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A Phase 1 Study of KHK4083 in subjects with Atopic Dermatitis

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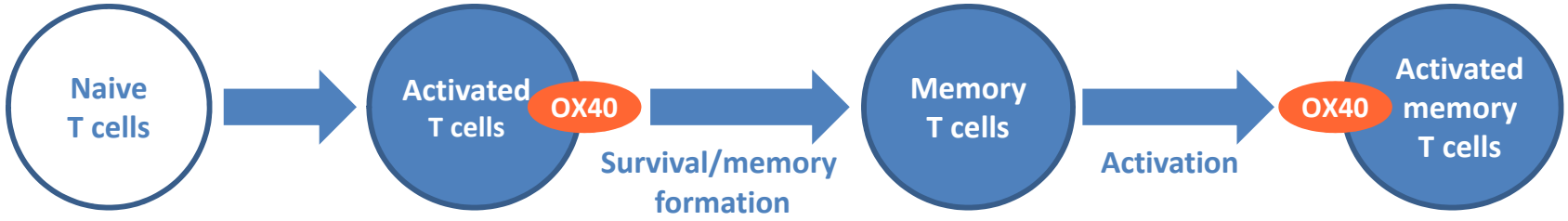
About target molecule OX40

■ OX40 (CD134):

- Type I membrane protein
- TNF receptor superfamily
- OX40 is expressed transiently on T cells when these become activated, and has been posited to significantly contribute to clonal expansion, survival and memory formation.



OX40 is a key molecule in autoimmune disease

Relationship between atopic dermatitis (AD) and OX40

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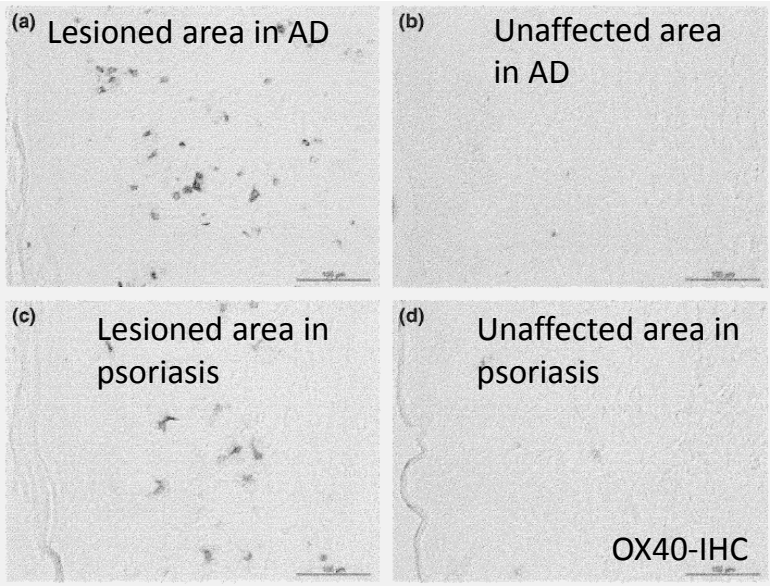
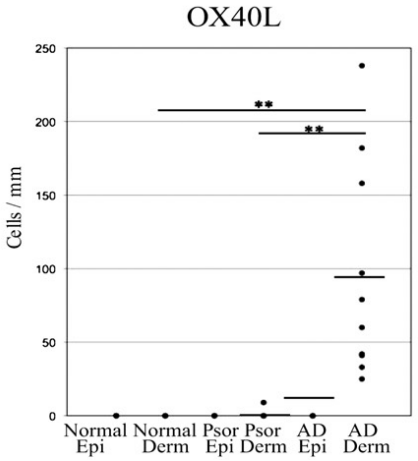
■ Pathogenic contribution of activated T cells

- Upregulation of OX40/OX40L in AD skin
  - A marked increase in OX40L-positive cells was found in lesioned areas.
  - Compared with unaffected areas, lesioned areas were found to exhibit an increase in the number of OX40-positive cells.



J. Eur. Acad. Dermatol. Venereol., **27**, e197-e205 (2013)

J. Allergy Clin. Immunol., **128**, 574-582 (2011)



Likelihood of OX40's involvement in AD pathology

OX40 as a therapeutic target for AD

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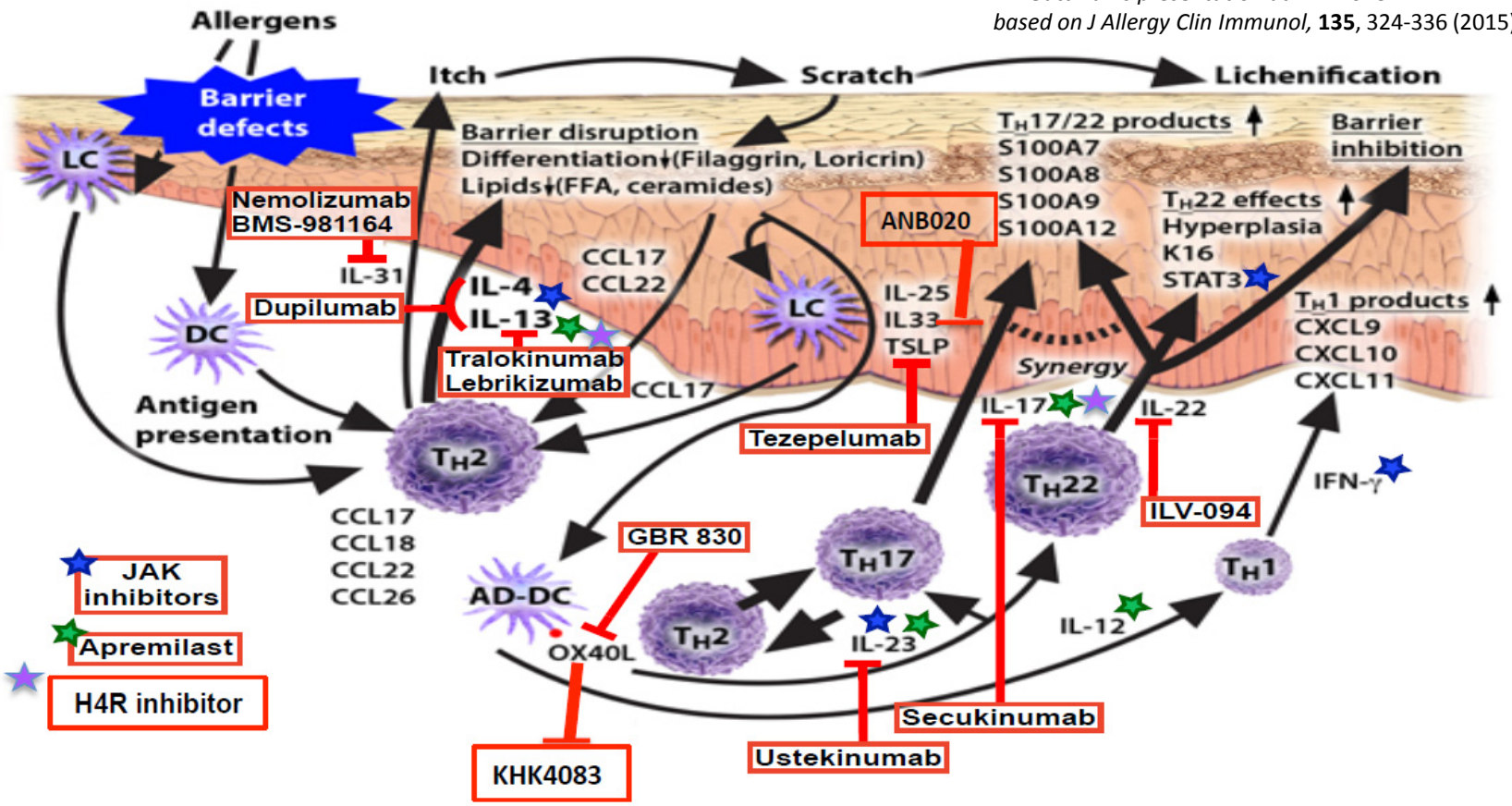
Dr. Guttman's presentation at AAD2018
based on J Allergy Clin Immunol, **135**, 324-336 (2015)



The involvement of various helper T cell subsets (Th1/2/17/22) in the pathophysiology of atopic dermatitis (AD) has been suggested.

⇒ Targeting OX40 may allow extensive control of helper T cells

About KHK4083

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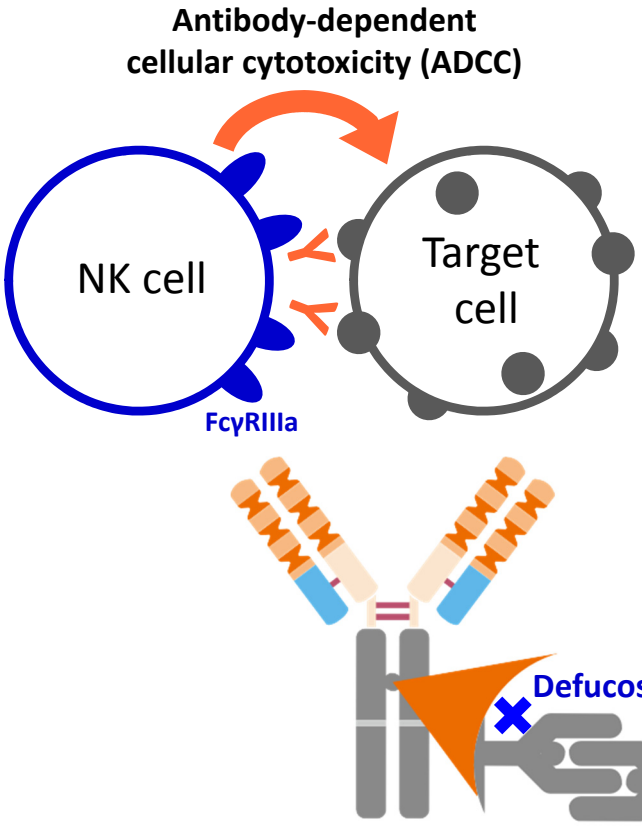
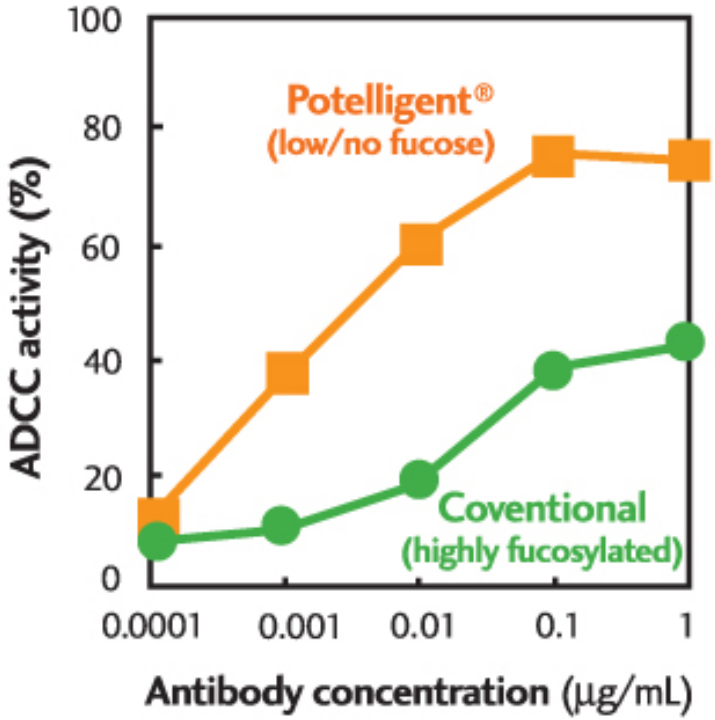
■ KHK4083: fully human anti-OX40 monoclonal antibody

- Created by using fully human antibody production technology
- ADCC activity increased by using Kyowa Hakko Kirin's POTELLIGENT® defucosylation technology





POTELLIGENT® technology

KHK4083 is an antibody drug incorporating Kyowa Hakko Kirin's antibody technology

Functions of KHK4083

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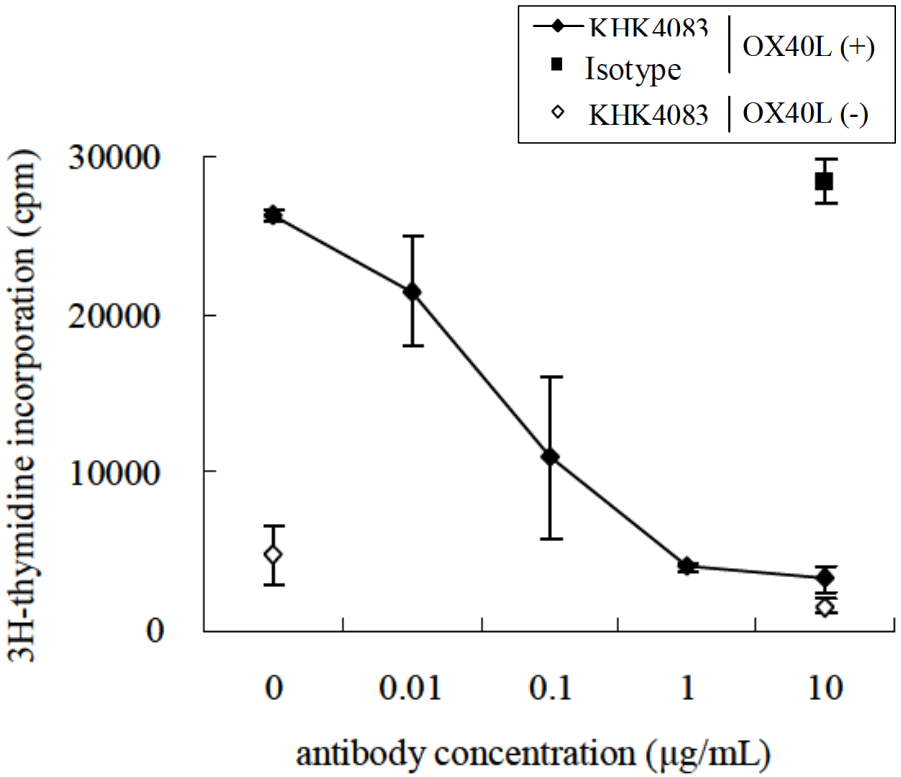
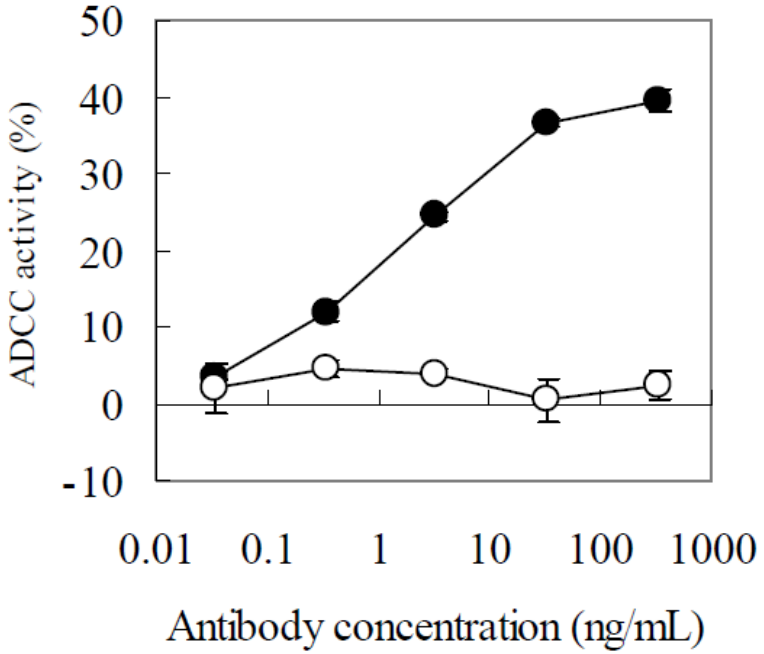
■ Antagonistic activity



Human CD4⁺ T cells are incubated in the presence of solid-phase CD3 antibodies, sOX40L and KHK4083; cell proliferation is then measured based on ^{3}H-thymidine incorporation.

■ ADCC activity



Human activated CD4⁺ T cells and PBMCs are incubated in the presence of either KHK4083 (●) or a negative control (○) (E/T ratio = 1:30). ADCC activity was measured using calcein released from calcein-labeled CD4⁺ T cells as an index.

Dual activities: antagonistic activity and ADCC activity

Results of pre-clinical pharmacological studies

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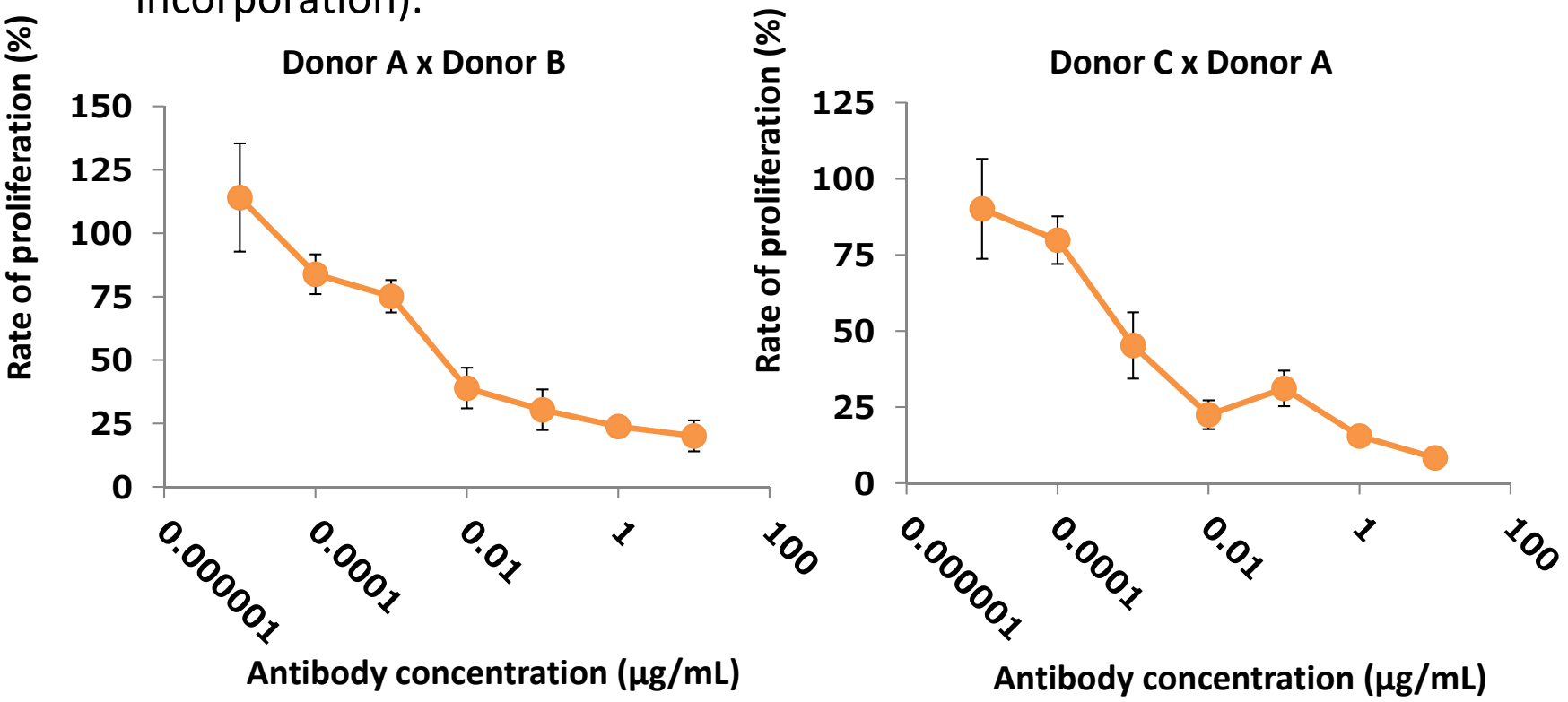
■ MLR (Mixed Lymphocyte Reaction) suppressing activity

- Ability to suppress lymphocyte activation during mixed incubation of PBMCs from different donors was assessed upon adding KHK4083 (by detecting ^{3}H incorporation).



Potential to suppress MLR at low doses was shown.

KHK4083's mechanism of action

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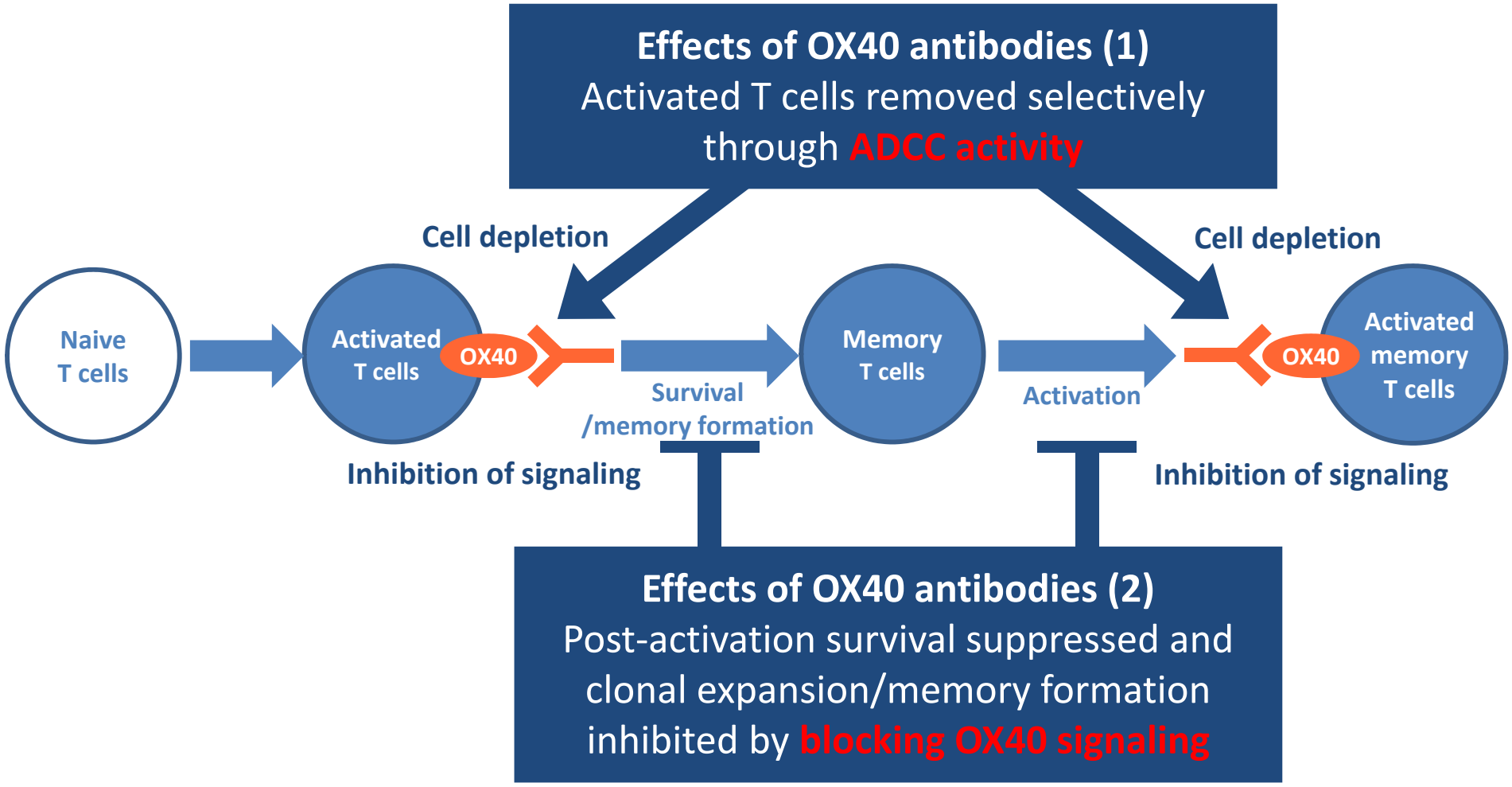

High efficacy can be expected based on powerful inhibition of acquired immunity through effects (1) and (2)

Overview of trial design

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Study design

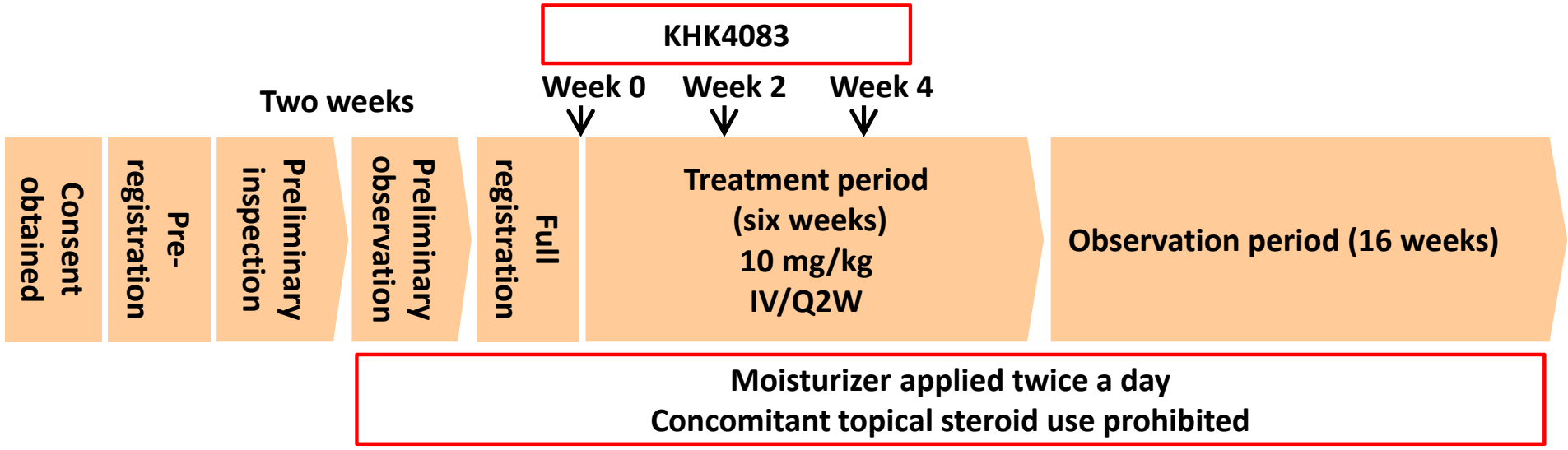
- Phase I repeated-dose
- 10 mg/kg of KHK4083 were administered intravenously every two weeks over a six-week period (three times in total).
- Concomitant administration of topical steroid medications was forbidden from one week before full registration to the end of the clinical trial (week 22).

Subjects

- Patients with moderate to severe AD (N = 22)
- Main inclusion criteria: EASI ≥ 12, IGA ≥ 3, BSA ≥ 10%, TARC ≥ 700 pg/mL

Endpoints

- Primary: safety
- Secondary: pharmacokinetics, immunogenicity
- Exploratory: pharmacodynamics (lymphocytes, serum cytokines, serum disease markers (TARC), flow cytometry, immunohistochemistry), clinical symptoms (EASI, etc.)



Patient background

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- 26 AD patients were assessed for eligibility to participate in the clinical trial, and the 22 patients who met the criteria were administered KHK4083 three times (at week 0, week 2 and week 4).
- During the 22-week trial period, four subjects received rescue therapy.

	N = 22 (average ± standard deviation) or (N (%))
Age [years]	33.6 ± 11.4
Men	18 (81.8)
BMI [kg/m^2]	23.96 ± 4.59
Disease score at baseline	
Rajka & Langeland AD severity	
Moderate	8 (36.4)
Severe	14 (63.6)
TARC [pg/mL]	6260 ± 6118
EASI (Eczema Area and Severity Index)	33.98 ± 9.68
IGA (Investigator's Global Assessment)	3.8 ± 0.6
BSA (Body Surface Area) [%]	57.4 ± 16.4
DLQI (Dermatology Life Quality Index)	8.9 ± 5.2
Pruritus NRS (Numerical Rating Scale)	7.0 ± 2.1
POEM (Patient-Oriented Eczema Measure)	15.3 ± 6.9

Primary endpoint: safety results

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- 17 out of 22 test subjects (77%) experienced adverse events.
- No fatal adverse events, serious adverse events, significant adverse events or adverse events leading to discontinuation occurred.

	KHK4083 10 mg/kg IV N = 22 (N (%))	
	Overall	With causal relationship
Test subjects who experienced adverse events	17 (77.3)	17 (77.3)
Fatal adverse events	0	0
Other serious adverse events	0	0
Other significant adverse events	0	0

Primary endpoint: safety results (list of adverse events)

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- "Pyrexia", affecting 11 subjects (50%), was most common, followed by "chills" (36.4%), affecting eight subjects (36.4%).

Event name	KHK4083 10 mg/kg IV N = 22 (N (%))
Total (adverse events)	17 (77.3)
Pyrexia	11 (50)
Chills	8 (36.4)
Aphthous ulcer	4 (18.2)
Nasopharyngitis	3 (13.6)
Raised blood uric acid	3 (13.6)
Stye	2 (9.1)
Erythema	2 (9.1)
Blepharitis	1 (4.5)
Gastrointestinal injury	1 (4.5)
Stomatitis	1 (4.5)
Vomiting	1 (4.5)
Fatigue	1 (4.5)
Angular cheilitis	1 (4.5)
Cellulitis	1 (4.5)
Folliculitis	1 (4.5)
Eczema impetiginous	1 (4.5)
Raised alanine aminotransferase	1 (4.5)
Decreased leukocytes	1 (4.5)
Hypertriglyceridemia	1 (4.5)
Sciatic neuralgia	1 (4.5)
Depressive symptoms	1 (4.5)
Asthma	1 (4.5)
Acne	1 (4.5)

Main exploratory endpoints: EASI/TARC

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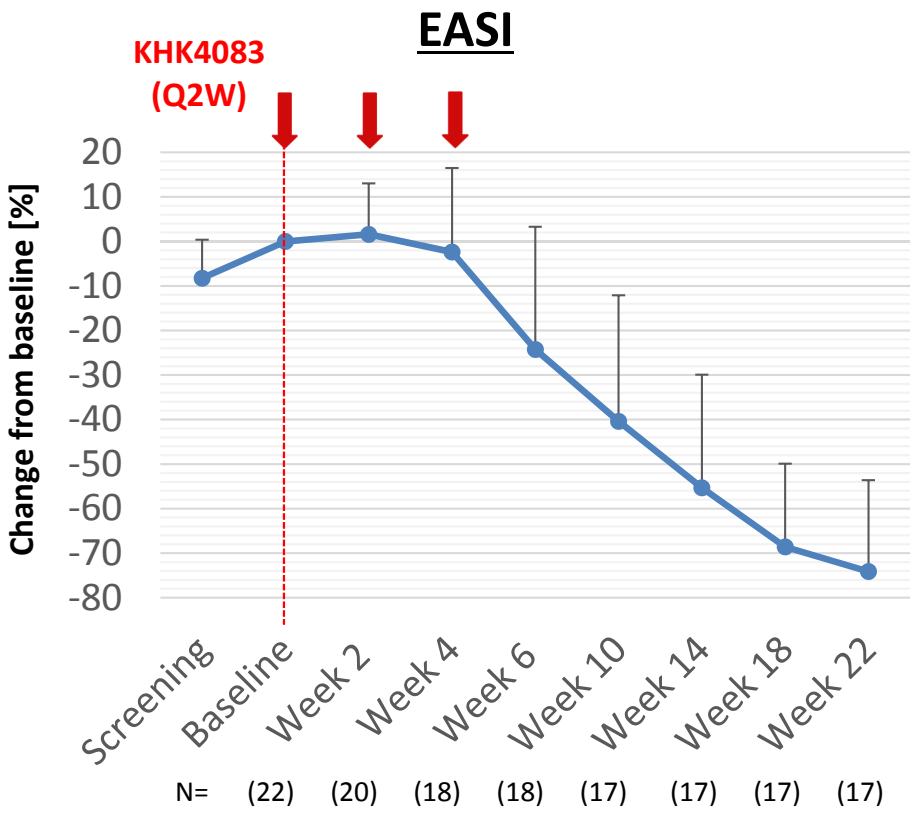
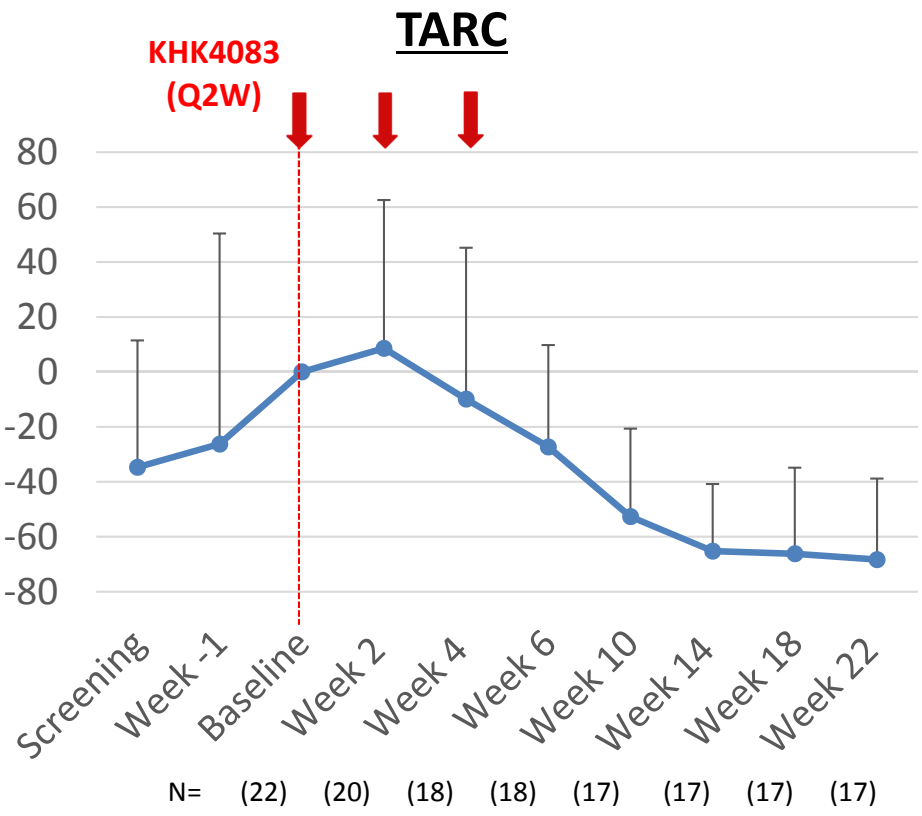
■ Rate of change from baseline (excluding data after rescue therapy)



EASI at week 22 had decreased by 74.12% from baseline



Increased until week 2 following discontinuation of topical steroids, then declined, maintaining this trend until week 22.

A beneficial effect was found to continue after the end of KHK4083 administration.

Main exploratory endpoints: other clinical symptoms

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Endpoints	Results at week 22
Ratio of patients reaching an IGA score of 0 or 1 (skin lesions disappeared or nearly disappeared)	35.0%
BSA improvement from baseline	28.9% (56.4% → 27.5%)
DLQI improvement from baseline	6.5 points (8.7 points → 2.2 points)
Pruritus NRS improvement from baseline	4.4 points (6.8 points → 2.4 points)
POEM improvement from baseline	8.8 points (14.9 points → 6.1 points)

4. Summary and future developments

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- OX40 is involved in T cell activation and is a key molecule in a variety of autoimmune disorders.
- In addition to Th2, the involvement of other helper T cell subsets in the pathophysiology of AD has also been suggested.
- Inhibiting OX40 may allow extensive control of helper T cells.
- Anti-OX40 antibodies KHK4083 exert ADCC activity and antagonistic activity, and can be expected to display high efficacy.
- The 4083-004/Phase I trial on AD subjects showed KHK4083's safety and tolerability in AD patients. Beneficial effects on clinical symptoms (EASI, etc.) were found to continue after the end of KHK4083 administration.
- We believe that KHK4083 will be an effective treatment option for moderate to severe AD.
- We have started global Phase II clinical trials on patients with moderate to severe AD (starting in October 2018; NCT03703102).

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The Kyowa Hakko Kirin Group companies strive to contribute to the health and well-being of people around the world by creating new value through the pursuit of advances in life sciences and technologies.

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