ORIGINAL ARTICLE

Phase I randomized study of KHK4083, an anti-OX40 monoclonal antibody, in patients with mild to moderate plaque psoriasis

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Abstract

Background OX40 (CD134) is expressed in lesional but not healthy skin of patients with psoriasis. KHK4083 is a fully human monoclonal antibody against OX40.

Objective The primary aim of this first-in-human phase 1 study was to determine the safety and tolerability of ascending single doses of KHK4083 in patients with mild to moderate plaque psoriasis. Secondary aims were to determine the pharmacokinetics and immunogenicity of KHK4083, and an exploratory objective was to assess clinical activity.

Methods In phase 1a, single doses of KHK4083 0.003 and 0.001 mg/kg IV were administered open label in two cohorts (each $n = 6$). Phase 1b had a multicentre, randomized, double-blind, placebo-controlled, ascending single-dose design in seven cohorts. Randomization was performed 3 : 1 to KHK4083 ($n = 6$) or placebo ($n = 2$) within each cohort. Ascending doses of KHK4083 were 0.03, 0.1, 0.3, 1.0, 3.0 and 10 mg/kg IV, and 1.0 mg/kg SC.

Results There were no severe or serious adverse events (AEs), or discontinuations because of AEs. The most frequent treatment-related AEs in the 55 patients who received KHK4083 were mild or moderate chills (9.1%), and infusion/injection site reactions (7.3%). No clinically meaningful or dose-related changes from baseline in laboratory values, vital signs, ECG recordings or physical examinations were observed. Some KHK4083 recipients (10/54) developed anti-KHK4083 antibodies following treatment. Mean elimination half-life ($t_{1/2}$) increased with dose, maximum serum concentration increased in a dose-proportional manner, and area under the serum concentration–time curve increased in a more than dose-proportional manner with increasing IV dose. Absolute bioavailability following SC administration was 73%. There was some indication of improvement in Psoriasis Area Severity Index (PASI) and sPGA scores at the highest IV doses (1.0 and 10 mg/kg) and the SC dose (1.0 mg/kg). The largest PASI 50 response and improvement in sPGA score ≥2 occurred with KHK4083 1.0 mg/kg SC.

Conclusion KHK4083 administration as a single dose up to 10 mg/kg IV or 1.0 mg/kg SC was generally safe and well tolerated in patients with mild to moderate plaque psoriasis with no dose-limiting AEs.

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Conflicts of interest

K.A.P. is an investigator, speaker, consultant and/or advisory board member for AbbVie, Akros, Allergan, Amgen, Astellas, Baxalta, Boehringer Ingelheim, Bristol-Meyers Squibb, Celgene, Dermira, Eli Lilly, Galderma, Genentech, Kyowa Kirin Pharmaceutical Development, Inc., Galxo Smith Kline, Janssen, Meiji Seika, MSD, Merck-Serono, Mitsubishi, Novartis, Pfizer, Regeneron, Roche, Sanofi-Genzyme, Sun Pharma, Takeda, UCB and Valeant. M.J.G. has been an investigator, speaker and/or consultant for AbbVie, Amgen, Boehringer Ingelheim, Celgene Inc., Dermira, Galderma, Kyowa Kirin Pharmaceutical Development, Inc., Eli Lilly, Glaxo Smith Kline, Janssen, Novartis, Pfizer, Takeda and UCB. The other authors declare no conflict of interests. V.S. is an employee of Kyowa Kirin Pharmaceutical Development, Inc. (Princeton, NJ, USA).

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Introduction

Psoriasis is a chronic autoimmune, inflammatory skin disease affecting about 2% of the global population or about 25 million people in North America and Europe.[1–3] The most common form (affecting ~80% of patients) is plaque psoriasis.[4] Plaque psoriasis often starts in late adolescence or early adulthood and usually persists as a chronic disease throughout adult life in about 90% of patients, which therefore necessitates continuous treatment.[1,5] The cause of psoriasis is not fully understood, but it is likely that there is combination of genetic and environmental components.[6]

The majority of patients (~80%) have mild to moderate psoriasis and receive first-line therapy with topical preparations and/or phototherapy.[5,7] Adherence to topic therapy is generally poor.[8,9] More recalcitrant moderate and severe disease necessitates progression to various systemic agents, e.g. cyclosporine, methotrexate, retinoids, apremilast, and biologic therapies such as etanercept, infliximab, adalimumab, ustekinumab, secukinumab and ixekizumab, which may be associated with certain severe and/or serious toxicities.[5,10–12]

OX40 (cluster of differentiation [CD]134, tumour necrosis factor receptor [TNFR]SF4), a TNFR family member, offers a novel therapeutic target as it is expressed in lesional but not healthy skin of patients with psoriasis.[13,14] OX40 plays a key role in maintaining late T-cell proliferation and survival by suppressing apoptosis, and in inducing T-cell memory formation (Fig. 1).[15–19] KHK4083 (Kyowa Kirin Pharmaceutical Development, Inc., Princeton, NJ, USA) is a fully human, non-fucosylated IgG_1 monoclonal antibody (mAb) specific for OX40. KHK4083 has shown antagonistic activity to OX40L *in vitro* and efficacy in animal models of graft-vs.-host disease and delayed-type hypersensitivity (unpublished data on file Kyowa Kirin Pharmaceutical Development, Inc.). The primary aim of this study was to determine the safety and tolerability of single, ascending doses of KHK4083 administered by intravenous (IV) infusion and a single dose administered by subcutaneous (SC) injection in patients with mild to moderate plaque psoriasis. Secondary aims were to determine the pharmacokinetics and immunogenicity of KHK4083, and an exploratory objective was to assess clinical activity.

Materials and methods

Patients

Male or female patients ≥18 years of age with a clinical diagnosis of mild to moderate plaque psoriasis according to the investigator for ≥6 months were eligible for study entry. Body surface area affected by psoriasis was ≥2% with at least one plaque suitable for biopsy (Cohort 1 had an upper limit of 10% for body surface area affected). Patients who had been previously treated with a biologic agent had to undergo an appropriate washout period for the relevant biologic agent or be naive to biologic treatment. Major exclusion criteria were as follows: a history of clinically significant cardiac, renal, pulmonary, immunologic or autoimmune disease apart from psoriasis; a history of drug-induced psoriasis; those requiring treatment with topical, oral or injectable corticosteroids during the study; and those receiving phototherapy. Full details of inclusion/exclusion criteria are provided as Supporting Information.

Study design

The study was conducted in accordance with US Code of Regulations and International Conference on Harmonization of Good Clinical Practice guidelines, and adhered to the ethical principles of the Declaration of Helsinki. The protocol and its subsequent amendments were approved by relevant Institutional Review Boards at the four participating study centres. All patients provided written informed consent prior to participation in the study.

The primary objective of this study was to determine the safety and tolerability of KHK4083 administered IV or SC as monotherapy in patients with mild to moderate plaque psoriasis. Secondary objectives were to evaluate its pharmacokinetic profile and immunogenicity. Exploratory objectives were to evaluate its pharmacodynamic profile assessed by changes in selected biomarkers in serum, peripheral blood and skin biopsies, its activity on functional health and health-related quality of life (HRoQL) and its efficacy compared to placebo.

There was no clinical experience with KHK4083 prior to this ascending single-dose study. The rationale for dose selection is detailed in Supporting Information. Patients were screened 3–28 days prior to single-dose administration of KHK4083 or placebo on Day 1. The study was divided into two parts: phase 1a and 1b (Table 1). Phase 1a was conducted at a single centre (Probity Medical Research, Inc., ON, Canada) with open-label administration of KHK4083 0.003 and 0.001 mg/kg IV over 60 min in cohorts 1 and 2, respectively (n = 6 in each cohort). Each patient in phase 1a and the first cohort of phase 1b (Cohort 3) received KHK4083 sequentially 1 week apart. All patients in cohorts 1–3 were enrolled at one site (K.A.P.), and safety data for these cohorts were reviewed by Health Canada before proceeding to subsequent cohorts recruited at four study centres. Phase 1b had a multicentre, randomized, double-blind, placebo-controlled, ascending single-dose design in seven cohorts (n = 8 in each cohort). Randomization was performed 3 : 1 to KHK4083 (n = 6) or placebo (n = 2) within each cohort using a random code for patient numbers. Cohorts 4–7 received KHK4083 0.03, 0.1, 0.3, 1.0 and 3.0 mg/kg, respectively, IV over 60 min. Cohort 8 received KHK4083 1.0 mg/kg SC. After completion of cohorts 7 and 8, and following protocol amendment, Cohort 9 was added and received KHK4083 10 mg/kg IV over 120 min.

KHK4083 was supplied in single-use vials containing 5 mL of 10 mg/mL product, and placebo was provided in similar appearing vials containing 5 mL of the formulation buffer of the active

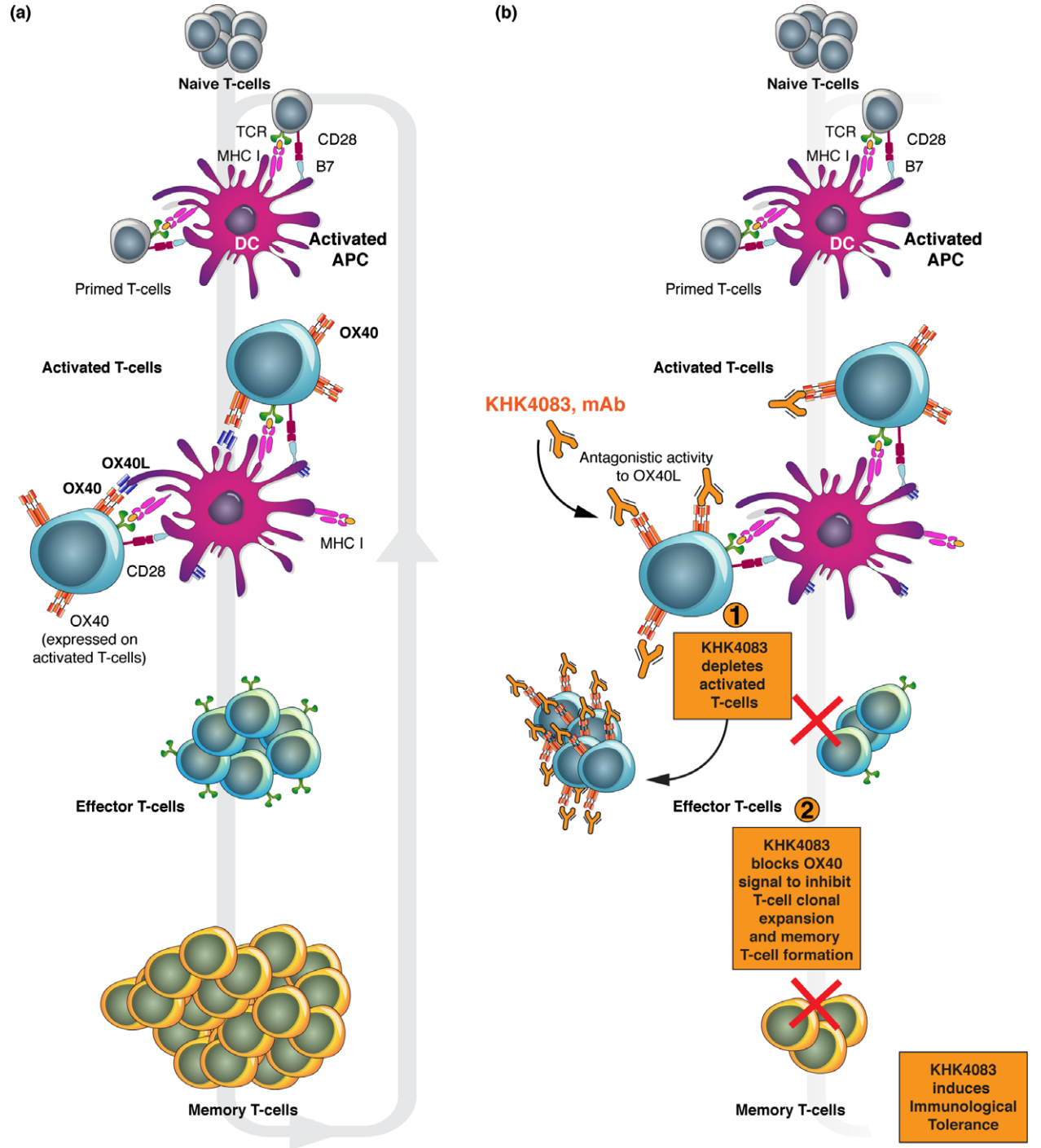

Figure 1 Effect of KHK-4083 on T-cell activation and memory cell expansion.

product. The required dose of KHK4083 or placebo was taken from the vial and diluted in sterile normal saline for IV infusion via a 0.2- or 0.22-μm low-protein-binding inline filter. Administration of KHK4083 (1.0 mg/kg) or placebo SC was given by direct injection from the vial without dilution. The sponsor, investigators and site personnel had no knowledge of the treatment assigned in phase 1b to maintain double-blind conditions; treatment allocation was only known by the pharmacist.

Table 1 Dose escalation schedule

Cohort*	Dose level	Administration route	No. of patients
Cohort 1	0.003 mg/kg	IV	6
Cohort 2	0.01 mg/kg	IV	6
Cohort 3	0.03 mg/kg	IV	8
Safety data reviewed by Health Canada before decision made to proceed to Cohort 4			
Cohort 4	0.1 mg/kg	IV	8
Cohort 5	0.3 mg/kg	IV	8
Cohort 6	1.0 mg/kg	IV	8
Cohort 7	3.0 mg/kg	IV	8
Cohort 8	1.0 mg/kg	SC	8
Cohort 9	10 mg/kg	IV	8

*Patients enrolled in cohorts 1 and 2 to receive only KHK4083 (phase 1a). Patients in cohorts 3–9 to receive either KHK4083 (n = 6) or placebo (n = 2) [phase 1b].
IV, intravenous; SC, subcutaneous.

Assessments

Patients were assessed at intervals from Day 1 (baseline) to Day 57 (cohorts 1–8) or 71 (Cohort 9).

Safety and tolerability were determined from adverse events (AEs), physical examination findings, electrocardiogram readings, vital sign measurements and clinical laboratory test results (serum chemistry, haematology, coagulation and urinalysis). AEs were recorded following observation by the investigator, in response to non-leading questioning, or spontaneous reporting by the subject. AEs were graded for intensity (mild, moderate or severe) and relationship to treatment (definite, probable, possible, unlikely or unrelated). The safety analysis population included all patients who received at least a partial dose of study medication. Immunogenicity was determined using a validated electrochemiluminescent ligand-binding assay for the detection of anti-KHK4083 antibodies in serum. Drug tolerance limit at 100 ng/mL of positive control was 10 μg/mL of KHK4083. There was no hook effect observed at up to 100 μg/mL of positive control.

Blood samples were taken for pharmacokinetic assessment. Serum samples were analysed using a validated electrochemiluminescent method for the determination of KHK4083 concentration. The lower limit of assay quantification was 25 ng/mL and the quantification range 25–10 000 ng/mL. Pharmacokinetic parameters were derived using non-compartmental analysis with WinNonlin, v6.3 (Pharsight Co., Mountain View, CA, USA).

Patients who received at least one full dose of KHK4083 or placebo and who had baseline data and at least one postdose activity assessment were included in the full analysis set (FAS) for determination of clinical activity. Psoriasis severity was graded using the Psoriasis Area Severity Index (PASI)[20] and a static Physician Global Assessment (sPGA) using a 6-point scale (0 = clear to 5 = severe). Response was determined according to change in mean PASI score, and the proportions of patients achieving PASI 50 or improvement in sPGA score ≥2.

Blood samples were taken for assessment of changes from baseline in the number and phenotypes of peripheral blood mononuclear cells by flow cytometry including total T lymphocytes and subsets, B lymphocytes, natural killer cells, monocytes, neutrophils, and naive, memory and effector T lymphocytes with and without OX-40 in response. The samples were analysed using available commercial assay kits and/or validated assay methods. Circulating OX40-positive T cells were measured. The measurement of soluble OX40 (sOX40) used a validated enzyme-linked immunosorbent assay (ELISA) method and soluble OX40 ligand (sOX40L) used a validated quantitative detection method for sOX40L carried out with modified use of the commercially available kit (Human sOX40L ELISA, MyBioSource, San Diego, CA). PASI scores were used to evaluate pharmacokinetic/pharmacodynamic correlations. Changes in skin mRNA keratin marker expression (K16), skin T cells and a wide array of cytokines and chemokines, transcription factors and other relevant markers were assessed for skin biopsy data for two biopsy punches, one from a target lesion and one from unaffected skin. All sections stained with markers for the presence of cytokines, leucocyte subsets, blood vessels and other markers were evaluated semiquantitatively and, if positive, further analysed using a confirmation assay.

Statistical analysis

Change from baseline in PASI and sPGA were analysed using a mixed-model repeated-measures (MMRM) analysis of all of the postbaseline PASI scores through to Day 57. Restricted maximum-likelihood estimation was used. The dependent variable was the change from baseline in PASI score. The model included dose level, route of administration and visit as fixed effects, the baseline PASI score as a covariate and visit as a repeated measure. An unstructured covariance matrix and the Kenward–Roger approximation were used to estimate the degrees of freedom. The contrast interest was between the KHK4083 and placebo groups for each route of administration on Day 57. Model-based least-squares means (LSMs) of the differences between the active treatment groups and placebo group on Day 57, along with 95% confidence intervals (CIs) and P values, were determined for each route of administration. The change from baseline to Day 29 in epidermal thickness was analysed using an analysis of covariance model with the baseline epidermal thickness as a covariate, and dose level and route of administration as fixed effects. The contrast interest was between the KHK4083 and placebo group for each route of administration. Model-based LSMs of the differences between the active treatment groups and placebo group on Day 29, along with 95% CIs and P values, were determined for each route of administration. P values <0.05 were considered statistically significant. Other results are described by descriptive statistics.

Results

Study population

The study was conducted from 21 December 2012 to 8 December 2014. All patients ($N = 68$) received at least a full or partial dose of study medication and were included in the safety analysis set. One patient in Cohort 5 was randomized to placebo IV but received KHK4083 0.3 mg/kg IV in error. The FAS included 67 patients as one patient in Cohort 2 (KHK4083 0.01 mg/kg IV) did not receive the full dose. The baseline demographic and clinical characteristics of these patients are summarized in Table 2. The groups treated with KHK4083 or placebo appeared balanced. Three patients in the FAS discontinued prematurely: one in Cohort 3 (0.03 mg/kg IV) on Day 51 lost to follow-up, one in Cohort 6 (1.0 mg/kg IV) on Day 20 due to lack of efficacy and one in Cohort 8 (1.0 mg/kg SC) on Day 45 due to withdrawal of consent.

Safety

The AE profile is summarized in Table 3. Treatment-emergent AEs occurred in similar proportions of patients in the KHK4083 and placebo groups and all were either mild or moderate in intensity. The percentages of patients with AEs were similar between the KHK4083 and placebo IV (59.2% vs. 54.5%, respectively) or SC (50% vs. 50%) dose cohorts. There were no dose-related trends in AE incidences across the KHK4083 IV dose cohorts. There were no severe AEs, discontinuations because of AEs or serious AEs. Treatment-related AEs only occurred in the patients treated with KHK4083 ($n = 11/55$, 20.0%), with the most commonly reported treatment-related AE being chills ($n = 5$, 9.1%) followed by infusion-related ($n = 3$, 5.5%) or injection-related ($n = 1$, 1.8%) reactions. One patient in Cohort 5 (0.3 mg/kg IV) developed pustular psoriasis on Day 50 that was considered possibly related to treatment: the patient started cyclosporine 200 mg twice daily from Day 57 and recovered by Day 78. There were no clinically meaningful or dose-related changes from baseline in laboratory values, vital signs, ECG recordings or physical examinations.

Immunogenicity

Immunogenicity was determined in the FAS ($n = 67$). Immunogenicity was negative on days 1 and 57 in all 11 placebo recipients and all six KHK4083 recipients who received SC administration. Three of 48 (6.3%) KHK4083 recipients who received IV administration showed confirmed positive anti-KHK4083 antibodies on Day 1 compared to 13 patients (27.1%) on Day 57. Positive anti-KHK4083 antibodies did not appear to affect pharmacokinetic exposure to the drug (data not shown).

Table 2 Baseline demographic and clinical characteristics

Variable	IV route (cohorts 1–7, 9)*		SC route (cohort 8)*		Total (cohorts 1–9) [*N* = 68]
	KHK4083 0.003–10 mg/kg (*n* = 49)	Placebo (*n* = 11)†	KHK4083 1.0 mg/kg (*n* = 6)	Placebo (*n* = 2)	
Age (years), mean (SD)	47.3 (13.0)	40.3 (10.8)	39.5 (13.4)	38.5 (9.2)	45.2 (12.9)
Gender, *n* (%)					
Male	39 (79.6)	7 (63.6)	3 (50.0)	0	49 (72.1)
Female	10 (20.4)	4 (36.4)	3 (50.0)	2 (100)	19 (27.9)
Race, *n* (%)					
Caucasian	45 (91.8)	10 (90.9)	4 (66.7)	2 (100)	61 (89.7)
Native American or Alaska native	2 (4.1)	0	2 (33.3)	0	4 (5.9)
BMI (kg/cm^2), mean (SD)	30.7 (6.99)	31.9 (4.62)	32.7 (12.1)	28.4 (9.44)	31.0 (7.15)
Time since diagnosis (years), mean (SD)	15.8 (11.7)	16.5 (11.3)	12.8 (9.2)	11.0 (12.7)	15.5 (11.3)
Prior use of psoriasis therapy, *n* (%)					
Yes	46 (93.9)	11 (100)	6 (100)	2 (100)	65 (95.6)
No	3 (6.1)	0	0	0	3 (4.4)
Type of prior psoriasis therapy, *n* (%)					
Topical‡	44 (89.8)	11 (100)	5 (83.3)	2 (100)	62 (91.2)
Oral/systemic§	17 (34.7)	7 (63.6)	1 (16.7)	0	25 (36.8)
Phototherapy	12 (24.5)	2 (18.2)	1 (16.7)	0	15 (22.1)

*Cohorts 1 and 2 received only KHK4083 IV; cohorts 3–7 and 9 received KHK4083 IV or placebo IV; and Cohort 8 received KHK4083 SC or placebo SC.
†One patient in Cohort 5 was randomized to placebo IV but received KHK4083 0.3 mg/kg IV in error.
‡Includes betamethasone, clobetasol, betamethasone/salicylic acid, betamethasone/calcipotriol, mometasone, halobetasol, etc.
§Includes methotrexate, oral retinoids, various biologic therapies (e.g. etanercept, tofacitinib, ustekinumab, apremilast, efalizumab, leflunomide) and investigational agents.
BMI, body mass index; IV, intravenous; PASI, Psoriasis Area Severity Index; SC, subcutaneous; SD, standard deviation.

Table 3 Adverse events

	IV route (cohorts 1–7, 9)*		SC route (Cohort 8)*		Total (cohorts 1–9) exposed to KHK4083 [*N* = 55]
	KHK4083 0.003–10 mg/kg (*n* = 49)	Placebo (*n* = 11)†	KHK4083 1.0 mg/kg (*n* = 6)	Placebo (*n* = 2)	
Any treatment-emergent AE	29 (59.2)	6 (54.5)	3 (50.0)	1 (50.0)	32 (58.2)
Mild	12 (24.5)	2 (18.2)	2 (33.3)	0	14 (25.5)
Moderate	17 (24.5)	4 (36.4)	1 (16.7)	1 (50.0)	18 (32.7)
Any treatment-related AE	10 (20.4)	0	1 (16.7)	0	11 (20.0)
Treatment-related AE by preferred term‡					
Chills	5 (10.2)	0	0	0	5 (9.1)
Infusion-related reaction	3 (6.1)	0	0	0	3 (5.5)
Injection-related reaction	0	0	1 (12.5)	0	1 (1.8)
Myalgia	2 (4.1)	0	0	0	2 (3.6)
Headache	2 (4.1)	0	0	0	2 (3.6)
Fatigue	1 (2.0)	0	0	0	1 (1.8)
Feeling cold	1 (2.0)	0	0	0	1 (1.8)
Hyperhidrosis	1 (2.0)	0	0	0	1 (1.8)
Pustular psoriasis	1 (2.0)	0	0	0	1 (1.8)
Anxiety	1 (2.0)	0	0	0	1 (1.8)

*Cohorts 1 and 2 received only KHK4083 IV; cohorts 3–7 and 9 received KHK4083 IV or placebo IV; and Cohort 8 received KHK4083 SC or placebo SC.
†One patient in Cohort 5 was randomized to placebo IV but received KHK4083 0.3 mg/kg IV in error.
‡Coded by MeDRA dictionary version 15.1.
AE, adverse event; IV, intravenous; SC, subcutaneous.

Table 4 Pharmacokinetics

	Mean ± SD						
	T_{max} (h)	C_{max} (μg/mL)	AUC_{0-t} (μg·h/mL)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	V_z or V_z/F* (mL/kg)	CL or CL/*F** (mL/h/kg)
Cohort 1 (0.003 mg/kg IV) [*n* = 6]	1.19 ± 0.452	0.090 ± 0.035	0.423 ± 0.222	1.19 ± 0.600‡	7.51 ± 2.22‡	29.5 ± 6.52‡	2.98 ± 1.27‡
Cohort 2 (0.01 mg/kg IV) [*n* = 6]	1.03 ± 0.0587	0.276 ± 0.048	3.37 ± 0.640	4.17 ± 0.985	9.62 ± 2.40	33.8 ± 6.74	2.52 ± 0.616
Cohort 3 (0.03 mg/kg IV) [*n* = 6]	1.20 ± 0.396	1.36 ± 0.942	27.9 ± 10.7	35.4 ± 11.1	27.9 ± 5.55	35.6 ± 8.96	0.900 ± 0.200
Cohort 4 (0.1 mg/kg IV) [*n* = 6]	1.23 ± 0.492	2.34 ± 1.19	182 ± 121	246 ± 85.2§	69.2 ± 19.1§	42.9 ± 13.1§	0.456 ± 0.191§
Cohort 5 (0.3 mg/kg IV) [*n* = 7]†	1.98 ± 1.02	8.32 ± 1.80	1320 ± 310	1420 ± 400	161 ± 67.8	49.6 ± 14.7	0.229 ± 0.0773
Cohort 6 (1.0 mg/kg IV) [*n* = 6]	2.35 ± 2.67	29.1 ± 4.01	6280 ± 1930	6740 ± 1760¶	214 ± 35.5	46.9 ± 6.11	0.156 ± 0.0383
Cohort 7 (3.0 mg/kg IV) [*n* = 6]	2.52 ± 2.17	86.2 ± 12.4	21 900 ± 5510	23 400 ± 6440	312 ± 100	57.3 ± 9.52	0.138 ± 0.0448
Cohort 8 (1.0 mg/kg SC) [*n* = 6]	124 ± 50.4	8.30 ± 3.10	4850 ± 1750	4940 ± 1790¶	185 ± 70.1	54.8 ± 13.5	0.228 ± 0.0877
Cohort 9 (10 mg/kg IV) [*n* = 6]	2.52 ± 0.804	320 ± 42.4	97 600 ± 15800	110 000 ± 18400	547 ± 86.4	72.7 ± 13.2	0.0930 ± 0.0181

*V_z/F and CL/*F* for SC dosing; V_z and CL for IV dosing.
†One patient in Cohort 5 was randomized to placebo IV but received KHK4083 0.3 mg/kg IV in error.
‡*n* = 4.
§*n* = 5.
¶Absolute bioavailability (*F*) = $AUC_{0-\infty}$ SC/$AUC_{0-\infty}$ IV = 4940/6740 × 100% = 73%.
AUC_{0-t}, area under the concentration–time curve from time zero to the time of the last measurable concentration (t); $AUC_{0-\infty}$, area under the concentration–time curve from time zero to infinity; C, total systemic clearance; CL/*F*, apparent systemic clearance; C_{max}, maximum serum concentration; *F*, absolute bioavailability; IV, intravenous; SC, subcutaneous; SD, standard deviation $t_{1/2}$, terminal elimination half-life; t_{max}, time to maximum serum concentration; V_z, volume of distribution; V_z/F, apparent volume of distribution.

Table 5 PASI score change from baseline

	Mean ± SD							
	Baseline	**Day 4**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 57**	**Day 71**
IV administration								
Cohort 1 (0.003 mg/kg) [*n* = 6]	5.25 ± 1.328	5.37 ± 1.394	5.15 ± 1.616	5.22 ± 1.289	4.68 ± 0.799	4.83 ± 1.069	4.32 ± 1.242	–
Cohort 2 (0.01 mg/kg) [*n* = 5]	7.06 ± 2.373	6.36 ± 2.182	6.52 ± 1.636	6.50 ± 2.258*	6.42 ± 1.770	6.32 ± 1.954	6.26 ± 1.483	–
Cohort 3 (0.03 mg/kg) [*n* = 6]	9.93 ± 5.816	10.24 ± 6.155†	9.70 ± 5.422	9.87 ± 6.246	9.03 ± 4.862	9.70 ± 6.893	12.20 ± 10.046†	–
Cohort 4 (0.1 mg/kg) [*n* = 6]	6.97 ± 3.492	6.78 ± 3.468	6.77 ± 3.405	6.85 ± 3.275	6.85 ± 3.203	6.53 ± 3.287	7.17 ± 4.539	–
Cohort 5 (0.3 mg/kg) [*n* = 7]	7.21 ± 3.884	6.99 ± 3.904	6.81 ± 4.231	6.94 ± 4.403	7.37 ± 4.638	6.63 ± 4.023	7.80 ± 4.560	–
Cohort 6 (1.0 mg/kg) [*n* = 6]	6.38 ± 4.322	6.42 ± 4.280	6.63 ± 4.731	5.73 ± 4.078	7.05 ± 4.993	6.17 ± 4.534	4.10 ± 2.265†	–
Cohort 7 (3.0 mg/kg) [*n* = 6]	6.70 ± 2.695	6.42 ± 2.515	6.35 ± 2.524	5.95 ± 2.577	6.02 ± 2.910	6.18 ± 2.919	6.60 ± 2.766	–
Cohort 9 (10 mg/kg) [*n* = 6]	5.30 ± 0.986	5.07 ± 1.078	4.48 ± 1.489	3.72 ± 1.243	3.67 ± 1.446	3.60 ± 1.497	3.63 ± 1.488	4.02 ± 1.294
Placebo [*n* = 11]	8.40 ± 6.993	8.44 ± 7.855	8.58 ± 8.427	8.40 ± 8.870	8.42 ± 8.900	8.45 ± 9.074	8.97 ± 8.903	7.95 ± 8.697‡
SC administration								
Cohort 8 (1.0 mg/kg) [*n* = 6]	4.90 ± 2.361	4.18 ± 1.794	3.18 ± 1.990	2.87 ± 2.084	3.35 ± 2.600	2.63 ± 2.026	2.60 ± 2.288	–
Placebo [*n* = 2]	7.55 ± 7.566	7.80 ± 7.212	7.40 ± 7.778	8.05 ± 6.859	7.80 ± 7.212	7.50 ± 6.788	2.50§	–

*n = 4; †n = 5; ‡n = 2; §n = 1.
IV, intravenous; PASI, Psoriasis Area Severity Index; SC, subcutaneous; SD, standard deviation.

Pharmacokinetics

Pharmacokinetic parameters of KHK4083 for the dose and route of administration are summarized in Table 4. Mean time to reach maximum serum concentration (t_{max}) was 1.03–2.52 h across IV dose levels. Mean pharmacokinetic exposure to KHK4083 increased in a dose-proportional manner for the 0.003–10 mg/kg IV dose range based on maximum serum concentration (C_{max}) but in a more than dose-proportional manner based on area under the serum concentration–time curves to the last measurable concentration and to infinity (AUC_{0-t} and $AUC_{0-\infty}$, respectively). Power analysis, in which the Ln C_{max} was regressed against Ln Dose (0.003–10 mg/kg), yielded a β value of 1.01 (95% CI 0.915–1.10). The power analysis of Ln AUC_{0-t} and Ln $AUC_{0-\infty}$ vs. Ln Dose yielded β values of 1.56 (95% CI 1.40–1.72) and 1.46 (95% CI 1.40–1.52), respectively. With increasing IV doses, mean elimination half-life ($t_{1/2}$) increased from 7.51 to 547 h, mean total systemic clearance decreased from 2.98 to 0.0930 mL/h/kg, and mean volume of distribution increased from 29.5 to 72.7 mL/kg. Following SC administration of KHK4083 1.0 mg/kg, mean t_{max} was 124 h and mean $t_{1/2}$ was 185 h, the latter being consistent with mean $t_{1/2}$ following the same IV dose of 1.0 mg/kg (214 h). Absolute bioavailability following SC administration was 73%.

Clinical activity

Changes in mean PASI and sPGA over time in the cohorts are detailed in Tables 5 and 6, respectively. Changes were minimal in the IV dose cohorts, with the largest improvements in patients who received KHK4083 10 mg/kg IV. Compared to placebo, the greatest improvements occurred in patients who received KHK4083 1.0 mg/kg SC. MMRM analysis did not find any statistically significant changes from baseline to Day 57 for PASI or sPGA, except for sPGA for KHK4083 1.0 mg/kg IV (LS mean −0.88, 95% CI −1.697 to −0.058; P = 0.036). The percentages of patients who achieved PASI 50 and improvement in sPGA score

Table 6 sPGA score change from baseline

	Mean ± SD							
	Baseline	**Day 4**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 57**	**Day 71**
IV administration								
Cohort 1 (0.003 mg/kg) [*n* = 6]	2.7 ± 0.82	2.5 ± 0.84	2.5 ± 0.55	2.5 ± 0.55	2.2 ± 0.75	2.5 ± 0.55	2.3 ± 0.52	–
Cohort 2 (0.01 mg/kg) [*n* = 5]	3.0 ± 0.00	2.4 ± 0.55	2.8 ± 0.45	2.8 ± 0.50*	3.0 ± 0.00	2.4 ± 0.55	2.3 ± 0.52	–
Cohort 3 (0.03 mg/kg) [*n* = 6]	2.7 ± 0.52	2.4 ± 0.55†	2.8 ± 0.41	2.5 ± 0.84	2.7 ± 0.52	2.5 ± 0.84	2.8 ± 0.45†	–
Cohort 4 (0.1 mg/kg) [*n* = 6]	2.5 ± 0.55	2.0 ± 0.89	2.0 ± 0.89	2.0 ± 0.89	2.0 ± 0.89	1.8 ± 0.98	2.2 ± 0.98	–
Cohort 5 (0.3 mg/kg) [*n* = 7]	2.4 ± 0.79	2.4 ± 0.79	2.6 ± 0.79	2.3 ± 0.76	2.6 ± 0.98	2.3 ± 0.76	2.4 ± 0.79	–
Cohort 6 (1.0 mg/kg) [*n* = 6]	2.3 ± 0.82	2.5 ± 0.84	2.3 ± 0.82	2.3 ± 0.82	2.3 ± 0.82	1.8 ± 0.75	1.4 ± 0.55†	–
Cohort 7 (3.0 mg/kg) [*n* = 6]	2.3 ± 0.82	2.2 ± 0.75	2.3 ± 0.52	2.3 ± 0.82	2.5 ± 1.05	2.5 ± 0.84	2.5 ± 0.84	–
Cohort 9 (10 mg/kg) [*n* = 6]	2.3 ± 0.82	2.3 ± 0.82	2.0 ± 0.63	1.8 ± 0.75	1.8 ± 0.75	2.0 ± 0.89	2.0 ± 0.89	1.8 ± 0.75
Placebo [*n* = 11]	2.5 ± 0.82	2.5 ± 0.82	2.5 ± 0.93	2.3 ± 0.79	2.5 ± 0.69	2.4 ± 0.81	2.5 ± 1.04	2.0 ± 1.41‡
SC administration								
Cohort 8 (1.0 mg/kg) [*n* = 6]	2.5 ± 1.05	2.2 ± 0.75	1.8 ± 0.75	1.7 ± 1.03	1.8 ± 0.41	1.3 ± 0.82	1.7 ± 1.21	–
Placebo [*n* = 2]	3.0 ± 1.41	3.0 ± 1.41	2.5 ± 2.12	3.0 ± 1.41	3.0 ± 1.41	3.0 ± 1.41	1.0§	–

*n = 4; †n = 5; ‡n = 2; §n = 1.
IV, intravenous; SC, subcutaneous; SD, standard deviation; sPGA, static Physician Global Assessment.

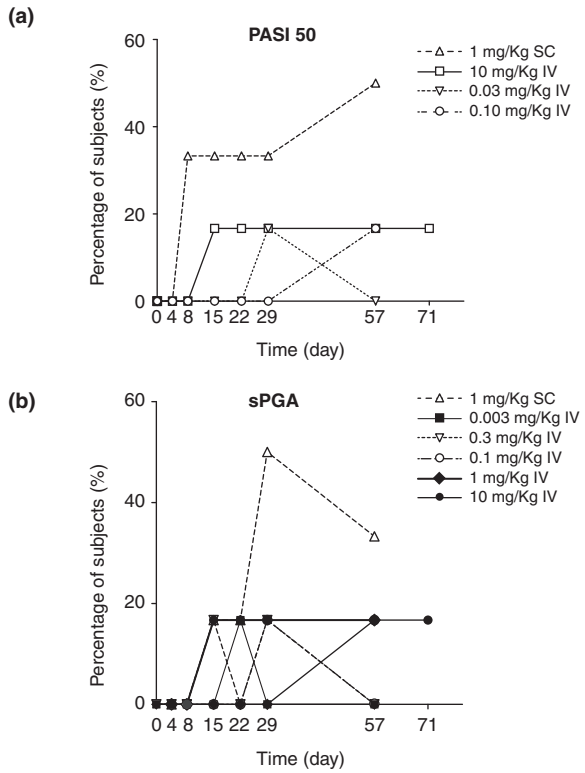

Figure 2 Percentage of patients achieving (a) PASI 50 or (b) improvement in sPGA score ≥2 in cohorts treated with KHK4083 or placebo administered IV or SC. Note: data points for no change not plotted.

≥2 over time in the cohorts are shown in Fig. 2. The largest percentage of patients (50%) achieving PASI 50 occurred in those receiving KHK4083 1.0 mg/kg SC. There were no consistent dose-related changes compared to placebo with respect to epidermal thickness change from Day 1 to Day 29 (data not shown): MMRM analysis only revealed statistically significant change from baseline for KHK4083 0.1 mg/kg (Cohort 4) [LS mean −110.53, 95% CI −178.875 to −42.182; P = 0.02].

Pharmacodynamics and pharmacodynamic/pharmacokinetic interactions

No meaningful or consistent dose-related changes could be reliably quantified due to the small sample size (data not shown).

Discussion

With respect to the primary endpoint of this first-in-human study, KHK4083 administration as a single dose up to 10 mg/kg IV or 1.0 mg/kg SC was generally safe and well tolerated in patients with mild to moderate plaque psoriasis with no dose-limiting AEs. There were no severe or serious AEs, or discontinuations because of AEs. The most frequent treatment-related AEs in the 55 patients who received KHK4083 were mild or moderate chills (9.1%), and infusion/injection site reactions (7.3%). There were no clinically meaningful or dose-related changes from baseline in laboratory values, vital signs, ECG recordings or physical examinations. Three of 48 (6.3%) KHK4083 recipients who received IV administration showed confirmed positive anti-KHK4083 antibodies at baseline compared to 13 patients (27.1%) at Day 57; none of the patients who received placebo or KHK4083 SC had positive antibodies at baseline or Day 57. Development of KHK4083 antibodies did not appear to affect pharmacokinetics.

With respect to pharmacokinetics, the main secondary endpoint, mean $t_{1/2}$, increased with dose, mean C_{max} increased in a dose-proportional manner, and mean AUC values increased in a

more than dose-proportional manner over the IV dose range from 0.003 to 10 mg/kg. Mean $t_{1/2}$ for the KHK4083 1.0 mg/kg SC dose was consistent with the $t_{1/2}$ for KHK4083 IV at the same dose level. Absolute bioavailability for KHK4083 1.0 mg/kg following SC administration was estimated to be 73%. Examination of exploratory pharmacodynamic endpoints and pharmacokinetic/pharmacodynamic correlations did not reveal any clinical meaningful or consistent results.

Exploratory analyses of clinical activity showed some indication of improvement in PASI and sPGA scores (not epidermal thickness of psoriasis skin biopsies) at the highest IV doses (1.0 and 10 mg/kg) and the SC dose (1.0 mg/kg) of KHK4083. The largest PASI 50 response and improvement in sPGA score ≥2 occurred with KHK4083 1.0 mg/kg SC. Clinical responses were not expected after single-dose administration of KHK4083 and the study was not sufficiently powered to detect improved clinical response compared to placebo given the limited number of patients enrolled overall and, more specifically, within each cohort.

The overall safety profile of KHK4083 supports the further phase 2 clinical evaluation of KHK4083 using high repeated doses in larger numbers of patients. KHK4083 SC (1.0 mg/kg) provided encouraging results (both immunogenicity and clinical activity) compared to less convenient IV administration at a higher dose (10 mg/kg), although these results need to be confirmed in higher numbers of patients. Phase 1 and phase 2 clinical development of KHK4083 is currently ongoing in patients with ulcerative colitis, another disease in which OX40 is indicated as a pathogenic target.[21]

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References

1 Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. *Nature* 2007; **445**: 866–873.
2 Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med* 2009; **361**: 496–509.
3 Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. *J Invest Dermatol* 2013; **133**: 377–385.
4 Mrowietz U, Reich K. Psoriasis: new insights into pathogenesis and treatment. *Dtsch Arztebl Int* 2009; **106**: 11–16.
5 Nast A, Boehncke WH, Mrowietz U *et al.* Deutsche Dermatologische Gesellshaft and Berufsverband Deutscher Dermatologen. S3 – Guidelines on the treatment of psoriasis vulgaris (English version). Update. *J Dtsch Dermatol Ges* 2012; **10**(Suppl. 2): S1–S95.
6 Bowcock AM, Krueger JG. Getting under the skin: the immunogenetics of psoriasis. *Nat Rev Immunol* 2005; **5**: 699–711.
7 Lebwohl M, Ali S. Treatment of psoriasis. Part 1. Topical therapy and phototherapy. *J Am Acad Dermatol* 2001; **45**: 487–498.
8 Fouéré S, Adjadj L, Pawin H. How patients experience psoriasis: results from a European survey. *J Eur Acad Dermatol Venereol* 2005; **19**(Suppl. 3): 2–6.
9 Augustin M, Holland B, Dartsch D, Langenbruch A, Radtke MA. Adherence in the treatment of psoriasis: a systematic review. *Dermatology* 2011; **222**: 363–374.
10 Otezla® (apremilast) prescribing information. Celgene Corporation, Summit, NJ. December 2015. URL https://www.celgene.com/content/uploads/otezla-pi.pdf (last accessed: 19 December 2016).
11 Cosentyx® (secukinumab) prescribing information. Novartis Pharmaceuticals Corporation, East Hanover, NJ. January 2015. URL https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/cosentyx.pdf (last accessed: 19 January 2017).
12 TALTZ™ (ixekizumab) prescribing information. Eli Lilly and Company, Indianapolis, IN. March 2016. URL http://pi.lilly.com/us/taltz-uspi.pdf (last accessed: 19 January 2017).
13 Matsumura Y, Hori T, Nishigori C *et al.* Expression of CD134 and CD134 ligand in lesional and nonlesional psoriatic skin. *Arch Dermatol Res* 2003; **294**: 563–566.
14 Ilves T, Harvima IT. OX40 ligand and OX40 are increased in atopic dermatitis lesions but do not correlate with clinical severity. *J Eur Acad Dermatol Venereol* 2013; **27**: e197–e205.
15 Salek-Ardakani S, Song A, Humphrey IR, Croft M. OX40:OX40L axis: emerging targets for immunotherapy of human disease. *Curr Immunol Rev* 2006; **2**: 37–53.
16 Croft M. The role of TNF superfamily members in T-cell function and diseases. *Nat Rev Immunol* 2009; **9**: 271–285.
17 Croft M, So T, Duan W, Soroosh P. The significance of OX40 and OX40L to T-cell biology and immune disease. *Immunol Rev* 2009; **229**: 173–191.
18 Croft M. Control of immunity by the TNFR-related molecule OX40 (CD134). *Annu Rev Immunol* 2010; **28**: 57–78.
19 Ishii N, Takahashi T, Soroosh P, Sugamura K. OX40-OX40 ligand interaction in T cell mediated immunity and immunopathology. *Adv Immunol* 2010; **105**: 63–98.
20 Fredriksson T, Pettersson U. Severe psoriasis: oral therapy with a new retinoid. *Dermatologica* 1978; **157**: 238–244.
21 Stüber E, Büschenfeld A, Lüttges J, von Freier A, Arendt T, Fölsch UR. The expression of OX40 in immunologically mediated diseases of the gastrointestinal tract (celiac disease, Crohn's disease, ulcerative colitis). *Eur J Clin Invest* 2000; **30**: 594–599.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Data S1. Inclusion and exclusion criteria, and rationale for dose selection in the study.