

# Update on KHK4083

## Inflammatory Skin Disease Summit (ISDS) 2021 Presentation

November 5, 2021

Kyowa Kirin Co., Ltd.

The logo for Kyowa Kirin, featuring a stylized 'K' icon followed by the text 'KYOWA KIRIN' in a bold, sans-serif font. The logo is positioned on an orange semi-circular background element in the bottom right corner of the slide.

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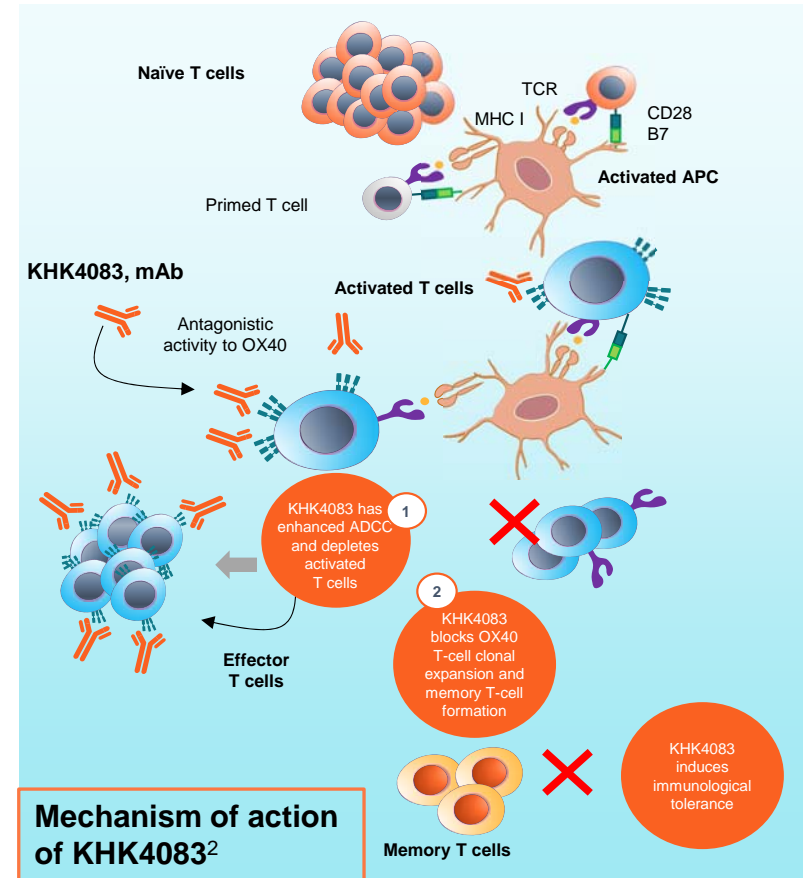
# Treatment with KHK4083/AMG 451, an antagonist of OX40, induces durable modulation of atopic dermatitis (AD)-related blood/skin biomarkers

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

- The OX40–OX40L axis plays a critical role in long-lasting T-cell responses
  - OX40 is expressed by activated T cells after antigen recognition 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 mAb with enhanced antibody-dependent cellular cytotoxicity (ADCC)<sup>1</sup> that acts by
  - Depleting activated T cells<sup>2</sup> ①
  - Blocking T-cell clonal expansion and memory T-cell formation<sup>2</sup> ②

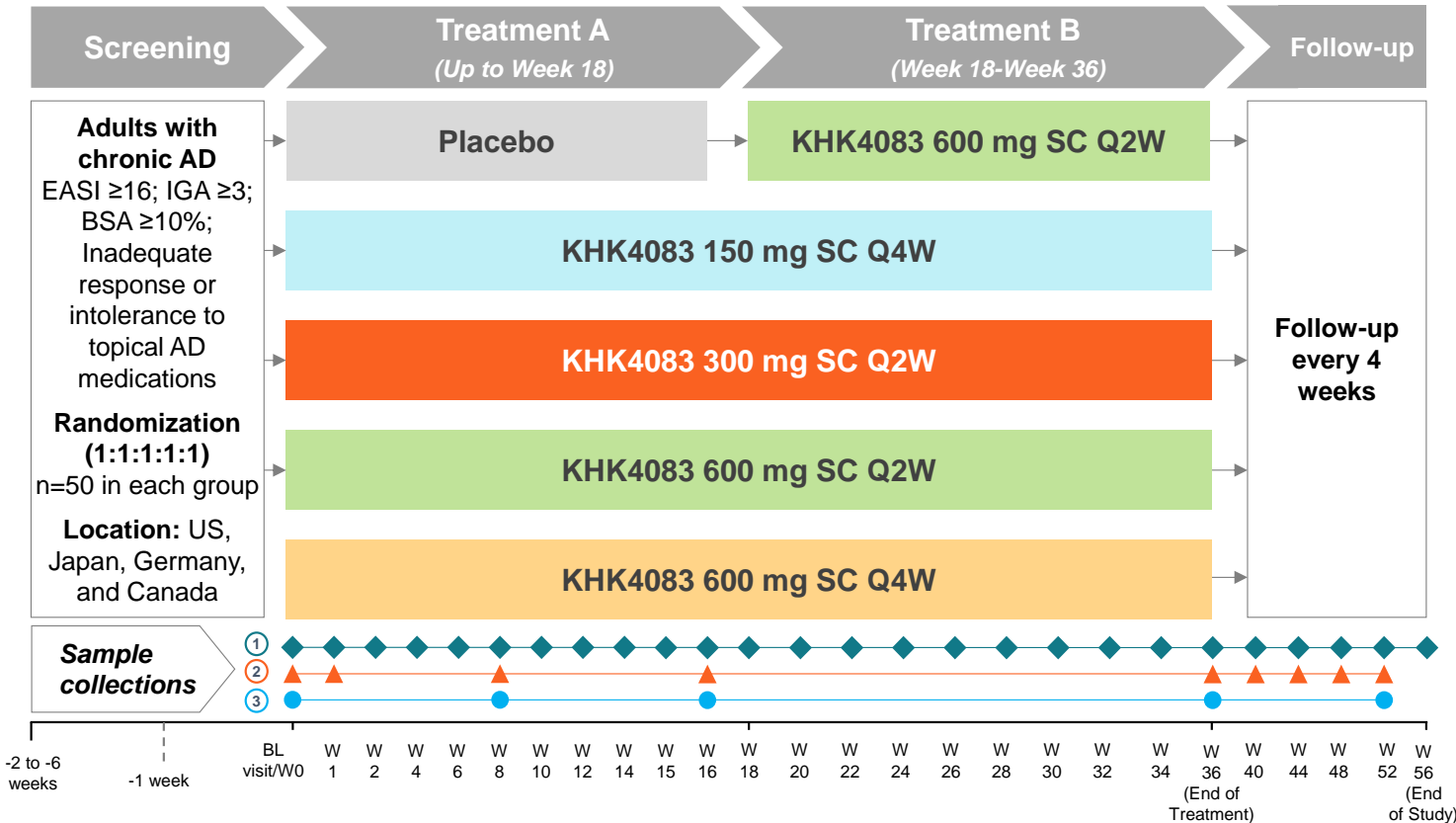


AD, atopic dermatitis; ADCC, antibody-dependent cellular cytotoxicity; APC, antigen-presenting cell; CD28, cluster of differentiation 28; IgG, immunoglobulin G; MHC, major histocompatibility complex; mAb, monoclonal antibody; TCR, T-cell receptor; Th2, T-helper 2  
<sup>1</sup>Nakagawa H et al. J Dermatol Sci. 2020; 99(2):82–89; <sup>2</sup>Papp KA et al. J Eur Acad Dermatol Venereol. 2017; 31(8):1324–1332.

## Objectives

- In a randomized, double-blind, placebo-controlled phase 2b study, we assessed the efficacy and safety of 4 dose regimens of KHK4083/AMG 451 in patients with moderate-to-severe AD
- We also monitored AD-related biomarkers (in blood) and target engagement biomarkers (in blood and skin)

# Phase 2 Study Design (NCT03703102)



- Primary efficacy endpoint**
- % change in EASI score from BL to W16
- Secondary efficacy endpoints**
- Reduction of  $\geq 50\%$ ,  $\geq 75\%$ , and  $\geq 90\%$  in EASI score (EASI 50/75/90) from BL
  - Achievement of an IGA score of 0/1 and a reduction of  $\geq 2$  points from BL (IGA0/1)
  - Achievement of a reduction of  $\geq 4$  points in Pruritus-NRS score from BL
- Safety evaluations**
- Adverse events
- Exploratory endpoints**
- Percent change from BL over time in
- Blood samples (All subjects):**
- TARC ①
  - Serum total IgE ①
  - IL-22 ②
- Blood and skin biopsy (Clinical biomarker substudy: subjects from Japan who provided additional consent)**
- Total OX40+ helper T cells in blood ②
  - Unoccupied OX40+ helper T cells in blood ②
  - OX40+ cells in skin ③

# Baseline Demographics and Disease Characteristics (Safety Analysis Set)

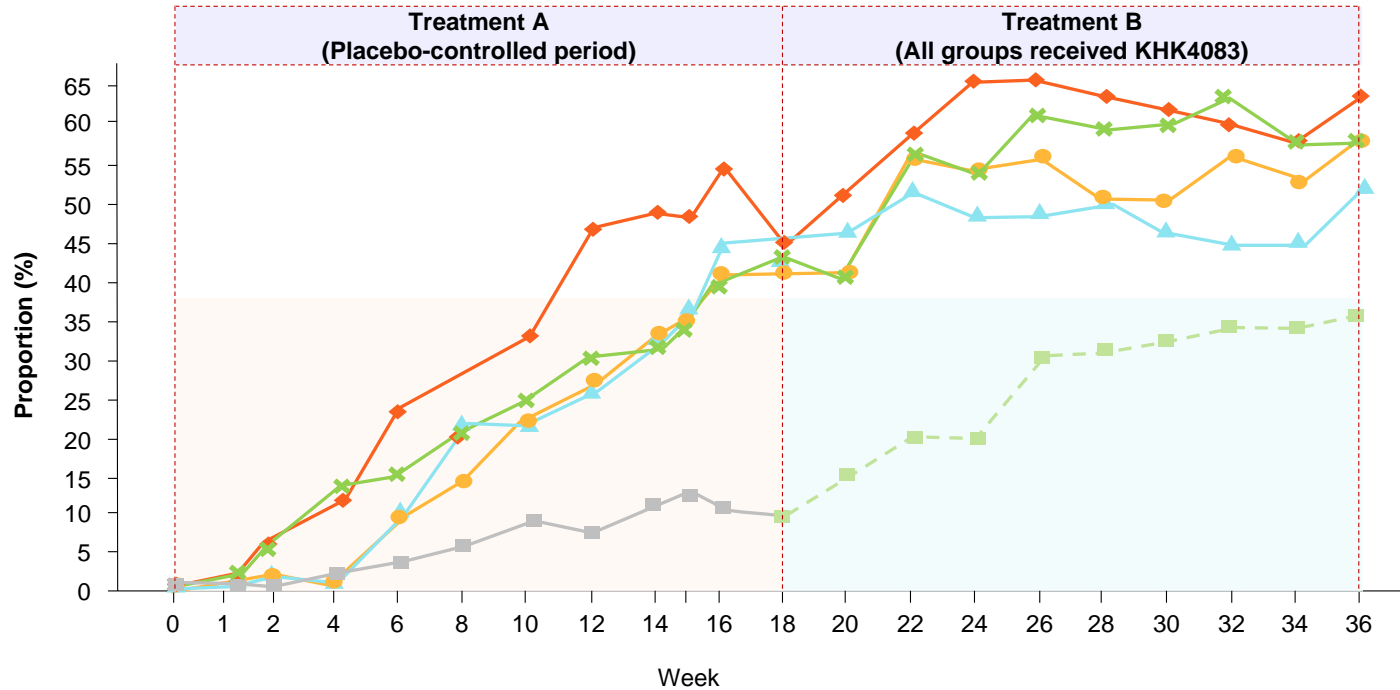
All baseline parameters were generally well-balanced among the treatment groups

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)	150 (54.9)
	Asian: Other	6 (11.1)	4 (7.5)	5 (9.1)	3 (5.6)	25 (9.2)
	Black or African American	3 (5.6)	1 (1.9)	2 (3.6)	1 (1.9)	13 (4.8)
	White	14 (25.9)	20 (37.7)	16 (29.1)	20 (37.0)	84 (30.8)
	Other	1 (1.9)	0	0	0	1 (0.4)
Body mass index at screening, kg/m <sup>2</sup>	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)	148 (54.2)
	4	24 (44.4)	25 (47.2)	25 (45.5)	25 (46.3)	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

# Proportion of Patients Who Achieved EASI-75 (Non-responder Imputation, Full Analysis Set)

Proportions of EASI-75 responders at Week 16 were significantly higher in all KHK4083-treated cohorts versus placebo



	Week 16	Week 24	Week 36
KHK4083 150 mg Q4W, %	44.2**	48.1	51.9
KHK4083 600 mg Q4W, %	40.4**	53.8	57.7
KHK4083 300 mg Q2W, %	53.8**	65.4	63.5
KHK4083 600 mg Q2W, %	38.9**	53.7	57.4
Placebo/KHK4083 600 mg Q2W, %	10.5	19.3	35.1

\*\*p<0.001 versus placebo, assessed at Week 16

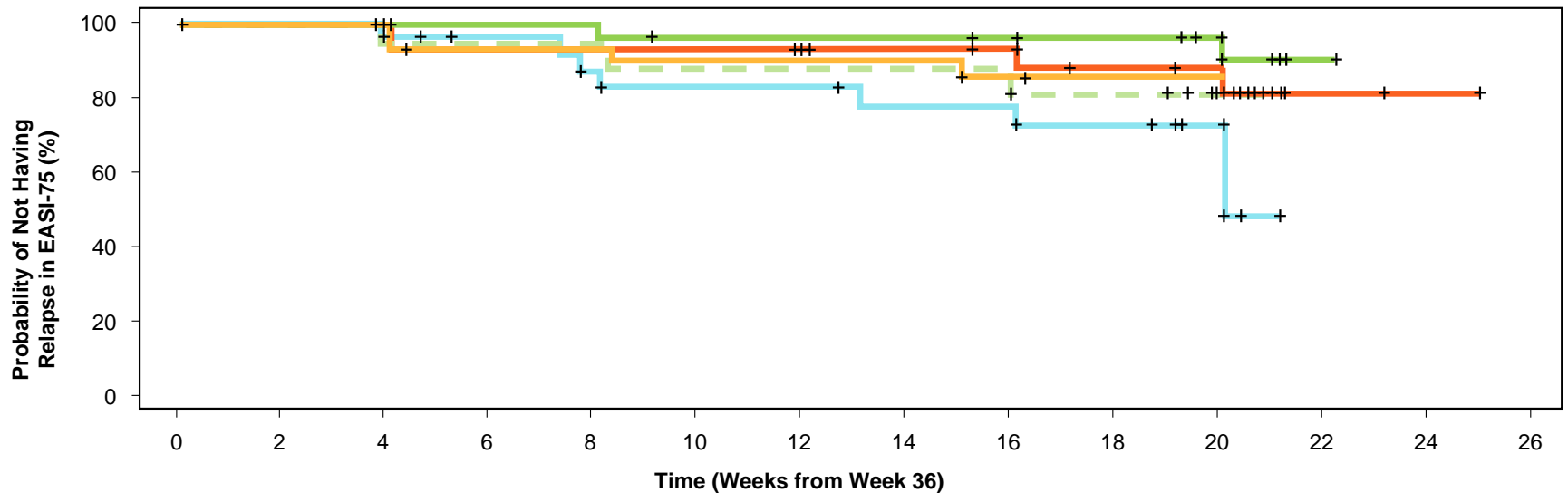
▲ KHK4083 150 mg Q4W   ● KHK4083 600 mg Q4W   ◆ KHK4083 300 mg Q2W   × KHK4083 600 mg Q2W   ■ / -■- Placebo/KHK4083 600 mg Q2W



# Durability of EASI-75 Response After Treatment Discontinuation in Subjects who Achieved EASI-75 at Week 36

EASI-75 response was durable even after discontinuation of KHK4083 at Week 36

The KM curve censored 37 (26%) EASI 75 responders who received rescue therapy during off-treatment



KHK4083 150 mg Q4W	27	26	26	22	19	17	17	15	15	13	9	0	0	0
KHK4083 600 mg Q4W	30	29	29	27	27	26	26	26	24	22	16	0	0	0
KHK4083 300 mg Q2W	33	30	29	25	25	25	24	22	21	18	13	2	1	0
KHK4083 600 mg Q2W	31	27	27	25	25	21	21	21	20	19	17	1	0	0
Placebo/KHK4083 600 mg Q2W	20	18	18	16	16	13	13	13	13	11	7	0	0	0

If patients use topical or systemic rescue therapy or dropped during the study in follow-up period, they are not treated as relapse as long as their EASI score meets EASI-75 criteria before taking rescue therapy and is displayed as “+”.

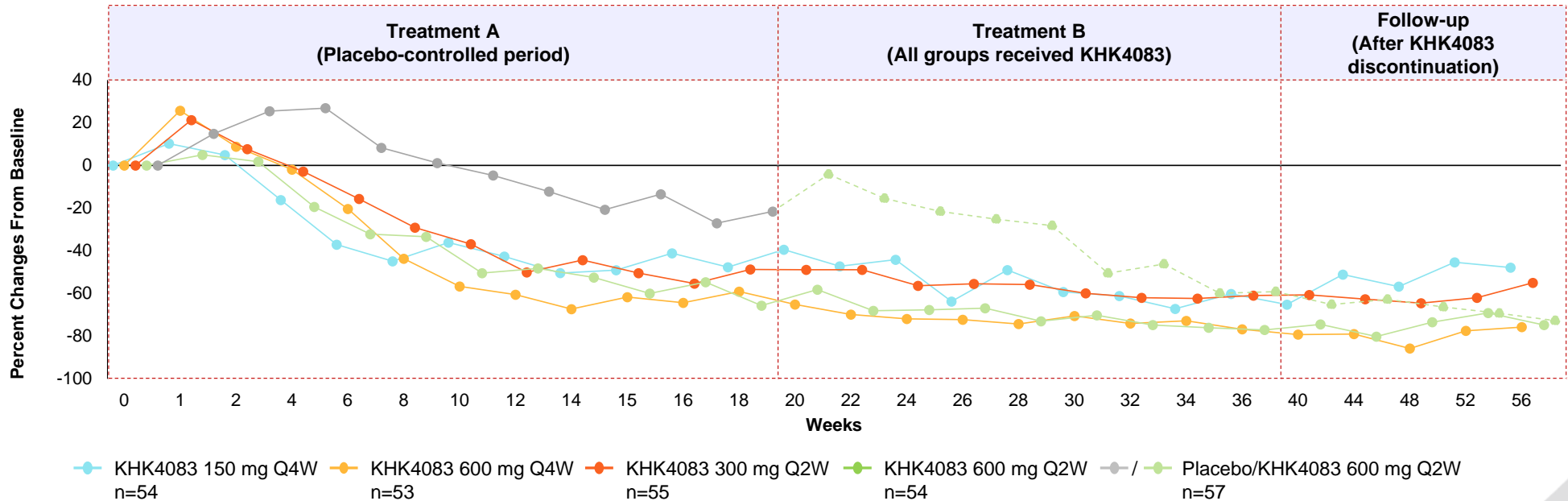
## TEAEs – Treatment A (Safety Analysis Set)

In Treatment A, 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)

# TARC: Median % Change From Baseline at Each Scheduled Visit (Safety Analysis Set)

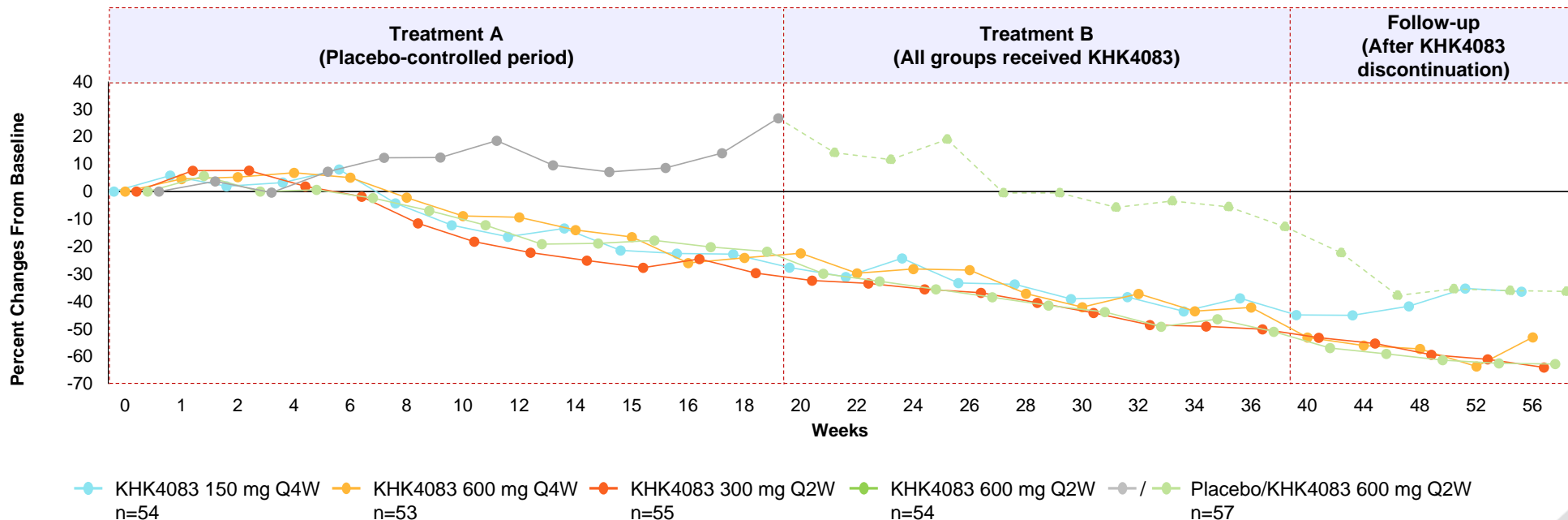
TARC levels clearly reduced in all KHK4083 groups. In the placebo/KHK4083 600 mg Q2W group, TARC reached almost the same levels as those in other KHK4083 groups around Week 32. TARC reduction was near maximum at Week 16 in all KHK4083 groups and sustained during off-treatment after Week 36



Q2W, every 2 weeks; Q4W, every 4 weeks; TARC, thymus and activation-regulated chemokine  
 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.

# IgE: Median % Change From Baseline at Each Scheduled Visit (Safety Analysis Set)

Total IgE was continuously reduced after Week 16 in KHK4083 groups and reached 50% reduction. This trend continued during off-treatment after Week 36 except in the KHK4083 150 mg Q4W group.

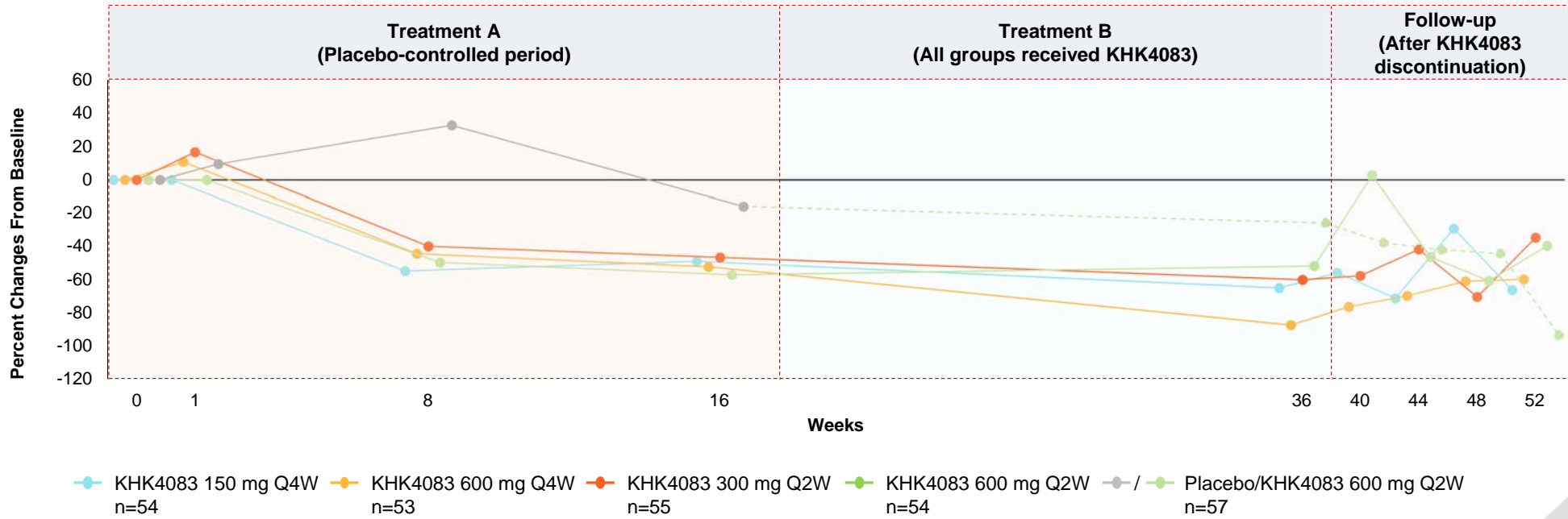


IgE, immunoglobulin E; Q2W, every 2 weeks; Q4W, every 4 weeks

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.

# IL-22: Median % Change From Baseline at Each Scheduled Visit (Safety Analysis Set)

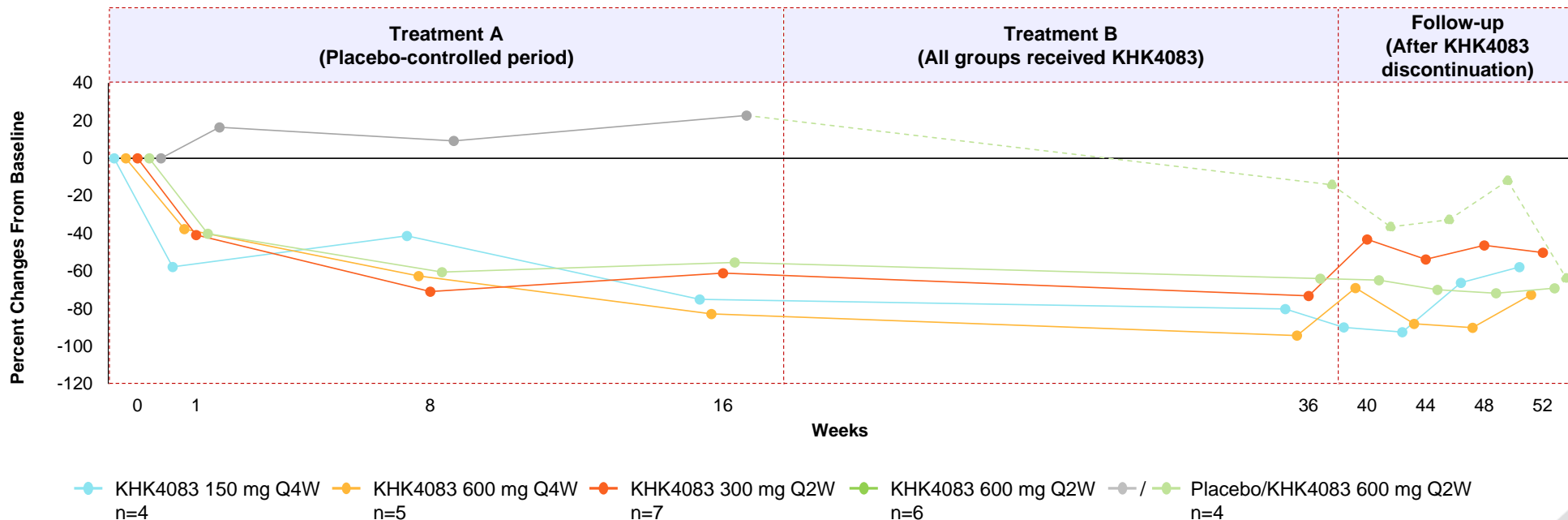
**IL-22 reduction was confirmed at Week 16 in all KHK4083 groups and continued after Week 16**  
**The reduction was maintained during off-treatment after Week 36**



IL, interleukin; Q2W, every 2 weeks; Q4W, every 4 weeks  
 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.

# Total OX40+ Helper T Cells in Peripheral Blood: Median % Change From Baseline at Each Scheduled Visit (Clinical Biomarker Statistical Analysis Set)

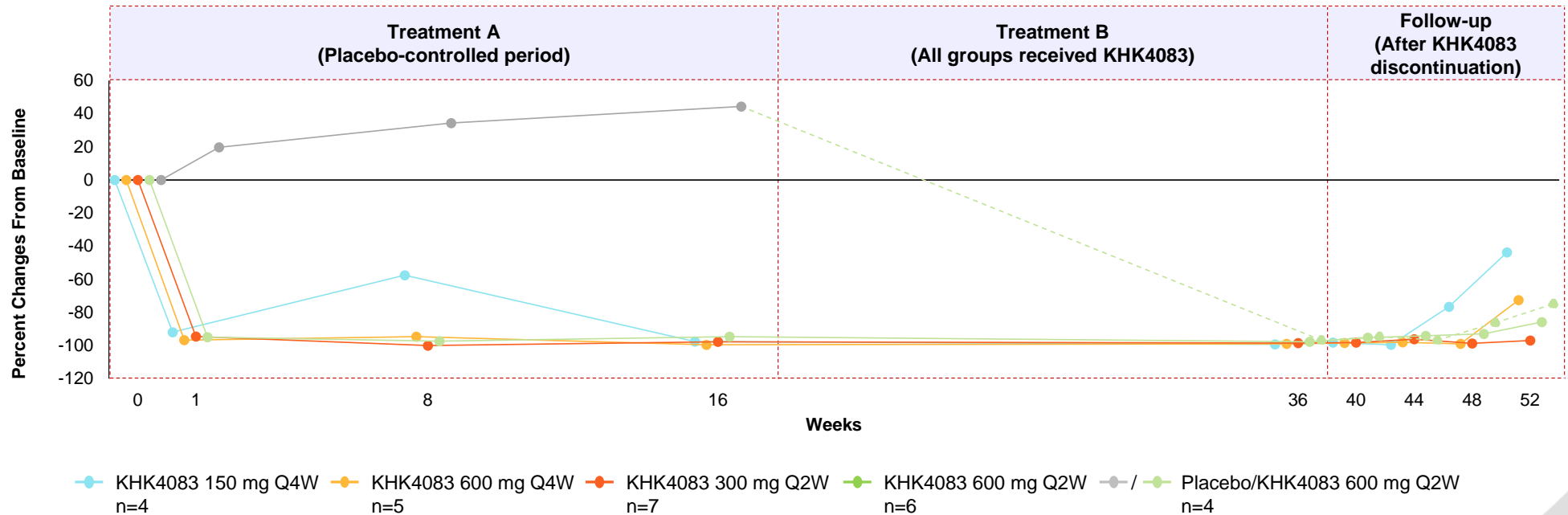
KHK4083 quickly showed reduction in OX40+ helper T cells in all KHK4083 groups  
This reduction persisted during off-treatment after Week 36



Q2W, every 2 weeks; Q4W, every 4 weeks  
Data presented from clinical biomarker statistical analysis set, which included 26 Japanese patients who provided additional consent.

# Unoccupied OX40+ Helper T Cells in Peripheral Blood: Median % Change From Baseline at Each Scheduled Visit (Clinical Biomarker Statistical Analysis Set)

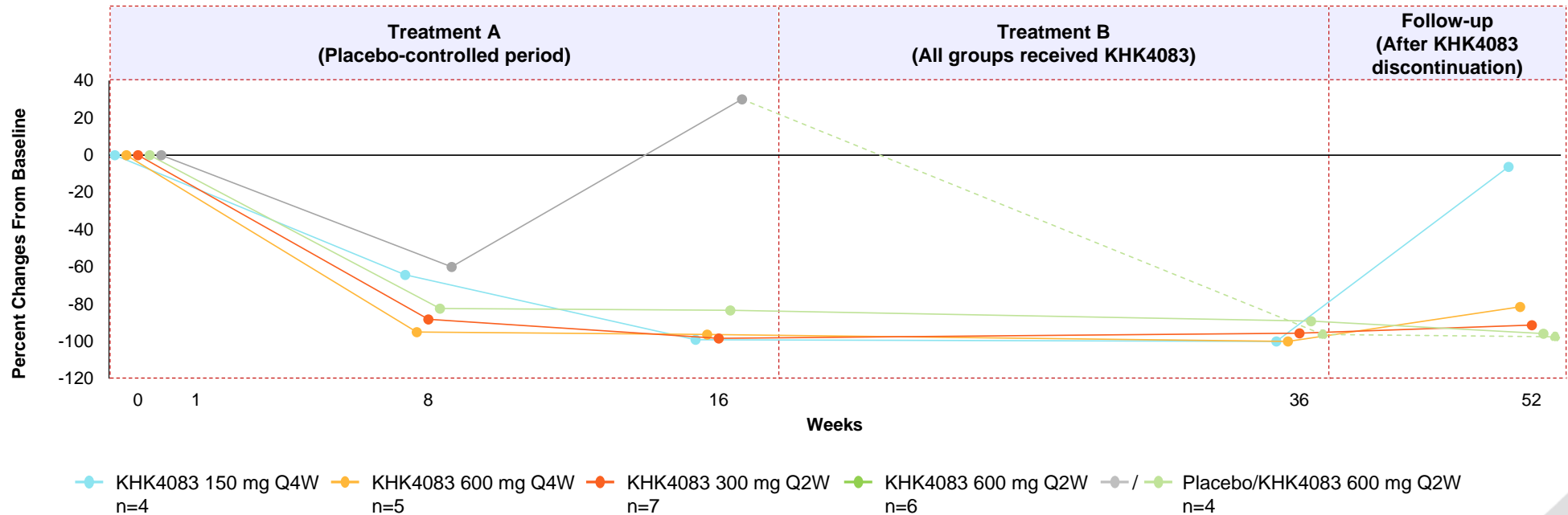
Unoccupied OX40+ helper T cells were detected at very low levels from Week 1 in all KHK4083 groups and retained at least 10 weeks after the last dose of KHK4083 at Week 34  
 The reductions persisted through Week 52 in the group randomized to 300 mg Q2W



Q2W, every 2 weeks; Q4W, every 4 weeks  
 Data presented from clinical biomarker statistical analysis set, which included 26 Japanese patients who provided additional consent.

# OX40+ Cells in the Upper Dermis (Skin Biopsy Lesion): Median % Change From Baseline at Each Scheduled Visit (Clinical Biomarker Statistical Analysis Set)

**OX40+ cells were removed from the upper dermis**  
**Faster reduction of OX40+ cells was observed in the 300 mg Q2W and 600 mg Q4W groups**  
**Removal of OX40+ cells was sustained during the off-treatment period (through Week 52), except in the 150 mg Q4W group**



Q2W, every 2 weeks; Q4W, every 4 weeks  
 Data presented from clinical biomarker statistical analysis set, which included 26 Japanese patients who provided additional consent.



## Conclusions

### In patients with moderate-to-severe AD

- KHK4083/AMG 451 groups demonstrated significant improvements in efficacy parameters, compared with the placebo group, at Week 16 and beyond
- KHK4083/AMG 451 induced significant modulation of AD-related biomarkers, including reduction in OX40+ T cells, TARC, IgE, and IL-22 in blood, that parallel the improvement in clinical measures observed across all KHK4083 groups at Week 16 and beyond
  - The sustained inhibition/depletion of OX40+ helper T cells (the drug target) may link closely to longer control of active disease following the withdrawal of treatment and potentially with a disease-modifying effect
- KHK4083/AMG 451 was well tolerated and did not show any new safety concerns
- KHK4083/AMG 451 may be a novel treatment option in patients with moderate-to-severe AD

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