Clinical trial results:
A Phase 2, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Study of an Anti-OX40 Monoclonal Antibody (KHK4083) in Subjects with Moderate to Severe Atopic Dermatitis

Summary

EudraCT number	2018-000998-72
Trial protocol	DE
Global end of trial date	12 November 2020

Results information

Result version number	v1 (current)
This version publication date	27 November 2021
First version publication date	27 November 2021

Trial information

Trial identification

Sponsor protocol code	4083-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03703102
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Kyowa Kirin Co., Ltd
Sponsor organisation address	1-9-2, Otemachi, Chiyoda-ku, Tokyo, Japan, 100-0004
Public contact	Regulatory Affairs Department, Kyowa Kirin Co., Ltd, +81 35205-7219,
Scientific contact	Regulatory Affairs Department, Kyowa Kirin Co., Ltd, +81 35205-7219,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of four dose regimens of KHK4083 compared to placebo as measured by the change from baseline in Eczema Area and Severity Index (EASI) score following multiple subcutaneous (SC) injections for 16 weeks in subjects with moderate to severe AD.

Protection of trial subjects:

The Investigators were responsible for conducting the study in full accordance with the October 2013 revision of the Declaration of Helsinki, the GCP Guideline, approved by the ICH, and any applicable national and local laws and regulations. The Investigators complied with the protocol on which the Principal Investigator and the Sponsor had agreed and which had been approved in writing by the IRB/IEC. Before enrollment, the Investigator fully informed each subject who was considered appropriate for the study about the description of the study based on the Information for Subjects/ICF, which was provided separately and written in a language understandable for the subject. The subject was given sufficient time to decide whether or not to participate in the study, and the Investigator obtained written consent from the subject on a voluntary basis before the screening examinations. After the subject signed and dated the ICF, the Investigator who had conducted the informed consent discussion also signed and dated it. The Investigator provided the subject with a copy of the signed ICF and the Information for Subjects. The Investigator retained the original for the investigative site’s record in accordance with the policy of each site.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	Japan: 159
Country: Number of subjects enrolled	United States: 57
Worldwide total number of subjects	274
EEA total number of subjects	33

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	256
From 65 to 84 years	17
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The screening period began in September 2018. A total of 61 sites in four countries (Canada, Germany, Japan, and the United States) screened 351 patients and enrolled 274. The screening period closed in September 2019.

Pre-assignment

Screening details:

A total of 351 subjects were screened. Of these, 77 were excluded. The top three reasons for exclusion were : EASI score ≥16 at screening and baseline (18 subjects), IGA score ≥3 at both screening and baseline (13 subjects). and BSA ≥10% at both screening and baseline (9 subjects).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	KHK4083 150 mg SC Q4W

Arm description:

Subjects in this arm received 150 mg of KHK4083 at Weeks 0 (Day 1), 4, 8, 12, 16, 20, 24, 28, and 32. To maintain the blind, they received placebo at Weeks 2, 6, 10, 14, 18, 22, 26, 30, and 34.

Arm type	Experimental
Investigational medicinal product name	KHK4083
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

150 mg of KHK4083 at Weeks 0 (Day 1), 4, 8, 12, 16, 20, 24, 28, and 32, done as three subcutaneous injections of 2 mL each.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

150 mg of placebo at Weeks 2, 6, 10, 14, 18, 22, 26, 30, and 34, done as three subcutaneous injections of 2 mL each.

Arm title	KHK4083 600 mg SC Q4W

Arm description:

Subjects in this arm received 600 mg of KHK4083 at Weeks 0 (Day 1), 4, 8, 12, 16, 20, 24, 28, and 32. To maintain the blind, they received placebo at Weeks 2, 6, 10, 14, 18, 22, 26, 30, and 34.

Arm type	Experimental

Investigational medicinal product name	KHK4083
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

600 mg of KHK4083 at Weeks 0 (Day 1), 4, 8, 12, 16, 20, 24, 28, and 32, done as three subcutaneous injections of 2 mL each.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

600 mg of placebo at Weeks 2, 6, 10, 14, 18, 22, 26, 30, and 34, done as three subcutaneous injections of 2 mL each.

Arm title	KHK4083 300 mg SC Q2W

Arm description:

Subjects in this arm received 300 mg of KHK4083 at Weeks 0 [Day 1], 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 34.

Arm type	Experimental
Investigational medicinal product name	KHK4083
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

300 mg of KHK4083 at Weeks 0 (Day 1), 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 34, done as three subcutaneous injections of 2 mL each.

Arm title	KHK4083 600 mg SC Q2W

Arm description:

Subjects in this arm received 600 mg of KHK4083 at Weeks 0 [Day 1], 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 34.

Arm type	Experimental
Investigational medicinal product name	KHK4083
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

600 mg of KHK4083 at Weeks 0 (Day 1), 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 34, done as three subcutaneous injections of 2 mL each.

Arm title	Placebo/KHK4083 600 mg

Arm description:

Subjects in this arm received placebo at Weeks 0 (Day 1), 2, 4, 6, 8, 10, 12, 14, and 16, and received KHK4083 600 mg at Weeks 18 (Day 127), 20, 22, 24, 26, 28, 30, 32, and 34.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details: 600 mg of placebo at Weeks 0 (Day 1), 2, 4, 6, 8, 10, 12, 14, and 16, done as three subcutaneous injections of 2 mL each.	
Investigational medicinal product name	KHK4083
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use
Dosage and administration details: 600 mg of KHK4083 at Weeks 18 (Day 127), 20, 22, 24, 26, 28, 30, 32, and 34, done as three subcutaneous injections of 2 mL each.	

Number of subjects in period 1[1]	KHK4083 150 mg SC Q4W	KHK4083 600 mg SC Q4W	KHK4083 300 mg SC Q2W
Started	54	53	55
Treatment Period A - completed	42	41	42
Treatment Period B - completed	33	39	37
Follow Up Period - completed	32	38	33
Completed	32	38	33
Not completed	22	15	22
Physician decision	2	2	2
Consent withdrawn by subject	7	5	5
Adverse event, non-fatal	4	3	7
Non-compliance with study drug	1	-	2
Lost to follow-up	-	1	1
Ineligibility	-	-	1
Lack of efficacy	4	-	1
Protocol deviation	4	4	3

Number of subjects in period 1[1]	KHK4083 600 mg SC Q2W	Placebo/KHK4083 600 mg
Started	54	57
Treatment Period A - completed	46	34
Treatment Period B - completed	38	26
Follow Up Period - completed	37	24
Completed	37	24
Not completed	17	33
Physician decision	2	4
Consent withdrawn by subject	5	9
Adverse event, non-fatal	3	13
Non-compliance with study drug	1	4
Lost to follow-up	2	2

Ineligibility	-	-
Lack of efficacy	4	1
Protocol deviation	-	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One subject who was randomized to the 600 mg Q4W group (US-09-08) did not receive any study treatment due to consent withdrawal before the start of the treatment. They are not included in any of the analysis sets.

Baseline characteristics

Reporting groups	
Reporting group title	KHK4083 150 mg SC Q4W
Reporting group description:	
Subjects in this arm received 150 mg of KHK4083 at Weeks 0 (Day 1), 4, 8, 12, 16, 20, 24, 28, and 32. To maintain the blind, they received placebo at Weeks 2, 6, 10, 14, 18, 22, 26, 30, and 34.	
Reporting group title	KHK4083 600 mg SC Q4W
Reporting group description:	
Subjects in this arm received 600 mg of KHK4083 at Weeks 0 (Day 1), 4, 8, 12, 16, 20, 24, 28, and 32. To maintain the blind, they received placebo at Weeks 2, 6, 10, 14, 18, 22, 26, 30, and 34.	
Reporting group title	KHK4083 300 mg SC Q2W
Reporting group description:	
Subjects in this arm received 300 mg of KHK4083 at Weeks 0 [Day 1], 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 34.	
Reporting group title	KHK4083 600 mg SC Q2W
Reporting group description:	
Subjects in this arm received 600 mg of KHK4083 at Weeks 0 [Day 1], 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 34.	
Reporting group title	Placebo/KHK4083 600 mg
Reporting group description:	
Subjects in this arm received placebo at Weeks 0 (Day 1), 2, 4, 6, 8, 10, 12, 14, and 16, and received KHK4083 600 mg at Weeks 18 (Day 127), 20, 22, 24, 26, 28, 30, 32, and 34.	

Reporting group values	KHK4083 150 mg SC Q4W	KHK4083 600 mg SC Q4W	KHK4083 300 mg SC Q2W
Number of subjects	54	53	55
Age categorical Units: Subjects			
Adults (18-64 years)	52	51	51
From 65-84 years	2	2	4
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	37.4	38.9	37.5
full range (min-max)	19 to 67	18 to 70	18 to 77
Gender categorical Units: Subjects			
Female	17	22	24
Male	37	31	31

Reporting group values	KHK4083 600 mg SC Q2W	Placebo/KHK4083 600 mg	Total
Number of subjects	54	57	273
Age categorical Units: Subjects			
Adults (18-64 years)	49	52	255
From 65-84 years	4	5	17
85 years and over	1	0	1

Age continuous Units: years			
arithmetic mean	37.3	38.7	
full range (min-max)	18 to 89	18 to 69	-
Gender categorical Units: Subjects			
Female	24	26	113
Male	30	31	160

End points

End points reporting groups

Reporting group title	KHK4083 150 mg SC Q4W

Reporting group description:

Subjects in this arm received 150 mg of KHK4083 at Weeks 0 (Day 1), 4, 8, 12, 16, 20, 24, 28, and 32. To maintain the blind, they received placebo at Weeks 2, 6, 10, 14, 18, 22, 26, 30, and 34.

Reporting group title	KHK4083 600 mg SC Q4W

Reporting group description:

Subjects in this arm received 600 mg of KHK4083 at Weeks 0 (Day 1), 4, 8, 12, 16, 20, 24, 28, and 32. To maintain the blind, they received placebo at Weeks 2, 6, 10, 14, 18, 22, 26, 30, and 34.

Reporting group title	KHK4083 300 mg SC Q2W

Reporting group description:

Subjects in this arm received 300 mg of KHK4083 at Weeks 0 [Day 1], 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 34.

Reporting group title	KHK4083 600 mg SC Q2W

Reporting group description:

Subjects in this arm received 600 mg of KHK4083 at Weeks 0 [Day 1], 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 34.

Reporting group title	Placebo/KHK4083 600 mg

Reporting group description:

Subjects in this arm received placebo at Weeks 0 (Day 1), 2, 4, 6, 8, 10, 12, 14, and 16, and received KHK4083 600 mg at Weeks 18 (Day 127), 20, 22, 24, 26, 28, 30, 32, and 34.

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

One subject in the 600 mg Q4W group (US-09-08) was excluded from all analysis sets as the subject was not exposed to IP. Two subjects in the 150 mg Q4W group (JP-23-01 and US-08-05), 1 subject in the 600 mg Q4W group (JP-20-03),and 3 subjects in the 300 mg Q2W group (JP-13-05, JP-15-04, and US-02-08) were excluded from the full analysis set. Those 6 subjects had no evaluable EASI score after the start of IP administration until Week 16.

Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

One subject in the 600 mg Q4W group (US-09-08) was excluded from all analysis sets as the subject was not exposed to IP. Two subjects in the 150 mg Q4W group (JP-23-01 and US-08-05), 1 subject in the 600 mg Q4W group (JP-20-03), and 3 subjects in the 300 mg Q2W group (JP-13-05, JP-15-04, and US-02-08) were excluded from the per protocol set. Those 6 subjects had no evaluable EASI score after the start of IP administration until Week 16.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who received at least one dose of KHK4083. One subject in the 600 mg Q4W group (US-09-08) was excluded as the subject was not exposed to IP.

Subject analysis set title	Pharmacokinetic Analysis Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with at least one sample collected and analyzed for plasma drug concentration. 25 subjects in the placebo group were excluded from the PKS as they were not exposed to KHK4083 during the Treatment B period.

Primary: Percent Change from Baseline in EASI Score at Week 16

End point title	Percent Change from Baseline in EASI Score at Week 16

End point description:

End point type	Primary

End point timeframe:

Every two weeks from Baseline to Week 16

End point values	KHK4083 150 mg SC Q4W	KHK4083 600 mg SC Q4W	KHK4083 300 mg SC Q2W	KHK4083 600 mg SC Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	54
Units: percent change				
least squares mean (confidence interval 95%)				
Overall Change	-48.33 (-62.62 to -34.04)	-49.72 (-62.47 to -35.17)	-61.07 (-75.19 to -46.96)	-57.35 (-71.27 to -43.43)

End point values	Placebo/KHK4083 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percent change				
least squares mean (confidence interval 95%)				
Overall Change	-15.01 (-28.60 to -1.43)			

Statistical analyses

Statistical analysis title	KHK4083 150 mg Q4W vs Placebo

Statistical analysis description:

The primary analysis will be performed in the percent change from baseline to Week 16 in EASI score, by applying ANCOVA with treatment, EASI score at baseline, and the following stratification factors:
• Severity of AD (IGA=3, IGA=4) at baseline
• Region (Japan, rest of world)
• Previous use of biological products (Yes, No) for the treatment of AD at baseline

Comparison groups	KHK4083 150 mg SC Q4W v Placebo/KHK4083 600 mg
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	ANCOVA

Notes:

[1] - The adjusted mean (LS mean) and the corresponding 95% confidence interval will be calculated from the ANCOVA model for each treatment group. A two-sided t-test with a significance level of 5% will be performed on the difference of LS mean between each KHK4083 group and the placebo group. A closed test procedure will be used to maintain overall type I error rate.

Statistical analysis title	KHK4083 600 mg Q4W vs Placebo

Statistical analysis description:

The primary analysis will be performed in the percent change from baseline to Week 16 in EASI score, by applying ANCOVA with treatment, EASI score at baseline, and the following stratification factors:
• Severity of AD (IGA=3, IGA=4) at baseline
• Region (Japan, rest of world)
• Previous use of biological products (Yes, No) for the treatment of AD at baseline

Comparison groups	Placebo/KHK4083 600 mg v KHK4083 600 mg SC Q4W
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.001
Method	ANCOVA

Notes:

[2] - The adjusted mean (LS mean) and the corresponding 95% confidence interval will be calculated from the ANCOVA model for each treatment group. A two-sided t-test with a significance level of 5% will be performed on the difference of LS mean between each KHK4083 group and the placebo group. A closed test procedure will be used to maintain overall type I error rate.

Statistical analysis title	KHK4083 300 mg Q2W vs Placebo

Statistical analysis description:

The primary analysis will be performed in the percent change from baseline to Week 16 in EASI score, by applying ANCOVA with treatment, EASI score at baseline, and the following stratification factors:
• Severity of AD (IGA=3, IGA=4) at baseline
• Region (Japan, rest of world)
• Previous use of biological products (Yes, No) for the treatment of AD at baseline

Comparison groups	Placebo/KHK4083 600 mg v KHK4083 300 mg SC Q2W
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001
Method	ANCOVA

Notes:

[3] - The adjusted mean (LS mean) and the corresponding 95% confidence interval will be calculated from the ANCOVA model for each treatment group. A two-sided t-test with a significance level of 5% will be performed on the difference of LS mean between each KHK4083 group and the placebo group. A closed test procedure will be used to maintain overall type I error rate.

Statistical analysis title	KHK4083 600 mg Q2W vs Placebo

Statistical analysis description:

The primary analysis will be performed in the percent change from baseline to Week 16 in EASI score, by applying ANCOVA with treatment, EASI score at baseline, and the following stratification factors:
• Severity of AD (IGA=3, IGA=4) at baseline
• Region (Japan, rest of world)
• Previous use of biological products (Yes, No) for the treatment of AD at baseline

Comparison groups	Placebo/KHK4083 600 mg v KHK4083 600 mg SC Q2W
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.001
Method	ANCOVA

Notes:

[4] - The adjusted mean (LS mean) and the corresponding 95% confidence interval will be calculated from the ANCOVA model for each treatment group. A two-sided t-test with a significance level of 5% will be performed on the difference of LS mean between each KHK4083 group and the placebo group. A closed test procedure will be used to maintain overall type I error rate.

Secondary: Achievement of 50%, 75%, or 90% reduction from baseline in Eczema Area and Severity Index (EASI) score (EASI-50, EASI-75, or EASI-90) at Week 16

End point title	Achievement of 50%, 75%, or 90% reduction from baseline in Eczema Area and Severity Index (EASI) score (EASI-50, EASI-75, or EASI-90) at Week 16

End point description:

In the EASI assessment, the severity of 4 elements of eczema (erythema, induration/papulation, excoriation, and lichenification) at each of 4 body regions (head and neck, trunk, upper extremities, and lower extremities) will be assessed on a scale of 0 to 3 (0 = None , 1 = Mild, 2 = Moderate, 3 = Severe). Half scores (1.5 and 2.5) are allowed, with the exception of 0.5. Any signs must be at least 1 (mild) in severity. In addition, the extent of eczema at each of the 4 body regions will be assessed on a scale of 0 to 6 (0 = 0%, 1 = 1% to 9%, 2 = 10% to 29%, 3 = 30% to 49%, 4 = 50% to 69%, 5 = 70% to 89%, 6 = 90% to 100%).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	KHK4083 150 mg SC Q4W	KHK4083 600 mg SC Q4W	KHK4083 300 mg SC Q2W	KHK4083 600 mg SC Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	54
Units: patients				
Achieved EASI-50 at Week 16	30	31	36	35
achieved EASI-75 at Week 16	23	21	28	21
achieved EASI-90 at Week 16	10	6	19	10

End point values	Placebo/KHK4083 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: patients				
Achieved EASI-50 at Week 16	17			
achieved EASI-75 at Week 16	6			
achieved EASI-90 at Week 16	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in EASI Score

End point title	Change from Baseline to Week 16 in EASI Score

End point description:

In the EASI assessment, the severity of 4 elements of eczema (erythema, induration/papulation, excoriation, and lichenification) at each of 4 body regions (head and neck, trunk, upper extremities, and lower extremities) will be assessed on a scale of 0 to 3 (0 = None , 1 = Mild, 2 = Moderate, 3 = Severe). Half scores (1.5 and 2.5) are allowed, with the exception of 0.5. Any signs must be at least 1 (mild) in severity. In addition, the extent of eczema at each of the 4 body regions will be assessed on a scale of 0 to 6 (0 = 0%, 1 = 1% to 9%, 2 = 10% to 29%, 3 = 30% to 49%, 4 = 50% to 69%, 5 = 70% to 89%, 6 = 90% to 100%).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	KHK4083 150 mg SC Q4W	KHK4083 600 mg SC Q4W	KHK4083 300 mg SC Q2W	KHK4083 600 mg SC Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	54
Units: score on a scale				
median (standard deviation)	-22.5 (± 14.7)	-20.7 (± 14.3)	-23.3 (± 9.0)	-19.9 (± 11.8)

End point values	Placebo/KHK4083 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: score on a scale				
median (standard deviation)	-9.8 (± 13.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change and Percent Change from Baseline to Week 16 in SCORAD Score

End point title	Change and Percent Change from Baseline to Week 16 in SCORAD Score

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	KHK4083 150 mg SC Q4W	KHK4083 600 mg SC Q4W	KHK4083 300 mg SC Q2W	KHK4083 600 mg SC Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	54
Units: percent				
least squares mean (confidence interval 95%)				
Change in score	-23.71 (-30.72 to -16.69)	-23.86 (-30.92 to -16.81)	-30.44 (-37.27 to -23.61)	-27.65 (-34.39 to -20.91)
% Change in score	-34.86 (-45.20 to -24.51)	-35.13 (-45.54 to -24.72)	-46.69 (-56.77 to -36.61)	-40.76 (-50.70 to -30.81)

End point values	Placebo/KHK4083 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percent				
least squares mean (confidence interval 95%)				
Change in score	-8.09 (-14.65 to -1.53)			
% Change in score	-11.90 (-21.59 to -2.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Achievement of an IGA Score of 0 or 1 and a Reduction from Baseline of ≥2 Points at Week 16

End point title	Achievement of an IGA Score of 0 or 1 and a Reduction from Baseline of ≥2 Points at Week 16

End point description:

In the IGA, the Investigator will evaluate the overall skin symptoms of subjects at each visit on a 5-point scale ranging from 0 (clear) to 4 (severe).

End point type	Secondary

End point timeframe:

Every two weeks from Baseline to Week 16

End point values	KHK4083 150 mg SC Q4W	KHK4083 600 mg SC Q4W	KHK4083 300 mg SC Q2W	KHK4083 600 mg SC Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	54
Units: number of patients				
number (confidence interval 95%)				
% of Patients who achieved IGA	19.2 (9.63 to 32.63)	15.4 (6.88 to 28.08)	30.8 (18.72 to 45.10)	18.5 (9.25 to 31.43)

End point values	Placebo/KHK4083 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: number of patients				
number (confidence interval 95%)				
% of Patients who achieved IGA	1.8 (0.04 to 9.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in Percent BSA

End point title	Change from Baseline to Week 16 in Percent BSA

End point description:

The Investigator will calculate the percentage (%) of the total body surface area affected by AD.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	KHK4083 150 mg SC Q4W	KHK4083 600 mg SC Q4W	KHK4083 300 mg SC Q2W	KHK4083 600 mg SC Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	54
Units: percent				
least squares mean (confidence interval 95%)				
Change in % BSA affected by AD	-22.86 (-30.30 to -15.42)	-21.48 (-29.07 to -13.89)	-27.92 (-35.30 to -20.54)	-25.04 (-32.33 to -17.76)

End point values	Placebo/KHK4083 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percent				
least squares mean (confidence interval 95%)				
Change in % BSA affected by AD	-7.87 (-14.96 to -0.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change and Percent Change from Baseline to Week 16 in Pruritus NRS Score

End point title	Change and Percent Change from Baseline to Week 16 in Pruritus NRS Score

End point description:

The worst degree of itch experienced during 24 hours before the time point will be assessed on a Numerical Rating Scale. The degree of itch will be scored on an 11-point scale, with 0 being "no itch" and 10 being the "worst itch imaginable."

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	KHK4083 150 mg SC Q4W	KHK4083 600 mg SC Q4W	KHK4083 300 mg SC Q2W	KHK4083 600 mg SC Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	54
Units: score				
least squares mean (confidence interval 95%)				
Change in Pruritis NRS Score	-2.04 (-2.90 to -1.18)	-3.02 (-3.90 to -2.15)	-3.60 (-4.44 to -2.75)	-2.81 (-3.64 to -1.97)
% Change in Pruritis NRS Score	-25.57 (-39.48 to -11.66)	-34.38 (-48.56 to -20.21)	-47.99 (-61.71 to -34.26)	-36.83 (-50.41 to -23.25)

End point values	Placebo/KHK4083 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: score				
least squares mean (confidence interval 95%)				
Change in Pruritis NRS Score	-1.31 (-2.12 to -0.49)			
% Change in Pruritis NRS Score	-6.18 (-19.37 to 7.01)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change and Percent Change from Baseline to Week 16 in Sleep Disturbance NRS Score

End point title	Change and Percent Change from Baseline to Week 16 in Sleep Disturbance NRS Score

End point description:

Daily sleep disturbance in the last 24 hours before the relevant time point will be assessed on a Numerical Rating Scale. Subjects will score the degree of their sleep disturbance on an 11-point scale ranging from 'no sleep loss' (0) to 'I cannot sleep at all" (10).

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	KHK4083 150 mg SC Q4W	KHK4083 600 mg SC Q4W	KHK4083 300 mg SC Q2W	KHK4083 600 mg SC Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	54
Units: score				
least squares mean (confidence interval 95%)				
Change in Sleep Disturbance NRS Score	-1.09 (-2.01 to -0.18)	-1.93 (-2.86 to -1.00)	-2.59 (-3.48 to -1.69)	-2.00 (-2.90 to -1.11)
% Change in Sleep Disturbance NRS Score	-8.19 (-44.32 to 27.95)	-7.02 (-44.96 to 30.93)	-41.58 (-78.30 to -4.86)	-33.17 (-69.08 to 2.74)

End point values	Placebo/KHK4083 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: score				
least squares mean (confidence interval 95%)				
Change in Sleep Disturbance NRS Score	-0.01 (-0.87 to 0.86)			
% Change in Sleep Disturbance NRS Score	46.54 (11.83 to 81.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in DLQI

End point title	Change from Baseline to Week 16 in DLQI

End point description:

DLQI (Dermatology Life Quality Index) consists of 6 subscales (symptoms and feelings, daily activities,

leisure, work and school, personal relationships, and treatment), which are scored from 0 to 3 on the basis of 10 questions. The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more QoL is impaired.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	KHK4083 150 mg SC Q4W	KHK4083 600 mg SC Q4W	KHK4083 300 mg SC Q2W	KHK4083 600 mg SC Q2W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	52	54
Units: score				
least squares mean (confidence interval 95%)				
Change in DLQI Score	-2.59 (-4.73 to -0.44)	-4.66 (-6.89 to -2.43)	-6.28 (-8.38 to -4.18)	-4.93 (-7.01 to -2.84)

End point values	Placebo/KHK4083 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: score				
least squares mean (confidence interval 95%)				
Change in DLQI Score	0.19 (-1.88 to 2.27)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded for reporting from the subject's written consent to participate in the study through the end of the study, up to 62 weeks (potential 6 week screening period up to Week 56).

Adverse event reporting additional description:

The Investigator will inquire about AEs at all subject visits by asking the subject a non-leading question such as: "How have you been feeling since your last visit?" All AEs, whether observed by the Investigator or reported by the subject, must be collected. Each AE will be coded by the Sponsor according to MedRA.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	KHK4083 150 mg SC Q4W
Reporting group description: -	
Reporting group title	KHK4083 600 mg SC Q4W
Reporting group description: -	
Reporting group title	KHK4083 300 mg SC Q2W
Reporting group description: -	
Reporting group title	KHK4083 600 mg SC Q2W
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	KHK4083 150 mg SC Q4W	KHK4083 600 mg SC Q4W	KHK4083 300 mg SC Q2W
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 54 (7.41%)	1 / 53 (1.89%)	4 / 55 (7.27%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			

subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectosigmoid cancer			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative ileus			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Atopic cataract			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Incarcerated umbilical hernia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestine ulcer			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract inflammation			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spinal stenosis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			

subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	KHK4083 600 mg SC Q2W	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 54 (1.85%)	2 / 57 (3.51%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 54 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectosigmoid cancer			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Atopic cataract			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Incarcerated umbilical hernia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine ulcer			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Spinal stenosis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			

subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	KHK4083 150 mg SC Q4W	KHK4083 600 mg SC Q4W	KHK4083 300 mg SC Q2W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 54 (87.04%)	50 / 53 (94.34%)	48 / 55 (87.27%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 54 (7.41%)	6 / 53 (11.32%)	6 / 55 (10.91%)
occurrences (all)	12	9	20
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 54 (3.70%)	3 / 53 (5.66%)	7 / 55 (12.73%)
occurrences (all)	2	3	10
Fatigue			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	1 / 55 (1.82%)
occurrences (all)	0	1	1
Injection site pain			
subjects affected / exposed	2 / 54 (3.70%)	3 / 53 (5.66%)	1 / 55 (1.82%)
occurrences (all)	4	4	13
Injection site swelling			
subjects affected / exposed	0 / 54 (0.00%)	2 / 53 (3.77%)	3 / 55 (5.45%)
occurrences (all)	0	2	4
Malaise			
subjects affected / exposed	0 / 54 (0.00%)	2 / 53 (3.77%)	1 / 55 (1.82%)
occurrences (all)	0	2	1
Pyrexia			
subjects affected / exposed	7 / 54 (12.96%)	9 / 53 (16.98%)	10 / 55 (18.18%)
occurrences (all)	7	9	11
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	2 / 54 (3.70%)	0 / 53 (0.00%)	3 / 55 (5.45%)
occurrences (all)	2	0	3
Gastrointestinal disorders			
Aphthous ulcer			
subjects affected / exposed	3 / 54 (5.56%)	11 / 53 (20.75%)	4 / 55 (7.27%)
occurrences (all)	3	18	5
Constipation			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	2 / 54 (3.70%)	4 / 53 (7.55%)	2 / 55 (3.64%)
occurrences (all)	2	4	6
Nausea			
subjects affected / exposed	3 / 54 (5.56%)	3 / 53 (5.66%)	2 / 55 (3.64%)
occurrences (all)	7	3	2
Stomatitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	3 / 55 (5.45%)
occurrences (all)	0	1	3
Vomiting			
subjects affected / exposed	1 / 54 (1.85%)	3 / 53 (5.66%)	1 / 55 (1.82%)
occurrences (all)	2	3	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 54 (7.41%)	0 / 53 (0.00%)	4 / 55 (7.27%)
occurrences (all)	4	0	6
Oropharyngeal pain			
subjects affected / exposed	1 / 54 (1.85%)	3 / 53 (5.66%)	0 / 55 (0.00%)
occurrences (all)	1	3	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 54 (1.85%)	5 / 53 (9.43%)	7 / 55 (12.73%)
occurrences (all)	1	6	8
Dermatitis atopic			
subjects affected / exposed	19 / 54 (35.19%)	12 / 53 (22.64%)	18 / 55 (32.73%)
occurrences (all)	21	12	21
Dermatitis contact			

subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	1 / 55 (1.82%)
occurrences (all)	0	1	1
Miliaria			
subjects affected / exposed	0 / 54 (0.00%)	3 / 53 (5.66%)	0 / 55 (0.00%)
occurrences (all)	0	3	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	3 / 55 (5.45%)
occurrences (all)	0	0	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 54 (1.85%)	2 / 53 (3.77%)	1 / 55 (1.82%)
occurrences (all)	1	3	1
Back pain			
subjects affected / exposed	3 / 54 (5.56%)	0 / 53 (0.00%)	0 / 55 (0.00%)
occurrences (all)	3	0	0
Infections and infestations			
Influenza			
subjects affected / exposed	5 / 54 (9.26%)	1 / 53 (1.89%)	1 / 55 (1.82%)
occurrences (all)	5	1	1
Kaposi's varicelliform eruption			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	13 / 54 (24.07%)	11 / 53 (20.75%)	12 / 55 (21.82%)
occurrences (all)	21	16	16
Oral herpes			
subjects affected / exposed	1 / 54 (1.85%)	2 / 53 (3.77%)	4 / 55 (7.27%)
occurrences (all)	1	2	6
Pharyngitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Tinea pedis			
subjects affected / exposed	2 / 54 (3.70%)	1 / 53 (1.89%)	3 / 55 (5.45%)
occurrences (all)	3	1	3
Upper respiratory tract infection			

subjects affected / exposed	1 / 54 (1.85%)	4 / 53 (7.55%)	4 / 55 (7.27%)
occurrences (all)	1	4	5

Non-serious adverse events	KHK4083 600 mg SC Q2W	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 54 (94.44%)	46 / 57 (80.70%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 54 (9.26%)	5 / 57 (8.77%)	
occurrences (all)	6	6	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	12 / 54 (22.22%)	1 / 57 (1.75%)	
occurrences (all)	14	1	
Fatigue			
subjects affected / exposed	3 / 54 (5.56%)	2 / 57 (3.51%)	
occurrences (all)	3	2	
Injection site pain			
subjects affected / exposed	1 / 54 (1.85%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Injection site swelling			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences (all)	0	0	
Malaise			
subjects affected / exposed	3 / 54 (5.56%)	0 / 57 (0.00%)	
occurrences (all)	5	0	
Pyrexia			
subjects affected / exposed	11 / 54 (20.37%)	3 / 57 (5.26%)	
occurrences (all)	11	3	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Aphthous ulcer			

subjects affected / exposed	3 / 54 (5.56%)	0 / 57 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	3 / 54 (5.56%)	0 / 57 (0.00%)	
occurrences (all)	4	0	
Diarrhoea			
subjects affected / exposed	3 / 54 (5.56%)	0 / 57 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	8 / 54 (14.81%)	2 / 57 (3.51%)	
occurrences (all)	8	2	
Stomatitis			
subjects affected / exposed	4 / 54 (7.41%)	1 / 57 (1.75%)	
occurrences (all)	10	1	
Vomiting			
subjects affected / exposed	2 / 54 (3.70%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 54 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 54 (3.70%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	3 / 54 (5.56%)	3 / 57 (5.26%)	
occurrences (all)	4	3	
Dermatitis atopic			
subjects affected / exposed	20 / 54 (37.04%)	24 / 57 (42.11%)	
occurrences (all)	22	28	
Dermatitis contact			
subjects affected / exposed	3 / 54 (5.56%)	1 / 57 (1.75%)	
occurrences (all)	3	1	
Miliaria			

subjects affected / exposed	0 / 54 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 54 (9.26%)	1 / 57 (1.75%)	
occurrences (all)	5	1	
Back pain			
subjects affected / exposed	2 / 54 (3.70%)	1 / 57 (1.75%)	
occurrences (all)	2	1	
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 54 (1.85%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Kaposi's varicelliform eruption			
subjects affected / exposed	0 / 54 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	4	
Nasopharyngitis			
subjects affected / exposed	19 / 54 (35.19%)	13 / 57 (22.81%)	
occurrences (all)	25	18	
Oral herpes			
subjects affected / exposed	4 / 54 (7.41%)	3 / 57 (5.26%)	
occurrences (all)	4	4	
Pharyngitis			
subjects affected / exposed	3 / 54 (5.56%)	1 / 57 (1.75%)	
occurrences (all)	4	1	
Tinea pedis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 54 (1.85%)	3 / 57 (5.26%)	
occurrences (all)	1	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 July 2018	2.0 • The dosing regimen of 150 mg Q2W was changed to 150 mg Q4W. • The inclusion criteria 4 was changed. • The exclusion criteria 22 was added. • The withdrawal criteria 5 was added. • The withdrawal criteria 1 and 6 were changed. • The length of waiting time for acute drug reaction after IP administration was changed. • The TB questionnaire was added to the Appendix 8 of the Clinical Protocol
04 December 2018	DE 2.0.1 • The inclusion criteria 8 was changed. • The exclusion criteria 2 and 21 were changed.
04 December 2018	2.1 • The inclusion criteria 8 was changed. • The exclusion criteria 2, 13, and 21 were changed.
19 April 2019	2.2 The length of waiting time for acute drug reaction after IP administration was changed.
31 January 2020	2.3 The description of safety follow-up for subjects who discontinued IP administration due to an AE was added.
11 June 2020	3.0 • The withdrawal criteria 3 was relaxed considering COVID-19 outbreak. • The scope of the data used for the interim analysis 2 was changed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported