Kyowa Kirin Co., Ltd.

KHK4083 Updates

October 4, 2021

Event Summary

[Event Name]	KHK4083 Updates	
[Date]	October 4, 2021	
[Number of Speakers]	2	
	Masutaka Furue	Professor Emeritus, Kyushu University
	Yoshifumi Torii	Executive Officer, Vice President, Head, R&D Division

Presentation

Moderator: We will now begin the briefing session. In today's session, we will provide an overview of the results of the Phase II study of KHK4083, which Kyowa Kirin is co-developing with Amgen Inc. These results were presented at the EADV Congress on October 2 at 5:00 PM Japan time.

Today's speakers are Professor Masutaka Furue, Professor Emeritus of Kyushu University, and Dr. Yoshifumi Torii, Executive Officer, Vice President, and Head of Research and Development.

First, Professor Furue will lecture on the pathogenesis of atopic dermatitis, and the latest treatment options. After that, Dr. Torii will give an overview of the results of the Phase 2 study presented at the conference. Afterwards, we will take questions from the audience. Before the lecture, Dr. Torii will provide an introduction of Professor Furue's work. Dr. Torii, please go ahead.

Torii: Thank you. Professor Furue is a specialist in the research and treatment of atopic dermatitis. He has been involved in the preparation of guidelines for the Japanese Dermatological Association, serving as the head of the Atopic Dermatitis Research Group of the Ministry of Health, Labour and Welfare. He has also served as the Chair of the Atopic Dermatitis Guidelines Committee of the Japanese Dermatological Association.

In addition, he has been making significant contributions to the field of dermatology in a wide range of areas, including research, clinical practice, education, and impacts on broader society. He has worked to disseminate information obtained through his research activities to the general public through his website in an easy-to-understand manner. In this way, he has promoted the spread of information about useful treatment methods.

Until March of this year, he served as the sixth Professor of Dermatology at the Kyushu University Graduate School of Medicine. After 23 1/2 years of work as a Professor, he became a Professor Emeritus of Kyushu University in April of this year. Thank you for joining us, Professor Furue.

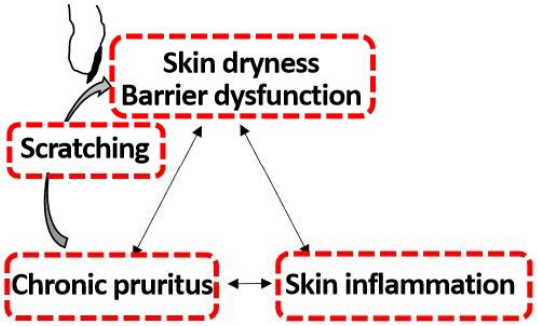
Furue: Thank you very much, Dr. Torii. I'm humbled by your introduction. I am Furue from Kyushu University. Today, I would like to talk about the pathogenesis of atopic dermatitis and the latest treatments.

As for conflicts of interest, I receive lecture fees and consulting fees from Kyowa Kirin Co., Ltd.

Top 20 prevalence of skin diseases in 67,448 patients

Rank	Name of Disease	67,448	
1	Miscellaneous eczema	12,590	18.67%
2	Atopic dermatitis	6,733	9.98%
3	Tinea pedis	4,379	6.49%
4	Urticaria/angioedema	3,369	4.99%
5	Tinea unguium	3,231	4.79%
6	Viral wart	3,028	4.49%
7	Psoriasis	2,985	4.43%
8	Contact dermatitis	2,643	3.92%
9	Acne	2,430	3.60%
10	Seborrheic dermatitis	2,213	3.28%
11	Hand eczema	2,024	3.00%
12	Miscellaneous benign skin tumors	1,666	2.47%
13	Alopecia areata	1,653	2.45%
14	Herpes zoster/ zoster-associated pain	1,609	2.39%
15	Skin ulcer (nondiabetic)	1,334	1.98%
16	Prurigo	1,229	1.82%
17	Epidermal cyst	1,194	1.77%
18	Vitiligo vulgaris	1,134	1.68%
19	Seborreic keratosis	1,095	1.62%
20	Drug eruption/toxicoderma	1,018	1.51%
Total		57,557	85.34%

Furue et al. J Dermatol. 2011;38:310-20



3

This slide shows the top 20 most common dermatological diseases, as published by the Japanese Dermatological Association in 2011.

The number one disease is miscellaneous eczema. Of the 67,448 patients with various types of dermatological disease, 12,590 patients, or 18.67%, had miscellaneous eczema.

Concerning atopic dermatitis, the number of patients is 6,733. It is a very common disease in dermatology, accounting for 9.98% of all cases.

Of course, there are people with mild, moderate, and severe disease states. Those with mild disease can be treated relatively easily. It can be challenging to manage the severe disease. This is even more true of atopic dermatitis than of other diseases. It is a prevalent disease, but it can have a significant impact on peoples' lives.

The symptoms of atopic dermatitis can be described in 4 main categories.

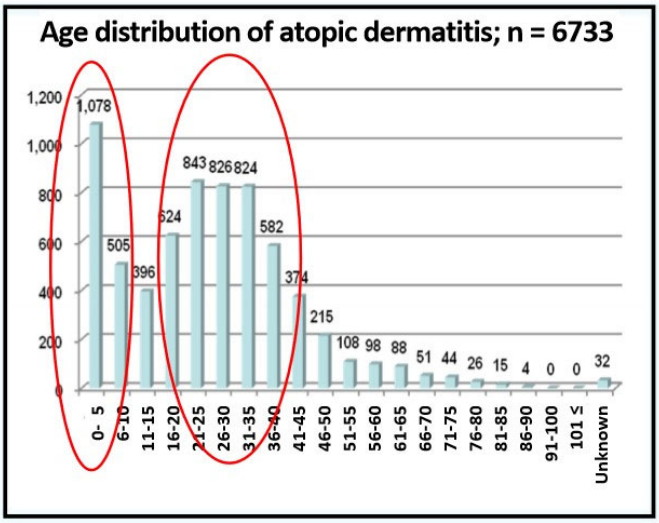
The first thing that happens is that the skin becomes very dry and no longer functions as a barrier. This will lead to skin irritation. This, in turn, leads to a very profound chronic itch. The more you scratch, the drier your skin becomes, and the more you scratch, the more you damage the skin barrier. That is why patients get this very itchy rash on their faces.

In the early stages of atopic dermatitis, the skin becomes dry, and the barrier is broken, which causes sweat to sink into the skin. This will cause itching in these areas. Sweating tends to accumulate in the creases of the

knees, elbows, wrists, and neck. Sweat accumulates in these areas, irritating them and causing them to itch, resulting in this very characteristic eczema.

Top 20 prevalence of skin diseases in 67,448 patients

Rank	Name of Disease	67,448	
1	Miscellaneous eczema	12,590	18.67%
2	Atopic dermatitis	6,733	9.98%
3	Tinea pedis	4,379	6.49%
4	Urticaria/angioedema	3,369	4.99%
5	Tinea unguium	3,231	4.79%
6	Viral wart	3,028	4.49%
7	Psoriasis	2,985	4.43%
8	Contact dermatitis	2,643	3.92%
9	Acne	2,430	3.60%
10	Seborrheic dermatitis	2,213	3.28%
11	Hand eczema	2,024	3.00%
12	Miscellaneous benign skin tumors	1,666	2.47%
13	Alopecia areata	1,653	2.45%
14	Herpes zoster/ zoster-associated pain	1,609	2.39%
15	Skin ulcer (nondiabetic)	1,334	1.98%
16	Prurigo	1,229	1.82%
17	Epidermal cyst	1,194	1.77%
18	Vitiligo vulgaris	1,134	1.68%
19	Seborreic keratosis	1,095	1.62%
20	Drug eruption/toxicoderma	1,018	1.51%
Total		57,557	85.34%



Furue et al. J Dermatol. 2011;38:310-20

4

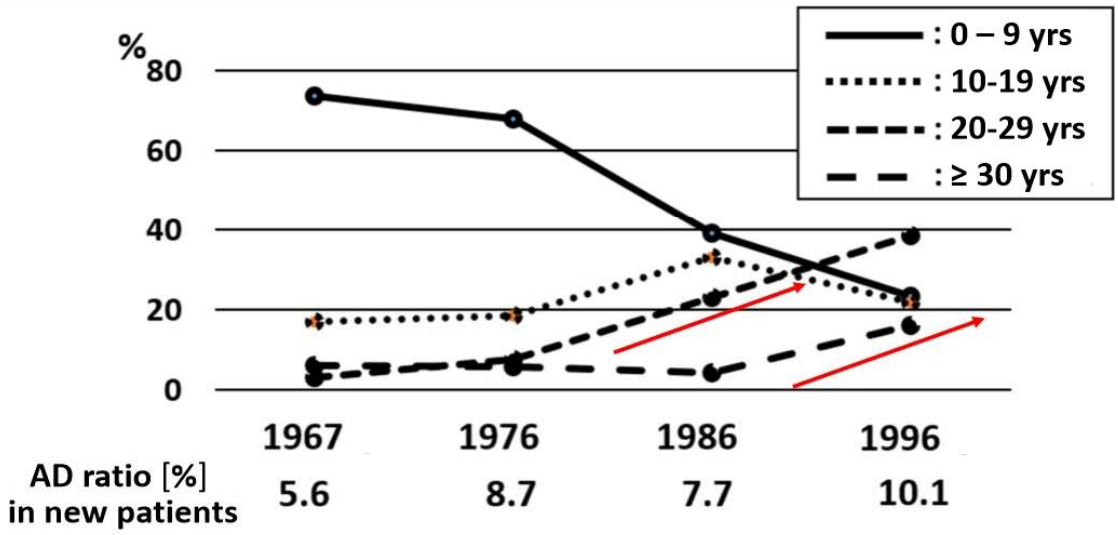
Now, let's look at the distribution of atopic dermatitis patients by age.

The right graph shows the age distribution of the 6,733 people I mentioned earlier, from 0 to 5 years old, and from 6 to 10 years old, in increments of 5 years, up to 100 years old or more.

As you can see, there are two prominent peaks in the age distribution of atopic dermatitis. The first peak is in the 0 to 5 age group. This is the reason why atopic dermatitis is said to be a disease of infants. However, the number of patients drops off in the 6 to 10 years group. Between the ages of 16 to 40, there is a second peak.

The symptoms in this group are stronger and last longer than those of children between the ages of 0 and 5 years old, and this is where the most severely ill patients accumulate. This is a very important time in peoples' lives. At a very critical time when people live very stressful lives working, building a social life, getting married, and having children, atopic dermatitis becomes stronger again.

Chronological age distribution of atopic dermatitis



Masutaka Furue, The Latest Treatment for Atopic Dermatitis, Gakushikai bulletin No.931, 115-120. 2018-IV

5

This slide shows the age distribution of the two major strata. The study population is first-time patients at the Dermatology Department of a hospital affiliated with the University of Tokyo. This slide shows the percentage of patients diagnosed with atopic dermatitis by age and the change in distribution over time.

In 1967, 5.6% of all first-time patients had atopic dermatitis. In 1976, the percentage was 8.7%; in 1986, 7.7%; and in 1996, 10.1%. This means that in the 30 years between 1967 and 1996, the percentage of patients visiting dermatology departments with atopic dermatitis nearly doubled, increasing to 10%.

This 10% figure was essentially unchanged in the 2011 figures I just showed, suggesting that the incidence of atopic dermatitis has not changed much since 1996. The number of patients doubled between 1967 and 1996. We notice something interesting when we look at the age distribution. In 1967, the percentage of children aged 0 to 9 was very high.

If you look at every 10 years from 1976, 1986, and 1996, the percentage of people between the ages of 20 and 29 has been increasing steadily. The percentage of people over 30 years old has been increasing since 1986, appearing to follow this trend. This is consistent with the distribution of atopic dermatitis in adolescents, as shown earlier.

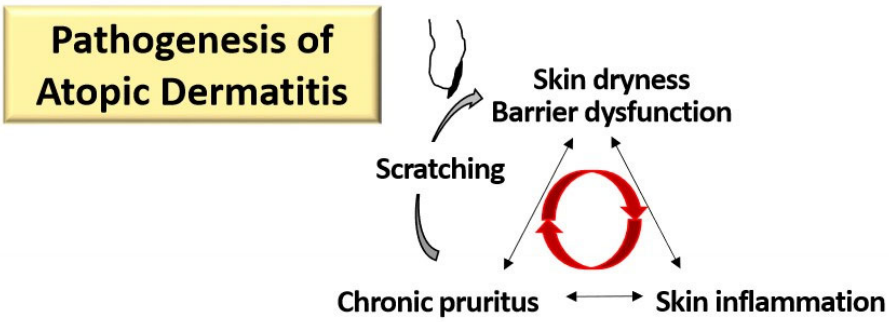
When the skin becomes dry and itchy, and eczema develops, the more you scratch it, the more eczema spreads from the skin creases to the whole body, and the more severe atopic dermatitis becomes.

Patients will complain of itching and sleeplessness, which are very severe symptoms.

Children with atopic dermatitis also suffer from insomnia. Children can be up all night, unable to sleep. This keeps the parents up, leading to insomnia for them as well. It can be called a familial disease.

Other issues can arise as symptoms progress. Patients may have difficulty attending school or have difficulty working.

As the disease progresses, it can lead to social phenomena like truancy and school withdrawal.



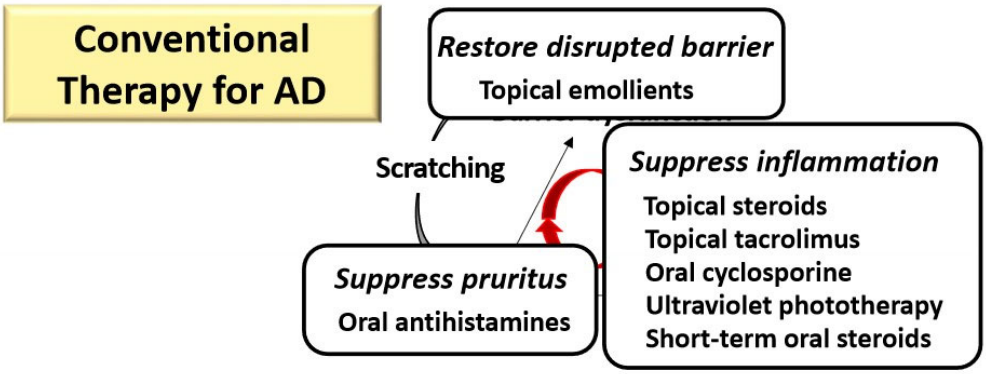
Furue M, Furue M. J Clin Med. 2021;10:2578.
Furue M. J Clin Med. 2020;9:3741

8

I would like to take a closer look at the pathogenesis of atopic dermatitis.

I mentioned earlier that there are four symptoms, and these are shown on the next slide.

These symptoms are inter-related, creating a very strong vicious cycle that can affect the whole body.



Furue M, Furue M. J Clin Med. 2021;10:2578.

Furue M. J Clin Med. 2020;9:3741

9

So far, we have seen this existing treatment for dry skin and skin barrier disorder. Moisturizers are applied externally to restore the barrier effect.

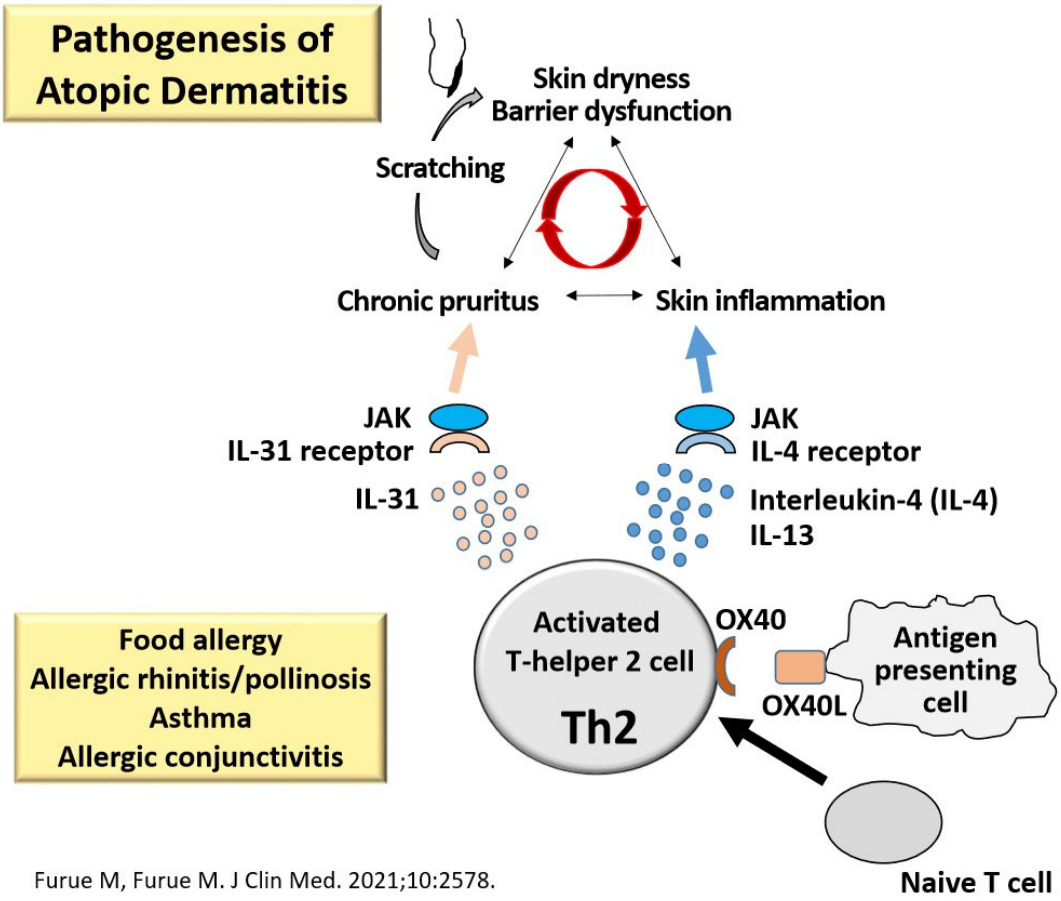
Next, there is skin inflammation. We use topical steroids, topical tacrolimus, oral cyclosporine, UV therapy, and short-term oral steroids to reduce inflammation.

Next is chronic itching. Antihistamines are the only medication known to reduce itching. As I will show later, itching in atopic dermatitis is completely different from itching in urticaria.

Antihistamines work very well for itching caused by urticaria. Unfortunately, they do little to suppress itching caused by atopic dermatitis. However, as there are no other treatment options, antihistamines have been used.

As I will discuss later, it has been discovered that interleukin 31 (IL-31) is the main cause of itching in atopic dermatitis.

Patients are actually not very satisfied with these existing treatments, as they are slow to take effect and not very effective.



Furue M, Furue M. J Clin Med. 2021;10:2578.

Furue M. J Clin Med. 2020;9:3741

10

Recently, however, we have learned more about the source of these conditions.

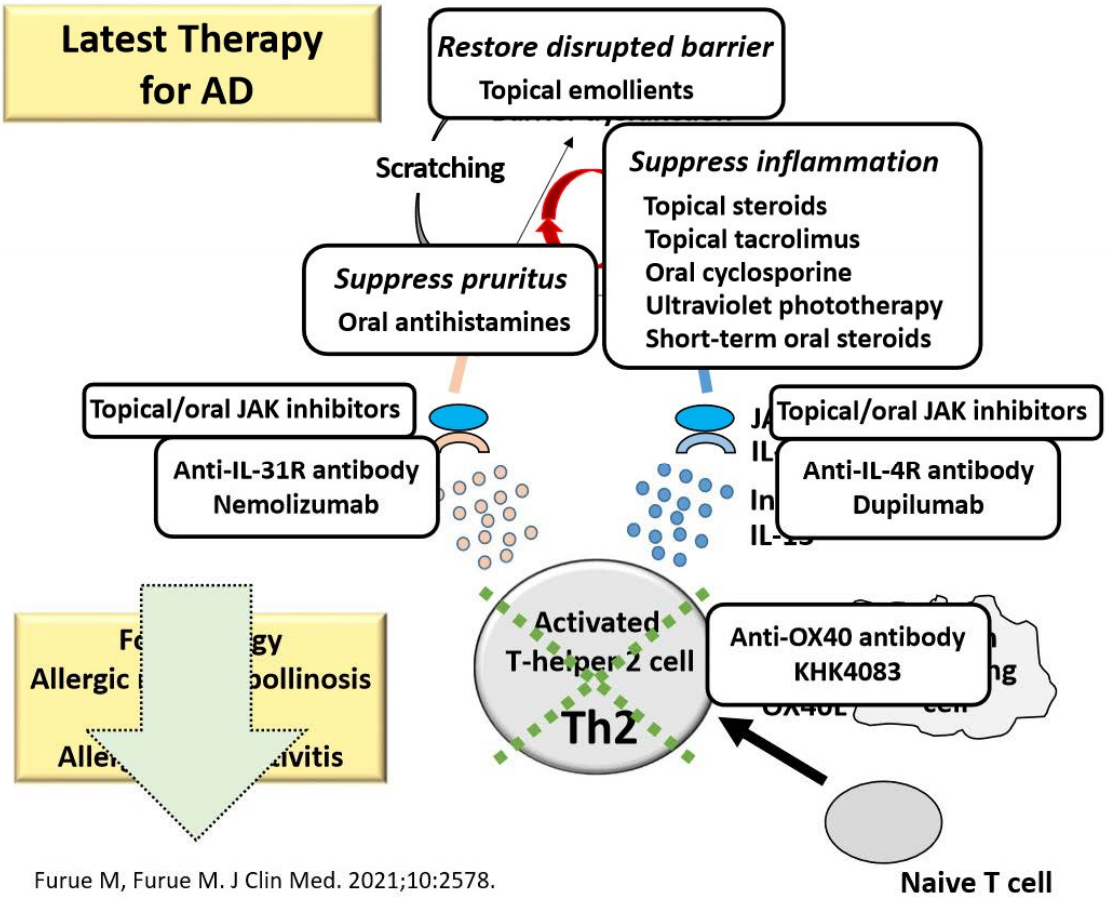
This is because the number of activated Th2 cells has significantly increased. These Th2 cells secrete cytokine proteins, such as interleukin-4, interleukin-13, IL-4, and IL-13. When this protein binds to the IL-4 receptor on skin cells, it activates a downstream protein called JAK, causing skin dryness, skin inflammation, and chronic itching.

Next, I'll say a bit more about this chronic itch. In addition to IL-4 and IL-13, Th2 cells produce a protein called IL-31, a cytokine, which binds to IL-31 receptors on skin cells, especially nerve cells, and activates JAK downstream, resulting in chronic itching. This is the etiology of the disease.

In order for Th2 cells to be activated, naive T cells must be stimulated by antigen-presenting cells. It has been found that stimulation via the OX40 receptor expressed on activated Th2 cells is very important here. This occurs through the OX40 ligand (OX40L). Conversely, activated Th2 cells expressing OX40 have been found to produce a large amount of IL-4, IL-13, and IL-31.

Other allergic diseases have also been found to involve activated helper T cells, Th2 cells. These include food allergies, allergic rhinitis, hay fever, asthma, and allergic conjunctivitis.

Because Th2 cell activation is the main cause of disease in all of these cases, atopic dermatitis and other allergic diseases are often seen together.



Furue M, Furue M. J Clin Med. 2021;10:2578.

Furue M. J Clin Med. 2020;9:3741

11

Let's move on to the latest treatments.

In addition to the existing treatments I just mentioned, the next slide shows treatments from the past 5 years. Receptor antibodies have been launched to suppress the activation of IL-4 and IL-13 receptors. This is dupilumab. Topical and oral JAK inhibitors are now available.

In addition, anti-IL-31 receptor antibodies have emerged to block the action of IL-31, which causes the itch. Clinical trials for anti-IL-31 receptor antibodies have now been completed, and an application has been submitted to the Ministry of Health, Labour and Welfare. JAK inhibitors, topical and oral, have also been shown to reduce itching.

Antibody therapy against OX40 is now being developed. This is KHK4083, the topic of today's talk.

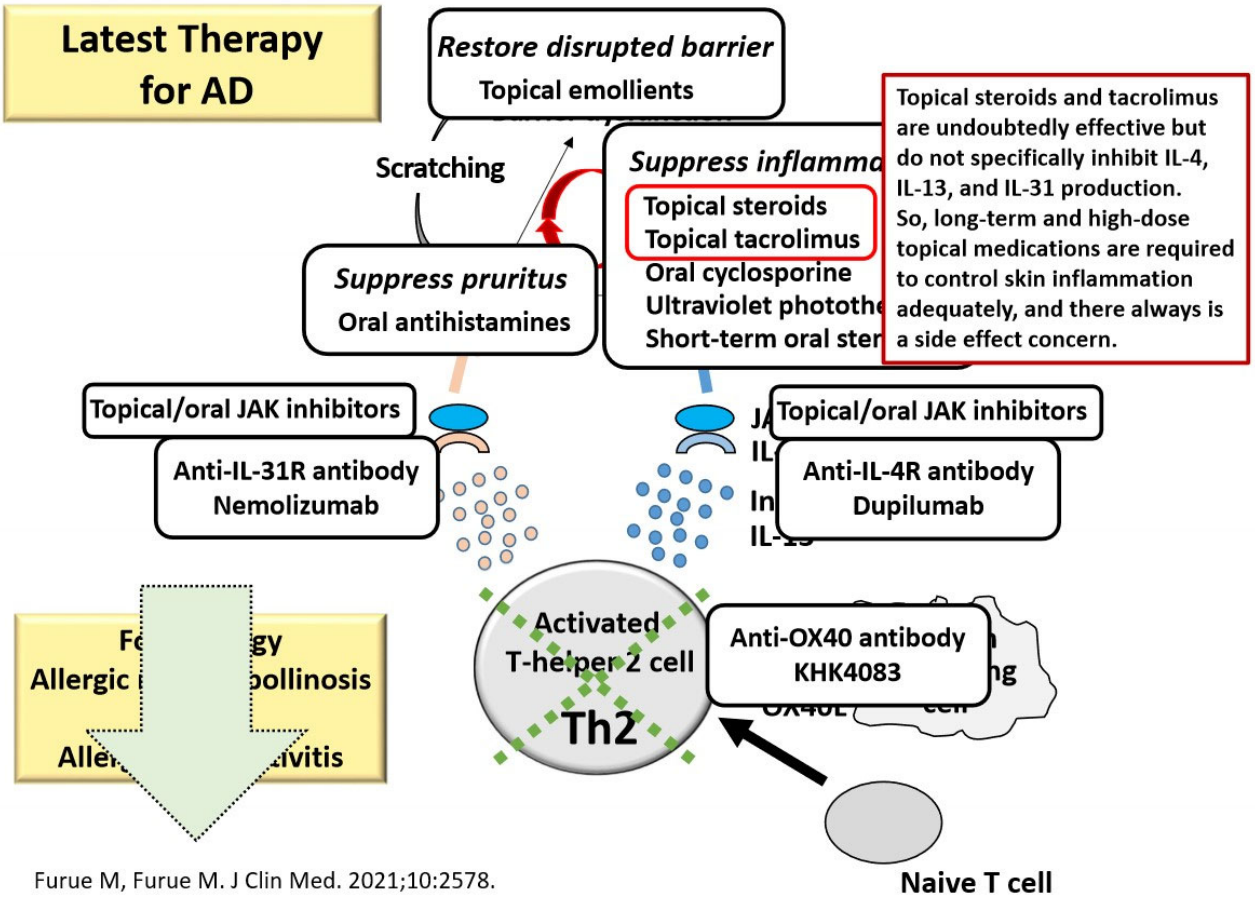
The goal of this therapy is to reduce the number of activated Th2 cells. As the root cause is the same, this therapy offers the potential to control food allergies and other allergic diseases, in addition to atopic dermatitis.

By the way, some people have concerns about treatment using topical steroids. However, topical steroids alone can improve the condition significantly. That’s the reason it has been commonly used as an existing therapy.

The downside is that it is very painful for the patients. Because it is for external use, patients have to apply it by themselves. For example, the area on the upper back is very difficult to reach, so patients need someone

to help them. In addition, it is very sticky and uncomfortable to sleep at night, and children do not want to apply it because of the stickiness.

Additionally, when applied regularly for an extended period, the hormonal effects of steroid hormones can cause the skin to become thinner, which is a very unpleasant side effect.



Furue M, Furue M. J Clin Med. 2021;10:2578.

Furue M. J Clin Med. 2020;9:3741

13

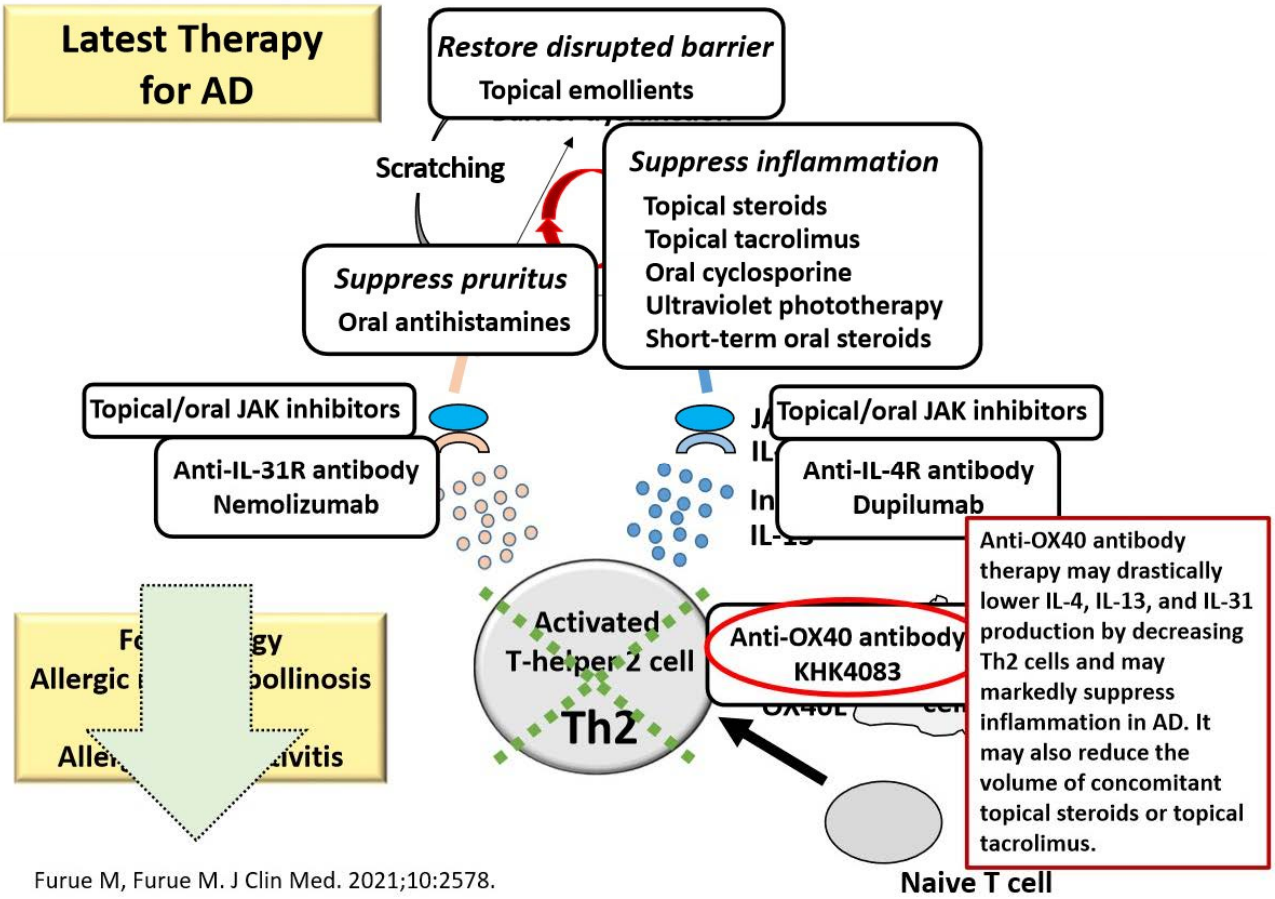
What element of the pathology of atopic dermatitis do these topical steroids and topical tacrolimus suppress?

As is shown in the square box, topical steroids and topical tacrolimus are certainly effective, but they do not suppress the production of IL-4, IL-13, or IL-31 in a pinpoint manner.

Therefore, long-term and high-dose topical medication are necessary to control skin inflammation adequately.

As a result, the occurrence of side effects has always been a concern.

The challenge with these treatments is balancing the desired effects and the side effects.



On the other hand, the topic of today's talk, KHK4083, is an anti-OX40 antibody.

KHK4083 causes a reduction in the number of Th2 cells.

As a result, the production of IL-4, IL-13, and IL-31 is thought to be drastically reduced. Therefore, atopic dermatitis can be markedly suppressed.

Although we cannot eliminate the use of topical steroids and topical tacrolimus, we can expect to reduce the amount of these drugs used and the amount used in combination therapy.

The benefit of an injectable drug is that the injection reduces systemic inflammation, reducing the level of topical application necessary to treat local inflammation when a rash inevitably appears.

Drug efficacy image of the latest therapy (personal opinion)

	Local skin inflammation		Systemic inflammation	
	IL-4/IL-13 axis inhibition	IL-31 axis inhibition	IL-4/IL-13 axis inhibition	IL-31 axis inhibition
Topical steroids	+ +	+ +	+	+
Topical tacrolimus	+ +	+ +	+	+
Oral steroids	+	+	+ +	+ +
Oral cyclosporin	+	+	+ +	+ +
Anti-IL-4R antibody	+ + +	+	+ + +	+
Anti-IL-31R antibody	+	+ + +	+	+ + +
Topical JAK inhibitors	+ +	+ +	+	+
Oral JAK inhibitors	+ +	+ +	+ +	+ +
Anti-OX40 antibody	+ + +	+ + +	+ + +	+ + +

15

This slide shows my impression of the effectiveness of these treatments, including more recent treatments.

The inflammation seen in atopic dermatitis can be divided into local skin inflammation and systemic inflammation. Immune activation and Th2 cell production occur in the bloodstream, and we refer to this as the systemic inflammation part. This can be further divided into two axes: the first is IL-4- and IL-13-mediated; the second is IL-31-mediated. We can also consider the effects of treatment by category.

Since the topical steroids in the left frame are for external use, they can suppress the IL-4/IL-13 and IL-31 axes of local skin inflammation to some extent. However, it does not spread to the whole body, so there is very little, if any, suppression of systemic inflammation. The same is true of topical tacrolimus.

The opposite is true for oral steroids, which have little effect on local skin inflammation but have a stronger effect on systemic inflammation. Oral cyclosporine has the same character as oral steroids, tending to reduce systemic inflammation rather than local skin inflammation.

Anti-IL-4 receptor antibodies are naturally able to very strongly inhibit the IL-4/IL-13 axis, either topically in the skin or systemically. On the other hand, there will be less inhibition of the IL-31 axis. Of course, the inhibition is not zero. This is because IL-4, IL-13, and IL-31 are also produced from the same activated Th2 cells. So, if the activation of Th2 cells is suppressed by inhibiting IL-4/IL-13 axis, naturally, IL-31 will be slightly suppressed as the number of Th2 cells decreases.

Conversely, anti-IL-31 receptor antibodies cause very strong suppression of IL-31 locally on the skin and throughout the body, but less suppression of the IL-4/IL-13 axis.

Topical JAK inhibitors are very similar to topical steroids and topical tacrolimus. They suppress both axes of IL-4/IL-13 and IL-31 for local skin inflammation, but they do not suppress systemic inflammation very well because they are topical.

However, since JAK inhibitors exist downstream of various receptors, high concentrations of JAK inhibitors can cause very strong side effects. This is why we take low doses, so the effect isn't as pronounced. That's why it's listed here as 2-plus.

On the other hand, this anti-OX40 antibody reduces the number of Th2 cells, suppressing both the IL-4/IL-13 axis and the IL-31 axis. Additionally, it acts both locally on the skin and systemically. As a result, we expect it to be the most powerful of the current treatment options.

This concludes my presentation. Thank you very much for your attention.

Moderator: Thank you very much, Professor Furue. Dr. Torii will now give an overview of the results of a Phase II trial of KHK4083. Dr. Torii, please go ahead.

Torii: Professor Furue, thank you very much for your very clear lecture on the pathogenesis and latest treatment of atopic dermatitis. I would now like to introduce the data that I presented at the EADV late-breaking session on October 2.

Here is the actual presentation title.

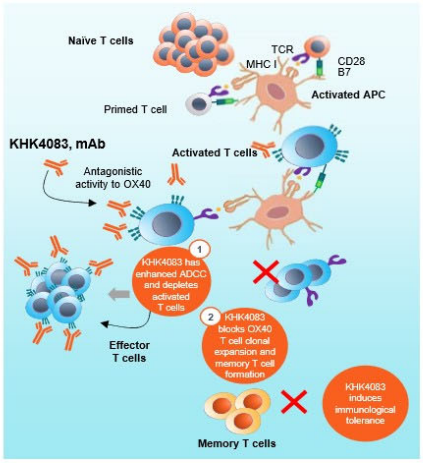
Of the results of the Phase II study of KHK4083 in moderate to severe atopic dermatitis, the efficacy and safety data were presented at the congress.

KYOWA KIRIN

EADV 2021

KHK4083/AMG 451 targets OX40 as a potential novel target for AD treatment

- Activation of Th2 and other T-cell subsets is central in atopic dermatitis (AD)
- The OX40–OX40L axis plays a critical role in long-lasting T-cell responses
  - OX40 is primarily expressed by activated T cells and binds OX40L on antigen-presenting cells (APCs), facilitating the effector function of T cells
- KHK4083/AMG 451 is a fully human, anti-OX40, non-fucosylated IgG1 monoclonal antibody with enhanced antibody-dependent cellular cytotoxicity (ADCC)[1]
  - It inhibits and depletes activated T cells, inhibiting T-cell clonal expansion and memory T-cell formation[2]



Mechanism of action of KHK4083[2]

CD28, cluster of differentiation 28; IgG, immunoglobulin G; MHC, major histocompatibility complex; mAb, monoclonal antibody; TCR, T-cell receptor; Th2, T-helper 2; TNF, tumor necrosis factor

[1]Nakagawa H et al. J Dermatol Sci. 2020; 99(2):82–89; [2]Papp KA et al. J Eur Acad Dermatol Venereol. 2017, 31(8):1324–1332.

4

This slide will explain again the mechanism of action of KHK4083.

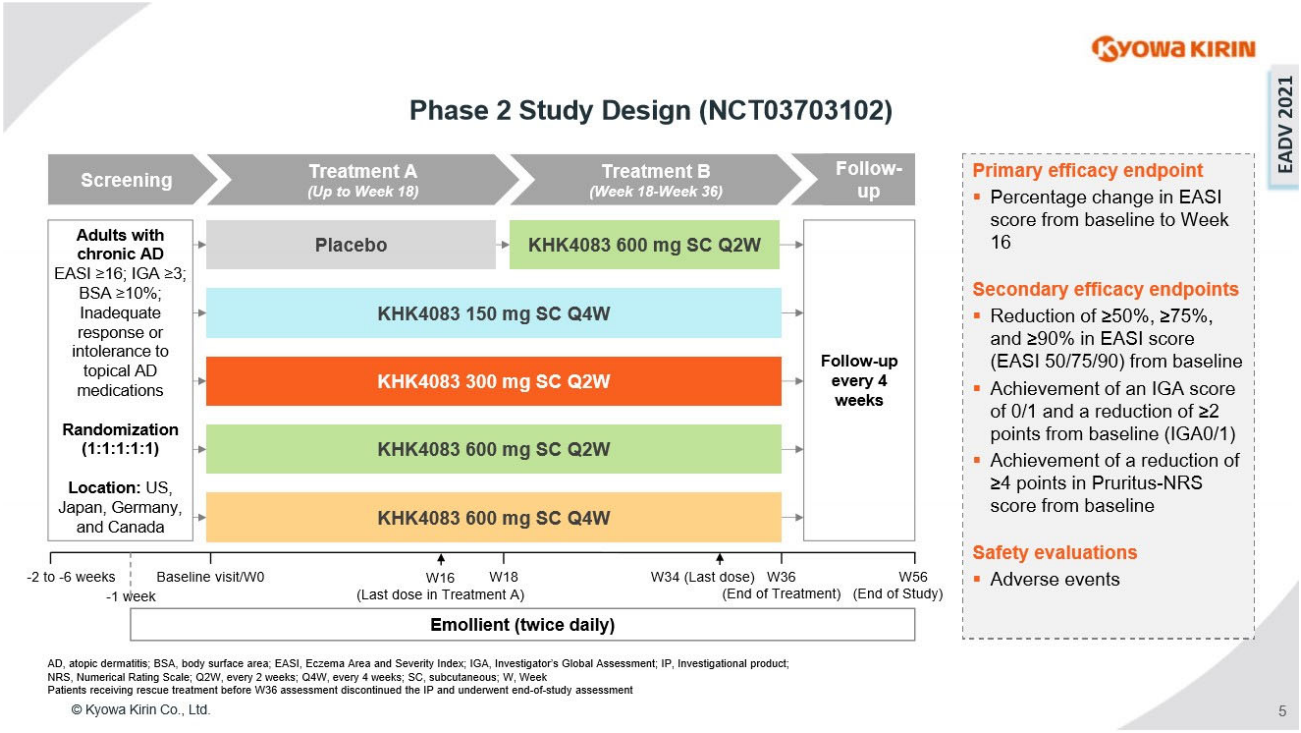
First of all, as Professor Furue explained earlier, activation of several T cell subsets, including Th2 cells, plays a central role in the pathogenesis of atopic dermatitis.

It is also known that OX40 and OX40 ligand signaling play an important role in long-term T-cell response. OX40, which is mainly expressed by activated T cells, promotes the effector function of T cells through binding with the OX40 ligand on antigen-presenting cells.

KHK4083 is a human anti-OX40 monoclonal antibody created with our Company's Potelligent technology, featuring enhanced ADCC activity. In addition to its potent inhibition of OX40 signaling, it has the ability to remove OX40-positive cells by ADCC activity. This inhibits the clonal expansion of T cells and the formation of memory T cells by suppressing or removing activated Th2 cells. As a result, there is prolonged suppression of immune overactivity in diseases such as atopic dermatitis.

Among several Phase I studies conducted to clarify the potential of KHK4083, the study in atopic dermatitis showed interesting results regarding tolerability and persistence of drug effect.

Subsequently, this Phase II study was conducted to evaluate the efficacy and safety of various dosing regimens.



Please see the next slide. This slide shows the design of the Phase II study.

The study was double-blind, placebo-controlled, and conducted at sites in Japan, the United States, Canada, and Germany. Subjects with moderate to severe adult chronic atopic dermatitis with an EASI score of at least 16, an IGA score of at least 3, and a BSA of at least 10% as of prior checkups and pre-administration tests were included.

Another inclusion criterion was insufficient response to topical therapy, or topical therapy not medically recommended in the 1-year period prior to the pretest.

After inclusion, subjects were randomly assigned to 5 groups: placebo group, KHK4083 subcutaneously at 150 mg every 4 weeks, 300 mg every 2 weeks, 600 mg every 2 weeks, and 600 mg every 4 weeks.

For all groups, moisturizers are available twice a day from 1 week before the first dose until the end of the treatment period, but topical steroids are not allowed.

In the placebo group, of the 56-week study period, the first 18 weeks were placebo-controlled treatment period A. This was followed by an 18-week treatment period B that all subjects shifted KHK4083 treatment with 600 mg every 2 weeks.

All groups then underwent a 20-week follow-up.

KYOWA KIRIN

EADV 2021

Baseline Demographics and Disease Characteristics (Safety Analysis Set)

All baseline parameters were generally well-balanced among the treatment groups

Characteristics*		KHK4083 150 mg Q4W N=54	KHK4083 600 mg Q4W N=53	KHK4083 300 mg Q2W N=55	KHK4083 600 mg Q2W N=54	Placebo/ KHK4083 600 mg Q2W N=57	Total N=273
Age, years		37.4 ± 13.6	38.9 ± 14.6	37.5 ± 14.1	37.3 ± 16.3	38.7 ± 14.4	38.0 ± 14.5
Sex, male, n (%)		37 (68.5)	31 (58.5)	31 (56.4)	30 (55.6)	31 (54.4)	160 (58.6)
Race, n (%)	Asian: Japanese	30 (55.6)	28 (52.8)	32 (58.2)	30 (55.6)	30 (52.6)	150 (54.9)
	Asian: Other	6 (11.1)	4 (7.5)	5 (9.1)	3 (5.6)	7 (12.3)	25 (9.2)
	Black or African American	3 (5.6)	1 (1.9)	2 (3.6)	1 (1.9)	6 (10.5)	13 (4.8)
	White	14 (25.9)	20 (37.7)	16 (29.1)	20 (37.0)	14 (24.6)	84 (30.8)
	Other	1 (1.9)	0	0	0	0	1 (0.4)
Body mass index at screening, kg/m^2		24.99 ± 4.81	24.69 ± 5.69	26.69 ± 7.24	25.19 ± 6.49	24.26 ± 5.23	25.16 ± 5.97
Duration from diagnosis of AD to randomization, years		6.47 ± 6.59	8.40 ± 8.32	8.59 ± 9.58	6.42 ± 5.69	6.41 ± 5.98	7.26 ± 7.32
Severity of AD - IGA, n (%)	3	30 (55.6)	28 (52.8)	30 (54.5)	29 (53.7)	31 (54.4)	148 (54.2)
	4	24 (44.4)	25 (47.2)	25 (45.5)	25 (46.3)	26 (45.6)	125 (45.8)
Pruritus-NRS score		7.8 ± 1.6	7.5 ± 2.3	7.5 ± 1.6	7.6 ± 1.9	7.2 ± 2.3	7.5 ± 2.0
EASI score		32.8 ± 13.1	32.5 ± 12.7	32.2 ± 13.4	31.1 ± 11.8	29.2 ± 13.3	31.5 ± 12.8
SCORAD score		68.75 ± 12.57	69.44 ± 13.64	68.52 ± 14.36	68.79 ± 14.36	66.35 ± 14.05	68.34 ± 13.76
Percent BSA		59.5 ± 23.7	59.1 ± 25.2	56.8 ± 21.8	55.3 ± 23.4	54.3 ± 23.5	56.9 ± 23.5
Previous use of biological products for treatment of AD, n (%)		7 (13.0)	5 (9.4)	8 (14.5)	8 (14.8)	9 (15.8)	37 (13.6)

AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; SCORAD, Severity scoring of atopic dermatitis; Q2W, every 2 weeks; Q4W, every 4 weeks
*Data presented as mean ± SD, unless specified otherwise. Data presented from safety analysis set, which included patients who received at least 1 dose of KHK4083; 273 of the 274 randomized patients were included in the safety analysis set.

6

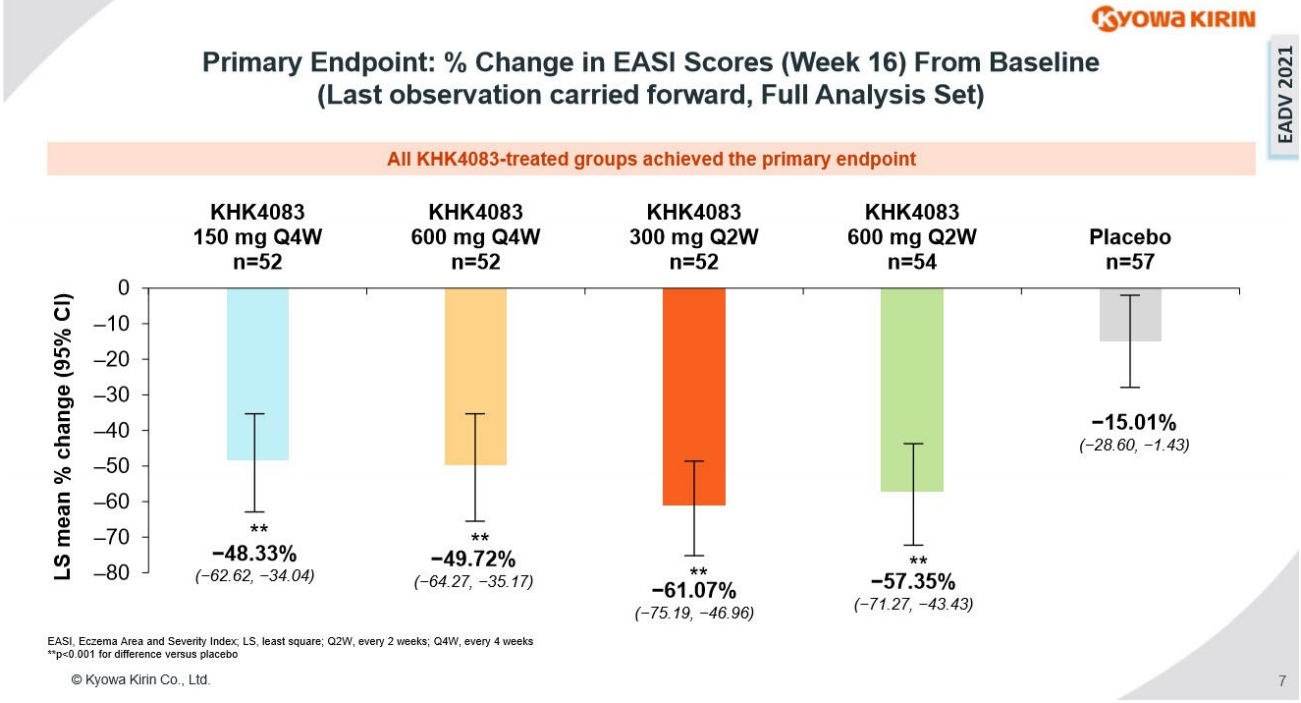
Here is the profile of the subjects at baseline in each group after randomization.

As you can see, all parameters, including EASI score, are roughly balanced over the all treatment groups.

10% to 15% of the subjects had been treated previously with biologics for atopic dermatitis.

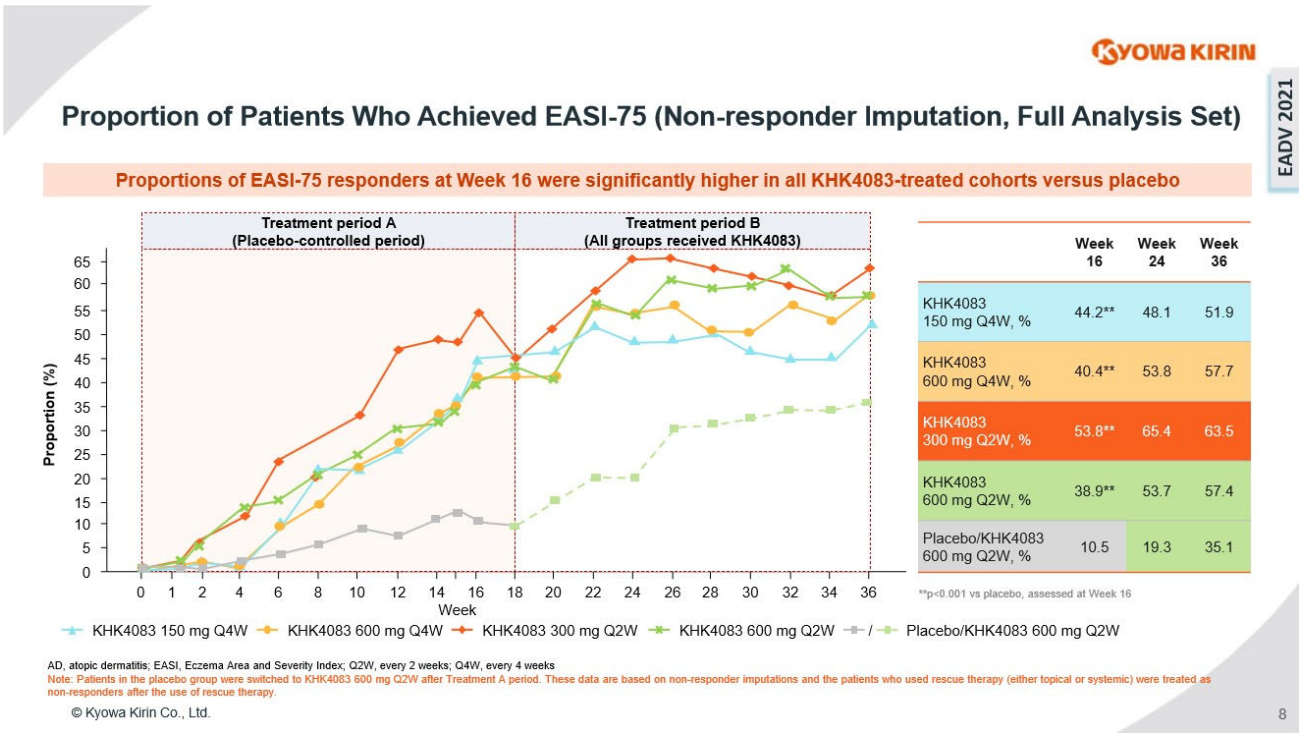
Many of the subjects had a history of treatment with topical steroids or oral immunosuppressive agents in the past.

Of the total 274 subjects subjected to randomization, the 273 subjects who received at least 1 dose of the actual drug were the target population for the safety analysis.



This shows the percentage change from baseline in EASI score at 16 weeks, which is the primary endpoint of this study.

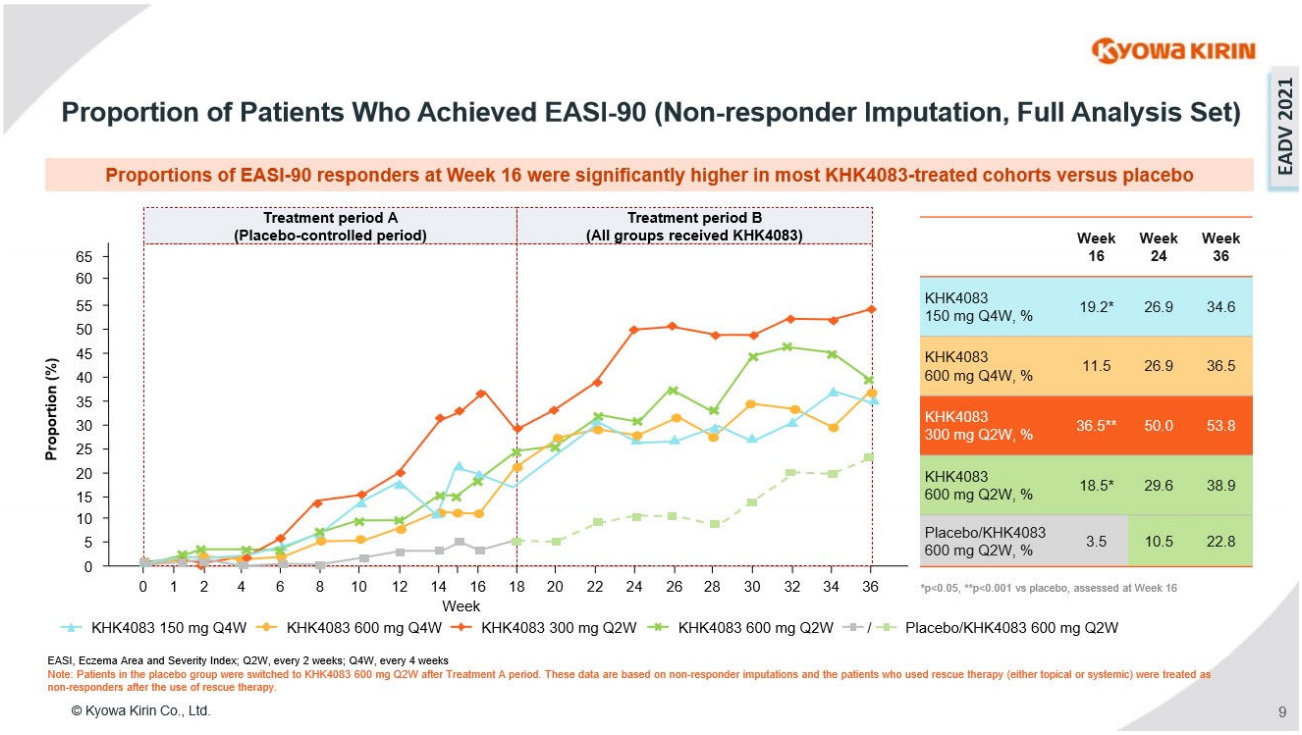
As you can see, the rate of change in all KHK4083 groups, regardless of the dosing regimen, was significantly greater than the rate of change in the placebo group.



This shows the EASI-75 achievement rate at 16 weeks, that is 1 of the secondary endpoints, and the trend until the end of treatment.

The percentage of patients who achieved EASI-75 at 16 weeks was significantly higher in all active drug groups than in the placebo group. The highest achievement rate was seen in the group that received 300 mg of the drug every 2 weeks.

Interestingly, further improvement in the EASI-75 achievement rate was observed in treatment period B after 16 weeks. In treatment period B, KHK4083 was also administered to patients in the placebo group in treatment period A. Substantial improvement in EASI-75 achievement was also observed in this group.



Here is the achievement rate of EASI-90.

The EASI-90 achievement rate at 16 weeks was significantly higher in most of the active drug groups than in the placebo group.

As with the EASI-75 achievement rate, the highest achievement rate was seen in the group that received 300 mg of the drug every 2 weeks.

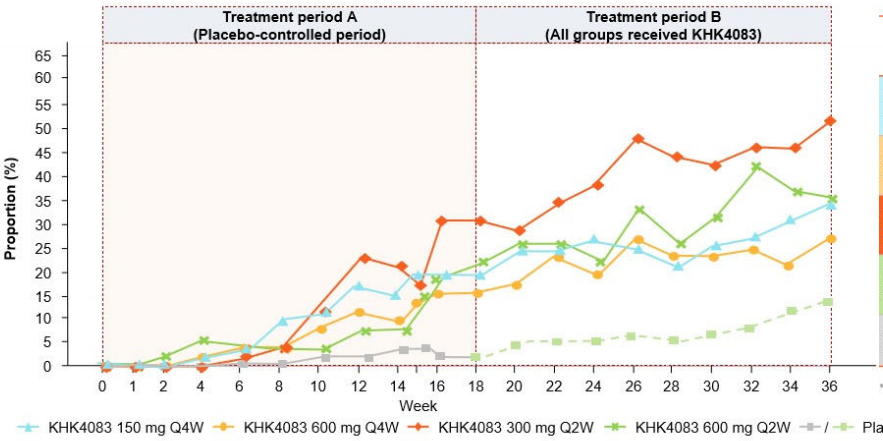
The EASI-90 achievement rate continued to increase from 16 to 36 weeks, and improvement was also seen in the group that switched from placebo to KHK4083 treatment in treatment period B.

KYOWA KIRIN

EADV 2021

Proportions of Patients Who Achieved an IGA Score of 0/1 and a Reduction of ≥2 Points from Baseline (Non-responder Imputation, Full Analysis Set)

In all KHK4083 groups, the proportion of subjects who achieved IGA score 0/1 gradually increased up to Week 36



	Week 16	Week 24	Week 36
KHK4083 150 mg Q4W, %	19.2*	26.9	34.6
KHK4083 600 mg Q4W, %	15.4*	19.2	26.9
KHK4083 300 mg Q2W, %	30.8**	38.5	51.9
KHK4083 600 mg Q2W, %	18.5*	22.2	35.2
Placebo/KHK4083 600 mg Q2W, %	1.8	5.3	14.0

*p<0.05, **p<0.001 vs placebo, assessed at Week 16

IGA, Investigator's General Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks

Note: Patients in the placebo group were switched to KHK4083 600 mg Q2W after Treatment A period. These data are based on non-responder imputations and the patients who used rescue therapy (either topical or systemic) were treated as non-responders after the use of rescue therapy.

Here is the achievement rate of IGA score improvement.

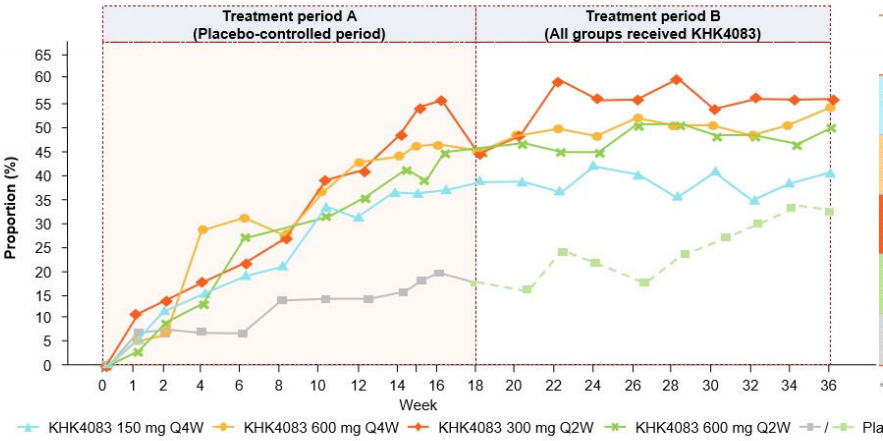
In the KHK4083 group, the percentage of subjects with an IGA score of 0 or 1 gradually increased through 36 weeks. In treatment period B, a substantial increase in the achievement rate was also observed in the group switching from placebo.

KYOWA KIRIN

EADV 2021

Proportions of Patients Who Achieved Reduction of ≥4 Points for Pruritus-NRS (Non-responder Imputation, Full Analysis Set)

Proportions of Pruritus-NRS responders at Week 16 were significantly higher in most KHK4083-treated groups versus placebo



	Week 16	Week 24	Week 36
KHK4083 150 mg Q4W, %	36.5	42.3	40.4
KHK4083 600 mg Q4W, %	46.2*	48.1	53.8
KHK4083 300 mg Q2W, %	55.8**	55.8	55.8
KHK4083 600 mg Q2W, %	44.4*	44.4	50.0
Placebo/KHK4083 600 mg Q2W, %	19.3	21.1	31.6

*p<0.05, **p<0.001 vs placebo, assessed at Week 16

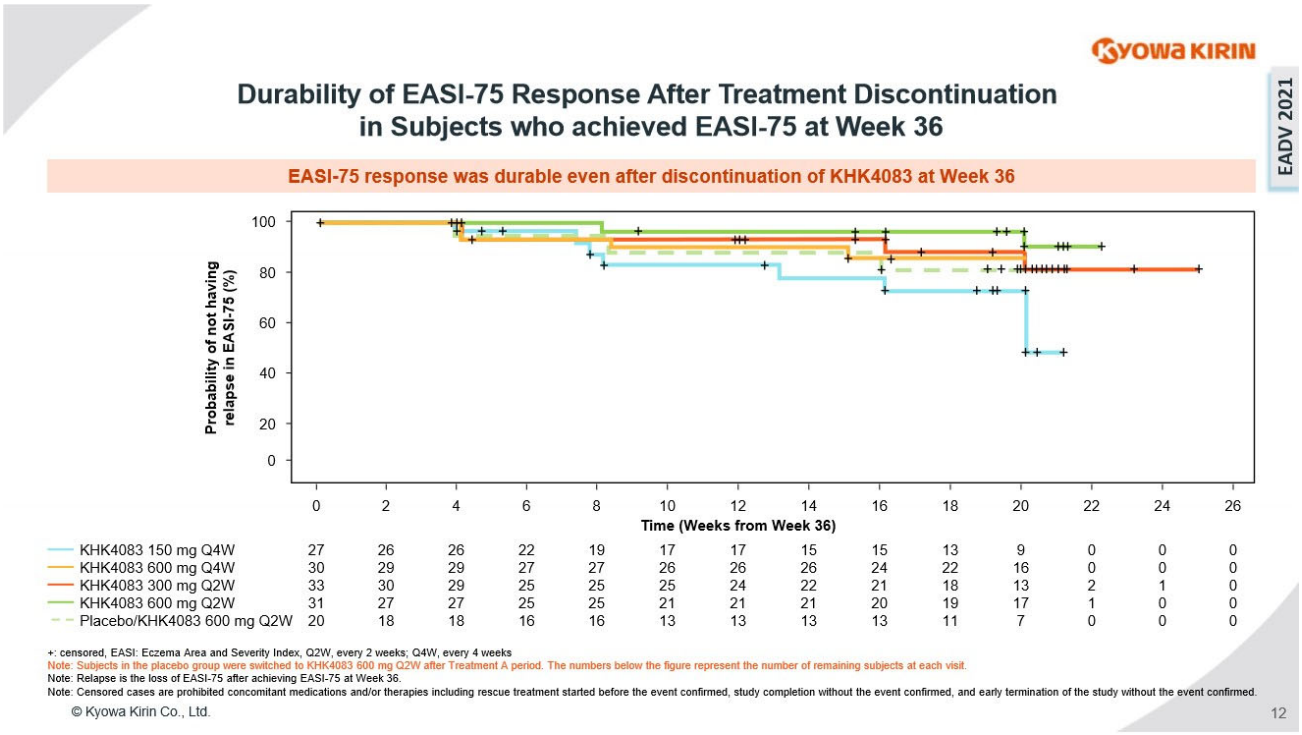
NRS, Numerical Rating Scale; Q2W, every 2 weeks; Q4W, every 4 weeks

Note: Patients in the placebo group were switched to KHK4083 600 mg Q2W after Treatment A period. These data are based on non-responder imputations and the patients who used rescue therapy (either topical or systemic) were treated as non-responders after the use of rescue therapy.

This is the achievement rate of improvement of 4 points or more in the pruritus-NRS score.

The percentage of subjects achieving improvement in the pruritus-NRS score at 16 weeks was higher in most of the active treatment groups than in the placebo group.

In addition, the increase in the achievement rate continued through to 36 weeks. In treatment period B, there was also an increase in the achievement rate in the group switching from placebo.



This slide shows the persistence of the EASI-75 response after the end of administration.

This graph shows the percentage of subjects who have achieved EASI-75 at 36 weeks after completing all treatment periods and have maintained EASI-75 over time.

At 56 weeks, or 20 weeks after the end of treatment, there was an approximate 70%-94% probability that the EASI-75 response maintained in all treatment groups.

KYOWA KIRIN

EADV 2021

TEAEs – Treatment A Period (Safety Analysis Set)

In Treatment A period, 81% TEAEs occurred in KHK4083 groups versus 72% in the placebo group

Category	KHK4083 150 mg Q4W N=54	KHK4083 600 mg Q4W N=53	KHK4083 300 mg Q2W N=55	KHK4083 600 mg Q2W N=54	KHK4083 Total N=216	Placebo N=57
Any TEAEs	37 (68.5)	45 (84.9)	47 (85.5)	46 (85.2)	175 (81.0)	41 (71.9)
Serious TEAEs	3 (5.6)	1 (1.9)	3 (5.5)	1 (1.9)	8 (3.7)	1 (1.8)
TEAEs leading to treatment discontinuation	5 (9.3)	3 (5.7)	7 (12.7)	4 (7.4)	19 (8.8)	12 (21.1)
All deaths	0	0	0	0	0	0
TEAEs with severity grade of ≥3	6 (11.1)	1 (1.9)	5 (9.1)	4 (7.4)	16 (7.4)	2 (3.5)

TEAE, treatment-emergent adverse event; Q2W, every 2 weeks; Q4W, every 4 weeks
Note: n=number of patients reporting at least 1 TEAE in that category except for all deaths. Data are presented as n (%).
Data presented from safety analysis set, which included patients who received at least 1 dose of investigational product; 273 of the 274 randomized patients were included in the safety analysis set.

13

The next slide covers TEAEs, Treatment-Emergent Adverse Events, during drug administration.

During treatment period A, TEAEs were observed in 81% of subjects across the active drug groups and 72% in the placebo group. Most of the TEAEs were mild to moderate, and there were no severe TEAEs attributable to administration of the study drug.

There were no cases of grade 5 or higher TEAE, no deaths, no hypersensitivity reactions, and no signs of increased risk of infection.

KYOWA KIRIN

EADV 2021

TEAEs in >5% of Subjects in the Total KHK4083 Group by Preferred Term – Treatment A Period (Safety Analysis Set)

- The most frequent TEAEs in KHK4083 groups were pyrexia, nasopharyngitis, worsening of AD, and chills
- Events of pyrexia and chills were mild to moderate in intensity and were mostly observed only after the first administration of KHK4083 and were not associated with any consequent treatment discontinuation
- No hypersensitivity reactions were observed

Preferred Term	KHK4083 150 mg Q4W N=54	KHK4083 600 mg Q4W N=53	KHK4083 300 mg Q2W N=55	KHK4083 600 mg Q2W N=54	KHK4083 Total N=216	Placebo N=57
Pyrexia	7 (13.0)	10 (18.9)	9 (16.4)	10 (18.5)	36 (16.7)	2 (3.5)
Nasopharyngitis	8 (14.8)	7 (13.2)	7 (12.7)	8 (14.8)	30 (13.9)	9 (15.8)
Dermatitis atopic	8 (14.8)	5 (9.4)	8 (14.5)	7 (13.0)	28 (13.0)	17 (29.8)
Chills	2 (3.7)	3 (5.7)	7 (12.7)	12 (22.2)	24 (11.1)	0
Headache	4 (7.4)	6 (11.3)	4 (7.3)	5 (9.3)	19 (8.8)	1 (1.8)
Aphthous ulcer	3 (5.6)	8 (15.1)	3 (5.5)	1 (1.9)	15 (6.9)	0
Nausea	3 (5.6)	2 (3.8)	1 (1.8)	7 (13.0)	13 (6.0)	1 (1.8)

PT, Preferred Term; TEAE, treatment-emergent adverse event; Q2W, every 2 weeks; Q4W, every 4 weeks
Note: Adverse events were coded using MedDRA version 23.0. Data are presented as **n (%)**.

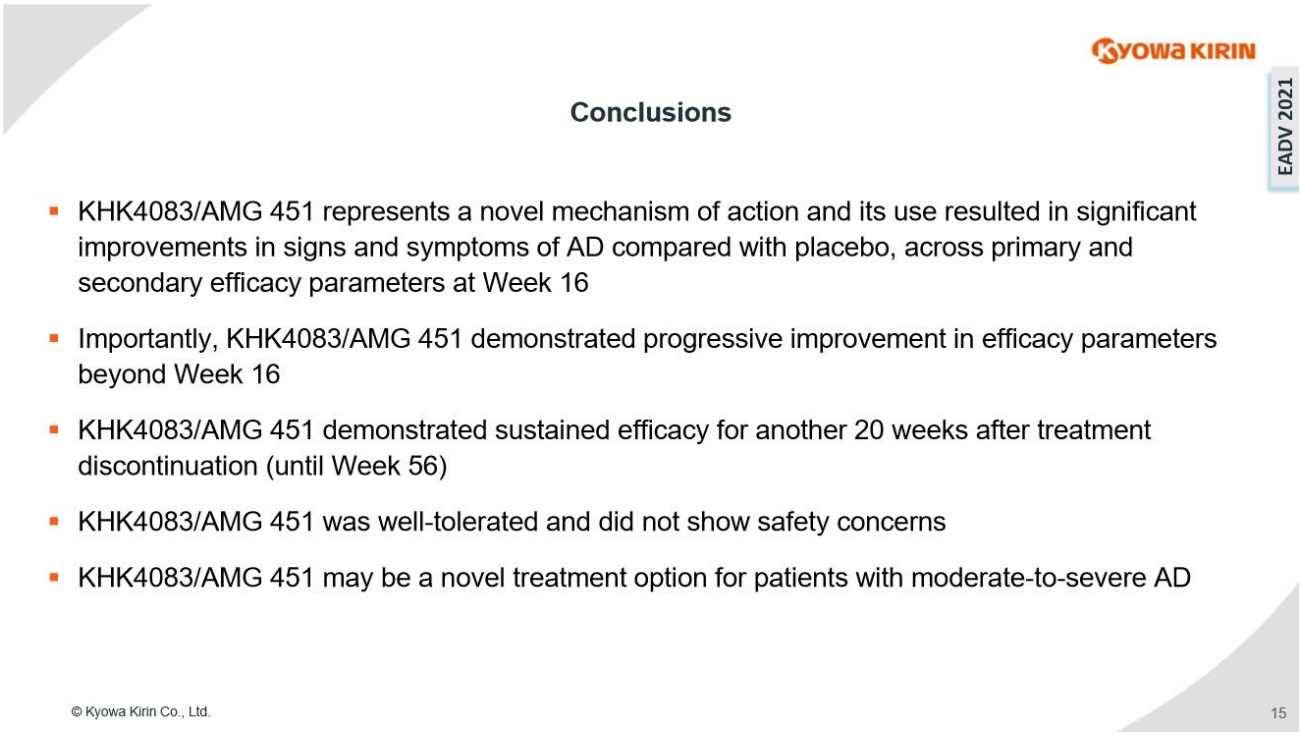
14

Here we have extracted TEAEs expressed in more than 5% of the subjects in all KHK4083 treatment groups.

The TEAEs with the highest incidence in the active drug group were fever in 16.7%, nasopharyngitis in 13.9%, worsening of atopic dermatitis in 13%, and chills in 11.1%.

Symptoms of fever and chills were mild to moderate, and they occurred only after the first dose.

In addition, there were no cases that led to discontinuation of administration.



Here is the conclusion.

KHK4083 has a novel mechanism of action and significantly improved the signs and symptoms of atopic dermatitis compared to the placebo group in the primary and secondary endpoints at 16 weeks.

Progressive improvement in efficacy parameters was also observed after 16 weeks, also indicating sustained efficacy even after 20 weeks from the end of treatment.

The drug was well tolerated, and no safety concerns were observed.

As a result, we believe that this therapy has the potential to be a new treatment option for moderate to severe atopic dermatitis.

Kyowa Kirin, in collaboration with its partner Amgen, will continue to develop the drug for atopic dermatitis and explore the applicability for other inflammatory diseases.

This concludes my presentation. Thank you very much for your attention.

Question & Answer

Moderator: I would now like to move on to the Q&A session.

Our first question comes from Mr. Yamaguchi of Citigroup Global Markets Japan.

Yamaguchi: This is Yamaguchi from Citigroup. Thank you for the explanation. I have 1 question for Professor Furue and 1 for Dr. Torii.

First, I would like to ask Professor Furue about the comparison between this data and that of Dupixent, which is the most commonly used biologic. In actual clinical use, I wonder if the anti-inflammatory effect of Dupixent tends to increase over a long period of time as it did in this case. Also, I think Dupi is administered once every 2 weeks. But if KHK4083 were to be administered once every 4 weeks, would that be a point of differentiation?

Furue: Thank you for your question. Of course, I can't say anything definite until this drug is actually released to the market, but I will state my personal opinion on the matter.

In this study, the treatment was stopped at 36 weeks, and patients were followed up thereafter. The first thing that is very interesting about this drug is that disease control was good even in the post-treatment phase.

Then if you look at the figure for the 36-week period presented today, the response at 16 weeks is already higher than that seen from Dupixent or existing antibodies, such as IL-31 receptor antibodies.

Continuing from there up to the 36-week timepoint, the response gradually becomes more pronounced. This is especially true of the red line. An EASI-75 score was achieved in 63.5% of patients in the 300 mg Q2W group, which is extremely high. Since this was not a head-to-head comparative study, we can only speak in terms of EASI. However, I suspect that the potential of this antibody is higher than that of other antibodies.

Yamaguchi: Thank you very much. In the case of Dupixent, it is administered once every 2 weeks, but I would like to ask about differentiation in the method of administration.

Furue: I agree that once every 4 weeks would be beneficial, but of course, this is something to be considered by the development team at Kyowa Kirin.

On the other hand, in the case of Dupixent, treatment is continued with Q2W administration for a matter of years. For this compound, there may be other options, such as a 36-week course of treatment. Other options could also include breaks in treatment.

Again, I think that these decisions will be made by Kyowa Kirin based on the overall study data.

Yamaguchi: Thank you very much. There is 1 thing that I would like to ask Dr. Torii. This is a comparison of administration methods. At a glance, to the untrained eye, the 300 mg Q2W dose seems to be the best, but for the convenience of patients, the 600 mg Q4W might also be a good choice.

Looking at it in the opposite way, it seems that there isn't much of an effect in the 600 mg Q2W group, or that the effect peaks out. Of course, decisions about dosing are the product of various future discussions, but what are your thoughts on this at present?

Torii: Thank you for your question, Mr. Yamaguchi. We are currently working on models and simulations and will be communicating with the FDA and other regulatory agencies on this issue.

As for the frequency of administration, 1 option could be 300 mg Q2W for initial induction, and after that, using a maintenance regimen with a slightly longer interval between doses. We will decide on this issue with the authorities in the future.

Yamaguchi: Thank you very much. That's all from me.

Moderator: Thank you very much. The next question comes from Mr. Kohtani of Nomura Securities.

Kohtani: I'm Kohtani from Nomura Securities. I think my first question is probably for Dr. Torii. Well, it might be 2 questions.

In the KHK4083 trial, it appears that the 600 mg twice a week is less effective. Dosage dependency seems to break down a bit here, so why is this higher dose less effective? I was wondering if you could tell me if you have a hypothesis about this.

Also, I would like to confirm this, but on page 13, there are TEAEs for which treatment has been discontinued. For the 300 mg Q2W group, the figure reached 13%. That seems a little higher than other groups. Treatment was discontinued for these patients, but I'm not entirely clear on the reason. Could you tell us why this figure is a little high?

Torii: Thank you for your question, Mr. Kohtani. As you mentioned, there is no clear difference in the dose response, but rather than a decline in efficacy in the 600 mg Q2W group, it seems that the effect peaks at 300 mg Q2W. Further improvement is limited even when the dosing is increased beyond that point. As I mentioned earlier, we are currently studying this issue using simulations and other methods.

Regarding TEAEs that led to discontinuation, we had contraindicated the use of TCS (Topical corticosteroids) even before the baseline. After that, if TCS was required as a rescue after the drug administration, we treated it as a discontinued case. For this reason, we recognize that the proportion of TEAEs that led to dose discontinuation in 300 mg Q2W group is slightly higher than in other treatment groups.

Kohtani: In short, this is because the rescue drug was used because the atopy worsened, and the administration was discontinued, right?

Torii: Yes, that is part of it.

Kohtani: Understood. The second question. I guess Dr. Michael Croft was also involved in the development of this drug. He wrote a paper in which he found a patient who was deficient in OX40. He found that the patient who had no OX40 at all had leishmaniasis and classic Kaposi's sarcoma. Kaposi's sarcoma is typically only seen in HIV patients, and I believe, in other such diseases affecting the immune system. The bottom line is that persistent immunity is lost without OX40.

I was wondering if there may be a concern about reduced immunity and risk of infectious diseases if this drug is kept administered for a long time. Professor Furue mentioned earlier about using an induction dose of once every 2 weeks and following that with a maintenance dose of once every 4 weeks, but by doing that and having a medication holiday, would the risk disappear? And would it be correct to assume that a next clinical trial to be carried out with such study design?

It may be difficult to comment as there was only 1 documented case of this, but could you tell us your thoughts on this?

Torii: Thank you for your question. As Professor Furue mentioned earlier, our anti-OX antibodies have a wider range of effects than other biologics. The risks include increased risk of infection, as you mentioned, and development of cancer due to suppression of Treg cells. At the moment, the number of patients is still small,

but we would like to proceed with development, while carefully assessing safety with regard to the risks you mentioned in large-scale Phase III trials.

Kohtani: So, at this point, the decision to include a medication holiday part in Phase III has not yet been made, right?

Torii As I mentioned earlier, the development of Phase III will be determined by the results of discussions with the regulatory authorities. We will present more information on that when it is confirmed.

Kohtani: Understood. Thank you very much.

Furue: This is Furue. I'd like to say a few words about the previous question, why the efficacy of the drug appears to be lower if the dose is higher. It is interesting to note that most antibody therapies show a phenomenon where the therapeutic effect is somewhat reduced when the amount of antibody is high.

This is 1 reason to conduct Phase I or Phase II studies to find best treatment regimen.

However, this is not limited to antibody therapy. There are also various drugs, such as FGF, which is a spray used to heal skin ulcers. This can be called high-dose inhibition. The higher the concentration of these biologic therapies, the less effective they are.

Before that decline, there is a point where the concentration is just right. The treatment effect can generally be seen in that way.

Kohtani: Thank you very much.

Moderator: Thank you very much. The next question is from Mr. Hashiguchi of Daiwa Securities.

Hashiguchi: My name is Hashiguchi from Daiwa Securities. Thank you. First, I would like to ask Professor Furue about his impression of this drug's effectiveness. I think you mentioned earlier that 63% of the EASI-75 is quite high, but in the Phase III study of Dupixent, 68.9% was achieved in combination with TCS, and over 50% was achieved in 16 weeks as a single agent. I believe there is also a study of nemolizumab that reported more than 60% at 64 weeks of long-term treatment.

If you simply compare the numbers, it doesn't look like KHK4083 is much stronger than the others at first glance. I would like to know about the background of the strength as a medication that you mentioned earlier.

Also, Professor Furue said earlier that the effect gets stronger. I can't tell from just looking at this because KHK4083 doesn't have a transition in the rate of change in today’s presentation, but if looking at the Dupixent data or transition in the rate of change, I get the impression that the score under Dupixent improves at a relatively early stage all at once. The onset of effect is somewhat rapid. What do you think on that point?

Furue: I'll take the second part of the question first. This is because Dupixent suppresses IL-4, which mediates inflammation to some extent. As a result, it works quickly. However, although IL-4 is suppressed, the number of activated Th2 cells doesn't change, so IL-4 continues to be steadily produced.

KHK4083 suppresses Th2 cells but does not kill them rapidly. Since it doesn't kill them straight away, they continue to produce IL-4 until they die, so the effect will be slower than Dupixent. However, when it starts to work, the number of Th2 cells, which is the main source of the disease, is reduced, so it becomes more effective.

Although we cannot compare it directly with Dupixent, the effect in combination with topical steroids is very high. I think that in the case of the KHK4083 trial too, if topical steroids were used, the 16-week achievement rate would be much higher.

I hope this answers your question.

Hashiguchi: Thank you very much. I thought that nemolizumab also had that characteristic, that the effect comes out relatively slowly, like at 64 weeks.

Furue: That's right. However, nemolizumab takes time to have an effect on inflammation, but acts very quickly against itching.

Hashiguchi: Okay, thank you very much. Also, I have a question for Dr. Torii. I heard that more than ten percent of the patients had a history of using biologics, but I don't know if I can say this clearly because the absolute number is small. Is there likely to be a difference in results between patients who have a history of using these drugs and those who don't?

Torii: Thank you for your question. We don't have enough patient number to say anything here, but what we can say now is that there were some patients who failed to respond to Dupixent and actually showed efficacy with KHK4083. We will wait for the results of the upcoming Phase III study to see if that actually becomes clear when the sample size is larger.

Hashiguchi: Thank you very much. That's all.

Moderator: Thank you very much. The next question comes from Mr. Wakao of JP Morgan Securities Japan.

Wakao: This is Wakao of JP Morgan. Thank you. I would just like to crystallize what we've heard so far by asking you both what KHK4083 can do in terms of efficacy and long-term regimens.

If I understand what you are saying now, if the drug is used for a long period of time, it is possible to achieve the same level of efficacy as Dupixent. Also, in terms of the interval between doses, there is a possibility to achieve a dosing method that surpasses existing drugs. Is that correct?

When I first looked at the data, I thought that there was an advantage in terms of long-term effects, but I thought that it was slightly inferior to Dupixent in terms of efficacy. From what you have just said, I got the impression that we can expect a high level of effectiveness from this compound.

I'm sorry if this is a repetition of others' questions, but I'd be grateful if you could sum things up.

Moderator: Professor Furue, would you like to answer?

Furue: Thank you for your question. It's true that it's difficult to make a head-to-head comparison with existing data. I'm particularly interested in the percentage of placebo and how it compares to that. At 16 weeks, the figure was 61.07% in the 300 mg Q2W group, compared to 15.1% in the placebo group. This is a very large difference.

The placebo in the Dupixent trial was a little bit more, I think it was around 30% to 40%, so if you compare that to the placebo for Dupixent, I personally think that this is very effective. I don't want to sound overly enthusiastic, but there is quite a difference there.

One more thing I'd like to mention is the difference between this antibody therapy and people born without OX40. This topic came up a little earlier. There is a difference between using antibody therapy to kill OX40 positive cells and being born without OX40, and I think it's important to clear this up.

People born without OX40 are exposed to the outside world when they are babies, and they are exposed to various microorganisms around them. Since OX40 is already absent at that birth, it is difficult for the baby to develop a strong immune system.

However, people with atopic dermatitis are not born with these antibodies, so they still have the immunity from the time they were born. In this case, the antibodies are used to suppress activated Th2 cells that are present in atopic dermatitis. So, the situation is completely different.

Another advantage of the OX40 or OX40 ligand is that it is expressed only in activated cells. For example, in the case of tuberculosis, a T cell develops that has immunity to tuberculosis. The T cell expresses OX40 when it is active. When it is not active, and it is acting as a 'memory' T cell, it does not express OX40.

So, the T cells that die from OX40 antibodies are only the activated ones, and the memory T cells that have immunity to tuberculosis actually survive. I think that's probably the reason why the side effect profile of this antibody was better than some might expect.

Moderator: Dr. Torii, please go ahead.

Torii: Thank you very much for your question, Mr. Wakao. The expectation of the Company developing the drug is that it is a new MOA. So far, at the 16-week stage in Phase IIb, the efficacy of the drug is equivalent or superior to that of Dupixent.

The dosing interval could also be extended to Q4W or even longer. Alternatively, efficacy may also be seen in patients who are refractory to Dupixent. These are the sort of points I am hoping for as points of differentiation.

Also, as the Doctor mentioned earlier, it is important to compare against the efficacy of placebo. Again, this is not a head-to-head comparison and is just for reference. As you can see now, this placebo is 15%, and the most effective treatment group, 300 mg Q2W, is 61.7%. The difference to the placebo is roughly 46.7%.

On the other hand, in the SOLO-1 study of dupilumab, a single-agent Phase III study, there was a delta of 36.2%, with a figure of 67.1% for the 300, Q2W group and 30.9% for the placebo. It is also notable that the placebo value is a little higher here.

I will share this information for your reference. That's all.

Wakao: Thank you very much. Secondly, I would like to ask Dr. Torii a question about differentiation. Efficacy of this drug is clearly an advantage, but I think the increased dosing interval is a benefit that is very easy to understand.

Considering a launch date in 2025 or 2026, I believe that by that time, Dupixent's market share will probably have increased further. Considering this, I think that rather than focusing on patients in whom Dupixent isn't effective. Patients who switch from Dupixent might be a more important group. Is there a possibility to include patients switching from Dupixent in the current Phase III trial?

While at the moment, I think it is more likely to be people who do not respond to topical agents or people who did not respond to biologics, but will there be a cohort of people who are using Dupixent and are stable, but who will switch for the longer dosing interval?

Torii: Thank you for your question. We are also discussing the development strategy for Phase III with Amgen, and this will be decided after negotiations with the regulatory authority. We are now planning strategies to maximize the value of this drug. We will disclose this information to you once it is finalized based on the results of negotiations with the FDA.

Wakao: Understood. In that case, the clinical trial itself is scheduled for early next year, so am I correct in understanding that the protocol will be known early next year?

Torii: That's right. We expect to be able to discuss it in the first half of next year.

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

Torii: Thank you very much.

Moderator: Thank you very much. The next question comes from Mr. Arai, Bank of America Securities Japan.

Arai: This is Arai of BofA Securities. Thank you for holding today's briefing. The first question is how KHK4083 would be used post-launch. This may be an add-on to the previous question, but for example, while there is a difference in convenience and effectiveness, I think there is also the benefit for Dupixent of familiarity among medical professionals, for example. What kind of difference in usage would occur after launch? Can you tell us about any thoughts you have on this? I would like to hear Professor Furue's opinion on this as well.

Moderator: Professor, could you say a few words?

Furue: I think it is difficult to say until this drug is actually released. As an image, of course, I have the impression that after 1 year of using Dupixent, the number of Th2 cells, which is the main source of allergic reactions, will decrease, and the overall allergic reaction in patients will decrease.

But 1 year is a very long time, actually. For example, if you compare 3 months, 6 months, and 1 year of medication, it may sound short in words. But in reality, there is a huge difference between 6 months and 1 year when it comes to patients themselves.

In the case of this antibody, KHK4083, the initial onset of the effect is a little slow, but the number of Th2 cells decreases, so the symptoms drop off dramatically during the course of the treatment. That is the unique feature of the treatment.

The benefit is that even if the treatment is stopped, the effect will persist for some time. For example, it may be possible to stop the treatment after about 6 months and monitor the patient's condition, which is a little different from Dupixent.

There are a lot of patients who cannot continue with Dupixent for even a year. Financial reasons are one factor. It's not easy to pay that much money all the time. That's why I think it's better to use a treatment method that permits a shorter administration period and allows the patient to be aware of the effects to some extent.

Arai: Thank you very much. The second question is how this compares to competing drugs. Trial data was announced at the EADV Congress for KY1005, which Sanofi bought in acquiring Kymab. I'm curious to see how it compares.

Of course, it is difficult to make a direct comparison since the disclosure of information by the other side has not yet progressed that far, but from a layman's point of view, I understand that the profile is quite similar in terms of efficacy and frequency of administration. How do you perceive the comparison with this drug at present? It would be helpful if you could explain the difference between the two agents.

Torii: Thank you for your question. As I explained earlier, our drug is an antibody to OX40. The Kymab drug is an antibody against OX40 ligand expressed on antigen-presenting cells, so that is where the difference lies. It was also presented just a few days ago at the EADV Congress. However, this is still in Phase IIa, so I think it is difficult to compare.

For reference, the percent change of EASI from baseline was 60.7% for our 2b and 15% for placebo, so the delta was 46.7%. The lower dose of the Kymab's antibody seems to be more effective, and the figure here was 80.1% in the treatment group compared with 49.9% in the placebo group. Again, the placebo was higher, so the delta was 30.2%. This is just for reference.

In fact, comparisons in terms of drug efficacy and safety will be made based on the results of Phase III trials. However, as we are about to start Phase III, we are ahead of the time schedule, and we would like to deliver the value of our drug to patients as soon as possible. That's all.

Arai: I am sorry to add this, but are there any differences in efficacy or safety profiles that can be inferred from the differences in the mechanism of action? I would like to ask Professor Furue about this, if he has any opinions.

Furue: I can't think of much difference in the mechanism of action, but the OX40 ligand is on the antigen-presenting cell side, and OX40 is on the T cell side. So, I think targeting OX40 would be more specific. Targeting the antigen-presenting cell side, the OX40 ligand, will affect a very large number of T cells. The most common cells expressing OX40 are Th1 and Th2 cells, but if we target antigen-presenting cells with OX40 ligand, this includes Th17 and Treg cells. The scale of the effect could be quite large.

Therefore, I think OX40 is more advantageous for targeting Th2 cells, and of course, KHK4083 has the ability to kill those cells. It works by reducing the number, which is different from other antibody therapies.

In the case of OX40 ligand antibodies, although the antibody does not kill cells, if the antibody has a killing effect, antigen-presenting cells will be attacked, and very strong side effects may occur. So, it is probably more efficient to use antibodies that do not kill.

Arai: In other words, there may be a difference in safety or sustained efficacy.

Furue: That's right.

Arai: I understand, thank you very much. That's all.

Moderator: Thank you very much. The next question comes from Mr. Ueda of Goldman Sachs Japan.

Ueda: I am Ueda from Goldman Sachs. First of all, I would like to ask Professor Furue about the expected profile of KHK4083. For example, what unmet needs exist with Dupixent treatment, for example, and what sort of profile would you like to see in KHK4083 to address those needs? You mentioned earlier that it is difficult to compare the two, but I would be very grateful if you could give me your thoughts. Thank you.

Furue: Indeed. First of all, I should probably refrain from talking too much about other companies, but as you know, one problem with Dupixent is that it doesn't work well for facial rashes. In addition, there are many people whose condition worsens on Dupixent, and they have to stop taking it. We don't know which people this will happen to and which people it won't, so if patients pay a lot of money and then have to stop because their face gets worse from the rash, they are wasting their money. That's where I'm having a little bit of trouble with Dupixent.

So far, there have been no reports relating to facial rash with KHK4083. The fact that side effects seen with Dupixent are likely absent, and that the effect is likely to be a bit stronger than Dupixent, I think that is what makes it different.

The other thing is, that there is a possibility that we can change the Q2W to Q4W. If the protocol allows us to have a treatment holiday and then administer the drug once more, rather than administering it all the time, I think that would make it easier to use.

Whether this will be the case or not remains to be seen, but we will have to wait and see how the clinical trials progress. That's all from me.

Ueda: Thank you very much. Secondly, I would like to know about the concept of the dose dependency in KHK4083, which was mentioned earlier. 1 of the reasons why this dose-dependence is not observed is that OX40-expressing cells, for example, may have been completely eliminated at a very low dose. If you have data on the percentage of OX40-expressing cells that have been eliminated, please introduce it to us.

Also, in terms of serious adverse events, it seems to be more common with lower doses. Could you comment on this?

Torii: Thank you for your question. We are going to make a presentation on biomarkers at the ISDS, the Inflammatory Skin Disease Summit, on November 4. I hope you can refer to that.

Ueda: In terms of the serious adverse events on this slide, it looks like they are a little higher at the lower dose. I would like to know if you have any opinions about the dose-dependent nature of the adverse events here.

Torii: Thank you for your question. It is difficult to make quantitative judgments about this part of the safety information, especially since we are still in the Phase II stage with a small number of cases. So, I would like to say that the Company does not consider that there is a clear difference in this part. I will provide more details if and when we get more detailed data relating to this in Phase III.

Ueda: Understood. Thank you very much, that's all.

Moderator: Thank you very much. The next question comes from Mr. Sakai of Credit Suisse Securities.

Sakai: My name is Sakai from Credit Suisse Securities. Thank you very much for your time today. I would like to ask Professor Furue something quite basic. I understood very well the patient profile and the historical process of atopic dermatitis when you showed it in the presentation.

Basically, I think that this kind of antibody therapy has emerged in the midst of the difficulty in finding a fundamental treatment. I guess the big question is what the fundamental cause is. I don't know if it can be called translational research, but to what extent have the underlying factors that are causing this been clarified? I'd be grateful if you could tell us something about this.

Furue: First of all, I believe the "fundamental cause" is probably consistent with what I consider the root cause. I think the one key point is this: why does it happen? We know part of the story, but to be honest, I don't really know what the most general difference is from the average person.

In the case of rheumatoid arthritis, it is a reaction within the body, but in the case of atopic dermatitis, it is a reaction to the outside world, and that is the bottleneck. The problem of reaction to the outside world is very complicated. There really is no single, all-encompassing answer to the question of why at the moment.

That's my answer.

Sakai: Understood. Various drugs for atopic dermatitis have been developed, and most of them are antibodies. I suppose that after this OX40 antibody, it's possible that the search for treatment continues.

Furue: I think you're right.

Sakai: Okay, thank you very much. One more thing. I think the name of nemolizumab was mentioned, and it is said to be effective for itching. If this comes out, I think it will probably come out before KHK4083, in the

sense that it will be made into a product. How do you think its use will compare with that of Dupixent when it comes out?

Furue: I think it will develop in a completely different direction. In fact, IL-31 is not only related to atopic dermatitis, but also to itching in many other situations. So, there is actually a possibility that it will help with all kinds of itching that antihistamines don't work on. If we just focus on atopic dermatitis, there are many patients who have no symptoms but only very strong itching. I expect that if this is used for such people, the satisfaction level of the patients will increase greatly.

Nemolizumab is also expected to be effective for people who have itching problems other than atopic dermatitis, such as people who itch only around their buttocks, or for people who suffer from itching related to varicose veins.

This latter case is called stasis dermatitis and is a very strong and intractable itching associated with varicose veins in the calves of both legs. Nemolizumab is expected to be very effective in this type of case. Therefore, I think it is expected to be used as an anti-itch drug, not only for allergic diseases, but also for many other diseases where itching is an important symptom.

Sakai: Understood. Thank you very much.

Moderator: Thank you very much. The next question is from Mr. Tanaka of Mizuho Securities.

Tanaka: This is Tanaka from Mizuho Securities. Thank you for your time today. Just one thing for Professor Furue. I just found out about nemolizumab, but I wanted to ask about something on your last slide, on page 15, the part about JAK. The US authority has issued a pretty strong warning about JAK inhibitors, but on the other hand, there is data that shows that they beat Dupixent in terms of efficacy. Doctor, since you have made it 2 plus, what are your current thoughts?

Furue: Topical JAK is similar to steroids, but oral JAK has 2 pluses for both systemic and local effects. So, if you put these together, I think the number of pluses would be the same as the IL-4 receptor antibody or the IL-31 receptor antibody.

On the other hand, while the side effects increase, it is an oral drug, so it is easy to use. It seems that the Japanese Dermatological Association has not yet decided on the best way to use this product in the Japanese market, or what position it should occupy in the current guidelines. We will have to wait and see what happens in the future. Although there is great potential for oral JAK, I am honestly concerned about the side effects.

Tanaka: The effectiveness of the product is not a problem, but you are worried about warnings from the FDA about Xeljanz.

Furue: Yes, that's right. Since it suppresses cytokine signaling in so many ways, it is difficult to predict what side effects will occur depending on individual differences.

Tanaka: Okay, thank you very much.

Moderator: Thank you very much. We have some people who would like to ask further questions, and I would like to ask them to restrict themselves to one question each.

The next question is from Mr. Yamaguchi, Citigroup Japan. Please go ahead.

Yamaguchi: Thank you very much. One question, please. In Professor Furue's presentation, the mechanism was very easy to understand, and he introduced other diseases, such as food allergy, that involve activated

helper T cells. Dupixent is increasingly being used for other diseases as well, although perhaps more peripherally, or rather, to suppress inflammation, and so on.

Putting aside the question of whether you will actually do it or not, is there any scientific evidence that targeting OX40 will work for these other diseases? Would it work better for some than others? Or do you have an impression that it would work for all of them?

Furue: Theoretically, I think it could work. I don't know the Company's data at all, so I'm not entirely sure myself.

Yamaguchi: The basis is that the same mechanism is involved in all of these diseases, is that right?

Furue: Yes, that's right.

Yamaguchi: I understand. Thank you, that's all.

Moderator: Thank you very much. The next question is from Mr. Hashiguchi of Daiwa Securities.

Hashiguchi: This is Hashiguchi, thank you. I think you have mentioned several times earlier that the effects of placebo vary greatly depending on the trial. In the first place, what is the reason why this clinical trial of atopic dermatitis shows improvement even with placebo? I would also like to know why it varies from test to test?

On page 6 of Dr. Torii's slides, he shows the patient background. Comparing this with the patient background of the SOLO trial of Dupixent, I felt that there was not much difference, for example in the IGA=4 ratio, EASI score, or severity of illness. Why do you think the placebo response is different?

Moderator: Doctor, could I pass the first part of the question to you?

Furue: Actually, there has been a lot of discussion for many years about why this placebo works. It's not just atopic dermatitis, but the placebo effect is very pronounced in allergic diseases. For example, if you look at clinical trials of antihistamines for rhinitis and hay fever, you can see that the placebo may be 40% or 50% effective, and antihistamines are 60% effective. The same is true of asthma.

Allergic diseases are completely different from other diseases, such as rheumatoid disease, tuberculosis, and so on. It is a disease that depends on how the body reacts to external reactions, rather than reactions within the body. I think the reason that the placebo is so effective is that the disease is very sensitive to external influences.

In other words, some people react very badly in the winter, but very well in the summer. I think allergic diseases can be affected by things such as symptoms getting better when work calms down a little. So, I think the placebo will inevitably be higher than in other trials.

Hashiguchi: Thank you very much. In light of that, I would like to ask Dr. Torii to tell us something. This study is supposed to be a double-blind study, but to what extent was the blinding ensured?

I believe that double-blindness is assured up to 18 weeks, but after that, all patients received the actual drug. The patients and the doctors in charge of the study were probably informed about the protocol. If that is the case, should I be concerned about the fact that the improvement after 18 weeks is to some extent influenced by the placebo effect?

Torii: Thank you for your question. First of all, as for blinding, this is done for both the actual drug and the placebo, where there is no distinction at the stage of supplying the investigational drug.

Also, at the facilities, this is basically a double-blind study, so we are aware that we are at the stage where we have ensured blinding there, and we have ensured blinding throughout the entire treatment period in this Phase IIb study.

Hashiguchi: Is it communicated to the patients that the actual drug will be administered in all cases after 18 weeks?

Torii: It is.

Hashiguchi: Understood. Thank you, that's all.

Moderator: Thank you very much.

Furue: Just to add a few words, from an ethical standpoint, the regulatory officer may think that it is unfortunate for patients to be in the placebo group rather than the treatment group. As a doctor who is in charge of patients, I think it would be unethical to continue with a placebo for a long time, and I think most clinical trials these days are conducted with that in mind. That's all.

Moderator: Thank you very much. This concludes today's briefing. Thank you very much for joining us today. Thank you for your continued support of Kyowa Kirin.

[END]