Update on KHK4083

EADV Follow-up

October 4, 2021

Yoshifumi Torii, Ph.D.
Executive Officer, Vice President, Head of R&D Division

Kyowa Kirin Co., Ltd.

This document contains certain forward-looking statements relating to such items as the company's (including its domestic and overseas subsidiaries) forecasts, targets and plans. These forward-looking statements are based upon information available to the company at the present time and upon reasonable assumptions made by the company in making its forecasts, but the actual results in practice may differ substantially due to uncertain factors.

These uncertain factors include, but are not limited to, potential risks of the business activities in the pharmaceutical industry in Japan and overseas, intellectual property risks, risk of side effects, regulatory risks, product defect risks, risks of changes to the prices for raw materials, risks of changes to market prices, as well as risks of changes to foreign exchange rates and financial markets.

This document is used only for the purpose of providing the information to investors. Though it may contain the information concerning pharmaceutical products (including products under development), it is not for the purpose of promotion, advertising, or medical advice.

EADV 2021

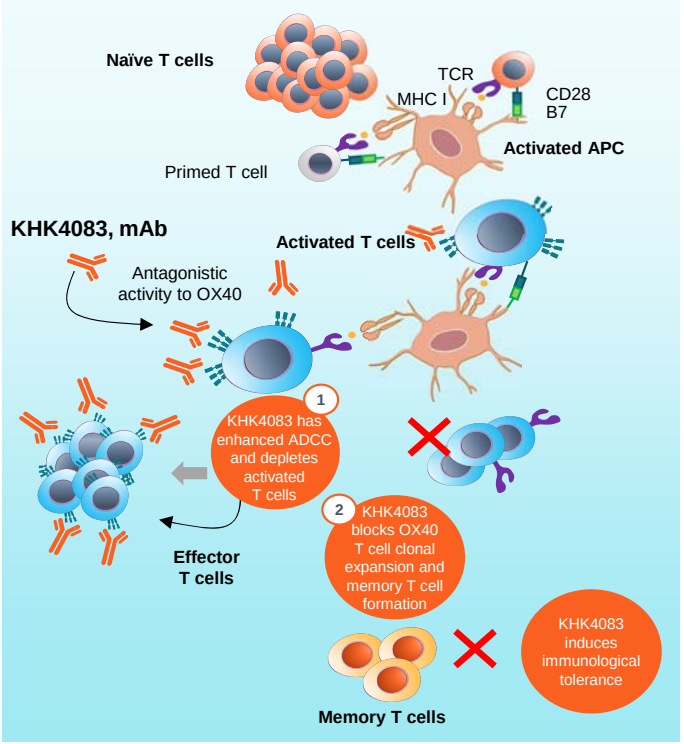
Efficacy and Safety Results of KHK4083/AMG 451 (Anti-OX40 mAb) in Subjects With Moderate to Severe Atopic Dermatitis: A Phase 2, Multicentre, Randomized, Double-blind, Parallel-Group, Placebo-Controlled Study

Emma Guttman-Yassky,[1] Eric Simpson,[2] Kristian Reich,[3] Kenji Kabashima,[4] Ken Igawa,[5] Hidetoshi Takahashi,[6] Keizo Matsuo,[7] Yoshihiko Katahira,[8] Kazutomo Toyofuku,[9] Masatoshi Abe,[10] Margrit Simon,[11] Oliver Weirich,[12] Tetsuya Suzuki,[13] Shunichiro Orihara,[13] Takeshi Matsui,[13] Ehsanollah Esfandiari,[14] Masutaka Furue[15]

[1]Icahn School of Medicine at Mount Sinai, New York, USA; [2]Oregon Health & Science University, Portland, USA; [3]Translational Research in Inflammatory Skin Diseases, Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [4]Kyoto University, Kyoto, Japan; [5]Dokkyo Medical University Hospital, Tochigi, Japan; [6]Takagi Dermatological Clinic, Hokkaido, Japan; [7]Matsuo Clinic, Fukuoka, Japan; [8]Katahira Dermatology Clinic, Kagoshima, Japan; [9]Yamate Dermatological Clinic, Tokyo, Japan; [10]Sapporo Skin Clinic, Hokkaido, Japan; [11]Interdisciplinary Study Association GmbH, Berlin, Germany; [12]Rosenpark Research GmbH, Darmstadt, Germany; [13]Kyowa Kirin Co., Ltd., Tokyo, Japan; [14]Kyowa Kirin International Plc, London, UK; [15]Kyushu University, Fukuoka, Japan

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]

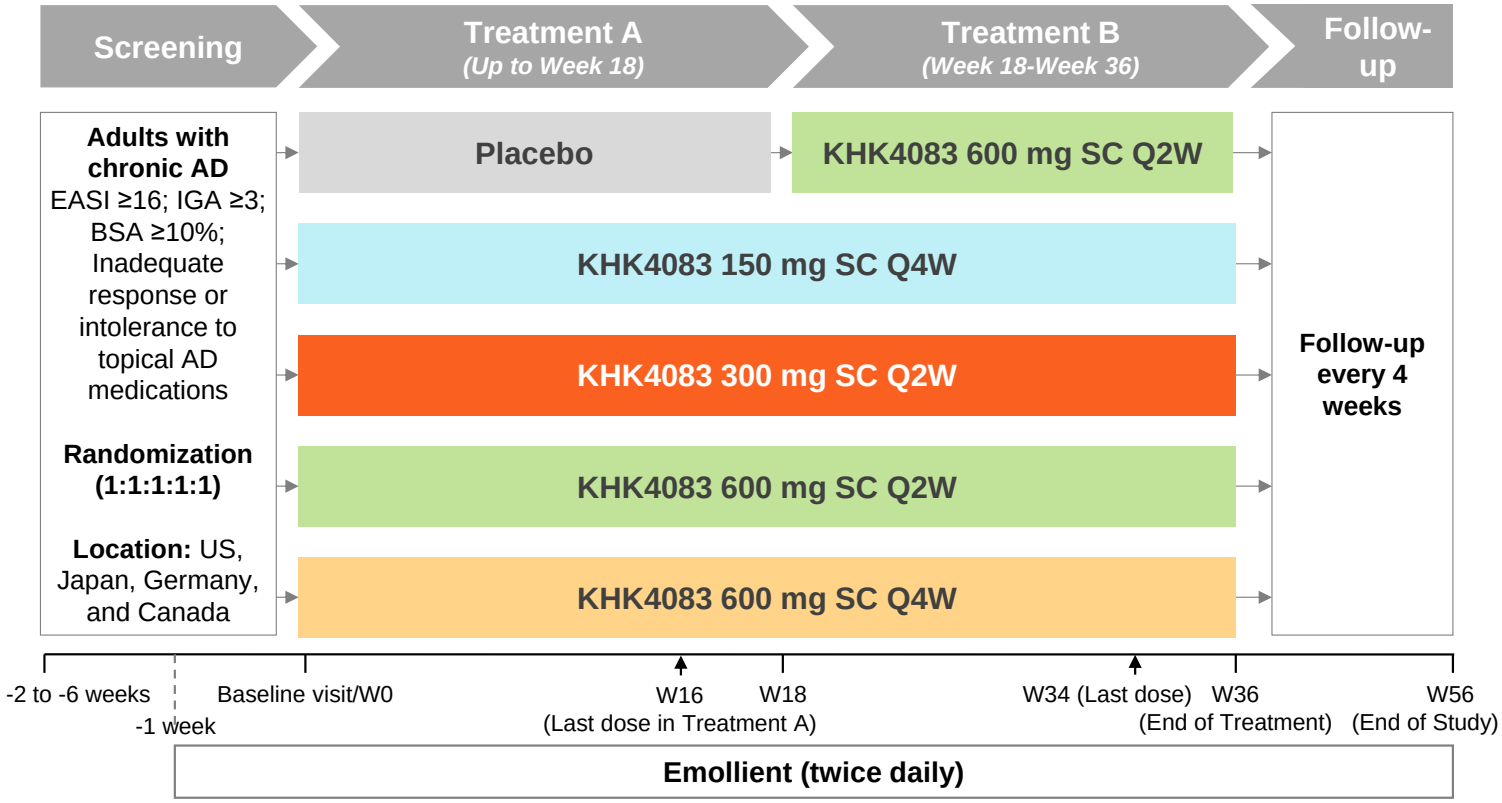


Mechanism of action of KHK4083[2]

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.

Phase 2 Study Design (NCT03703102)



Primary efficacy endpoint

- Percentage change in EASI score from baseline to Week 16

Secondary efficacy endpoints

- Reduction of ≥50%, ≥75%, and ≥90% in EASI score (EASI 50/75/90) from baseline
- Achievement of an IGA score of 0/1 and a reduction of ≥2 points from baseline (IGA0/1)
- Achievement of a reduction of ≥4 points in Pruritus-NRS score from baseline

Safety evaluations

- Adverse events

AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IP, Investigational product; NRS, Numerical Rating Scale; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous; W, Week
Patients receiving rescue treatment before W36 assessment discontinued the IP and underwent end-of-study assessment

Baseline Demographics and Disease Characteristics (Safety Analysis Set)

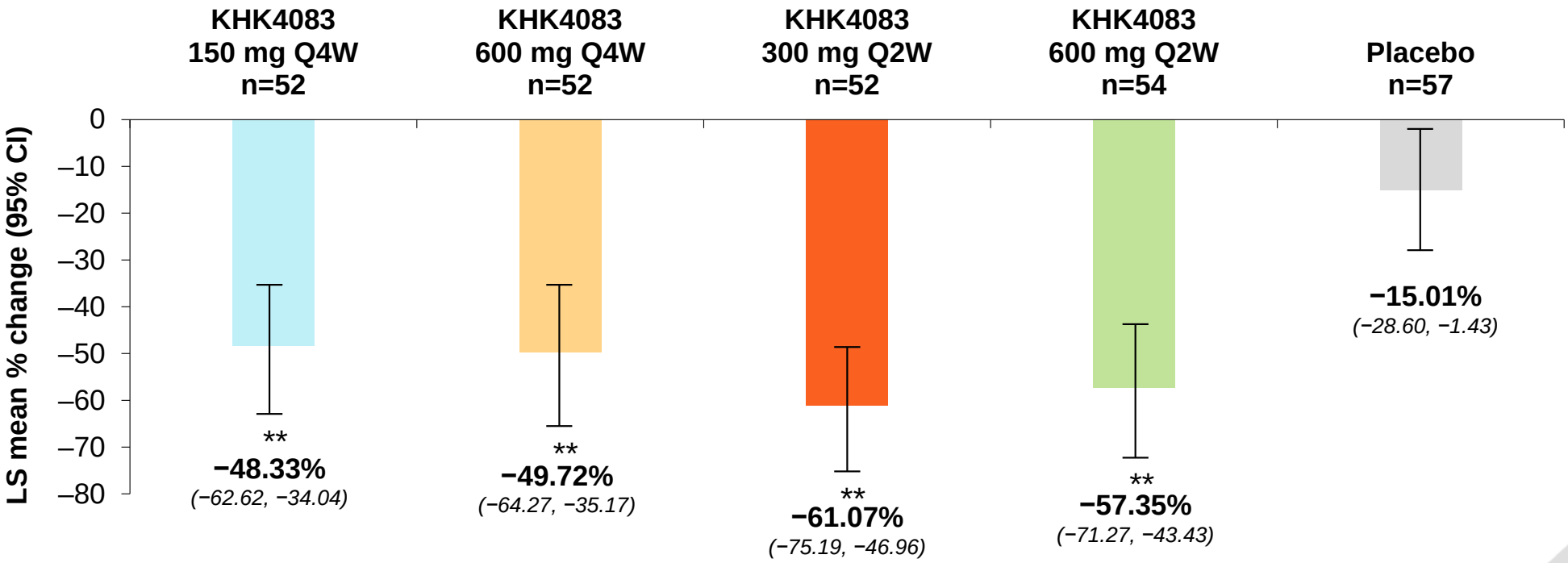
All baseline parameters were generally well-balanced among the treatment groups

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.

Primary Endpoint: % Change in EASI Scores (Week 16) From Baseline (Last observation carried forward, Full Analysis Set)

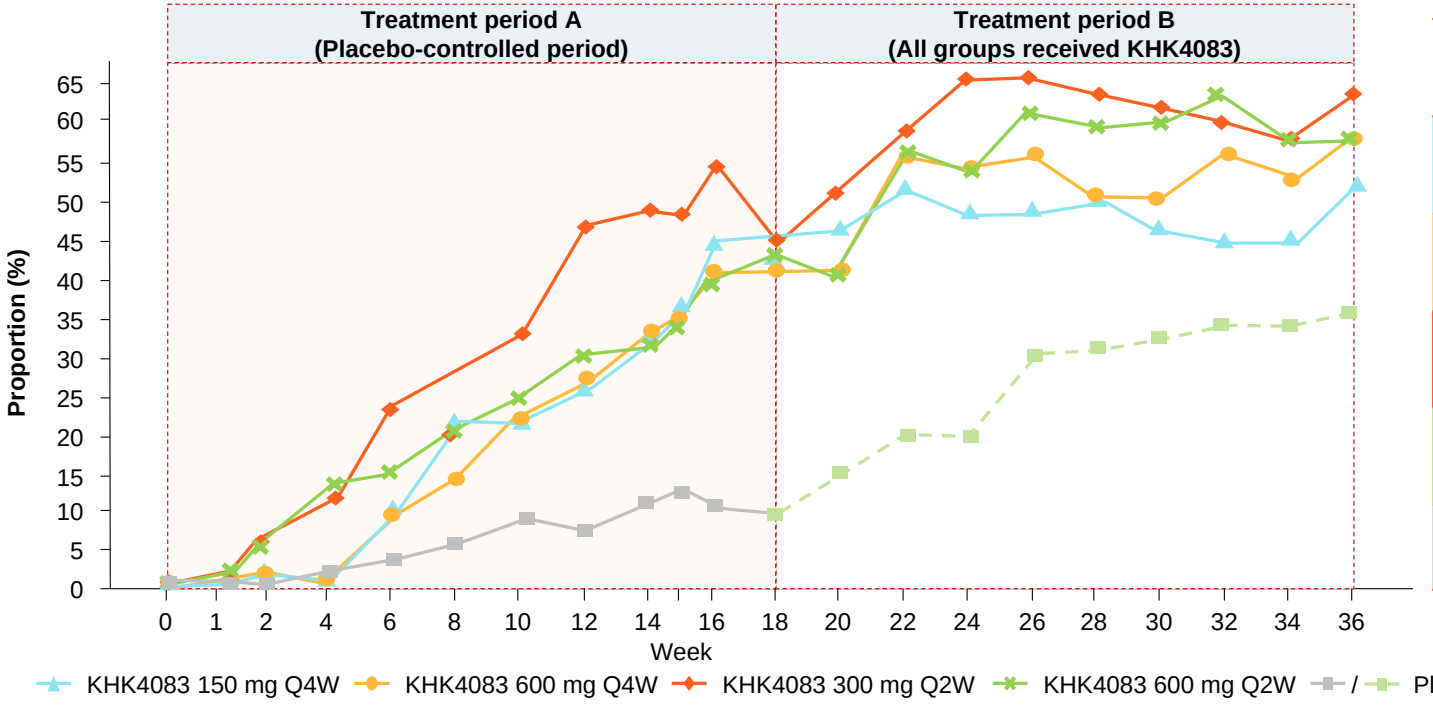
All KHK4083-treated groups achieved the primary endpoint



EASI, Eczema Area and Severity Index; LS, least square; Q2W, every 2 weeks; Q4W, every 4 weeks
**p<0.001 for difference versus placebo

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

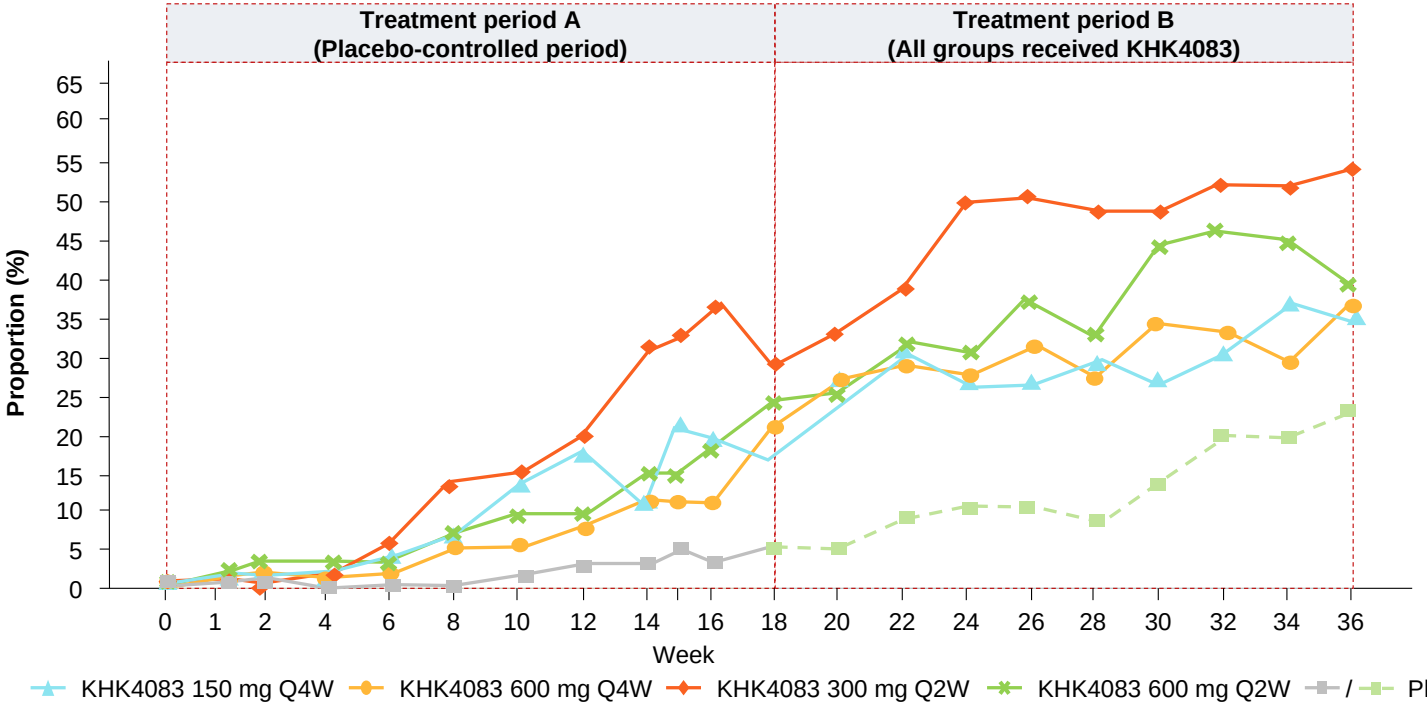
**p<0.001 vs placebo, assessed at Week 16

AD, atopic dermatitis; EASI, Eczema Area and Severity Index; 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.

Proportion of Patients Who Achieved EASI-90 (Non-responder Imputation, Full Analysis Set)

Proportions of EASI-90 responders at Week 16 were significantly higher in most KHK4083-treated cohorts versus placebo



	Week 16	Week 24	Week 36
KHK4083 150 mg Q4W, %	19.2*	26.9	34.6
KHK4083 600 mg Q4W, %	11.5	26.9	36.5
KHK4083 300 mg Q2W, %	36.5**	50.0	53.8
KHK4083 600 mg Q2W, %	18.5*	29.6	38.9
Placebo/KHK4083 600 mg Q2W, %	3.5	10.5	22.8

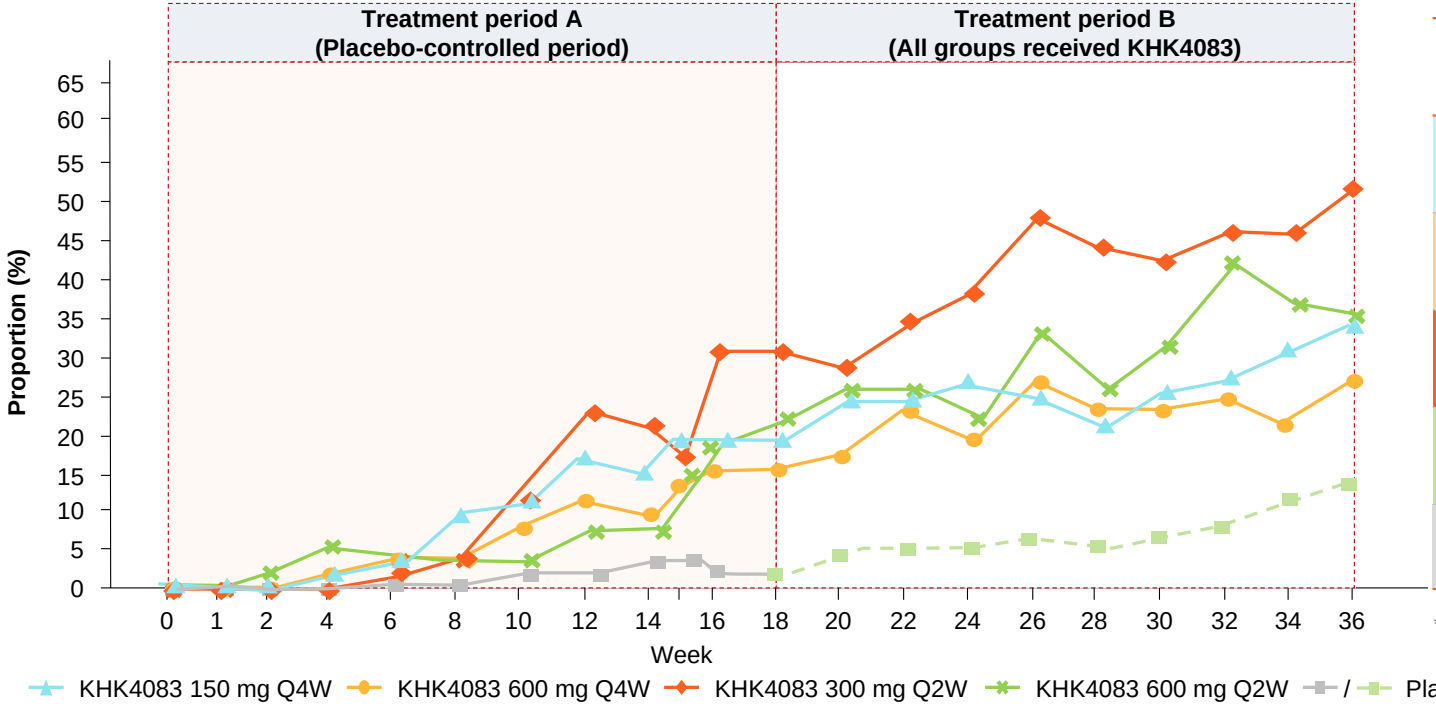
*p<0.05, **p<0.001 vs placebo, assessed at Week 16

EASI, Eczema Area and Severity Index; 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.

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

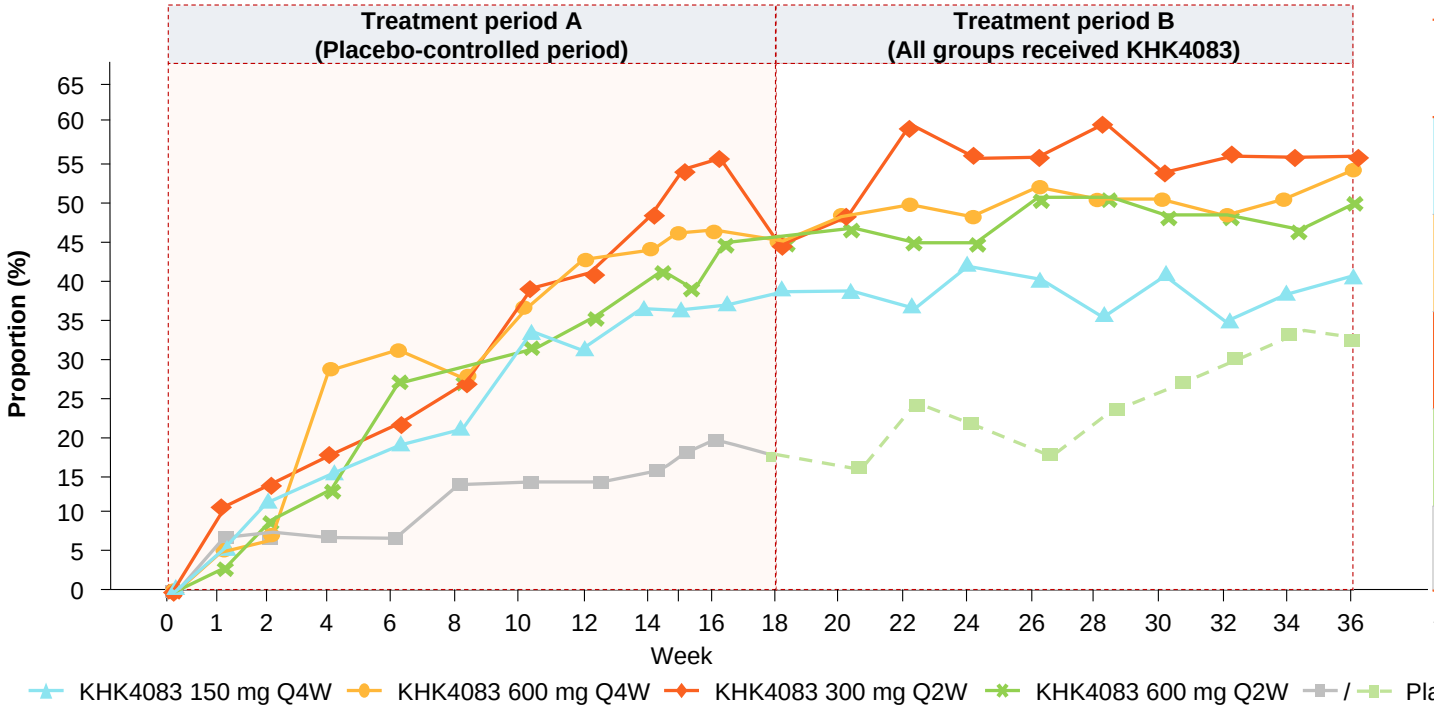
*p<0.05, **p<0.001 vs placebo, assessed at Week 16

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.

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

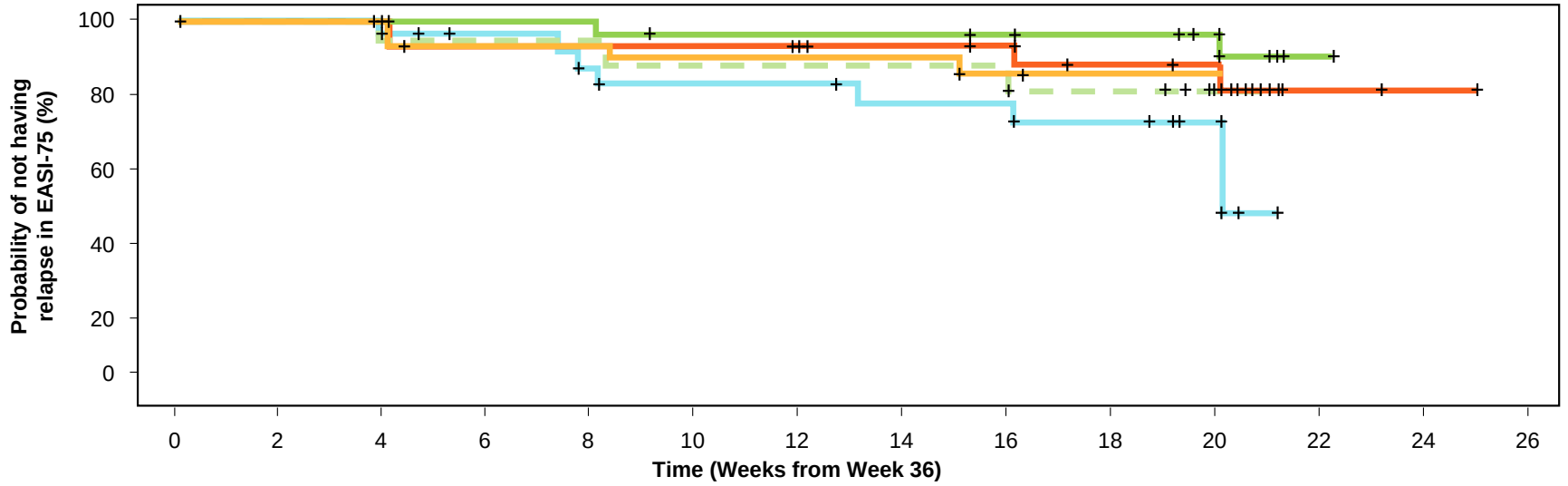
*p<0.05, **p<0.001 vs placebo, assessed at Week 16

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.

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



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

+: censored, EASI: Eczema Area and Severity Index, Q2W, every 2 weeks; Q4W, every 4 weeks
Note: Subjects in the placebo group were switched to KHK4083 600 mg Q2W after Treatment A period. The numbers below the figure represent the number of remaining subjects at each visit.
Note: Relapse is the loss of EASI-75 after achieving EASI-75 at Week 36.
Note: Censored cases are prohibited concomitant medications and/or therapies including rescue treatment started before the event confirmed, study completion without the event confirmed, and early termination of the study without the event confirmed.

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.

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 (%)**.

Conclusions

- KHK4083/AMG 451 represents a novel mechanism of action and its use resulted in significant improvements in signs and symptoms of AD compared with placebo, across primary and secondary efficacy parameters at Week 16
- Importantly, KHK4083/AMG 451 demonstrated progressive improvement in efficacy parameters beyond Week 16
- KHK4083/AMG 451 demonstrated sustained efficacy for another 20 weeks after treatment discontinuation (until Week 56)
- KHK4083/AMG 451 was well-tolerated and did not show safety concerns
- KHK4083/AMG 451 may be a novel treatment option for patients with moderate-to-severe AD


Kyowa KIRIN