CLINICAL PROTOCOL

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 (AD)

Protocol Number:	4083-006
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Phase:	2
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Sponsor:	Kyowa Kirin Co., Ltd [redacted]

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Title: 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

Protocol Number: 4083-006

Version: 3.0

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Any supplemental information (e.g., protocol amendment, Investigator's Brochure, and study manuals) that may accompany this document are also proprietary to Kyowa Kirin Co., Ltd. and should be handled consistent with the terms stated above.

I, the undersigned, have reviewed this protocol, including appendices. I will conduct the clinical study in compliance with the protocol, study manuals, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Principal Investigator:

Signature	Date
Printed Name	Title
Institution Address	Telephone Number

PROTOCOL SIGNATURE PAGE

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[redacted]

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CLINICAL STUDY PROTOCOL SYNOPSIS

I Study Title

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 (AD)

II Study Objectives and Endpoints

Primary Objective	Endpoint
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.	• Percent change from baseline to Week 16 in EASI score
Secondary Objectives	**Endpoints**
To evaluate the effects on **skin symptoms** following multiple SC injections of KHK4083 for 16 weeks in comparison with placebo in subjects with moderate to severe AD.	• Achievement of 50%, 75%, or 90% reduction from baseline in EASI score (EASI-50, EASI-75, or EASI-90) at Week 16 • Change from baseline to Week 16 in EASI score • Change and percent change from baseline to Week 16 in Severity Scoring of Atopic Dermatitis (SCORAD) score • Achievement of an Investigator's Global Assessment (IGA) score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16 • Change from baseline to Week 16 in percent body surface area of involvement of AD (BSA)
To evaluate the effects on **itching and sleeping** following multiple SC injections of KHK4083 for 16 weeks in comparison with placebo in subjects with moderate to severe AD.	• Change and percent change from baseline to Week 16 in pruritus Numerical Rating Scale (NRS) score • Change and percent change from baseline to Week 16 in sleep disturbance NRS score
To evaluate the effects on **quality of life (QoL)** following multiple SC injections of KHK4083 for 16 weeks in comparison with placebo in subjects with moderate to severe AD.	• Change from baseline to Week 16 in Dermatology Life Quality Index (DLQI)

To evaluate the effects on **skin symptoms** following multiple SC injections of KHK4083 for 36 weeks in subjects with moderate to severe AD.	• Change and percent change from baseline in EASI score at each time point • Achievement of EASI-50, EASI-75, or EASI-90 at each time point • Change and percent change from baseline in SCORAD score at each time point • Achievement of an IGA score of 0 or 1 and a reduction from baseline of ≥2 points at each time point • Change from baseline in percent BSA at each time point
To evaluate the effects on **itching and sleeping** following multiple SC injections of KHK4083 for 36 weeks in subjects with moderate to severe AD.	• Change and percent change from baseline in pruritus NRS score at each time point • Change and percent change from baseline sleep disturbance NRS score at each time point
To evaluate the effects on **QoL** following multiple SC injections of KHK4083 for 36 weeks in subjects with moderate to severe AD.	• Change from baseline in DLQI at each time point
Safety Objective	**Endpoints**
To evaluate the safety of multiple SC injections of KHK4083 in subjects with moderate to severe AD.	• Treatment-emergent adverse events (TEAEs) • Laboratory values • Vital signs • Standard 12-lead electrocardiogram (ECG)
Exploratory Objectives	**Endpoints**
To investigate pharmacokinetics and immunogenicity following multiple SC injections of KHK4083 in subjects with moderate to severe AD.	• Pharmacokinetic assessment – Serum KHK4083 concentration – Pharmacokinetic parameters (e.g., C_{max}, C_{trough}) • Anti-KHK4083 antibody
To assess pharmacodynamics following multiple SC injections of KHK4083 in subjects with moderate to severe AD.	• Pharmacodynamic assessment – Serum disease markers (thymus and activation-regulated chemokine [TARC], serum total IgE)

III Summary of Study Design

This is a Phase 2, multicenter, randomized, placebo-controlled, double-blind, parallel-group study consisting of a screening period of at least 2 weeks (a maximum 6 weeks), an 18-week placebo-controlled treatment period (Treatment A period), followed by an 18-week treatment period (Treatment B period), and a 20-week follow-up period.

Subjects will receive SC doses of investigational product (IP) every 2 weeks under double-blind conditions (Weeks 0 [Day 1], 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 34). The last dose will be administered at Week 34, and subjects will complete the treatment period at Week 36 (end of treatment [EOT]). Subsequently, subjects will be followed up at Weeks 40, 44, 48, 52, and 56. The study period will be a maximum of 60 weeks.

1) Screening Period

The Investigator will register subjects who provide written informed consent in an interactive web response system (IWRS) to start screening those subjects within 4 weeks after the date of subject's signature on informed consent. Subjects will undergo baseline assessments at least 2 weeks but not later than 6 weeks after the start of screening.

A total of approximately 250 subjects who are considered eligible as a result of the screening and baseline assessments will be enrolled.

Subjects will be required to apply a topical emollient, as a rule, twice daily for at least 1 week before baseline visit through the end of the study. The use of topical corticosteroids will be prohibited from at least 1 week before baseline visit through Week 36 assessment.

2) Treatment Period (Day 1 to Week 36)

Randomization will be performed within 3 days after baseline visit.

Subjects will start study treatment on the day of or the day after randomization (date of the first dose of IP will be regarded as Day 1). The treatment period is defined as the period between Day 1 and the end of the Week 36 assessment.

The study consists of 2 treatment periods.

Treatment A period (last dose at Week 16)

All subjects who meet the inclusion criteria and none of the exclusion criteria during the screen phase will be randomized to one of the treatment groups (placebo, KHK4083 150 mg Q4W, 300 mg Q2W, 600 mg Q2W, or 600 mg Q4W). In the 150 mg Q4W group and the 600 mg Q4W group, placebo will be administered between KHK4083 injections to ensure blinding.

Treatment A period is defined as the period between Day 1 and Week 18 pre (before IP administration at Week 18).

In order to ensure the study blind, the efficacy data until Week 16 shall be entered into the electronic Clinical Outcome Assessment (eCOA).

Treatment B period (last dose at Week 34)

Treatment B period is an extension phase where all subjects will receive KHK4083 for an additional 18 weeks under double-blind conditions (from Week 18 post [IP administration at Week 18] through Week 36).

In Treatment B period, subjects randomized to the placebo group in Treatment A period will receive SC injections of 600 mg KHK4083 every 2 weeks starting at Week 18. Subjects randomized to any of the KHK4083 groups in Treatment A period will receive KHK4083 at the same dose and dosing interval as in Treatment A period.

Subjects who meet withdrawal criterion 5) (Section 4.4.1) based on the IGA score at Week 26 will discontinue IP administration at Week 26, undergo end-of-study assessments, and then be withdrawn from the study.

Subjects receiving rescue treatment (See Section 6.3.3) during the period between the start of IP administration and the end of the Week 36 assessment will discontinue IP, undergo end-of-study assessments, and subsequently be withdrawn from the study.

3) Follow-up Period (up to Week 56)

Subjects will enter the follow-up period after the end of the Week 36 assessment and will be followed up every 4 weeks until Week 56. Subjects who received rescue treatment after Week 36 will not be withdrawn from the study and will be observed until the end of the study up to Week 56.

4) Other Potential Study Assessments (optional)

Sampling for exploratory biomarkers: Exploratory biomarkers to characterize KHK4083 pharmacodynamic activity will be assessed. At selected investigative sites in the United States and Canada, blood and skin samples will be collected from subjects who voluntarily provide consent to undergo both serum analyses (including but not limited to serum cytokines

and chemokines) and skin biopsy. At all investigative sites in Japan, blood and skin samples will be collected from subjects who voluntarily provide consent to undergo both flow cytometry (OX40-positive T cell and cutaneous lymphocyte-associated antigen [CLA]-positive T memory cell) and skin biopsy.

Pharmacogenetic testing: The purpose of this assessment is to explore the association between individual differences in responses to KHK4083 and mutations in DNA sequence. Blood samples will be collected before IP injection at Week 0 from subjects who voluntarily provide consent.

IV Number of Subjects

A total of approximately 250 subjects will be randomly assigned by a 1:1:1:1:1 ratio to 4 active treatment groups (50 subjects in each group) and one placebo group (50 subjects) in Treatment A period.

V Target Subjects

Subjects with moderate to severe AD whose disease cannot be adequately controlled with topical medications or for whom topical treatment is medically inadvisable.

To allow efficacy and safety assessments in subjects without previous use of biological products, enrollment of subjects who have received previous treatment with biological products for treatment of AD will be limited to not more than 50% of total enrollment.

VI Inclusion Criteria

Subjects who meet all of the following criteria will be enrolled in this study:

1) Voluntarily signed informed consent to participate in the study;
2) Men and women ≥18 years at the time of informed consent;
3) Chronic AD, according to American Academy of Dermatology Consensus Criteria (Eichenfield et al, 2014) or the local diagnostic criteria, that has been present for at least 1 year before screening;
4) EASI score ≥16 at screening and baseline;
5) IGA score ≥3 (moderate) at both screening and baseline;
6) BSA ≥10% at both screening and baseline;

7) Documented recent history (within 1 year prior to screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks);

   Note:

   - *Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0 = clear to 2 =mild) despite treatment with a daily regimen of topical corticosteroid of medium to higher potency (± topical calcineurin inhibitors as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super-potent topical corticosteroids), whichever is shorter.*
   - *Patients with documented systemic treatment for AD in the past 1 year are also considered as inadequate responders to topical treatments and are potentially eligible for treatment with KHK4083 after appropriate washout.*
   - *Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the Investigator or by the patient's treating physician.*

8) Women of childbearing potential (WOCBP) and fertile men must agree to use highly effective contraceptive methods per the approved local guidance in each country from the time of informed consent to 6 months after the last dose of IP (for women) or from the start of IP administration to 6 months after the last dose of IP (for men). WOCBP must have a negative serum pregnancy test result at screening and a negative urinary pregnancy test result at baseline assessments.

   For the United States and Canada, WOCBP who have sexual intercourse with a non-surgically sterilized male partner must agree and commit to the use one of the following highly effective methods of contraception (Clinical Trials Facilitation Group, 2014) from the time of informed consent to 6 months after the last dose of IP. Contraceptive methods considered acceptable for use in this study include:

   a) Established use (≥2 months prior to the screening visit) of oral, injected, transdermal or implanted combined estrogen-progestogen hormonal methods of contraception. Subjects who have used such methods for less than 2 months at the screening visit are required to use one of the methods described under b) or c) until the establishment of hormonal contraception methods.

   b) Double barrier contraception: use of occlusive diaphragm (cap or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. In countries where spermicidal condoms are not allowed ordinary condoms could be used in combination with spermicidal creams. Appropriate measures are to be determined by the investigator together with the subject, in accordance with the standard of care in the country where treatment is administered. A female condom and a male condom should not be used together as friction between the two can result in either, or both product(s) failing.

   c) An intrauterine device or system.

   For Germany, WOCBP and fertile men must agree to use highly effective contraceptive methods that can achieve a failure rate of less than 1% per year from the time of informed consent to 6 months after the last dose of IP (for women) or from the start of IP administration to 6 months after the last dose of IP (for men). WOCBP must have a

negative serum pregnancy test result at screening and a negative urinary pregnancy test result at baseline assessments and at each dose interval.

Birth control methods considered highly effective used consistently and correctly include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study treatments).

Note:

- *WOCBP exclude women who have undergone permanent sterilization, those who are postmenopausal [defined as the absence of menstruation for at least 12 consecutive months without any other medical reason (or in postmenopausal range per local laboratory standards)], and those anatomically having no childbearing potential.*

VII Exclusion Criteria

Subjects must be excluded from the study if they meet any of the following criteria.

1) Current or past history of clinically significant illness(es) deemed by the Investigator to be likely to affect the study conduct and assessments. Examples include, but are not limited to, clinically significant cardiovascular (e.g., New York Heart Association [NYHA] Class III or IV), uncontrolled diabetes (HbA1c ≥9%), liver (e.g., Child-Pugh class B or C), renal, respiratory, hematologic, central nervous system, psychiatric, or autoimmune diseases/disorders;
2) Any of the following laboratory abnormalities at screening:
   - Serum creatinine: >1.5 mg/dL
   - AST or ALT: ≥2.5 times the upper limit of normal
   - Neutrophil count: $<1.5\times10^3/\mu L$

- Other laboratory abnormalities that may affect the completion or evaluation of the study, as judged by the Investigator;

3) Active malignancies, or onset or a history of treatment of malignancies within 5 years prior to informed consent (except curatively treated in situ cervical carcinoma, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma);
4) Past history of alcohol or substance abuse within 1 year before screening visit; active alcohol dependence or drug dependence;
5) Current or past history of any suicidal behavior;
6) History of major immunologic reaction (e.g., serum sickness, anaphylaxis, or anaphylactic reaction) to any other biologic product or any excipient of KHK4083;
7) History of ≥3 systemic infections requiring systemic administration (excluding oral administration) of antimicrobials, antifungals, or antivirals within 1 year prior to baseline visit;
8) Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks before the baseline visit, or superficial skin infections within 2 weeks before the baseline visit;
9) Treatment with live vaccination (e.g., BCG, polio, measles, or rubella) within 12 weeks prior to baseline visit. Inactivated vaccination (e.g., hepatitis, pneumococcal, meningococcal, tetanus, diphtheria toxoid, acellular pertussis, inactivated polio, human papilloma and influenza-except intranasal influenza) is allowed;
10) Treatment with any biological product (including an IP) within 12 weeks (16 weeks for Japan) or 5 half-lives, whichever is longer, prior to baseline visit;
11) Treatment with 3 or more biological products (including an IP) within 2 years before the baseline visit;
12) Participation in a clinical or equivalent study and use of an IP (other than biologics) or unapproved medical device within 4 weeks (16 weeks for Japan) or 5 half-lives, whichever is longer, prior to baseline visit;
13) Treatment with any of the following medications or therapies within 4 weeks or 5 half-lives, whichever is longer, prior to baseline visit;
    - Systemic corticosteroids (inhaled corticosteroids, eye, ear, or nasal drops containing corticosteroids are allowed, suppositories or enemas containing corticosteroids are not allowed)
    - Systemic treatment with methotrexate, mycophenolate, calcineurin inhibitors, thalidomide, or other immunosuppressants
    - Phototherapy (e.g., psoralen ultraviolet A [PUVA] therapy, ultraviolet B [UVB] therapy, narrow-band UVB therapy, ultraviolet A1 [UVA1] therapy , excimer light) for the treatment of AD
    - Janus kinase inhibitors

14) Treatment with any of the following medications for the treatment of AD within 1 week prior to baseline visit;

- Topical corticosteroids
- Topical calcineurin inhibitors or other immunosuppressive agents
- Topical agents including crotamiton, Eucrisa®/crisaborole
- Combination topical agents containing a corticosteroid or a calcineurin-inhibiting component or other immunosuppressive agents
- Chinese herbal medicines (e.g., jumi-haidoku-to, shofu-san, saiko-seikan-to, hochu-eki-to)

15) Any planned surgical treatment or invasive procedure (for instance dental implant installation or non-emergency low invasive intra-cardiac manipulation) during the study;

16) Any conditions not allowing for discontinuation of prohibited concomitant drugs or therapies;

17) Pregnant or breastfeeding women, or women willing to become pregnant;

18) Evidence of HIV infection or are positive for HIV antibodies at screening; or current acquired, common variable or inherited, primary or secondary immunodeficiency;

19) Positive test for active hepatitis B (HB) infection at screening defined as:

- Positive for HB surface antigen;
- Positive for anti-HB core antibody or positive for HBV-DNA; or
- For subjects enrolled in Japan, positive for anti-HB core antibody and/or positive for anti-HB surface antibody, and positive for HBV-DNA. However, HBV-DNA measurement will not be required for subjects who are positive for antibodies produced after HB vaccination and who are not affected with hepatitis B at screening.

If any of HB tests has an indeterminate or the result cannot be interpreted with certainty, confirmatory testing as per local guidelines will be performed.

20) Positive for anti-hepatitis C (HC) virus antibody at screening, and confirmed infection with HC virus by RNA or other confirmation test. If the HC test has an indeterminate result, confirmatory testing will be performed by an alternative method that is locally accepted;

21) Evidence or history of active tuberculosis (TB), either treated or untreated; or latent TB (defined as a positive purified protein derivative [PPD] or interferon-gamma release assay [IGRA] test without evidence of clinically manifested active TB), the treatment of which was completed more than 12 months before baseline visit or untreated. Evaluation for TB will be conducted according to the local standards of care or as determined by local guidelines and will include PPD or IGRA tests and may consist of history, physical examinations and chest X-ray.

Subjects with latent TB who meet either of the following conditions can be enrolled:

- Subjects with latent TB who have completed an appropriate course of anti-TB treatment as per local guidelines or standards of care within 12 months before baseline visit.
- Subjects with latent TB who have been receiving appropriate anti-TB treatment as per local guidelines or standards of care (for instance isoniazid) for at least 28 days (21 days in Japan) before baseline visit.

22) Previous participation in a study of KHK4083 and use of an IP;

23) Other conditions unsuitable for participation in the study in the opinion of the Investigator.

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LIST OF TERMS

List of Abbreviations

Abbreviation	Expanded Form
AD	Atopic dermatitis
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
BSA	Body surface area of involvement of AD
CFR	Code of Federal Regulations
CLA	Cutaneous lymphocyte-associated antigen
CRO	Contract research organization
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic data capture
FAS	Full analysis set
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identifier
IEC	Independent Ethics Committee
IGA	Investigator's global assessment
IRB	Institutional Review Board
IP	Investigational product
IV	Intravenous
IWRS	Interactive web response system
JAK	Janus kinase
KKD	Kyowa Kirin Pharmaceutical Development, Inc.
mAb	Monoclonal antibody
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical rating scale
NYHA	New York Heart Association
PK	Pharmacokinetic(s)
PT	Preferred term
PPD	Purified protein derivative
PPS	Per protocol set
PUVA	Psoralen ultraviolet A
Q2W, Q4W	every 2 weeks, every 4 weeks

Abbreviation	Expanded Form
QoL	Quality of life
SAE	Serious adverse event
SC	Subcutaneous
SCORAD	Severity scoring of atopic dermatitis
SOC	System organ class
TARC (CCL17)	Thymus and activation-regulated chemokine
TB	Tuberculosis
TCS	Topical corticosteroid
TEAE	Treatment-emergent adverse event
Th	T-helper
TNFR	Tumor necrosis factor receptor
TSLP	Thymic stromal lymphopoietin
UC	Ulcerative colitis
US	United States
UVA1	Ultraviolet A1
UVB	Ultraviolet B
WOCBP	Women of childbearing potential

List of Definitions

Term	Definition
ANCOVA	Analysis of covariance
C_{max}	Maximum observed serum concentration
CTCAE	Common terminology criteria for adverse events
C_{trough}	Serum trough concentration
DNA	Deoxyribonucleic acid
EASI-50, -75, -90	50%, 75%, or 90% reduction from baseline in EASI score
FcγRIIIa	Receptors group III encoded by gene A recognizing the Fc portion of IgG mAbs
HBc	Hepatitis B virus core
HBs	Hepatitis B virus surface
HBV-DNA	Hepatitis B virus DNA
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HTLV-1	Human T-cell lymphotropic virus type-1
Injection reaction	Any systemic injection-related reaction
Injection site reaction	Any local injection-related reaction
IgE	Immunoglobulin E
Investigator	Principal Investigator or sub-Investigator
RNA	Ribonucleic acid
t_{max}	Time of maximum observed serum concentration

List of Clinical Laboratory Assessments (clinical laboratory evaluation, standard 12-lead electrocardiogram)

Term	Clinical Laboratory Assessment
WBC	Leukocytes
RBC	Erythrocytes

Term	Clinical Laboratory Assessment
Ht	Hematocrit
Hb	Hemoglobin
PLT	Platelets
Baso	Basophils/Leukocytes
Eosino	Eosinophils/Leukocytes
Neutro	Neutrophils/Leukocytes
Mono	Monocytes/Leukocytes
Lymph	Lymphocytes/Leukocytes
CRP	C Reactive Protein
γ-GTP	Gamma Glutamyl Transferase
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
Alb	Albumin
K	Potassium
Ca	Calcium
Cre	Creatinine
Cl	Chloride
BUN	Blood Urea Nitrogen
Glu	Glucose
T-Cho	Cholesterol
T-Bil	Bilirubin
TP	Protein
TG	Triglycerides
Na	Sodium
LDH	Lactate Dehydrogenase
UA	Urate
P	Phosphate
HbA1c	Hemoglobin A1c
HR	Heart rate
PR interval	The time from the onset of the P wave to the start of the QRS complex.
QRS interval	The time from the start of the Q wave to the end of the S wave.
QT interval	The time from the start of the Q wave to the end of the T wave.
QTc interval	The corrected QT interval

Study Participation Period

The study participation period for each subject in this study is defined as the period from the date of obtaining informed consent through the completion of the last protocol-specified assessment.

Time points for Investigational Product Administration, Observation, and Examinations

The date of the first dose of investigational product (IP) is defined as Day 1 (the start date of IP administration). The date that is Xth day of IP administration is regarded as Day X. The day before the start of IP administration is defined as Day −1. The week in which IP administration is started is defined as Week 0. The week that is Y weeks after Week 0 is regarded as Week Y.

1 INTRODUCTION

1.1 Medical Background

[redacted]

[redacted]

[redacted]

1.2 Atopic Dermatitis

[redacted]

[redacted]

1.3 KHK4083

[redacted]

[redacted]

[redacted]

[redacted]

1.3.1 Non-Clinical Studies

[redacted]

1.3.2 Clinical Studies

[redacted]

[redacted]

1.4 Risks and Benefits

1.4.1 Risks

[redacted]

1.4.2 Benefits

[redacted]

1.5 Rationale for Conducting the Study

[redacted]

2 STUDY OBJECTIVES AND ENDPOINTS

The primary, secondary, safety, and exploratory objectives of the study are as follows:

1) Primary Objective

Primary Objective	Endpoint
To assess the efficacy of four dose regimens of KHK4083 compared to placebo as measured by the change from baseline in EASI score following multiple subcutaneous (SC) injections for 16 weeks in subjects with moderate to severe AD.	• Percent change from baseline to Week 16 in EASI score

2) Secondary Objectives

Secondary Objectives	Endpoints
To evaluate the effects on **skin symptoms** following multiple SC injections of KHK4083 for 16 weeks in comparison with placebo in subjects with moderate to severe AD.	• Achievement of 50%, 75%, or 90% reduction from baseline in EASI score (EASI-50, EASI-75, or EASI-90) at Week 16 • Change from baseline to Week 16 in EASI score • Change and percent change from baseline to Week 16 in SCORAD score • Achievement of an Investigator's Global Assessment (IGA) score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16 • Change from baseline to Week 16 in percent body surface area of involvement of AD (BSA)
To evaluate the effects on **itching and sleeping** following multiple SC injections of KHK4083 for 16 weeks in comparison with placebo in subjects with moderate to severe AD.	• Change and percent change from baseline to Week 16 in pruritus NRS score • Change and percent change from baseline to Week 16 in sleep disturbance NRS score
To evaluate the effects on **quality of life (QoL)** following multiple SC injections of KHK4083 for 16 weeks in comparison with placebo in subjects with moderate to severe AD.	• Change from baseline to Week 16 in Dermatology Life Quality Index (DLQI)

To evaluate the effects on **skin symptoms** following multiple SC injections of KHK4083 for 36 weeks in subjects with moderate to severe AD.	• Change and percent change from baseline in EASI score at each time point • Achievement of EASI-50, EASI-75, or EASI-90 at each time point • Change and percent change from baseline in SCORAD score at each time point • Achievement of an IGA score of 0 or 1 and a reduction from baseline of ≥2 points at each time point • Change from baseline in percent BSA at each time point
To evaluate the effects on **itching and sleeping** following multiple SC injections of KHK4083 for 36 weeks in subjects with moderate to severe AD.	• Change and percent change from baseline in pruritus NRS score at each time point • Change and percent change from baseline in sleep disturbance NRS score at each time point
To evaluate the effects on **QoL** following multiple SC injections of KHK4083 for 36 weeks in subjects with moderate to severe AD.	• Change from baseline in DLQI at each time point

3) Safety Objective

Safety Objective	Endpoints
To evaluate the safety of multiple SC injections of KHK4083 in subjects with moderate to severe AD.	• Treatment-emergent adverse events (TEAEs) • Laboratory values • Vital signs • Standard 12-lead electrocardiogram (ECG)

4) Exploratory Objectives

Exploratory Objectives	Endpoints
To investigate PK and immunogenicity following multiple SC injections of KHK4083 in subjects with moderate to severe AD.	• PK assessment – Serum KHK4083 concentration – PK parameters (e.g., C_{max}, C_{trough}) • Anti-KHK4083 antibody
To assess pharmacodynamics following multiple SC injections of KHK4083 in subjects with moderate to severe AD.	• Pharmacodynamic assessment – Serum disease markers (TARC, serum total IgE)

3 STUDY DESIGN

3.1 Study Design and Duration

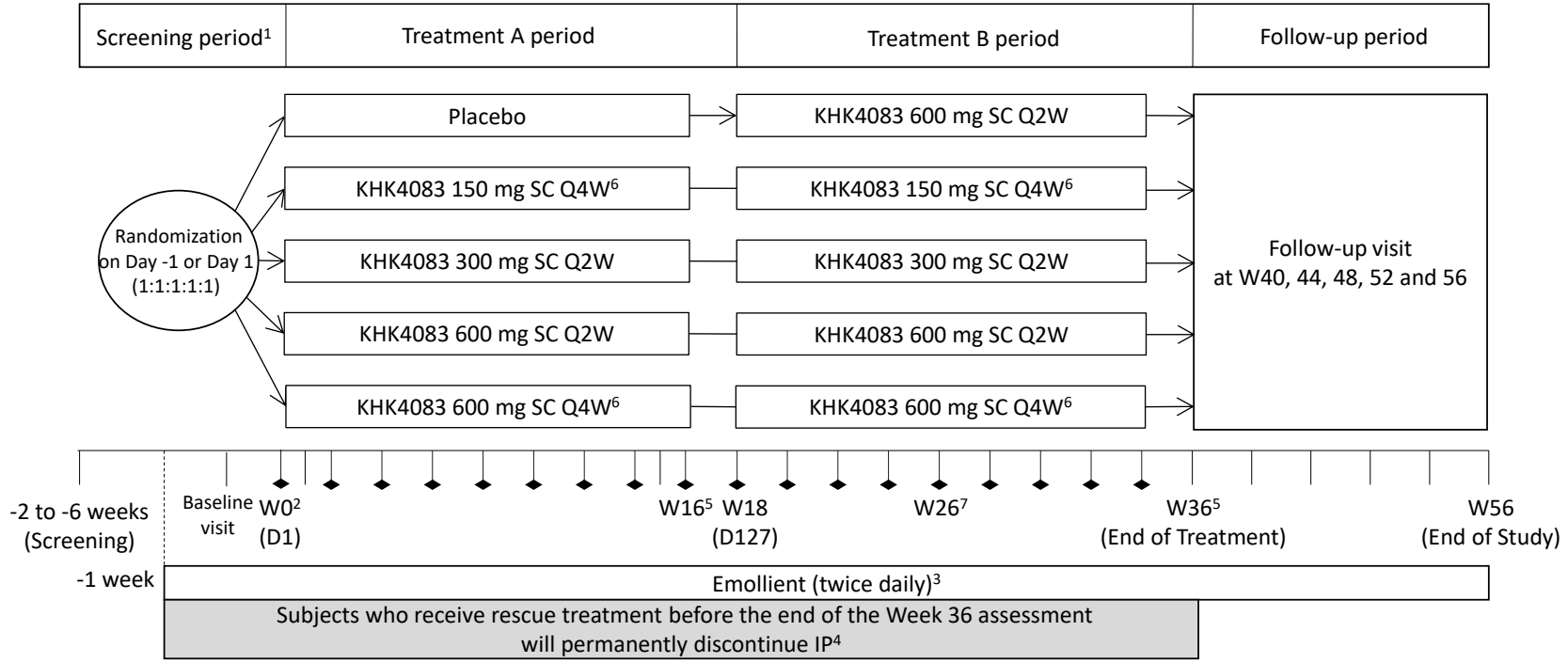
This is a Phase 2, multicenter, randomized, placebo-controlled, double-blind, parallel-group study consisting of a screening period of at least 2 weeks (a maximum 6 weeks), an 18-week placebo-controlled treatment period (Treatment A period), followed by an 18-week treatment period (Treatment B period), and a 20-week follow-up period.

Subjects will receive SC doses of IP every 2 weeks under double-blind conditions (Weeks 0 [Day 1], 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 34). The last dose will be administered at Week 34, and subjects will complete the treatment period at Week 36 (end of treatment [EOT]). Subsequently, subjects will be followed up at Weeks 40, 44, 48, 52, and 56. The study period will be a maximum of 60 weeks.

The study is expected to start in the third quarter of 2018 and end by the first quarter of 2021.

The study design is outlined in Figure 3.1-1.

Figure 3.1-1 Overall Study Design



IP=investigational product, SC=subcutaneous, Q2W=every 2 weeks, Q4W=every 4 weeks, W=Week, D=Day, Day 1= the date of the first dose of IP, ◆: IP administration

1: Randomization will be performed within 3 days after baseline visit. 2: Subjects will start study treatment on the day of or the day after randomization. 3: Subjects will apply a topical emollient by the simple method from at least 1 week before baseline visit through Week 36. Subjects may continue using the emollient throughout the study. 4: Subjects receiving rescue treatment (See Section 6.3.3) before the end of the Week 36 assessment will discontinue IP, undergo end-of-study assessments, and then be withdrawn from the study. 5: The study will be blinded to all study personnel/consultants, investigative site personnel, and study subjects. At the time when all subjects (excluding withdrawn subjects) have reached Week 16 and Week 36, the study will be unblinded to selected personnel to conduct interim analyses. 6: Subject who are randomized to the KHK4083 150 mg Q4W group and 600 mg Q4W group will receive KHK4083 alternating every 2 weeks with placebo. 7: Subjects who meet withdrawal criterion 5) (Section 4.4.1) based on the IGA score at Week 26 will discontinue IP administration at Week 26, undergo end-of-study assessments, and then be withdrawn from the study.

3.1.1 Screening Period

The Investigator will register subjects who provide written informed consent in an interactive web response system (IWRS) to start screening those subjects within 4 weeks after the date of subject's signature on informed consent. Subjects will undergo baseline assessments at least 2 weeks but not later than 6 weeks after the start of screening.

A total of approximately 250 subjects who are considered eligible as a result of the screening and baseline assessments will be enrolled.

Subjects will be required to apply a topical emollient, as a rule, twice daily for at least 1 week before baseline visit through the end of the study. The use of TCSs will be prohibited from at least 1 week before baseline visit through Week 36 assessment.

3.1.2 Treatment Period (Day 1 to Week 36)

Randomization will be performed within 3 days after baseline visit.

Subjects will start study treatment on the day of or the day after randomization (date of the first dose of IP will be regarded as Day 1). The treatment period is defined as the period between Day 1 and the end of the Week 36 assessment.

The study consists of 2 treatment periods.

Treatment A period (last dose at Week 16)

All subjects who meet the inclusion criteria and none of the exclusion criteria during the screen phase will be randomized to one of the treatment groups (placebo, KHK4083 150 mg Q4W, 300 mg Q2W, 600 mg Q2W, or 600 mg Q4W). In the 150 mg Q4W group and the 600 mg Q4W group, placebo will be administered between KHK4083 injections to ensure blinding.

Treatment A period is defined as the period between Day 1 and Week 18 pre (before IP administration at Week 18).

In order to ensure the study blind, the efficacy data until Week 16 shall be entered into the electronic Clinical Outcome Assessment (eCOA).

Treatment B period (last dose at Week 34)

Treatment B period is an extension phase where all subjects will receive KHK4083 for an additional 18 weeks under double-blind conditions (from Week 18 post [IP administration at Week 18] through Week 36).

In Treatment B period, subjects randomized to the placebo group in Treatment A period will receive SC injections of 600 mg KHK4083 every 2 weeks starting at Week 18. Subjects randomized to any of the KHK4083 groups in Treatment A period will receive KHK4083 at the same dose and dosing interval as in Treatment A period.

Subjects who meet withdrawal criterion 5) (Section 4.4.1) based on the IGA score at Week 26 will discontinue IP administration at Week 26, undergo end-of-study assessments, and then be withdrawn from the study.

Subjects receiving rescue treatment (See Section 6.3.3) during the period between the start of IP administration and the end of the Week 36 assessment will discontinue IP, undergo end-of-study assessments, and subsequently be withdrawn from the study.

3.1.3 Follow-up Period (up to Week 56)

Subjects will enter the follow-up period after the end of the Week 36 assessment and will be followed up every 4 weeks until Week 56. Subjects who received rescue treatment after Week 36 will not be withdrawn from the study and will be observed until the end of the study up to Week 56.

3.1.4 Other Potential Study Assessments (optional)

Sampling for exploratory biomarkers: Exploratory biomarkers to characterize KHK4083 pharmacodynamic activity will be assessed. At selected investigative sites in the United States and Canada, blood and skin samples will be collected from subjects who voluntarily provide consent to undergo both serum analyses (including but not limited to serum cytokines and chemokines) and skin biopsy. At all investigative sites in Japan, blood and skin samples will be collected from subjects who voluntarily provide consent to undergo both flow cytometry (OX40-positive T cell and cutaneous lymphocyte-associated antigen [CLA]-positive memory T cell) and skin biopsy.

Pharmacogenetic testing: The purpose of this assessment is to explore the association between individual differences in responses to KHK4083 and mutations in DNA sequence. Blood samples will be collected before IP injection at Week 0 from subjects who voluntarily provide consent.

3.2 Rationale for Study Design

[redacted]

3.3 Enrollment

A total of approximately 250 subjects with moderate to severe AD will be enrolled in this study.

The Investigator will enroll subjects according to the following procedure.

1) Before starting the study-specific procedures, written informed consent (or assent, if applicable) should be obtained from potentially eligible subjects.
2) At each investigative site, a subject identifier (ID) will be assigned through the IWRS to each subject who provides consent, according to the following rule. The same ID will be used from the time of informed consent through the end of the study.

   ID: 4083-006-XX-YY-ZZ

   XX: Country code (e.g., JP, Japan, US, the United States, CA, Canada, GE, Germany)

   YY: Investigative site code

   ZZ: Sequential number for subjects providing consent at the investigative site

   For example, the subject ID of the first subject who provides consent at ### hospital (investigative site code: 01) in Japan is 4083-006-JP-01-01.
3) Subjects will be assessed for eligibility.
4) Eligible subjects will be registered as an enrolled subject in the IWRS.
5) A subject who is not eligible may be re-screened at the discretion of the Investigator after re-obtaining written informed consent. Subjects will be permitted to be re-screened only once. Chest X ray (or CT scan) at re-screening may be omitted upon consultation with the Sponsor only if there are no findings suggestive of tuberculosis (TB) at the initial screening. The subject ID of re-screened subjects will be the same as that initially assigned.

Details of the subject enrollment method are specified in separate written procedures.

3.4 Randomization and Blinding

3.4.1 Randomization

Randomization will be performed through the IWRS in the order of enrollment. Subjects who meet all of the eligibility criteria will be randomly assigned to receive 150 mg Q4W, 300 mg Q2W, 600 mg Q2W, or 600 mg Q4W KHK4083 or placebo in a 1:1:1:1:1 ratio by the IWRS according to a dynamic allocation procedure. Randomization will be performed within 3 days after baseline assessments. The severity of AD (moderate, IGA=3; severe, IGA=4) at baseline, region (Japan, rest of world), and previous use of biological products (Yes, No) for the treatment of AD at baseline will be used as stratification factors for randomization by prioritizing them. Detailed written procedures for randomization will be provided separately from the protocol.

Randomization transaction of IWRS would decide each subject treatment arm allocation and at the same time indicated drug number (Kit No.) to be dispensed. The Kit No. shall be entered into the electronic Case Report Form (eCRF).

3.4.2 Blinding

3.4.2.1 Creation and Storage of Allocation Table

[redacted] will prepare a drug randomization list and allocate IP to each subject with the IWRS according to separate written procedures.

The drug randomization will be adaptive based on separate written procedures. The subject treatment group will be allocated by the IWRS according to the separate written procedures. [redacted] will create treatment assignment list that will be provided at the interim analysis following separate written procedures and will provide a record of emergency unblinding from the IWRS as required.

3.4.2.2 Blinding Method

The study will be blinded to all study personnel/consultants, investigative site personnel, and study subjects. However, the study will be unblinded to selected personnel as follows.

In this study, a pharmacist who is unblinded to treatment assignment ("unblinded pharmacist") (or qualified designee) will be registered at each investigative site beforehand. The unblinded pharmacist (or qualified designee) will prepare the IP dose for SC injection according to the assigned treatment. Details are specified in the Pharmacy Manual, which is separately provided.

Persons to be unblinded from the start of this study include unblinded pharmacist (or qualified designee), unblinded drug supply managers responsible for managing IP logistics and unblinded monitor responsible for monitoring the IP is stored, controlled and prepared according to the procedures of the Contract Research Organization (CRO), and safety personnel of the Sponsor who reports certain serious adverse events (SAEs) to the regulatory authorities; and persons to be unblinded after the interim analysis at Week 16 include personnel at interim analysis center of CRO and person responsible for PK and biomarkers of the Sponsor. The individuals will be identified in the separate document of Blinding Plan and Unblinding Processes.

The allocation of IP to the subject will be managed by the IWRS, the unblinded pharmacist (or qualified designee) will be given information on the IP allocation electronically via the IWRS.

3.4.2.3 Measures Taken to Maintain Blindness Assignment Based on Known Information on KHK4083

Test results on serum KHK4083 concentrations, anti-KHK4083 antibodies, TARC, serum total IgE, OX40-positive cells in skin and peripheral blood, and CLA-positive memory T cells in peripheral blood (Japan only) may unblind the subject treatment group based on serum drug concentration, immune response or KHK4083 mechanism of action. Therefore, those results must not be provided to the Investigator or site staff, who are involved in treatment or clinical assessments of subjects, or Sponsor/CRO personnel (except personnel at interim analysis center of CRO and person responsible for PK and biomarkers of the Sponsor) until the study is unblinded by the Sponsor, with the exception of when the knowledge of the test result is necessary to ensure subject safety or to submit an expedited report of a Suspected Unexpected Serious Adverse Reaction (SUSAR) to the Regulatory agencies. The Investigator must notify the Sponsor if they become aware of any test result regardless of the reason.

3.4.2.4 Unblinding

The Sponsor reserves the right to unblind an individual subject's treatment for the purposes of fulfilling regulatory requirements for expedited reporting of adverse events (AEs) and/or subject safety. A subject’s treatment assignment should only be unblinded by the Investigator or Sponsor when knowledge of the treatment is essential for the further management of the subject or may impact the safety of subjects in current and/or subsequent cohorts. The emergency unblinding process will be identified in the separate document of Emergency Unblinding Procedure.

In the following cases, the Investigator will immediately notify the Sponsor and withdraw the relevant subject from the study.

- Any study staff (the Principal Investigator, sub-Investigator, or clinical research coordinator) other than the unblinded pharmacist becomes aware of the treatment assignment of the subject.
- The knowledge of the treatment group of the subject is necessary to take measures against a TEAE. (The Investigator should report to the Sponsor before disclosing the emergency key code.)

After all subjects have completed the scheduled assessments and the database has been locked, the study will be unblinded to all study personnel.

3.5 Safety Monitoring Plan

The Sponsor and CRO will monitor subjects' safety and compliance with the protocol (e.g., inclusion and exclusion criteria, concomitant medications, and study visits) according to the procedures of the Sponsor.

The Sponsor has primary responsibility for the ongoing medical review of safety data throughout the study.

Recommendations will be made with the input of the Medical Monitor to the Principal Investigator and other appropriate designated staff regarding further conduct of the study.

Currently, based on safety observations from existing clinical trials, the infusion or injection reactions are identified as AE of special interest for KHK4083. [redacted] Detailed written procedures for the follow-up AEs of special interest will be provided separately from the protocol.

[redacted]

3.5.1 Injection-related Reaction

The Investigator should monitor subjects for acute drug reactions at the investigative site for at least 2 hours after IP administration for visits at Day 1, Weeks 2, 4, 18, 20, and 22. At all other visits subjects will be monitored for acute drug reactions at the investigative site for at least 30 minutes after IP administration. However, subjects will stay longer at the site for observation whenever it is clinically required and at the discretion and clinical judgment of the Investigator. Refer to Section 6.2.3 for detail on measures to be taken for acute reactions. No pre-medication (e.g., acetaminophen, anti-emetic; 5HT3 blocker; histamine H1 and/or H2 blocker[s]) is planned to be routinely/prophylactically administered prior to IP administration

in this study. However, pre-medication may be used prior to IP administration as per the decision of the Investigator upon approval of the Sponsor; or the Sponsor may recommend the pretreatment of subjects to the Principal Investigator if consistent mild (Grade 1) and/or moderate (Grade 2) injection reactions are observed during the course of the study. Refer to Section 7.9.8.1 for reporting an injection-related reaction including descriptions of specific symptoms observed or reported by the subject.

Each investigative site must have trained staff and immediate access to emergency supplies and equipment including, but are not limited to, drugs needed to treat a subject in case of a life threatening emergency.

3.5.2 Contraception

The Investigator will instruct subjects to use highly effective contraceptive methods per the approved local guidance in each country from the day of providing informed consent through 6 months after the last dose of IP for women of childbearing potential (WOCBP) and from the start day of IP administration through 6 months after the last dose of IP for men with reproductive capability. The Investigator will thoroughly explain the risks in pregnancy and the effective contraceptive methods to the subjects.

Actions will be taken according to Section 7.9.8.3, if a female subject becomes pregnant after providing informed consent, or if a partner of a male subject becomes pregnant after the start of IP administration until 6 months after the last dose of IP.

4 SUBJECT ELIGIBILITY AND WITHDRAWAL CRITERIA

4.1 Target Subjects

Subjects with moderate to severe AD whose disease cannot be adequately controlled with topical medications or for whom topical treatment is medically inadvisable.

To allow efficacy and safety assessments in subjects without previous use of biological products, enrollment of subjects who have received previous treatment with biological products for the treatment of AD will be limited to not more than 50% of total enrollment.

4.2 Inclusion Criteria

Subjects who meet all of the following criteria will be enrolled in this study:

1) Voluntarily signed informed consent to participate in the study;
2) Men and women ≥18 years at the time of informed consent;
3) Chronic AD, according to American Academy of Dermatology Consensus Criteria (Eichenfield et al, 2014) or the local diagnostic criteria, that has been present for at least 1 year before screening;
4) EASI score ≥16 at screening and baseline;
5) IGA score ≥3 (moderate) at both screening and baseline;
6) BSA ≥10% at both screening and baseline;
7) Documented recent history (within 1 year prior to screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks);

   Note:

   - *Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0 = clear to 2 =mild) despite treatment with a daily regimen of TCS of medium to higher potency (± topical calcineurin inhibitors as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super-potent TCSs), whichever is shorter.*
   - *Patients with documented systemic treatment for AD in the past 1 year are also considered as inadequate responders to topical treatments and are potentially eligible for treatment with KHK4083 after appropriate washout.*
   - *Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the Investigator or by the patient's treating physician.*

8) WOCBP and fertile men must agree to use highly effective contraceptive methods per the approved local guidance in each country from the time of informed consent to 6 months after the last dose of IP (for women) or from the start of IP administration to 6 months after the last dose of IP (for men). WOCBP must have a negative serum pregnancy test result at screening and a negative urinary pregnancy test result at baseline assessments.

   For the United States and Canada, WOCBP who have sexual intercourse with a non-surgically sterilized male partner must agree and commit to the use one of the following highly effective methods of contraception (Clinical Trials Facilitation Group, 2014) from the time of informed consent to 6 months after the last dose of IP. Contraceptive methods considered acceptable for use in this study include:

   a) Established use (≥2 months prior to the screening visit) of oral, injected, transdermal or implanted combined estrogen-progestogen hormonal methods of contraception. Subjects who have used such methods for less than 2 months at the screening visit are

required to use one of the methods described under b) or c) until the establishment of hormonal contraception methods.

b) Double barrier contraception: use of occlusive diaphragm (cap or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. In countries where spermicidal condoms are not allowed ordinary condoms could be used in combination with spermicidal creams. Appropriate measures are to be determined by the investigator together with the subject, in accordance with the standard of care in the country where treatment is administered. A female condom and a male condom should not be used together as friction between the two can result in either, or both product(s) failing.

c) An intrauterine device or system.

For Germany, WOCBP and fertile men must agree to use highly effective contraceptive methods that can achieve a failure rate of less than 1% per year from the time of informed consent to 6 months after the last dose of IP (for women) or from the start of IP administration to 6 months after the last dose of IP (for men). WOCBP must have a negative serum pregnancy test result at screening and a negative urinary pregnancy test result at baseline assessments and at each dose interval.

Birth control methods considered highly effective used consistently and correctly include:

- Comb Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study treatments).

Note:

•WOCBP exclude women who have undergone permanent sterilization, those who are postmenopausal [defined as the absence of menstruation for at least 12 consecutive months without any other medical reason (or in postmenopausal range per local laboratory standards)], and those anatomically having no childbearing potential.

4.3 Exclusion Criteria

Subjects must be excluded from the study if they meet any of the following criteria.

1) Current or past history of clinically significant illness(es) deemed by the Investigator to be likely to affect the study conduct and assessments. Examples include, but are not limited to, clinically significant cardiovascular (e.g., New York Heart Association [NYHA] Class III or IV), uncontrolled diabetes (HbA1c ≥9%), liver (e.g., Child-Pugh class B or C), renal, respiratory, hematologic, central nervous system, psychiatric, or autoimmune diseases/disorders;
2) Any of the following laboratory abnormalities at screening:
   - Serum creatinine: >1.5 mg/dL
   - AST or ALT: ≥2.5 times the upper limit of normal (ULN)
   - Neutrophil count: $<1.5\times10^3/\mu L$
   - Other laboratory abnormalities that may affect the completion or evaluation of the study, as judged by the Investigator;
3) Active malignancies, or onset or a history of treatment of malignancies within 5 years prior to informed consent (except curatively treated in situ cervical carcinoma, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma);
4) Past history of alcohol or substance abuse within 1 year before screening visit; active alcohol dependence or drug dependence;
5) Current or past history of any suicidal behavior;
6) History of major immunologic reaction (e.g., serum sickness, anaphylaxis, or anaphylactic reaction) to any other biologic product or any excipient of KHK4083;
7) History of ≥3 systemic infections requiring systemic administration (excluding oral administration) of antimicrobials, antifungals, or antivirals within 1 year prior to baseline visit;
8) Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks before the baseline visit, or superficial skin infections within 2 weeks before the baseline visit;
9) Treatment with live vaccination (e.g., BCG, polio, measles, or rubella) within 12 weeks prior to baseline visit. Inactivated vaccination (e.g., hepatitis, pneumococcal, meningococcal, tetanus, diphtheria toxoid, acellular pertussis, inactivated polio, human papilloma and influenza-except intranasal influenza) is allowed;
10) Treatment with any biological product (including an IP) within 12 weeks (16 weeks for Japan) or 5 half-lives, whichever is longer, prior to baseline visit;
11) Treatment with 3 or more biological products (including an IP) within 2 years before the baseline visit;

12) Participation in a clinical or equivalent study and use of an IP (other than biologics) or unapproved medical device within 4 weeks (16 weeks for Japan) or 5 half-lives, whichever is longer, prior to baseline visit;

13) Treatment with any of the following medications or therapies within 4 weeks or 5 half-lives, whichever is longer, prior to baseline visit;

- Systemic corticosteroids (inhaled corticosteroids, eye, ear, or nasal drops containing corticosteroids are allowed, suppositories or enemas containing corticosteroids are not allowed)
- Systemic treatment with methotrexate, mycophenolate, calcineurin inhibitors, thalidomide, or other immunosuppressants
- Phototherapy (e.g., psoralen ultraviolet A [PUVA] therapy, ultraviolet B [UVB] therapy, narrow-band UVB therapy, ultraviolet A1 [UVA1] therapy, excimer light) for the treatment of AD
- Janus kinase (JAK) inhibitors

14) Treatment with any of the following medications for the treatment of AD within 1 week prior to baseline visit:

- TCSs
- Topical calcineurin inhibitors or other immunosuppressive agents
- Topical agents including crotamiton, Eucrisa®/crisaborole
- Combination topical agents containing a corticosteroid or a calcineurin-inhibiting component or other immunosuppressive agents
- Chinese herbal medicines (e.g., jumi-haidoku-to, shofu-san, saiko-seikan-to, hochu-eki-to)

15) Any planned surgical treatment or invasive procedure (for instance dental implant installation or non-emergency low invasive intra-cardiac manipulation) during the study;

16) Any conditions not allowing for discontinuation of prohibited concomitant drugs or therapies;

17) Pregnant or breastfeeding women, or women willing to become pregnant;

18) Evidence of HIV infection or a positive result for HIV antibodies at screening; or current acquired, common variable or inherited, primary or secondary immunodeficiency;

19) Positive test for active hepatitis B (HB) infection at screening defined as:

- Positive for HB surface antigen;
- Positive for anti-HB core antibody or positive for HBV-DNA; or
- For subjects enrolled in Japan, positive for anti-HB core antibody and/or positive for anti-HB surface antibody, and positive for HBV-DNA. However, HBV-DNA measurement will not be required for subjects who are positive for antibodies produced after HB vaccination and who are not affected with hepatitis B at screening.

If any of HB tests has an indeterminate or the result cannot be interpreted with certainty, confirmatory testing as per local guidelines will be performed.

20) Positive for anti-hepatitis C (HC) virus antibody at screening, and confirmed infection with HC virus by RNA or other confirmation test. If the HC test has an indeterminate result, confirmatory testing will be performed by an alternative method that is locally accepted;

21) Evidence or history of active TB, either treated or untreated; or latent TB (defined as a positive purified protein derivative [PPD] or interferon-gamma release assay [IGRA] test without evidence of clinically manifested active TB), the treatment of which was completed more than 12 months before baseline visit or untreated. Evaluation for TB will be conducted according to the local standards of care or as determined by local guidelines and will include PPD or IGRA tests and may consist of history, physical examinations and chest X-ray.

    Subjects with latent TB who meet either of the following conditions can be enrolled:

    - Subjects with latent TB who have completed an appropriate course of anti-TB treatment as per local guidelines or standards of care within 12 months before baseline visit.
    - Subjects with latent TB who have been receiving appropriate anti-TB treatment as per local guidelines or standards of care (for instance isoniazid) for at least 28 days (21 days in Japan) before baseline visit.

22) Previous participation in a study of KHK4083 and use of an IP;

23) Other conditions unsuitable for participation in the study in the opinion of the Investigator.

4.4 Criteria and Procedure for Removal from Study

4.4.1 Subject Removal

If a subject's treatment is discontinued due to safety concerns such as AEs, the Investigator will take appropriate actions for the subject to be withdrawn from the study after appropriate follow-up. The Investigator will examine the safety of each subject who has discontinued treatment and promptly perform early termination assessments. Subjects who meet withdrawal criterion 4) or 5) will be performed the end-of-study assessments.

A subject who stops visiting the investigative site after exposure to IP but before completing planned assessment will be followed and assessed safety to the extent possible, in a way that will protect the subject's human rights. In the absence of a medical contraindication or significant protocol violation, every effort will be made by the Investigator to keep the subject in the study. However, if the Investigator concludes that it is in the best interest of the

subject to discontinue IP administration or should the subject decide to discontinue study treatment, all efforts will be made to complete and report the observations as thoroughly as possible.

Subject will be withdrawn from the study if any of the following events occur:

1) Subject is found to be ineligible after the start of the study, not meeting the eligibility criteria. This may include, but is not limited to, the following events:
   - Diagnosis of a malignancy during study
   - Active TB or opportunistic infection
2) Subject experiences a serious, acute injection reaction despite administration of a prophylactic regimen or subject experiences anaphylaxis regardless of having received a pre-medication regimen or not;
3) Two consecutive doses of IP are not administered as scheduled or 3 or more doses are skipped during the treatment period. However, the subject who meets this criterion due to the logistical issue caused by the COVID-19 outbreak such as restriction on traveling, isolation etc., is allowed to remain in the study by the Investigator's discretion. Once the subject is able to make visits, he or she continues with IP administration and other procedures required by this protocol. However, missed visits may not be repeated. For example, if a subject missed Week 26 and 28 visits, and then makes a visit to the site again on the scheduled date for Week 30, assessments for Week 30 should be conducted instead of Week 26 assessments. If a subject returns to the site on Week 36 or later, no IP administration should occur;
4) Subject receives rescue treatment (See Section 6.3.3) during the treatment period;
5) IGA score at Week 26 remains unchanged or has worsened from both baseline (Week 0) and Week 18;
6) Subject experiences an AE, and the Investigator determines that treatment should be discontinued and the subject should be withdrawn from the study after follow-up. This may include, but is not limited to, the following events:
   - CTCAE v4.0 Grade 2 or higher cardiovascular AE
   - Any MACE
   - CTCAE v4.0 Grade 2 or higher Blood and Lymphatic System Disorders (System Organ Class [SOC])
   - Any CTCAE v4.0 Grade 3 or higher AEs, such as:
     – Severe pulmonary, kidney, liver, neurologic or systemic disorders including but not limited to central nervous system hemorrhage or thrombosis/embolism or renal failure
     – Hypersensitivity reactions (including anaphylactic and serum sickness-like reactions)

  - Neuropsychiatric events (including suicidal ideation and behavior)
- Severe laboratory abnormalities, such as:
  - Neutrophil count $\leq 0.5 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$
  - ALT and/or AST values >3 × ULN with total bilirubin >2 × ULN (unless elevated bilirubin is related to confirmed Gilbert's Syndrome)
  - Confirmed AST and/or ALT >5 × ULN

7) Subject or his/her legally acceptable representative decides to withdraw consent to participate the study in the absence of a medical need for withdrawal as determined by the Investigator;
8) Subject cannot undergo necessary observations and examinations anymore due to inconvenience to the subject;
9) Subject becomes pregnant, or wishes to become pregnant;
10) The emergency key code for the subject is opened during the study period;
11) The Investigator determines that the subject should be withdrawn from the study for a reason other than above (e.g., if use of any of the prohibited medications defined in 1) to 3) of Section 6.3.2 is considered necessary);
12) The Sponsor determines that this study should be terminated.

The Investigator will identify the date of withdrawal and the reason for withdrawal and will record the information on the eCRF.

In addition, subjects who discontinued IP administration due to an AE will be followed up until the AE is recovered/resolved. For the subject, safety follow up should be conducted under the Investigator's responsibility. However, no further eCRF entry is required other than AE data. The subject is followed up to 28 days (+14 days) after the last dose of the IP or until the date of early termination/end of study assessments, whichever is later, and if the AE is not recovered/resolved by then, the subject's current AE data will be recorded on the eCRF. After that, the subject will be followed up until AE is resolved unless medical judgment is obtained, but without further recording of the data on the eCRF.

4.4.2 Premature Termination or Suspension of the Entire Study or the Study at Individual Investigative Site

The Sponsor reserves the right to terminate or suspend the entire study or the study at individual investigative sites at any time. Reasons for study termination include, but may not be limited to, manufacturing problems, a request to discontinue the study from a regulatory

authority, a corporate decision to discontinue development of KHK4083, AE incidence or severity not consistent with the potential benefit of the drug, poor enrollment, or inadequate adherence to ICH-GCP guidelines.

In terminating the study, the Sponsor and the Principal Investigator will ensure that adequate consideration is given to the protection of the subjects' interest.

If the study is terminated prematurely, the IEC/IRB and regulatory authorities (if required) will be notified. Should the Principal Investigator choose to prematurely discontinue participation in the study, the site must promptly notify the Sponsor and IRB/IEC in accordance with local GCP guidelines.

5 INVESTIGATIONAL PRODUCTS

5.1 Investigational Drug and Comparator

5.1.1 Investigational Drug

Company code: KHK4083

Non-proprietary name: TBD

Strength and dosage form:

[redacted]

5.1.2 Comparator

Placebo

Strength and dosage form:

Placebo for KHK4083 is supplied in the same container closure system and contains the same deliverable volume and excipients as KHK4083 IP without the active ingredient.

5.2 Packaging and Labelling

5.2.1 Packaging

Seven vials (KHK4083 and/or placebo) per box

5.2.2 Labeling

Labels will bear the appropriate text as required by local regulatory requirements.

5.3 Storage

[redacted]

Guidance of the recommended storage conditions for IPs can be found in the Pharmacy Manual.

5.4 Delivery, Storage, Accountability, and Return of Investigational Product

After signing a Clinical Trial Agreement, the Sponsor will dispense IP to each investigative site through a carrier company with which the Sponsor appropriately concludes a contract. Separate written procedures will be followed for dispensing IP. The Sponsor will develop written procedures for controlling IP and provide it to each investigative site.

The IP manager at each investigative site (unblinded pharmacist or qualified designee) will properly store and control IP according to the procedures and will document the status of IP such as inventory, use, return, and disposal. All IPs (used and unused) should be stored until the record is finalized after verification of the unblinded monitor of CRO. The IP manager will properly check unused and used IP supplies (including empty vials and boxes) against the IP management record. All unused or expired drugs after accountability will be either destroyed at site or returned to the depot upon authorization by the Sponsor and/or the CRO

according to the investigative site's biohazards waste procedures and local regulations. After study completion or at the delivery of a new batch, the IP manager will seal all unused supplies.

It will be the Principal Investigator's responsibility to arrange for disposal of all IPs with containers, provided that procedures for proper disposal have been established according to applicable regulations and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

A copy of the certificate of destruction must be placed in the Sponsor's Trial Master File. Refer to the Pharmacy Manual for additional details on the destruction of IP.

6 TREATMENT PLAN AND CONCOMITANT THERAPY

6.1 Dose and Duration of Treatment

Dose: KHK4083 at 150 mg or 600 mg every 4 weeks, 300 mg or 600 mg every 2 weeks, or placebo.

Duration of treatment: 36 weeks (a total of 18 visits for injections)

6.2 Mode of Administration

6.2.1 KHK4083 or Placebo

To maintain the double blind and randomization schedule, the following treatment administration schedule will be followed (Table 6.2.1-1).

Subjects who are randomized to the KHK4083 150 mg or 600 mg Q4W group will receive 150 mg or 600 mg KHK4083 at Weeks 0 (Day 1), 4, 8, 12, 16, 20, 24, 28, and 32, and will receive placebo at Weeks 2, 6, 10, 14, 18, 22, 26, 30, and 34.

Subjects who are randomized to the KHK4083 300 mg or 600 mg Q2W group will receive 300 mg or 600 mg KHK4083 at Weeks 0 (Day 1), 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 34.

Subjects who are randomized to the placebo group will receive placebo at Weeks 0 (Day 1), 2, 4, 6, 8, 10, 12, 14, and 16, and will receive KHK4083 600 mg at Weeks 18 (Day 127), 20, 22, 24, 26, 28, 30, 32, and 34.

Table 6.2.1-1 Dosing Schedule for Randomized Treatment Groups

	Treatment A period									Treatment B period								
Weeks	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Placebo	P	P	P	P	P	P	P	P	P	600	600	600	600	600	600	600	600	600
150 mg Q4W	150	P	150	P	150	P	150	P	150	P	150	P	150	P	150	P	150	P
300 mg Q2W	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300
600 mg Q2W	600	600	600	600	600	600	600	600	600	600	600	600	600	600	600	600	600	600
600 mg Q4W	600	P	600	P	600	P	600	P	600	P	600	P	600	P	600	P	600	P

P = Placebo, 150 = KHK4083 150 mg, 300 = KHK4083 300 mg, 600 = KHK4083 600 mg

The volume of SC injection will be 6 mL (divided into three syringes) per dose regardless of treatment assigned to subject. Each subject will receive three SC injections of 2 mL each at every dosing visit. For subjects who complete all 18 dosing visits from Week 0 until Week 34, the total number of injections during the study will be 54. The procedure for preparing the KHK4083 dose for SC injection is provided in the Pharmacy Manual.

A designated unblinded pharmacist (or qualified designee) at each investigative site will withdraw the required amount of IP from designated 7 vials into syringes. The method of IP administration is specified in the Pharmacy Manual.

The Principal Investigator, sub-Investigator, clinical research coordinator (nurse), or other healthcare professional will administer IP subcutaneously in the abdomen, thigh, upper arm, or other appropriate sites. The site of injection should be rotated so that IP is not injected into the same site consecutively. Before IP administration, the Investigator should make sure that there are no skin disorders such as erythema, redness, pain, or swelling in the area for injection.

6.2.2 Dose Modification

No dose modifications of IP will be permitted in this study.

IP administration may be suspended only if dose interruption is considered necessary because of an AE. IP administration may be resumed if the symptom has resolved and the Investigator determines that the subject can be rechallenged with IP. Subjects will discontinue IP according to the withdrawal criteria, as indicated in Section 4.4.1, if two consecutive doses

are not administrated or a total of 3 or more doses are skipped during the treatment period (both A and B) due to the reason other than the logistical issues caused by the COVID-19 outbreak.

6.2.3 Measures to be taken for Acute Reactions

Fully human antibodies such as KHK4083 may be associated with acute reactions, especially with the first injection. Therefore, the Investigator must carefully monitor subjects for injection-related reactions or other TEAEs occurring after each IP administration to confirm the safety of each subject after injection as specified below.

Day 1, Weeks 2, 18, and 20: Vital signs will be measured before IP administration. Subjects will remain and be monitored at the investigative site for at least 2 hours after IP administration. In addition, vital signs will be measured 2 hours (±10 minutes) after IP administration.

Weeks 4 and 22: Vital signs will be measured before IP administration. Subjects will remain and be monitored at the investigative site for at least 2 hours after IP administration.

Administration time points other than above: Vital signs will be measured before IP administration. Subjects will remain and be monitored at the investigative site for at least 30 minutes after IP administration. However, subjects will stay longer at the site for observation whenever it is clinically required and at the discretion and clinical judgment of the Investigator.

No pre-medication (e.g., acetaminophen, anti-emetic; 5HT3 blocker; histamine H1 and/or H2 blocker[s]) is planned to be routinely/prophylactically administered prior to KHK4083 injection in this study. However, appropriate measures should be selected to treat individual subjects at the discretion of the Investigator upon approval of the Sponsor. If consistent mild (Grade 1) and/or moderate (Grade 2) injection reactions are observed, the Sponsor may recommend the pretreatment of subjects to the Principal Investigator.

Any subject experiencing an acute reaction must receive immediate medical assessment and indicated supportive management according to the institutional standard of care and local Principal Investigator judgment until the signs/symptoms of the reaction have resolved. Refer to Section 7.9.8.1 for reporting an injection-related reaction including descriptions of specific symptoms observed or reported by the subjects.

6.2.4 Rationale for Route of Administration, Dosing Regimen, and Treatment Duration

[redacted]

[redacted]

[redacted]

6.3 Concomitant Medications and Therapies

The following information will be recorded on the eCRF, if a subject receives any medication or therapy during the period from day of informed consent until the end (early termination) of the study:

- Generic name of medication or therapy
- Route of administration
- Start date and end date of medication
- Reason for use (indication)

Regarding the name of medicine, the generic names are preferred. For combination drugs, the brand names are allowed.

6.3.1 Concomitant Medications

In this study, an emollient prescribed by the Investigator will be used concomitantly as background treatment during the study period between at least 1 week before baseline visit and the end of the study. If the subject is using any emollient as prior medication, the dosing regimen of the emollient must be switched to that prescribed by the Investigator at least 1 week before baseline visit. If the subject is not using any emollients as prior medication, an emollient designated by the Investigator will be newly prescribed at least 1 week before baseline visit. Subjects will be required to apply a topical emollient, as a rule, twice daily during the study period. The application of the emollient must be continued at the same regimen throughout the study period even after improvement of AD symptoms.

In the United States, Canada, and Germany, over-the-counter emollients can be used instead of prescription emollients from at least l week before baseline visit through the end of the study with approval from the Investigator.

6.3.2 Prohibited Concomitant Medications and Therapies

1) The following medication will be prohibited from 12 weeks (16 weeks for Japan) or 5 half-lives, whichever is longer, before baseline visit through the end of study (or early termination)
   - Biological products (including IPs)
2) The following medication will be prohibited from 4 weeks (16 weeks for Japan) or 5 half-lives, whichever is longer, before baseline visit through the end of study (or early termination)
   - Other IPs (excluding biological products)
3) The following medication will be prohibited from 12 weeks before baseline visit through the end of study (or early termination)
   - Vaccination with live vaccines (e.g., BCG, oral polio, measles, rubella)
4) The following medications and therapies will be prohibited from 4 weeks or 5 half-lives, whichever is longer, before baseline visit through the end of study (or early termination)
   - Systemic corticosteroids (inhaled corticosteroids, eye, ear, or nasal drops containing corticosteroids are allowed, suppositories or enemas containing corticosteroids are not allowed)
   - Systemic treatment with methotrexate, mycophenolate, calcineurin inhibitor, thalidomide, or other immunosuppressants
   - Phototherapy (e.g., PUVA therapy, UVB therapy, narrow-band UVB therapy, UVA1 therapy, excimer light) for the treatment of AD
   - JAK inhibitors
5) The following medications for the treatment of AD will be prohibited from 1 week before baseline visit through the end of study (or early termination). Subjects who received rescue treatment after Week 36 will not be withdrawn from the study and will be observed until the end of the study up to Week 56.
   - TCSs
   - Topical calcineurin inhibitors or other immunosuppressive agents
   - Topical agents including crotamiton, Eucrisa®/crisaborole
   - Combination topical agents containing a corticosteroid or a calcineurin-inhibiting component or other immunosuppressive agents
   - Chinese herbal medicines (e.g., jumi-haidoku-to, shofu-san, saiko-seikan-to, hochu-eki-to)

6.3.3 Rescue Treatments

Rescue treatment is defined as the use of any of the prohibited medications or therapies defined in 4) and 5) of Section 6.3.2 for exacerbation of AD. Subjects who have received rescue treatment until Week 36 assessment will discontinue further IP administration and will be withdrawn from the study. The use of a prohibited concomitant medication or therapy for rescue treatment will not be regarded as a protocol deviation. Subjects who received rescue treatment after Week 36 will not be withdrawn from the study and will be observed until the end of the study up to Week 56.

6.4 Treatment Compliance

IP should be administered within the allowable window for each visit specified in Section 7.1. The dose should be skipped if IP cannot be administered within the specified allowable window. Study treatment should be discontinued if the scheduled dosing is skipped twice consecutively or three times in total during the treatment period. Details are described in Section 4.4.1.

7 STUDY PROCEDURES

7.1 Overall Schedule

The Investigator will assign subject IDs to subjects who provide written informed consent followed by a transaction within the IWRS to start screening those subjects within 4 weeks after the date of subject's signature on informed consent. The Investigator will register eligible subjects in the IWRS and randomize them. Subsequently, subjects will start study treatment and undergo observation, investigations, and examinations according to the schedule provided in Table 7.1-1 to Table 7.1-3. Detailed study procedures are described in Section 7.2 to Section 7.8.

Day 1 will be the starting point when scheduling study visits and examinations during the study. **Examinations and observations for efficacy assessment must be performed before IP administration of the study visit.**

Table 7.1-1 Study Schedule of Events - Screening, Baseline, and Treatment A period

STUDY PROCEDURE	SCREENING		TREATMENT A PERIOD : Day 1 to Week 18 pre (Last dose at Week 16)											
	Screening	Baseline	Week 0	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 15	Week 16	Week 18 pre
			Day 1	Day 8 ±3 days	Day 15 ±3 days	Day 29 ±3 days	Day 43 ±3 days	Day 57 ±3 days	Day 71 ±3 days	Day 85 ±3 days	Day 99 ±3 days	Day 106 ±3 days	Day 113 ±3 days	Day 127 ±3 days
SCREENING/BASELINE:														
Written Informed Consent	X*													
Inclusion/Exclusion Criteria	X	X												
Medical History/Demographics	X													
Registration on IWRS	X	X												
Randomization		X												
Training on eCOA[1]	X													
TREATMENT:														
IP Administration[3]			X[2]		X	X	X	X	X	X	X		X	
Prior/Concomitant Medications	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X
EFFICACY:														
EASI, SCORAD, IGA, BSA	X	X		X	X	X	X	X	X	X	X	X	X	X
Pruritus NRS[5]	X	X		X	X	X	X	X	X	X	X	X	X	X
Sleep disturbance NRS[5]	X	X		X	X	X	X	X	X	X	X	X	X	X
DLQI[5]	X	X		X	X	X	X	X	X	X	X	X	X	X
Photograph of AD area (optional)[6]	X	X		X	X	X	X	X	X	X	X	X	X	X
SAFETY:														
Weight	X	X			X			X						X
Height	X													
Physical Examination[7]	X	X												X
Brief Physical Examination[8]			X	X	X	X	X	X	X	X	X	X	X	
Vital Sign[9]	X	X	X[3]	X	X[3]	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X			X			X					X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*: The Investigator will start screening subjects providing written informed consent within 4 weeks after the date of informed consent.

Table 7.1-1 Study Schedule of Events - Screening, Baseline, and Treatment A period (Continued)

STUDY PROCEDURE	SCREENING		TREATMENT A PERIOD : Day 1 to Week 18 pre (Last dose at Week 16)											
	Screening	Baseline	Week 0	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 15	Week 16	Week 18 pre
			Day 1	Day 8 ±3 days	Day 15 ±3 days	Day 29 ±3 days	Day 43 ±3 days	Day 57 ±3 days	Day 71 ±3 days	Day 85 ±3 days	Day 99 ±3 days	Day 106 ±3 days	Day 113 ±3 days	Day 127 ±3 days
LABORATORY:														
Infection Test[10]	X													
HBV-DNA[11]	X					X		X		X			X	
TB test[12]	X												X	
Urinary Drug Screen	X													
Serum Pregnancy[13]	X													
Urinary Pregnancy[13]		X				X		X		X			X	
Urinalysis	X	X				X		X		X			X	
Chemistry	X	X			X	X	X	X	X	X	X		X	X
Hematology	X	X		X	X	X	X	X	X	X	X	X	X	X
TARC, Serum total IgE	X	X		X	X	X	X	X	X	X	X	X	X	X
Serum IL-22		X		X				X					X	
PK/DRUG CONCENTRATION and ANTI-DRUG ANTIBODY SAMPLING:														
Serum KHK4083 concentration sample[14]		X		X	X	X	X	X	X	X	X	X	X	X
Anti-KHK4083 antibody sample[15]		X				X		X		X			X	
OTHER POTENTIAL STUDY ASSESSMENTS (optional):														
Serum cytokines and chemokines (at only selected US and Canada sites)[16]		X						X					X	
Skin biopsy(at only selected US and Canada sites, and all Japan sites)[17]		X (NL, L)						X (L)					X (NL, L)	
Flow cytometry (at only Japan sites)[18]	X	X		X				X					X	
Stored blood for pharmacogenetics[19]		X												

Table 7.1-2 Study Schedule of Events - Treatment B period

STUDY PROCEDURE	TREATMENT B PERIOD : Weeks 18 post to 36 (Last dose at Week 34)									
										End of Treatment
	Week 18 post	Week 20	Week 22	Week 24	Week 26	Week 28	Week 30	Week 32	Week 34	Week 36
	Day 127 ±3 days	Day 141 ± 3 days	Day 155 ± 3 days	Day 169 ± 3 days	Day 183 ± 3 days	Day 197 ± 3 days	Day 211 ± 3 days	Day 225 ± 3 days	Day 239 ± 3 days	Day 253 ± 3 days
TREATMENT:										
IP Administration[3]	X	X	X	X	X	X	X	X	X	
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X
EFFICACY:										
EASI, SCORAD, IGA, BSA		X	X	X	X	X	X	X	X	X
Pruritus NRS[5]		X	X	X	X	X	X	X	X	X
Sleep disturbance NRS[5]		X	X	X	X	X	X	X	X	X
DLQI[5]		X	X	X	X	X	X	X	X	X
Photograph of AD area (optional)[6]		X	X	X	X	X	X	X	X	X
SAFETY:										
Weight										X
Height										
Physical Examination[7]										X
Brief Physical Examination[8]		X	X	X	X	X	X	X	X	
Vital Sign[9]	X[3]	X[3]	X	X	X	X	X	X	X	X
12-lead ECG				X				X		
Adverse Events	X	X	X	X	X	X	X	X	X	X

Table 7.1-2 Study Schedule of Events - Treatment B period (Continued)

STUDY PROCEDURE	TREATMENT B PERIOD : Weeks 18 post to 36 (Last dose at Week 34)									
										End of Treatment
	Week 18 post	Week 20	Week 22	Week 24	Week 26	Week 28	Week 30	Week 32	Week 34	Week 36
	Day 127 ±3 days	Day 141 ± 3 days	Day 155 ± 3 days	Day 169 ± 3 days	Day 183 ± 3 days	Day 197 ± 3 days	Day 211 ± 3 days	Day 225 ± 3 days	Day 239 ± 3 days	Day 253 ± 3 days
LABORATORY:										
Infection Test[10]										
HBV-DNA[11]		X		X		X		X		X
TB test [12]										X
Urinary Drug Screen										
Serum Pregnancy[13]										
Urinary Pregnancy[13]		X		X		X		X		X
Urinalysis		X	X	X	X	X	X	X	X	X
Chemistry		X	X	X	X	X	X	X	X	X
Hematology		X	X	X	X	X	X	X	X	X
TARC, Serum total IgE		X	X	X	X	X	X	X	X	X
Serum IL-22										X
PK/DRUG CONCENTRATION and ANTI-DRUG ANTIBODY SAMPLING:										
Serum KHK4083 concentration sample[14]		X	X	X	X	X		X		X
Anti-KHK4083 antibody sample[15]		X				X				X
OTHER POTENTIAL STUDY ASSESSMENTS (optional):										
Serum cytokines and chemokines (at only selected US and Canada sites) [16]										X
Skin biopsy (at only selected US and Canada sites, and all Japan sites) [17]										X (L)
Flow cytometry (at only Japan sites)[18]										X

Table 7.1-3 Study Schedule of Events - Follow-up Period and Early Termination

STUDY PROCEDURE	FOLLOW-UP					Early Termination (if applicable)
					End of Study	
	Week 40	Week 44	Week 48	Week 52	Week 56	
	Day 281 ± 3 days	Day 309 ± 7 days	Day 337 ± 7 days	Day 365 ± 7 days	Day 393 ± 7 days	
TREATMENT:						
Concomitant Medications	X	X	X	X	X	X
EFFICACY[20]:						
EASI, SCORAD, IGA, BSA	X	X	X	X	X	X
Pruritus NRS[5]	X	X	X	X	X	X
Sleep disturbance NRS[5]	X	X	X	X	X	X
DLQI[5]	X	X	X	X	X	X
Photograph of AD area (optional)[6]	X	X	X	X	X	X
SAFETY:						
Weight		X			X	X
Brief Physical Examination[8]	X	X	X	X	X	X
Vital Sign[9]	X	X	X	X	X	X
12-lead ECG	X		X		X	X
Adverse Events	X	X	X	X	X	X
LABORATORY:						
HBV-DNA[11]	X	X	X	X	X	
TB test [12]					X	X
Urinary Pregnancy[13]	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X
Hematology	X	X	X	X	X	X
TARC, Serum total IgE	X	X	X	X	X	
Serum IL-22	X	X	X	X		
PK/DRUG CONCENTRATION and ANTI-DRUG ANTIBODY SAMPLING:						
Serum KHK4083 concentration sample	X	X	X	X	X	X
Anti-KHK4083 antibody sample	X		X		X	X
OTHER POTENTIAL STUDY ASSESSMENTS (optional):						
Serum cytokines and chemokines (optional, at only selected US and Canada sites) [16]				X		
Skin biopsy (optional, at only selected US and Canada, and all Japan sites)[17]				X (L)		
Flow cytometry (optional, at only Japan sites)[18]	X	X	X	X		

Footnotes to Table 7.1-1 to Table 7.1-3

Week 18 pre: Before IP administration at Week 18.
Week 18 post: After IP administration at Week 18.

1: Subjects will be trained on how to use an eCOA device at the screening visit and complete pruritus NRS, sleep disturbance NRS, SCORAD (part C), and DLQI and record of emollient use on the eCOA device.
2: The first dose of IP will be administered on the day of or the day after randomization.
3: All subjects are required to remain at the investigative site to be carefully monitored for injection reactions, injection site reactions or other TEAEs after each injection. The safety of subjects after injection will be confirmed as specified below.

Day 1, Weeks 2, 18, and 20: Vital signs will be measured before the IP administration and 2 hours (±10 minutes) after injection. Subjects will remain and be monitored at the site for at least 2 hours after injection.

Weeks 4 and 22: Vital signs will be measured before the IP administration. Subjects will remain and be monitored at the site for at least 2 hours after injection.

Weeks 6, 8, 10, 12, 14, 16, 24, 26, 28, 30, 32, and 34: Vital signs will be measured before the IP administration. Subjects will remain and be monitored at the site for at least 30 minutes after injection. However, subjects will stay longer at the site for observation whenever it is clinically required and at the discretion and clinical judgment of the Investigator.

4: For all subjects, information on the use of concomitant medications will be obtained by visit or phone etc. on Day −7.
5: Pruritus NRS, sleep disturbance NRS, SCORAD (part C), and DLQI should be completed before the assessments of EASI, SCORAD (part A and B), IGA, and BSA.
6: Photographs of AD lesions will be obtained only from subjects who provide separate consent. The sites to be photographed are the front and back sides of the body (from the neck down) in principle, but may be determined by the Investigator.
7: Complete physical examination includes general appearance, examination of the HEENT (head, eyes, ears, nose, and throat) and body systems (including, but not limited to, cardiovascular, respiratory, abdominal, musculoskeletal, extremities, lymph nodes, and skin).
8: Brief physical examination only includes the HEENT, cardiovascular, respiratory, abdominal, and skin examinations.
9: Blood pressure, pulse, respiration rate, and body temperature will be measured.
10: Infection tests include HBs antigen/antibody, HBc antibody, HCV antibody, HIV antigen/antibody, and HTLV-1 antibody.
11: HBV-DNA will be measured every 4 weeks in subjects who test negative for HBs antigen but positive for HBc and/or HBs antibodies.
12: Chest X-ray (or chest CT scan) and/or a test according to the local guideline (e.g., QuantiFERON, T-Spot, PPD test) will be conducted at screening. TB risk assessment questionnaire provided in Appendix 8 may be conducted at Weeks 16, 36, and 56, and at early termination.
13: Only WOCBP will undergo urinary pregnancy test.
14: PK samples must be collected before IP administration.
15: Samples for anti-KHK4083 antibodies must be collected before IP administration, at the same time as PK samples.
16: Blood samples will be collected from subjects providing consent (optional) to undergo both skin biopsy and serum analyses at the selected investigative sites in the United States and Canada.
17: Skin samples will be collected from subjects providing consent (optional) at the selected investigative sites in the United States and Canada, and all investigative sites in Japan. NL = non-lesion, L = lesion
18: At all investigative sites in Japan, blood samples for flow cytometry will be collected from subjects providing consent (optional) to undergo both skin biopsy and flow cytometry analysis. OX40-positive T cells and CLA-positive memory T cells in peripheral blood will be measured by flow cytometry.
19: Blood samples will be collected from subjects providing consent (optional) to pharmacogenetic testing.
20: In the follow-up period, efficacy assessments may be omitted for subjects who have received rescue treatment for exacerbation of AD, at the time points (including early termination) after receiving the rescue treatment.

7.2 Investigation Items

7.2.1 Demographics

The following demographic information of subjects will be recorded on the eCRF:

- Date of informed consent
- Sex
- Year of birth/age
- Race/Ethnicity
- Current medical history
- Past medical history
- Previous use of biological products for the treatment of AD (Yes/No); if Yes, generic name of the biological product and reason for discontinuation of treatment
- Time of diagnosis of AD

Time points: screening.

7.2.2 Exposure

The following information on the status of IP administration will be collected in the eCRF:

- Kit No.
- Date and time of administration
- Status of administration (per protocol/not per protocol)
- Location sites of administration
- Reason for dose interruption (if applicable)

Time points: Week 0 (Day 1), Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18 (Day 127), 20, 22, 24, 26, 28, 30, 32, and 34.

7.3 Efficacy Assessments

Examinations and observations must be performed before IP administration. However, in the follow-up period, efficacy assessments may be omitted for subjects who have received any of the medications or therapies specified in items 1) to 5) of Section 6.3.2 for exacerbation of AD, at the time points (including early termination) after receiving the medication or therapy.

7.3.1 Eczema Area and Severity Index (EASI)

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 (see Appendix 1). 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%).

Scores calculated according to the expression "total score of 4 elements of eczema × area score of eczema" will be multiplied by 0.1 for head and neck, 0.2 for upper extremities, 0.3 for trunk, and 0.4 for lower extremities. The 4 region scores obtained will then be summed up (maximum score: 72) as EASI score. To ensure consistent evaluation, individual subjects should be evaluated by the same assessor (whenever possible) at baseline and all subsequent visits. The Investigator will complete the EASI assessment on the eCOA device at each visit.

Time points: screening, baseline, Week 1 to 56, early termination.

7.3.2 SCORing Atopic Dermatitis (SCORAD)

In the SCORAD assessment, the extent of AD will be calculated as the sum of the percentage of each defined body area, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The severity of 6 specific symptoms of AD will be assessed using the following scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe, with a maximum score of 18 (assigned as "B" in the overall SCORAD calculation). Itch and sleeplessness will be assessed by subjects on a visual analogue scale (VAS), where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum score of 20 (assigned as "C" in the overall SCORAD calculation). The SCORAD score is calculated as A/5 + 7B/2 + C.

Refer to Appendix 2 for the SCORAD assessment tool. Subjects will complete SCORAD (C) on the eCOA device at each visit before the assessments of EASI, SCORAD (A and B), IGA, and BSA. To ensure consistent evaluation, individual subjects should have the same representative area evaluated by the same assessor (whenever possible) at baseline and at all

subsequent visits. The Investigator will complete the SCORAD assessment on the eCOA device at each visit.

Time points: screening, baseline, Week 1 to 56, early termination.

7.3.3 Investigator's Global Assessment (IGA)

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).

Refer to Appendix 3 for the IGA assessment tool. To ensure consistent evaluation, individual subjects should be evaluated by the same assessor (whenever possible) at all visits. The Investigator will complete IGA on the eCOA device at each visit.

Time points: screening, baseline, Week 1 to 56, early termination.

7.3.4 Body Surface Area of Involvement of AD (BSA)

The Investigator will calculate the percentage (%) of the total body surface area affected by AD and complete BSA on the eCOA device at each visit. To ensure consistent evaluation, individual subjects should be evaluated by the same assessor (whenever possible) at all visits.

Time points: screening, baseline, Week 1 to 56, early termination.

7.3.5 Pruritus Numerical Rating Scale (NRS)

The worst degree of itch experienced during 24 hours before the time point will be assessed on a NRS (see Appendix 4). The degree of itch will be scored on an 11-point scale, with 0 being "no itch" and 10 being the "worst itch imaginable."

Subjects will complete pruritus NRS on the eCOA device at each visit before the assessments of EASI, SCORAD (A and B), IGA, and BSA.

Time points: screening, baseline, Week 1 to 56, early termination.

7.3.6 Sleep Disturbance Numerical Rating Scale (NRS)

Daily sleep disturbance in the last 24 hours before the relevant time point will be assessed on a NRS (see Appendix 5). 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).

Subjects should complete the sleep disturbance NRS on the eCOA device at each visit before the assessments of EASI, SCORAD (A and B), IGA, and BSA.

Time points: screening, baseline, Week 1 to 56, early termination.

7.3.7 Dermatology Life Quality Index (DLQI)

The effects of skin symptoms on daily living in the last 1 week will be assessed by DLQI (see Appendix 6). DLQI consists of 6 subscales (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment), which are scored on the basis of 10questions. The scoring of each question is as follows:

Response	Score
very much	scored 3
a lot	scored 2
a little	scored 1
not at all / not relevant / question unanswered	scored 0
Question 7: "prevented work or studying"	scored 3

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.

Subjects will complete DLQI on the eCOA device at each visit before the assessments of EASI, SCORAD (A and B), IGA, and BSA.

Time points: screening, baseline, Week 1 to 56, early termination.

7.3.8 Photograph (Optional)

Photographs will be obtained only from subjects who provide separate consent. The sites to be photographed are the front and back sides (from the neck down) in principle but may be determined by the Investigator. Photographs involving the face should be taken with due consideration so that the subject is not identifiable. Photograph data will be submitted to the Sponsor according to separate written procedures.

Time points: screening, baseline, Week 1 to 56, early termination.

7.4 Pharmacodynamic Assessments

7.4.1 Serum Disease Markers

TARC and serum total IgE will be measured as serum disease markers. Blood should be collected before IP injection if the administration of IP is scheduled at the same time. Details are specified in a separate Laboratory Manual provided to the investigative sites. Residual samples, after measurement, may be utilized for the improvement of serum biomarker assay. The date of blood collection will be entered into the eCRF.

Time points: screening, baseline, Weeks 1, 2, 4, 6, 8, 10, 12, 14, 15, 16, 18 pre, 20, 22, 24, 26, 28, 30, 32, 34, 36, 40, 44, 48, 52, and 56.

7.4.2 Serum IL-22

Blood samples for measuring serum IL-22 should be collected before IP injection if the administration of IP is scheduled at the same time. Details are specified in a separate Laboratory Manual provided to the investigative sites. Residual samples, after measurement, may be utilized for the improvement of serum biomarker assay. The date of blood collection will be entered into the eCRF.

Time points: baseline, Weeks 1, 8, 16, 36, 40, 44, 48, and 52.

7.5 Pharmacokinetic Concentrations and Immunogenicity Specimen Assessment

7.5.1 Serum KHK4083 Concentration

Drug concentrations will be measured by a PK bioanalytical laboratory. Serum samples should be collected prior to IP injection if the administration of IP is scheduled at the same time. Details of the collection, storage, and shipment of samples are described in the Laboratory Manual. The date and time of blood collection and IP administration will be entered into the eCRF.

Residual samples after measurement may be removed from the study and utilized for the improvement of serum KHK4083 concentration assay.

Time points: baseline, Weeks 1, 2, 4, 6, 8, 10, 12, 14, 15, 16, 18 pre (Day 127), 20, 22, 24, 26, 28, 32, 36, 40, 44, 48, 52, and 56, early termination.

7.5.2 Anti-KHK4083 Antibody

Anti-KHK4083 antibodies will be measured by a PK bioanalytical laboratory. Evaluation of neutralizing activity may also be measured by a PK bioanalytical laboratory, if necessary. Serum samples should be collected prior to IP administration, at the same time as PK sampling. Details of the collection, storage, and shipment of samples are described in the Laboratory Manual. The date and time of blood collection will be entered into the eCRF.

Residual samples after measurement may be removed from the study and utilized to improve anti-KHK4083 antibody assay.

Time points: baseline, Weeks 4, 8, 12, 16, 20, 28, 36, 40, 48, and 56, early termination.

7.6 Exploratory Biomarker Measurement (Optional)

7.6.1 Skin Biopsy (To be Performed at the Selected Investigative Sites in the United States and Canada and the Investigative Sites in Japan)

At the selected investigative sites in the United States and Canada, skin samples will be collected from subjects providing additional consent to undergo both skin biopsy and serum cytokines and chemokines, as described in Section 7.6.2. Samples should be collected before IP injection if the administration of IP is scheduled at the same time. Gene expression tests (excluding gene sequence analysis), pathological staining, and immunohistochemical staining will be conducted using the samples collected. The tests will be performed at a facility working with the Sponsor. Details of the collection, storage, and shipment of samples are described in the Laboratory Manual and Punch Biopsy Procedure provided separately. The date of consent, the date of skin biopsy collection and the location of skin biopsy collection will be entered into the eCRF. The laboratory reports will be provided to the Sponsor. The results of this exploratory biomarker research may be reported separately and may not form part of the Clinical Study Report.

At the investigative sites in Japan, skin samples will be collected from subjects providing additional consent to undergo both skin biopsy and flow cytometry, as described in Section 7.6.3. Samples should be collected before IP injection if the administration of IP is scheduled at the same time. Gene expression tests (excluding gene sequence analysis) and immunohistochemical staining will be conducted using the samples collected. The tests will be performed at a facility working with the Sponsor. Details of the collection, storage, and shipment of samples are described in the Laboratory Manual. The date of consent, the date of skin biopsy collection and the location of skin biopsy collection will be entered into the eCRF. The laboratory reports will be provided to the Sponsor. The results of this exploratory biomarker research may be reported separately and may not form part of the Clinical Study Report.

Time of sampling: baseline (non-lesions and lesions), Week 8 (lesions), Week 16 (non-lesions and lesions), Week 36 (lesions), and Week 52 (lesions).

7.6.2 Serum Cytokines and Chemokines (To be Performed at the Selected Investigative Sites in the United States and Canada Only)

At the selected investigative sites in the United States and Canada, blood samples for serum cytokines and chemokines will be collected from subjects providing additional consent to undergo both skin biopsy and serum cytokines and chemokines, as indicated in Section 7.6.1. Samples should be collected before IP injection if the administration of IP is scheduled at the same time. Serum cytokines and chemokines will be measured by a facility working with the Sponsor. Details of the collection, storage, and shipment of samples are described in the Laboratory Manual. The date of consent and the date of blood collection will be entered into the eCRF. The laboratory reports will be provided to the Sponsor. The results of this exploratory biomarker research may be reported separately and may not form part of the Clinical Study Report.

Time of sampling: baseline, Weeks 8, 16, 36, and 52.

7.6.3 Flow Cytometry (To be Performed in Japan Only)

At the investigative sites in Japan, blood samples for flow cytometry will be collected from subjects providing additional consent to undergo both skin biopsy and flow cytometry, as indicated in Section 7.6.1. Samples should be collected before IP injection if the administration of IP is scheduled at the same time. OX40+ cell counts and CLA+ memory T

cell counts will be determined. Analysis will be performed by a facility working with the Sponsor. Details of the collection, storage, and shipment of samples are described in the Laboratory Manual. The date of consent and the date of blood collection will be entered into the eCRF. The laboratory reports will be provided to the Sponsor. The results of this exploratory biomarker research may be reported separately and may not form part of the Clinical Study Report.

Time points: screening, baseline, Weeks 1, 8, 16, 36, 40, 44, 48, and 52.

7.7 Pharmacogenetics

The purpose of the pharmacogenetic testing is to explore the association between individual differences in responses to KHK4083 (e.g., efficacy, adverse drug reactions, pharmacokinetics, and pharmacodynamics) and mutations in DNA sequence (e.g., genetic polymorphism). Only subjects who provide additional consent to participation in the study and to the collection, storage, and use of blood samples for pharmacogenetic testing will be involved in this exploratory assessment.

Blood sampling for the pharmacogenetic testing should be completed before IP administration at Day 1. The blood samples will be anonymized with subject IDs and stored at a sample-archiving facility. The date of consent and the date of blood collection will be entered into the eCRF.

If a subject withdraws consent to the collection, storage, and use of blood samples for the pharmacogenetic testing, the investigative site should immediately notify the Sponsor of the withdrawal. The Sponsor will instruct the sample-archiving facility to destroy the relevant samples. The sample-archiving facility will destroy the samples and submit a certificate of destruction to the Sponsor. The Sponsor will designate a biobanking manager.

[redacted]

When the schedule or contents of pharmacogenetic testing using samples is specified, a "Pharmacogenetic Testing Protocol" will also be prepared before the testing is initiated. Measurement of pharmacogenetics will be conducted by the Sponsor or a company working

with the Sponsor. The results of this pharmacogenetics may be reported separately and may not form part of the Clinical Study Report.

The scientific reliability, such as accuracy or certainty, of results obtained from pharmacogenetic testing using archived samples is unknown at present. Therefore, any obtained results (e.g., pharmacogenetic test results) will not be disclosed to subjects. However, the obtained information will be disclosed to subjects (1) when the subject requests disclosure of test results according to laws related to personal information protection and the claim is considered to meet relevant requirements; or (2) when an ethics review committee established by the Sponsor determines after its deliberations that the disclosure of the information is necessary. As a general rule, the information will be disclosed only to the subject in both cases.

The samples derived from the subjects who have provided consent for the storage and use of samples for pharmacogenetics will be stored for 15 years after the completion of scheduled assessments of the last subject, until the research is considered unnecessary, or until the subject withdraws consent for the storage and use of samples, whichever is the earliest. The samples will then be discarded after being treated appropriately so that they cannot be used by other persons for other research.

7.8 Safety Assessments

7.8.1 Clinical Laboratory Evaluation

All prespecified laboratory tests, except for the investigative site controls will be performed by a central laboratory. The central laboratory will provide the required materials for processing the samples, and will also provide details of the collection, storage, and shipment of samples as the Laboratory Manual. The Investigator will receive a laboratory report for information on a per visit basis. Clinical significance will be reported as AEs including any related comments.

Clinical laboratory parameters are shown in Table 7.8.1-1. Each test will be performed according to the test schedule provided in Section 7.1. Samples should be collected before IP injection if the administration of IP is scheduled at the same time.

Table 7.8.1-1 Clinical Laboratory Assessments

Hematology	WBC, RBC, Ht, Hb, PLT, differential WBC (Baso, Eosino, Neutro, Mono, Lymph)
Chemistry	T-Bil, ALP, LDH, AST, ALT, γ-GTP, TP, Alb, Glu, T-Cho, TG, BUN, Cre, UA, Na, K, Cl, Ca, P, CRP, HbA1c[a] a: To be measured only at screening.
Urinalysis	Specific gravity, pH, qualitative parameters (glucose, protein, bilirubin, urobilinogen, occult blood, ketone body)
Urinary drug screen	Phencyclidine, benzodiazepine, cocaine, psychostimulants, cannabis, morphine, barbiturates, tricyclic antidepressants
Infection test (blood test)	HBs antigen, HBs antibody, HBc antibody, HCV antibody, HIV antigen/antibody, HTLV-1 antibody Any indeterminate result should be confirmed by a local alternative test method.
HBV-DNA (blood test)	HBV-DNA will be measured if the subject is negative for HBs antigen and positive for HBc antibody and/or HBs antibody at screening. Subjects enrolled with an HBV-DNA level below the limit of detection will undergo measurement of HBV-DNA according to the schedule specified in the protocol.
TB test	Chest X-ray (or chest CT scan) and/or a test according to the local guideline (e.g., QuantiFERON, T-Spot, PPD test) will be conducted at screening. TB risk assessment questionnaire provided in Appendix 8 may be conducted at Weeks 16, 36, and 56, and at early termination.
Pregnancy test (blood or urinary test)	Information such as the presence or absence of menstruation, menstrual cycle, and surgical history will be obtained through interview. WOCBP (excluding women who have undergone permanent contraception, post-menopausal women [defined as the absence of menstruation for at least 12 months without any other medical reason], or women who anatomically have no childbearing potential) will undergo pregnancy test. The reason for not undergoing pregnancy test should be described in source documents, if applicable.
	Urinary hCG (serum hCG at screening)

7.8.2 Physical Examination

The Investigator will observe subjects for any changes in symptoms or finding and for any new symptoms or findings after the start of IP administration according to the schedule provided in Section 7.1. At each visit, the Investigator will observe subjects for skin disorders (including late responses) such as erythema, redness, pain, and swelling at the sites of injection.

Complete physical examinations include general appearance, examination of the HEENT (head, eyes, ears, nose, and throat) and body systems (including, but not limited to, cardiovascular, respiratory, abdominal, musculoskeletal, extremities, lymph nodes, and skin) at screening, baseline, Weeks 18 and 36.

Brief physical examinations only include the HEENT, cardiovascular, respiratory, abdominal, and skin examinations at Weeks 1, 2, 4, 6, 8, 10, 12, 14, 15, 16, 20, 22, 24, 26, 28, 30, 32, 34, 40, 44, 48, 52, and 56 and at early termination.

If there are any unfavorable or unintended signs or symptoms, they will be reported as AEs.

7.8.3 Height and Weight

Body weight will be measured at screening, baseline, Weeks 2, 8, 18, 36, 44, and 56, and early termination. Body weight should be measured before IP injection if the administration of IP is scheduled at the same time. Height will be measured only at screening.

7.8.4 Vital Signs

Vital signs include systolic and diastolic blood pressure, pulse, respiration rate, and body temperature and should be measured in the supine or semi-supine position after at least 5-minute rest. Vital signs will be measured at all study visits for screening and during the treatment period and the follow-up period. Vital signs should be measured before IP injection if the administration of IP is scheduled at the same time. In addition, on Day 1 and at Weeks 2, 18, and 20, vital signs should be measured 2 hours (±10 minutes) after IP administration.

Additional vital sign measurements will be performed at the discretion of the Investigator if any clinically significant signs or symptoms occur. Refer to Section 6.2.3 for detail on measures to be taken for acute reactions.

Time points: screening, baseline, Week 0 (Day 1) to 56, early termination

Note: If baseline visit and Day 1 are same day, one measurement can be allowed for baseline assessment and Day 1 assessment before IP administration.

7.8.5 Standard 12-Lead Electrocardiogram

Standard 12-lead ECG parameters include heart rate, PR interval, QRS interval, QT interval, and QTc interval (QTcB, QTcF), which will be recorded after the subject has rested in a supine position for at least 5 minutes, but before blood collection for drug concentration measurement.

The Investigator will check for any clinically abnormal findings and if any, determine whether the abnormality is clinically significant or not (Interpretation: normal or abnormal, not clinically significant/abnormal, clinically significant). The interpretation will be recorded on the eCRF.

Time points: screening, baseline, Weeks 2, 8, 16, 24, 32, 40, 48, and 56, early termination

7.9 Adverse Events

7.9.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical study subject and does not necessarily have a causal relationship with the study treatment. An AE can therefore be any unfavorable and/or unintended sign (e.g., an abnormal laboratory finding), symptom or disease whether or not considered related to the product.

An AE includes but is not limited to:

- Any clinically significant* worsening of a pre-existing condition;
- A clinically significant* new/worsened laboratory abnormality;
- Any clinically important changes noted during interim or final physical examinations, 12-lead ECGs, X-rays, or any other potential safety assessments, whether or not these procedures are required by the protocol;
- An AE occurring from overdose (i.e., a dose higher than that prescribed by a healthcare professional for clinical reasons, or a dose higher than that described on the marketed product label) of an investigational or marketed product, whether accidental or intentional;
- An AE occurring from abuse (e.g., use for non-clinical reasons) of an investigational or marketed product.

*Clinically significant may include, but is not limited to, abnormalities that meet the definition of "serious" (see Section 7.9.5), or an event that leads to an intervention such as premature discontinuation of IP or the addition of concomitant/corrective therapy.

The collection of AE and SAE information commences following the subject's written consent to participate in the study. 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. If a subject experiences an AE or SAE, the subject will receive appropriate treatment and supportive care as necessary, and the Investigator will continue to follow up

until there is a return to the subject's baseline condition, or until a clinically satisfactory resolution is achieved.

In addition to the Investigator's own description of the AEs, each AE will be coded by the Sponsor according to the Medical Dictionary for Regulatory Activities (MedDRA).

7.9.2 Actions for Subjects

If an AE occurs, the Investigator will take appropriate actions as needed, such as providing a proper medical intervention or withdrawal from the study, to ensure the safety of the subject.

If it is necessary to identify the treatment (drug) received by the subject, the emergency key code for the subject will be opened according to the procedure provided in Section 3.4.2.4.

7.9.3 Urgent Safety Measures

In accordance with the principles of ICH E6-GCP, the Investigator(s) has/have primary responsibility for assuring subject safety throughout the performance of study procedures. An urgent safety measure is defined as any measure which an Investigator may need to implement, which is a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to study subjects without prior IEC/IRB approval/favorable opinion.

The Investigator may take appropriate urgent safety measures in order to protect the subjects of the clinical study against any immediate hazards to their health or safety. However, **the Investigator must inform the Sponsor within 24 hours of having taken such measures,** and the AE resulting in the Urgent Safety Measure must also be reported within 24 hours, following the SAE reporting instruction in Section 7.9.5.1.

7.9.4 Reporting of Adverse Events

The following information will be recorded on the eCRF from the subject's written consent to participate in the study through the end of the study. However, information on AEs leading to discontinue of IP administration will be collected in accordance with Section 4.4.1. The Sponsor retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

1) Reported AE term: Events of injection reaction or injection site reaction with study treatment will be entered for 'Yes: Was this an injection reaction/ this an injection site reaction associated with Study Treatment?' in addition to AE term.
2) Start date/time of AE: The date and time of onset will be entered for injection reactions or injection site reactions. Only the date of onset will be entered for other AEs.
3) Severity, as indicated in Section 7.9.4.1;
4) Serious event
    - Serious (Y): AEs defined in Section 7.9.5.
    - Non-serious (N): AEs other than those defined in Section 7.9.5.
5) Action taken with study treatment
    - Dose not changed
    - Drug interrupted
    - Drug withdrawn
    - Not applicable
6) Other action taken
    - None
    - Other drug taken
    - Other therapy received
    - Other
7) Outcome of AE
    - Recovered/resolved
    - Recovering/resolving
    - Not recovered/not resolved
    - Recovered/resolved with sequelae
    - Fatal
    - Unknown
8) End date/time of AE: The date and time of outcome identification will be entered for injection reactions or injection site reactions. Only the date of outcome identification will be entered for other AEs.
9) Relationship to study treatment: Causal relationships to the IP will be classified into 3 categories, as indicated in Section 7.9.4.2.
    - Related
    - Not related

- Unknown

7.9.4.1 Assessment of Intensity

All AEs will be classified either as Grade 1 to 5 in intensity as defined below:

- **Grade 1** (Mild) − Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** (Moderate) − Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money).
- **Grade 3** − Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- **Grade 4** − Life-threatening consequences; urgent intervention indicated.
- **Grade 5** − Death related to an AE (fatal).

The Investigator will be instructed to closely monitor each subject who experiences an AE (whether ascribed to the IP or not) until the outcome of the AE has been determined. The AE must be monitored until the return to the subject's baseline condition or until clinically satisfactory resolution is achieved (e.g., Grade 1 or stable).

7.9.4.2 Assessment of Relationship to Study Treatment

The causal relationship to study treatment should be assessed as one of the following:

- **Related** − There is a reasonable causal relationship between the IP administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.
- **Not related** − There is not a reasonable causal relationship between the IP administration and the AE.
- **Unknown** − The causal relationship cannot be determined.

7.9.5 Definition of Serious Adverse Events

An SAE is an event defined as below.

- **Death**
- **Life-threatening** − The term "life-threatening" as part of the definition of "serious" refers to an event in which the subject was at risk of immediate death at the time of the

event; it does not refer to an event that hypothetically might have caused death if it were more severe;

- **Hospitalization** or **prolongation of existing hospitalization** − Hospitalizations for procedures planned prior to study entry are not considered SAEs;
- **Persistent** or **significant disability**
- **Congenital anomaly** or **birth defect**
- **Other medically important** are those that may not result in death, be life threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, or blood dyscrasias that does not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

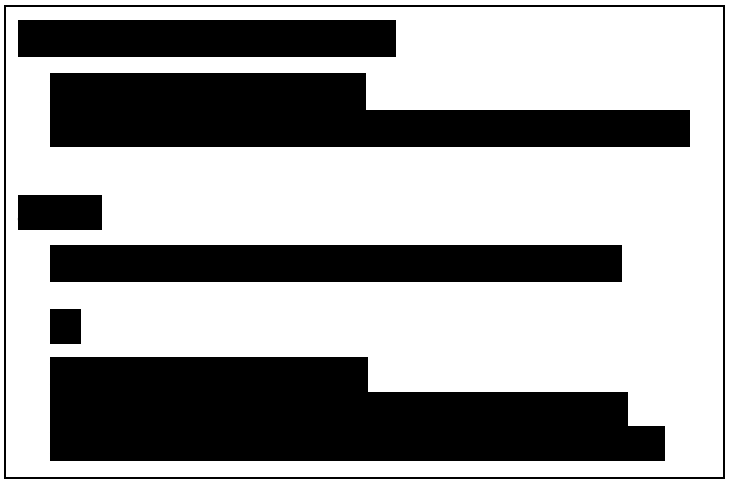
All AEs, whether non-serious or serious, must be recorded on the AE page of the eCRF. In addition, any AE that is initially considered serious or becomes serious must be reported on the SAE form. The SAE information entered on the eCRF must be consistent with the information entered on the SAE form.

7.9.5.1 Reporting of Serious Adverse Events

SAEs require expeditious handling to comply with regulatory requirements. **Any SAE occurring in a clinical study and follow-up must be reported to the Sponsor or designee within 24 hours of the Investigator having knowledge of the SAE.**

The Investigator or other qualified individual at the investigative site must complete the SAE form, sign it, and fax or e-mail it to the Sponsor or designee. If the Investigator is unable to sign the form that is initially submitted within 24 hours, the form must be resubmitted with signature within 72 hours. All telephone communication regarding an SAE must be followed by a written report.

Serious Adverse Event Contacts



The Investigator will ensure that information reported immediately by telephone or other means and information entered on the SAE report form are accurate and consistent. For all SAEs, the Investigator is obligated to pursue and provide information as requested by the Sponsor in addition to that requested on the SAE report form. Information must include a description of the AE in sufficient detail to allow for a complete, independent medical assessment of the case and independent determination of causality. Supporting documentation such as hospital discharge summaries or pertinent laboratory reports should also be sent to the Sponsor. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor.

Within 7 days of being aware of the SAE, the Principal Investigator will submit a detailed written report using the SAE report form (Detailed Report) to the Sponsor. For Japan sites only, the SAE report form must also be submitted to the director of the investigative site. Serious, unexpected drug-related AEs should be identified when reporting to the director of the investigative site.

7.9.5.2 Notification of Serious Adverse Events to Institutional Review Board or Ethics Committee

The Investigator must comply with the applicable regulatory requirements related to the reporting of SAEs and the Sponsor's safety information to the IRB/IEC as per standard operating procedures.

The Investigator will provide additional information upon request from the Sponsor, IRB/IEC, and where applicable, the director of the investigative site in Japan.

The investigative site will consult with the IRB/IEC and Sponsor whether to continue the subject in the study. For Japan only, the director of the investigative site will consult with the IRB/IEC whether to continue the study at the site.

7.9.6 Definition of Treatment-Emergent Adverse Events

A treatment-emergent adverse event (TEAE) is herein defined as any untoward medical occurrence in a subject who received an IP (KHK4083 or placebo). A TEAE can therefore be any unfavorable or unintended signs (including any abnormal laboratory findings), symptoms, or disease that occurred after treatment with the IP, whether or not considered related to the IP.

A TEAE of which causal relationship to IP is assessed as “related” or “unknown” is defined as a drug-related TEAE.

Results of laboratory tests will be checked against the normal range for any deviations (abnormal test results) and any abnormal test results will be compared with those obtained prior to treatment with the IP to determine whether such a change is clinically significant (abnormal change).

Any abnormal changes in signs, symptoms, and laboratory data associated with a disease (diagnosis) are regarded as an AE whose name is consistent with the diagnosis. If an injection reaction occurs, the presenting signs or symptoms of the reaction will be regarded as TEAEs (Section 7.9.8.1). Any individual atypical or extremely severe signs or symptoms of the disease will be regarded as independent AEs, separately from the diagnosis.

7.9.7 Definition of Other Significant Treatment-Emergent Adverse Events

Other significant TEAEs are defined as any non-serious TEAEs that lead to interruption or discontinuation of IP.

7.9.8 Other Significant Treatment-Emergent Adverse Events Requiring Special Handling

7.9.8.1 Reporting of Injection-related Reactions

The signs and symptoms of an injection reaction usually develop shortly after drug injection and generally resolved completely within 24 hours of completion of the injection. **The**

presenting sign or symptom should be reported as TEAE term(s). Acute injection reactions should not be classified as anaphylaxis unless symptomatic bronchospasm and/or allergy-related edema/angioedema is/are the principal clinical manifestation(s). Refer to Appendix 7 for the clinical criteria for diagnosis of anaphylaxis.

The time of onset of the injection reaction or injection site reaction and the time of outcome identification should be entered into the eCRF.

7.9.8.2 Overdose

Overdoses should be reported, whether or not the overdose was associated with an AE/SAE, using an SAE form within 24 hours of the Investigator having knowledge of the error. Follow the SAE reporting instructions in Section 7.9.5.1.

7.9.8.3 Pregnancy Reporting

Pregnancy in a female subject or partner of a male subject must be avoided.

When a female study subject reports a pregnancy: The subject must be advised by the Investigator immediately if she suspects she may be pregnant. The Investigator is obligated to immediately report to the Sponsor or designee any pregnancy occurring at any time after the subject signs the Informed Consent Form (ICF) and within 6 months after the last dose of IP.

When a male study subject reports a pregnancy of a female partner: The subject must be advised by the Investigator immediately if he suspects his partner became pregnant after the subject received IP. The Investigator is obligated to immediately report to the Sponsor or designee any pregnancy occurring at any time after the start of IP administration and within 6 months after the last dose of IP.

When a female study subject reports a pregnancy (or a male study subject reports a pregnancy of a female partner), IP administration should be stopped immediately for the female subject and a pregnancy test should be arranged for the female subject/female partner by the Investigator within seven (7) days of the pregnancy being reported. In the case of pregnancy, the Investigator must immediately notify the Sponsor of this event and report the pregnancy on the Pregnancy Surveillance Form. This includes a study subject as well as the partner of a study subject who becomes pregnant while the subject was receiving IP. If a partner of a male subject becomes pregnant, voluntary written informed consent (a separate ICF will be provided) should be obtained from the partner before conducting necessary

follow-up. Every attempt will be made to follow the pregnancy to conclusion to obtain information regarding the outcome.

7.9.9 Other Handling

Safety data will be summarized and reported as required by regulatory authorities.

8 DATA MANAGEMENT

8.1 Source Documents (Source Data)

Subjects' data are obtained from source documents, where data are first recorded. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarized into the eCRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the subject will be referred to by the subject ID, not by name.

8.2 Access to Data

By signing this protocol, the Principal Investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Personal Information Protection Law, the Health Insurance Portability and Accountability Act (HIPAA), the General Data Protection Regulation (GDPR), and their implementing regulations. During the Sponsor's monitoring and auditing, the IRB/IEC's review, and inspections by domestic and foreign regulatory authorities, the Investigator and the investigative site should allow them direct access to (and copying of, if required) all study-related records including source documents.

8.3 Electronic Case Report Forms (eCRFs)

An electronic data capture (EDC) system will be used for collecting data in this study. The EDC system allows each investigative site to enter data in the eCRF, check the input data, and respond to the Sponsor's inquiries on the input data, as well as to append electronic signatures. The entered data will be encrypted and transferred to the EDC server via the Internet. This EDC system is designed to meet requirements and guidelines of regulatory

agencies (Food and Drug Administration [FDA], Code of Federal Regulations [CFR], Title 21, ICH GCP, European Medicines Agency [EMA] and Ministry of Health, Labour and Welfare [MHLW]).

The Principal Investigator will fill out an eCRF for each subject and, after ascertaining that all data are accurate and complete, append his/her electronic signature through the EDC system. If an eCRF is filled out by a sub-Investigator or clinical research coordinator, the Principal Investigator will check the accuracy and completeness of data prior to appending his/her electronic signature. The Guide for Changes or Corrections to an Electronic Case Report Form, which will be supplied by the Sponsor, must be followed to fill out the eCRF.

In this study, the subject data stored in the EDC server will be regarded as the original eCRF. In this regard, however, once the eCRF data are relocated to a non-rewritable medium (e.g., DVD), or to the electronic document control system, the data in such medium/system will be handled as the original. Data should be migrated to the electronic document control system according to prespecified written procedures.

The Sponsor will provide a copy of eCRFs and change or correction histories to each investigative site.

By signing this protocol, the Principal Investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations. In addition for the investigative sites in the United States, compliance is required with all applicable provisions of the HIPAA and its implementing regulations.

The Principal Investigator, sub-Investigator, or clinical research coordinator will change or correct entries in the eCRF according to the Guide for Changes or Corrections to an Electronic Case Report Form provided by the Sponsor. The change or correction history to the eCRF is automatically recorded on the EDC system.

8.4 Data Collection Using eCOA System

An eCOA system will be used to collect data on EASI, IGA, BSA, SCORAD, pruritus NRS, sleep disturbance NRS, DLQI, and record of emollient use in this study. Since data collected by eCOA system will be regard as source data, paper instruments will not be used and will not be available as source documents.

The eCOA system consists of an eCOA device and an eCOA server.

The eCOA device, which will be used by subjects and Investigator, provides functions such as entering data, checking entered data, and obtaining audit trails on entered data. Data that are entered are transferred to and saved on the eCOA server. In addition, the investigative sites and the Sponsor are allowed to access data through the eCOA system on the eCOA server.

The eCOA device will be provided to each investigative site. The Investigator will complete EASI, IGA, BSA and SCORAD (A and B) data on the eCOA device at each visit. Subjects will complete pruritus NRS, sleep disturbance NRS, SCORAD (C), and DLQI data and record emollient use on the eCOA device at each visit. Written procedures provided by the Sponsor will be followed for data entry into the eCOA system. Data cannot be changed or corrected by subjects once they are saved on the eCOA device or the eCOA server.

If any change or correction is required for data saved on the eCOA server, the Principal Investigator, sub-Investigator, or clinical research coordinator will change or correct the relevant data according to written procedures provided by the Sponsor. Histories of changes or corrections on the eCOA system will be obtained by the system.

If the eCOA is filled out by a sub-Investigator, the Principal Investigator have to check the accuracy and completeness.

Since the eCOA system uses the device, data (including audit trails) saved on the eCOA device will be regarded as source data from data entry into the device until data transfer to the eCOA system, and data on the eCOA server will be regarded as source data after data transfer to the eCOA system. If data (including audit trails) on the eCOA server are migrated to a non-rewritable medium (e.g., CD-R, DVD-R), data on the medium will be regarded as source data and provided to the investigative site. The Sponsor will retain a copy of the source data.

8.4.1 Other Instructions Related to Creation of eCOA

The following data obtained until Week 16 from subjects who have completed the Week 16 assessment should be immediately entered into the eCOA. The data entered must be reviewed by the Sponsor and the CRO by the day before Week 18.

- EASI score
- SCORAD score
- IGA score
- BSA

- Pruritus NRS
- Sleep disturbance NRS
- DLQI score

8.5 Record Keeping and Archiving

The investigative site and the Sponsor will retain the clinical trial master file and medical files of subjects for at least 25 years after the end of the study. If the investigative site's situation is such that retaining can no longer be ensured, the investigative site must inform the Sponsor and the relevant records will be transferred to mutually agreed-upon destination.

8.6 Study Monitoring

The monitor will check and ensure that the study has been conducted in compliance with the ICH E6-GCP, the protocol, applicable local regulations, and written procedures for this study and that the entries of eCRF coincide with the source data. Detailed procedures will be given in a monitoring plan document or alternative written procedures.

9 STATISTICAL ANALYSIS

9.1 Statistical Methods

Subjects will be summarized according to randomized treatment group. Subjects in the placebo group will be summarized as a treatment group of 'Placebo in Treatment A period and 600 mg Q2W in Treatment B period' and never combined with 600 mg Q2W group.

Unless otherwise specified, categorical data will be summarized with frequency and percentage. Continuous variables will be summarized with descriptive statistics including number of subjects, mean, standard deviation, minimum, median, and maximum. In addition to these descriptive statistics for PK parameters, coefficient of variation and geometric mean will also be calculated.

9.1.1 Primary Efficacy Analysis

Percent Change from Baseline to Week 16 in EASI Score

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

The percent change from baseline is defined as below,

Percent change from baseline (%) = 100 × (Post-dosing value − Value at baseline) / Value at baseline.

The adjusted mean (least squares [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. The test will be performed in sequence, starting with 600 mg Q2W vs. placebo and continue in the order of 300 mg Q2W vs. placebo, 600 mg Q4W vs. placebo, and 150 mg Q4W vs. placebo, from the highest dose to lowest dose until statistical significance at 5% is not achieved.

9.1.2 Secondary Efficacy Analyses

9.1.2.1 Efficacy Endpoints at Week 16

Continuous endpoints will be analyzed by ANCOVA model with treatment, the relevant baseline value and the stratification factors. The LS mean and the corresponding 95% confidence interval will be calculated from the ANCOVA model for each treatment group. The difference between the placebo group and each KHK4083 group and the corresponding 95% confidence intervals will also be calculated.

Categorical endpoints will be summarized by treatment group by number and percentage of subjects achieving the endpoint and their exact 95% confidence intervals. The difference

between the placebo group and each KHK4083 group and the corresponding 95% confidence intervals will also be calculated. The following secondary endpoints will be analyzed:

- Achievement of 50%, 75%, or 90% reduction from baseline in EASI score (EASI-50, EASI-75, or EASI-90) at Week 16
- Change from baseline to Week 16 in EASI score
- Change and percent change from baseline to Week 16 in SCORAD score
- Achievement of an IGA score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16
- Change from baseline to Week 16 in percent BSA
- Change and percent change from baseline to Week 16 in pruritus NRS score
- Change and percent change from baseline to Week 16 in sleep disturbance NRS score
- Change from baseline to Week 16 in DLQI

9.1.2.2 Efficacy Endpoints at Each Time Point

The following endpoints will be analyzed at each time point (scheduled visit until Week 56) by treatment group:

- Percent change from baseline in EASI score at each time point
- Achievement of EASI-50, EASI-75, or EASI-90 at each time point
- Change and percent change from baseline in SCORAD score at each time point
- Achievement of an IGA score of 0 or 1 and a reduction from baseline of ≥2 points at each time point
- Change from baseline in percent BSA at each time point
- Change and percent change from baseline in pruritus NRS score at each time point
- Change and percent change from baseline sleep disturbance NRS score at each time point
- Change from baseline in DLQI at each time point

9.1.3 Safety Analyses

TEAEs will be summarized for Treatment A period and the whole study period. For the placebo group, TEAEs that occur after the start of administration of KHK4083 will be presented along with TEAEs that occur after the start of administration of IP in the whole study period.

As for safety assessments other than TEAEs, they will be presented for each treatment group.

9.1.3.1 Adverse Events

All TEAEs will be summarized for each treatment group. The incidence of TEAEs will be summarized by frequency and percentage using MedDRA, by SOC and Preferred Term (PT). Multiple occurrences of TEAEs of the same term and classification in the same subject will be counted only once. The latest version of MedDRA at the time of database lock will be used for coding TEAEs.

9.1.3.2 Laboratory Values

Laboratory test values will be listed. Descriptive statistics of continuous variables at each time point (scheduled visit until Week 56) will be presented by treatment group. Categorical variables before and after administration will be presented in a shift table.

9.1.3.3 Vital Signs

Vital sign data will be listed. Descriptive statistics of continuous variables at each time point (scheduled visit until Week 56) will be presented by treatment group.

9.1.3.4 Standard 12-lead Electrocardiogram

Standard 12-lead ECG data will be listed.

9.1.4 Exploratory Analyses

9.1.4.1 Pharmacokinetics

The following analyses will be conducted in the PK analysis set.

9.1.4.1.1 Serum KHK4083 Concentration

The descriptive statistics of serum KHK4083 concentrations at each blood sampling point will be presented by treatment group. Plots of serum KHK4083 concentration-time profiles will be prepared.

9.1.4.1.2 Pharmacokinetics Parameters Calculated from Serum KHK4083 Concentrations

PK parameters (e.g., C_{max}, C_{trough}) will be calculated from serum KHK4083 concentrations for 4 treatment groups (KHK4083 150 mg Q4W, 300 mg Q2W, 600 mg Q2W, or 600 mg Q4W)

and will be presented by treatment group. For the Q2W treatment groups (KHK4083 300 mg Q2W and 600 mg Q2W), the C_{max} will be calculated only after administration of KHK4083 on Week 1 and Week 14. Following a single SC administration of KHK4083, the mean t_{max} was approximately 1 week (5.2 day, 7.0 day: minimum, maximum) in Study 4083-001 and Study 4083-003 (preliminary unaudited data), thus the C_{max} for Week 1 and Week 14 administrations will be defined as observed KHK4083 concentration at Week 1 (Day 8) and Week 15 (Day 106) within the acceptable ranges (±3 days), respectively. The C_{trough} will be defined as the observed KHK4083 concentrations at Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 32, and 36. Accumulation ratio based on C_{max} and C_{trough} will be calculated using each PK parameters in Week 1 and Week 14 administrations. For the Q4W treatment groups (KHK4083 150 mg Q4W and 600 mg Q4W), the C_{max} for Week 1 and Week 14 administrations will be defined as observed maximum KHK4083 concentration after administration. The C_{trough} will be defined as the observed KHK4083 concentrations at Weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36.

9.1.4.1.3 Anti-KHK4083 Antibody

All anti-KHK4083 antibody test values will be listed for each subject.

9.1.4.2 Pharmacodynamics

Pharmacodynamic analysis will be conducted using safety analysis set.

9.1.4.2.1 Serum Disease Markers

Changes in TARC and serum total IgE over time will be presented in a graph. The descriptive statistics of TARC and serum total IgE at each blood sampling point will be presented by treatment group.

9.1.4.3 Other Testing

9.1.4.3.1 Serum IL-22

Changes in serum IL-22 over time will be presented in a graph. The descriptive statistics of serum IL-22 at each blood sampling point will be presented by treatment group.

9.2 Target Number of Subjects

A total of approximately 250 subjects will be randomly assigned in a 1:1:1:1:1 ratio to 4 active treatment groups (50 subjects in each group) or one placebo group (50 subjects) in Treatment A period.

9.2.1 Rationale for Target Number of Subjects

[redacted]

9.3 Significance Level

The significance level for the primary efficacy endpoint will be 5% (two-sided). The statistical test for the primary efficacy endpoint will be conducted only at the first interim analysis as the final result. A closed test procedure will be used to maintain overall type I error rate.

9.4 Early Termination Criteria

No criteria for early termination of the study based on statistical evidence will be specified.

9.5 Handling of Missing, Unused, and Abnormal Data

Any efficacy data obtained after prohibited concomitant medications and therapies will be deemed as missing.

Any missing data of the primary endpoint and other continuous endpoints at Week 16 will be imputed by the LOCF method. For dropout subjects (including subjects who receive rescue treatment), data at the last assessment point will be defined as data obtained prior to dropout or receiving rescue treatment, while Week 16 data will be used for all other subjects. Subjects with any missing data of categorical endpoints at Week 16 will be counted as non-responder. Sensitivity analysis such as complete case analysis and multiple imputation will be performed to assess the robustness of primary endpoint analysis results.

If it is necessary to discuss how to handle data of a particular subject because of an event unexpected at study initiation, handling of such data to be used in the interim analysis (Section 9.8) should be decided before database is frozen (The "Freeze" status in EDC will be used) and the other data handling should be decided before database lock.

9.6 Development of Statistical Analysis Plan and Procedure for Reporting Deviations from the Original Statistical Analysis Plan

Details of the final analysis plan should be established in a statistical analysis plan that will be finalized before the database is frozen for the primary analysis. Major changes to the analysis plan will be described in the clinical study report.

9.7 Selection of Subjects to be Included in Analyses

The following populations are defined as analysis sets. Subjects included in the full analysis set (FAS) should be determined before the primary analysis and those include in other analysis sets should be determined before database lock.

9.7.1 Full Analysis Set (FAS)

The primary analysis set for the efficacy endpoints will be the FAS. The FAS is defined as a population of randomized subjects excluding those who meet either of the following conditions:

- Subjects who are not exposed to IP
- Subjects without any evaluable EASI score after the start of IP administration until Week 16

9.7.2 Per Protocol Set (PPS)

The per protocol set (PPS) will consist of all the FAS subjects excluding those who meet either of the following conditions. This analysis set has been selected to confirm the robustness of the result in the primary analysis.

- Subjects who failed to meet any major eligibility criteria
- Subjects with a major deviation from the protocol that may affect the primary endpoint

9.7.3 Safety Analysis Set

The safety analysis set is defined as a population of randomized subjects excluding those who meet the following condition. Analysis will be conducted according to the randomized treatment received by subjects.

- Subjects who are not exposed to IP

9.7.4 Pharmacokinetic Analysis Set

The PK analysis set is defined as a population of subjects excluding those who meet either of the following conditions:

- Subjects who are not exposed to KHK4083

- Subjects who do not undergo PK blood sampling at all after the administration of KHK4083

9.8 Interim Analysis

Interim analyses will be conducted at two time points: when all subjects (excluding early withdrawn subjects) have reached Week 16 and Week 36. All data for the interim analysis 1 should be frozen (The "Freeze" status in EDC will be used). However, only frozen efficacy data and SDVed safety data will be included in the interim analysis 2 (The "Verified" status in EDC will be used). The primary analysis will be performed in the FAS. The purpose of each interim analysis is as described below.

- **Interim analysis 1**, Week 16: To confirm a clinically significant difference in efficacy between KHK4083 and placebo and to obtain preliminary information for planning a future study.
- **Interim analysis 2**, Week 36: To obtain preliminary safety and efficacy information of KHK4083 for planning a future study.

The interim analysis 1 will be conducted for efficacy endpoints with the FAS after the database is frozen. The interim analysis 2 will be conducted for efficacy and safety (also including study withdrawal, demography). The cutoff date will be the date when the data is provided for the analysis after all subjects (excluding early withdrawn subjects) have reached Week 36 visit. However, only efficacy data that have been frozen as of the cutoff date and safety data that have been SDVed as of the cutoff date will be included in the interim analysis 2. The efficacy and safety analyses of the interim analysis 2 will be conducted with the FAS and the safety analysis set, respectively. These analyses will be performed for only pre-specified efficacy and safety analyses by a separate group which is different from the group for final analysis to maintain the blind at the subject level until final database lock. This group will share with the Sponsor only the summarized results (tables or figures) but not individual data listings. Further details of the interim analyses will be described in the statistical analysis plan that will be finalized before the database is frozen for the primary analysis conducted at the interim analysis 1. In addition, these interim analyses will be conducted for pre-specified exploratory endpoints, serum IL-22, and exploratory biomarkers with existing data at the time of interim analysis.

10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Compliance with GCP, the Protocol, and Other Applicable Regulatory Requirements

The Principal Investigator and sub-Investigator are responsible for conducting the study in full accordance with US FDA CFR21, Parts 50, 56, and 312, 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 Principal Investigator and sub-Investigator will comply with the protocol on which the Principal Investigator and the Sponsor have agreed and which has been approved in writing by the IRB/IEC.

If the IRB/IEC approves the collection, storage, and use of biological samples, a research protocol will be developed, and the research will be conducted in compliance with ethical principles based on the Declaration of Helsinki, any applicable laws and regulations in each country and related notifications, the protocol for this study, and the research protocol.

10.2 Institutional Review

Before starting this study, the protocol (authorized by the Sponsor) will be submitted to the regulatory/local health authorities (in accordance with local regulations) in the countries involved in the study and to the IRB/IEC for evaluation. The protocol will also be signed by the Principal Investigator before submission to the IRB/IEC. The study will not start before the IRB/IEC gives written approval or a favorable opinion in accordance with ICH E6-GCP and all applicable regulatory/local health authorities give approval or a favorable opinion as required.

When the Sponsor amends the protocol, the Sponsor will fully inform each Investigator using the amended version of the protocol or a written description of the amendment to obtain his/her agreement. The Principal Investigator will conduct the study according to the amended protocol after receiving the written approval of the IRB/IEC based on its prior review. Protocol amendments should be submitted to the IRB/IEC without delay. Any significant deviation from the protocol when no approved amendment exists will be regarded as a protocol violation, and will be addressed as such during the reporting of the study. However, this does not apply to amendments that only involve administrative issues (e.g., changes in affiliation, job title, address, or telephone number).

At least once a year or upon request, the site must submit a brief summary of the study progress to the IRB/IEC in accordance with local regulations.

10.3 Deviations from or Changes to the Protocol

The Investigator must not deviate from or change the protocol without obtaining the Sponsor's prior written agreement and the IRB/IEC's written approval based on its prior review. In the event of a deviation from or change to the protocol, the Investigator will make a record of all of the relevant actions regardless of the reason.

For medical reasons such as the need to eliminate immediate hazards to the subjects, the Investigator may deviate from or change the protocol without the Sponsor's prior written agreement or the IRB/IEC's prior written approval. In such a case, a document describing the nature of and the reason for the deviation or change should be submitted to the Sponsor. The site will also submit the document to the IRB/IEC for its approval, and in addition, will obtain the written approval from the Sponsor. For Japan sites only, written approval must also be obtained from the director of the investigative site.

10.4 Investigator's Responsibilities

10.4.1 Selection of Subjects to be enrolled in the Study and Assurance of Their Safety

In order to protect the human rights of all subjects, the Investigator must carefully examine the eligibility of each subject. For example, individuals who may be put at a disadvantage in case of refusal to participate (socially vulnerable people) should not be coerced into participating in the study.

The Investigator will determine whether each subject is eligible for enrollment according to the inclusion and exclusion criteria to ensure that the study will not include any subjects whose safety cannot be secured.

Throughout the study, the Investigator will keep track of the subject's condition by ensuring emergency contact or any other method, and will collect and share information that may be relevant to the safety of IP. If a TEAE occurs, the Investigator will ensure the safety of the subject by taking such measures as providing appropriate treatment to the subject and discontinuing IP administration, if necessary.

10.4.2 Protection of Subjects' Personal Information and Privacy

In filling out the eCRF, the Investigator will identify each subject with his/her subject ID to ensure that the subject's personal information is protected.

No individual who belongs to the Sponsor's units involved in the study may disclose, without a valid reason, confidential information on a subject to which he/she has access in the performance of his or her duties.

10.4.3 Subject Informed Consent

The Investigator will fully inform each subject before enrollment who is considered appropriate for the study about the description of the study based on Information for Subjects/ ICF as provided separately in a language understandable by the subject. The subject will be given sufficient time to decide whether or not to participate in the study, and the Investigator will obtain written consent (using the ICF provided separately) from the subject on a voluntary basis before the screening examinations.

After the subject signs and dates the ICF, the Investigator who has conducted the informed consent discussion will also sign and date it.

The Investigator will provide the subject with a copy of the signed ICF and the Information for Subjects. The Investigator will retain the original for the investigative site's record in accordance with the policy of each site.

Information for Subjects/ICF must contain the information specified by the local GCP guidelines and any applicable laws and regulations in the region.

When any new information that may influence the subject's willingness to continue participation in the study becomes available, the Investigator will promptly provide the subject with the updated information, confirm his/her willingness to continue the study, and document the details of the explanation given, the date of explanation, the name of person who confirmed the subject's decision, and the content of the subject's decision in medical records.

If the Information for Subjects/ICF needs revising in terms of the explanation given to the subject, the Principal Investigator will promptly revise it and obtain the IRB/IEC's approval. The Investigator will again give an explanation to the subject using the revised Information

for Subjects/ICF, and obtain written informed consent from the subject or his/her legally acceptable representative for further participation in the study in the same manner as in the case of the initial consent.

10.5 Audit and Inspection

The Sponsor or designee will verify, through monitoring and auditing, that the study, data generation, recording, and reporting are conducted in compliance with the protocol and ICH E6-GCP. According to ICH E6-GCP, the Sponsor or regulatory authorities may audit the investigative site. The Quality Assurance Unit of the Sponsor, independent of the Clinical Research and Development Department, is responsible for auditing the study.

The Principal Investigator must accept that domestic and foreign regulatory authorities may conduct an inspection to verify compliance of the study with GCP.

The management and quality assurance of data will be conducted according to the Sponsor's standard operating procedures for clinical studies and auditing.

10.5.1 Investigator Information

By agreeing to this protocol, the Principal Investigator recognizes that certain personal identifying information with respect to the Principal Investigator, and all sub-Investigators and study investigative site personnel, may be used and disclosed for study management purposes, as part of regulatory submissions, and as required by law. This information may include:

- name, address, telephone number, and email address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials;
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, affiliates, and agents of the Sponsor, in the country of the Investigator or other countries, including those that do not have laws protecting such information. Additionally, the Principal Investigator's name and business contact information may be included when reporting certain SAEs to regulatory agencies in the countries involved in the study or to other Principal Investigators. By agreeing to this protocol, the Principal Investigator expressly consents to these uses and disclosures.

In order to facilitate contact between Principal Investigators, the Sponsor may share a Principal Investigator's name and contact information with other participating Principal Investigators upon request.

10.5.2 Compliance with Law, Audit, and Debarment

By agreeing to this protocol, the Principal Investigator agrees to:

1) Conduct the study in an efficient and diligent manner and in compliance with this protocol, GCP, and all applicable regulatory requirements.
2) Complete, and/or update the FDA Form 1572 (or any other forms as equivalent) in a timely manner, and conduct the study in accordance with ICH GCP.
3) Allow monitoring, audits, IRB/IEC review, and inspection by domestic and foreign regulatory agencies of study-related documents and procedures; and provide for direct access to all study related source data and documents.
    - Promptly and fully disclose to the Sponsor, and make available all source documentation at their investigative site upon the request for inspection by representatives of the Sponsor, IRB/IEC, or any regulatory agencies.
    - Promptly inform the Sponsor of any regulatory agency inspection conducted for this study.
    - Promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.
4) Upon completion of the protocol-specified dosing and observation in all the subjects at an investigative site, the Investigator will promptly notify the IRB/IEC and the Sponsor of the completion of the study in writing in accordance with local procedures and any applicable laws and regulations.
5) For Japan sites only, upon completion of the protocol-specified dosing and observation of all the subjects at an investigative site, the Principal Investigator will report to the director of the investigative site on study-completion information and outline study results in writing.
6) Immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the Principal Investigator's knowledge, threatened. Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on the Sponsor's studies.
7) Provide to the Sponsor accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by US FDA regulations (CFR, Title 21, Part 54), and other financial regulatory agencies. The Principal Investigator further agrees to provide this information on a Financial

Disclosure/Certification Form that is provided. This requirement extends to sub-Investigators. This may involve the transmission of information to countries that do not have laws protecting personal data. Refer to Section 10.5.3 for additional details.

The ICH E6-GCP guidelines recommend that the Principal Investigator inform the subject's primary physician about the subject's participation in the study, if the subject has a primary physician and if the subject agrees to the primary physician being informed.

In the event the Sponsor prematurely terminates a particular investigative site, the Sponsor will promptly notify that investigative site's IRB/IEC.

10.5.3 Financial Disclosure

According to US FDA CFR, Title 21, Part 54, the Sponsor is required to completely and accurately disclose or certify information concerning the financial interests of an Investigator (or investigative site) who is not a full-time or part-time employee to the FDA. Therefore, the Principal Investigators and sub-Investigators (or investigative site) must provide the Sponsor with sufficient, accurate financial certification that none of the financial arrangements described in US FDA CFR, Title 21, Part 54.2 exist with the Sponsor or fully disclose the nature of the arrangement. This financial disclosure also applies to any financial arrangements that exist between the Sponsor and the Investigator's spouse(s) or dependent children.

10.6 Expenses Related to the Study

The details related to the expenses during the study treatment period for examinations and medical treatment such as administration or injection of pharmaceutical products with similar indications or therapeutic effects to those of IP are specified in the Clinical Trial Agreement.

In order to reduce the burden to subjects resulting from participation in the study, the Sponsor will bear the compensation/reimbursements for incurred expenses to the subjects through the relevant investigative site, in accordance with the applicable rules of each investigative site.

10.7 Compensation for Health Injury

In the event of any study-related disease or health injury in a subject, appropriate therapeutic measures will be taken in accordance with the clauses on compensation in the Information for Subjects/ICF or the Clinical Trial Agreement. An information leaflet containing essential

information about the compensation can be provided upon request of the subject (or attached to the ICF in Japan).

10.8 Publication Policy

The study is part of a multicenter study; accordingly, the investigative site and the Principal Investigator agree that the first publication of the results of the study shall be made in conjunction with the presentation of a joint, multicenter publication of the study results with the Principal Investigators and the investigative sites from all appropriate sites contributing data, analyses and comments. However, if such a multicenter publication is not submitted within 12 months after the database has been locked, abandonment or termination of the study at all sites, or after Sponsor confirms there will be no multicenter study publication, the investigative site and/or such Principal Investigator may publish the results from the institution site individually in accordance with the Sponsor's publication policy. Prior to submission of any materials for publication or presentation, the investigative site will provide such materials or manuscript to the Sponsor for review and approval. Details of the Sponsor's publication policy can be found in the Clinical Trial Agreement.

11 STUDY ADMINISTRATIVE STRUCTURE

11.1 Sponsor

[redacted]

11.2 Clinical Trial Manager (Sponsor Signatory)

[redacted]

[redacted]

11.3 Medical Monitor

[redacted]

[redacted]

[redacted]

Back-up Medical Monitor:

[redacted]

[redacted]

For further information on the study administrative structure, refer to other study documents and vendors' procedures that are provided separately.

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13 APPENDICES/ATTACHMENTS

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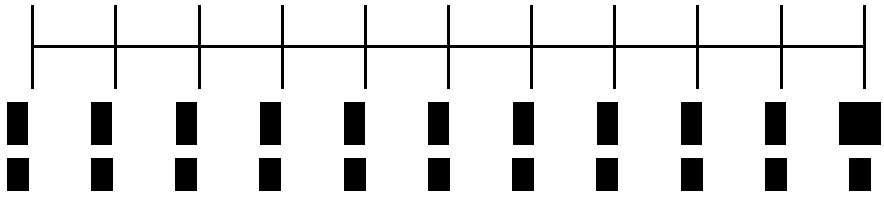

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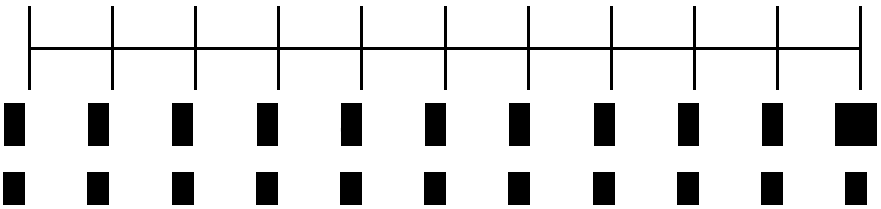

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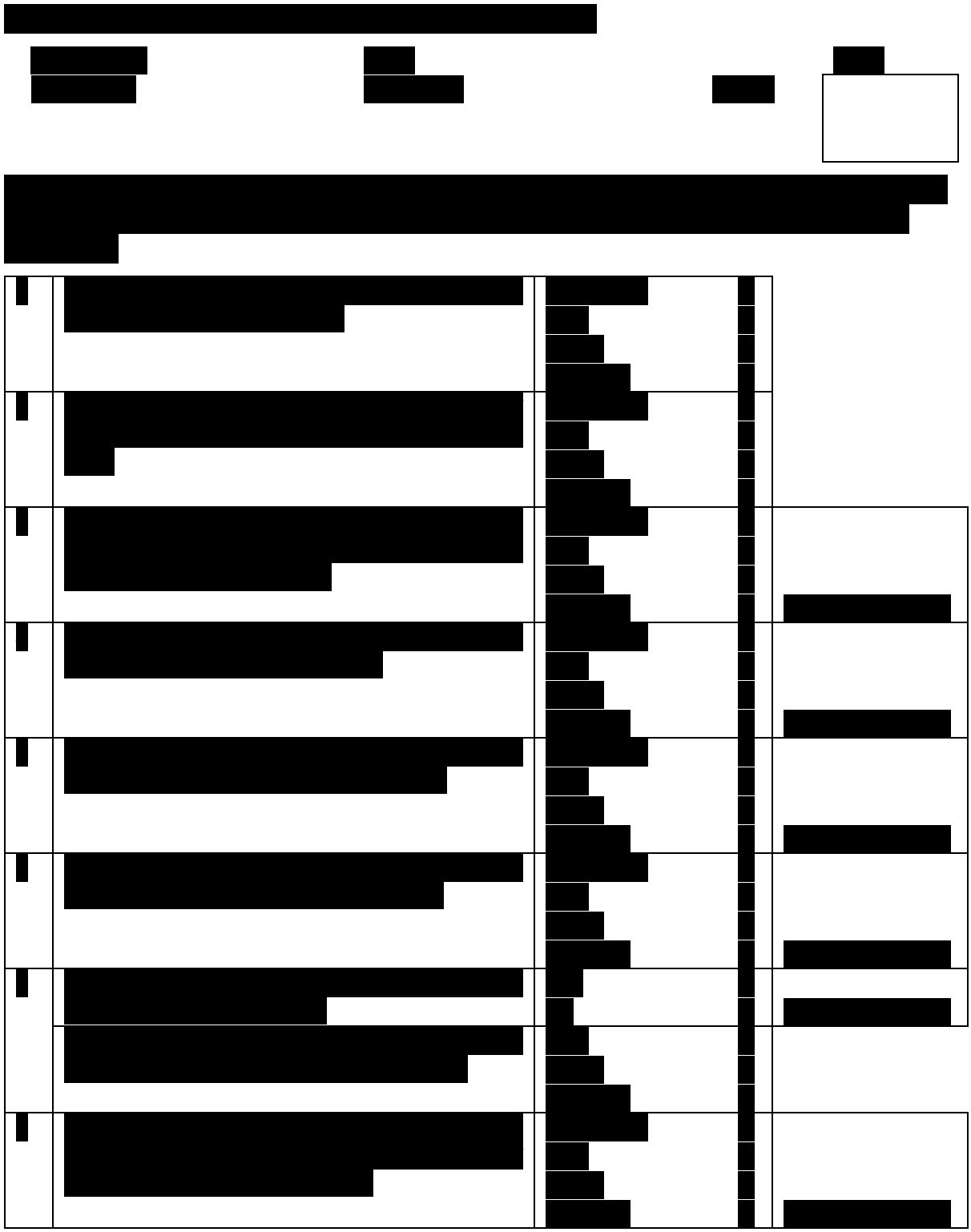

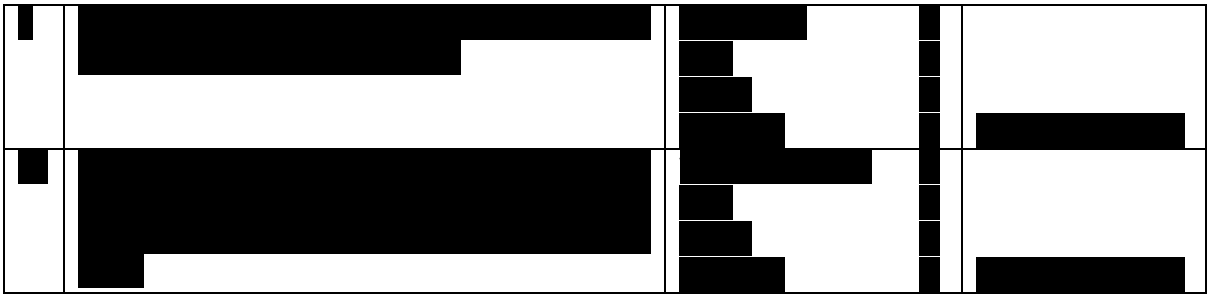

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