

**A Phase 3 Multicenter, Randomized,  
Double-blind, Placebo-controlled Study  
with an Open Label Extension to Evaluate  
the Efficacy and Safety of KHK4827 in  
Subjects with Axial Spondyloarthritis**

**Protocol**

**Sponsor: Kyowa Kirin Co., Ltd.**

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## [List of Abbreviations and Definitions of Terms]

### List of Abbreviations

Abbreviation	Expanded Form
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis international Society
ASDAS-CRP	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life Questionnaire
axSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
CMH	Cochran-Mantel-Haenszel
C-SSRS	Columbia-Suicide Severity Rating Scale
DMARDs	disease modifying antirheumatic drugs
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
ET	early termination
HLA-B27	human leukocyte antigen B27
IL	interleukin
IL-17R	interleukin-17 receptor
IL-17RA	interleukin-17 receptor A
IWRS	interactive web response system
MRI	magnetic resonance imaging
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
nr-axSpA	non-radiographic axial spondyloarthritis
NSAIDs	non-steroidal anti-inflammatory drug
PHQ-8	Patient Health Questionnaire-8 depression scale
PK	Pharmacokinetic(s)
PsA	psoriatic arthritis
Q2W	every 2 weeks
SC	subcutaneous
SF-36	Short Form Health Survey
SID	subject identifier
SpA	spondyloarthritis
PsO	psoriasis
SPARCC	Spondyloarthritis Research Consortium of Canada
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
ULN	upper limit of normal
WPAI	Work Productivity and Activity Impairment Questionnaire

## List of Definitions of Terms

Term	Definition
ASAS 20	ASAS 20 response is defined as an improvement of $\geq 20\%$ and absolute improvement of $\geq 1$ unit [on a 10-unit scale] in at least three of the four main ASAS domains (i.e. Patient Global Assessment (PGA) of axSpA, the average of total and nocturnal PGA of spinal pain, BASFI score, and the mean of BASDAI Q5 and Q6), with no worsening by $\geq 20\%$ and $\geq 1$ unit in the remaining domain.
ASAS 40	ASAS 40 response is defined as an improvement of $\geq 40\%$ and absolute improvement of $\geq 2$ units [on a 10-unit scale] in at least three of the four main ASAS domains (i.e. PGA of axSpA, the average of total and nocturnal PGA of spinal pain, BASFI score, and the mean of BASDAI Q5 and Q6) and no worsening at all in the remaining domain
AUC <sub>0-<math>\tau</math></sub>	area under the serum KHK4827 concentration-time curve up to the next dose
C <sub>max</sub>	maximum observed serum KHK4827 concentration
CTCAE v4.0	The Common Terminology Criteria for Adverse Events version 4.0
FAS	full analysis set
HBc antibody	hepatitis B core antibody
HBs antigen	hepatitis B virus surface antigen
HBs antibody	hepatitis B virus surface antibody
hCG	human chorionic gonadotropin
HCV antibody	hepatitis C virus antibody
HIV antigen/antibody	human immunodeficiency virus antigen/antibody
HTLV-1	human T-lymphotropic virus type-1 antibody
ICH	The international Council for Harmonization of Technical Requirements for Pharmaceuticals for human use
IRB	institutional review board
MedDRA	The ICH Medical Dictionary for Regulatory Activities
PPS	per protocol set
PT	MedDRA preferred term
SOC	MedDRA system organ class
t <sub>max</sub>	time to maximum observed serum KHK4827 concentration
Pharmaceutical and Medical Device Act	Japanese law to ensure the quality, efficacy, and safety of pharmaceuticals, quasi-drugs, cosmetics, and medical devices
Comparator	A drug or other substances that are used as a reference in a clinical study
Investigational product	Investigational drug and its comparator (for investigational use only)
Investigational drug	A drug that is tested in a clinical study
Investigators	investigator or subinvestigator
Drug-related treatment-emergent adverse event	Any treatment-emergent adverse event for which a causal relationship to the investigational product is assessed as “related” or “unknown.”

## List of Laboratory Parameters

Parameter	Abbreviation	Display Name on Case Report Form
White blood cell count	WBC	Leukocytes

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Red blood cell count	RBC	Erythrocytes
Hematocrit	Ht	Hematocrit
Hemoglobin concentration	Hb	Hemoglobin
Platelet count	PLT	Platelets
Basophils	basophils	Basophils/Leukocytes
Eosinophils	eosinophils	Eosinophils/Leukocytes
Neutrophils	neutrophils	Neutrophils/Leukocytes
Monocytes	monocytes	Monocytes/Leukocytes
Lymphocytes	lymphocytes	Lymphocytes/Leukocytes
Sodium	Na	Sodium
Potassium	K	Potassium
Chloride	Cl	Chloride
Total protein	TP	Protein
Albumin	ALB	Albumin
Calcium	Ca	Calcium
Magnesium	Mg	Magnesium
Phosphate	P	Phosphate
Blood glucose	Glu	Glucose
Blood urea nitrogen	BUN	Blood Urea Nitrogen
Creatinine	Cr	Creatinine
Uric acid	UA	Urate
Total bilirubin	T-Bil	Bilirubin
Direct bilirubin	D-Bil	Direct Bilirubin
Alkaline phosphatase	ALP	Alkaline Phosphatase
Aspartate aminotransferase	AST	Aspartate Aminotransferase
Alanine aminotransferase	ALT	Alanine Aminotransferase
HLA-B locus genotyping	HLA-B locus genotyping	HLA-B locus genotyping
C-reactive protein	CRP	C-reactive protein
Urine specific gravity	–	Specific Gravity
Urine pH	–	pH
Urine occult blood	–	Occult Blood
Urine protein	–	Protein
Urine glucose	–	Glucose
Urine bilirubin	–	Bilirubin
Urine urobilinogen	–	Urobilinogen
Urine ketone bodies	–	Ketone Bodies
Diastolic blood pressure	–	Diastolic Blood Pressure
Systolic blood pressure	–	Systolic Blood Pressure
Respiratory rate	–	Respiratory Rate
Body height	–	Height
Body temperature	–	Temperature
Body weight	–	Weight
Pulse rate	–	Pulse Rate

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### Study participation period

The study participation period for each subject in this study is defined as the period from the day of obtaining informed consent through the completion of the final examination stipulated by the protocol.

### Definition of day 1 (week 0) and week X

The date of first dose of the investigational product is defined as day 1 (the start date of investigational product administration). The Xth day from the start date of investigational product administration inclusive is regarded as day X. The day before the start of investigational product administration is defined as day -1. The week in which investigational product administration is started is defined as week 0. The week corresponding to X weeks after week 0 is regarded as week X.

## PROTOCOL SYNOPSIS

### I Title

A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled Study With an Open Label Extension to Evaluate the Efficacy and Safety of KHK4827 in Subjects With Axial Spondyloarthritis

### II Objectives

Primary Objective:

To evaluate the efficacy of KHK4827 in axSpA (ankylosing spondylitis [AS] and non-radiographic axial spondyloarthritis [nr-axSpA]) subjects compared to placebo, as measured by the proportion of axSpA subjects achieving an Assessment of SpondyloArthritis international Society (ASAS) 40 response at week 16.

Secondary Objectives:

- To evaluate the efficacy of KHK4827 in axSpA (AS and nr-axSpA) subjects on ASAS 20 at week 16
- To evaluate the efficacy of KHK4827 in AS subjects as measured by ASAS 40 at week 16
- To evaluate the efficacy of KHK4827 in nr-axSpA subjects as measured by ASAS 40 at week 16
- To evaluate the efficacy of KHK4827 in axSpA (AS and nr-axSpA) subjects on Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP) at week 16

Safety Objective:

- To assess the safety profile of KHK4827 in axSpA (AS and nr-axSpA) subjects

Pharmacokinetics Objective:

- To characterize the pharmacokinetics (PK) of KHK4827 in axSpA (AS and nr-axSpA) subjects

### III Study Phase

Phase 3

## IV Endpoints

### Primary Endpoint:

- ASAS 40 at week 16 in axSpA (AS and nr-axSpA) subjects

### Secondary Endpoints:

- ASAS 20 at week 16 in axSpA (AS and nr-axSpA) subjects
- ASAS 40 at week 16 in AS subjects
- ASAS 40 at week 16 in nr-axSpA subjects
- ASDAS-CRP change from baseline at week 16 in axSpA subjects

### Exploratory Endpoints:

- BASFI
- BASDAI
- Patient Global Assessment of Spine Pain and axSpA
- ASQoL
- SF-36v2
- WPAI
- Enthesitis
- BASMI
- Swollen joint count
- MRI substudy

### Safety Endpoints:

- Adverse events
- Anti-KHK4827 antibodies

### PK Endpoints:

- Serum KHK4827 concentration
- PK parameters ( $t_{\max}$ ,  $C_{\max}$ ,  $AUC_{0-\tau}$ ) of weeks 14 to 16 and weeks 30 to 32

## V Target Indication

Axial spondyloarthritis (axSpA)

## VI Inclusion Criteria

- 1) Personally submitted written voluntary informed consent to participate in the study (if a minor at the time of consent, written informed consent must be obtained from his or her legally acceptable representative as well)
- 2) Aged  $\geq 18$  years at the time of consent (the cut-off age depends on the local law)

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- 3) Subject with age at onset <45 years and continuous chronic back pain for  $\geq 3$  months fulfills the ASAS classification criteria of axial spondyloarthritis (with the exception of the Crohn's disease)
- AS subjects:* Subject has radiographic evidence of sacroiliitis grade  $\geq 2$  bilaterally or grade 3 to 4 unilaterally (image obtained within 6 months prior to the time of consent may be used; centrally read) and at least one of the SpA features specified in the ASAS classification criteria of axial spondyloarthritis (with the exception of Crohn's disease)
- OR
- nr-axSpA subjects:* Subject does not have radiographic evidence of sacroiliitis grade  $\geq 2$  bilaterally or grade 3 to 4 unilaterally (image obtained within 6 months prior to the time of consent may be used; centrally read)
- AND
- Subject meets either of the following criteria:
- Presence of inflammatory lesions of sacroiliac joint on MRI of Spondyloarthritis Research Consortium of Canada (SPARCC) level  $\geq 2$  (centrally read) and at least one of the SpA features specified in the ASAS classification criteria of axial spondyloarthritis (with the exception of Crohn's disease)
  - Positive test for HLA-B27\* and the presence of at least 2 of the SpA features specified in the ASAS classification criteria of axial spondyloarthritis (with the exception of Crohn's disease), one of which must be elevated CRP\*\* (> upper limit of normal [ULN])
- \* Previous positive test result or positive result at screening
- \*\* Limited to the elevation of centrally measured CRP that is attributable to axSpA.
- 4) Subject has Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score  $\geq 4$  at screening and enrollment
- 5) Subject has spinal pain score (BASDAI question #2)  $\geq 4$  at screening and enrollment
- 6) Subject has had adequate therapy with non-steroidal anti-inflammatory drugs (oral NSAIDs) for back pain for at least 3 months with inadequate treatment response before enrollment (however, subjects with contraindication or intolerance to oral NSAIDs may be enrolled even if the subject does not meet the above criterion).
- 7) For subjects receiving non-biologic DMARDs (methotrexate or sulfasalazine): the subject has received treatment for  $\geq 3$  months prior to initiation of investigational product, with a stable dose for  $\geq 4$  weeks prior to initiation of investigational product.
- 8) For subject receiving oral corticosteroids: the subject has received treatment for  $\geq 4$  weeks prior to initiation of investigational product.
- 9) No findings in chest X-ray (or chest computed tomography (CT) scan) suggestive of active tuberculosis, meeting any of the following criteria at screening:
- Negative QuantiFERON or T-spot test
  - "Borderline" or "invalid" result of QuantiFERON or T-spot test, and negative result in re-testing

- “Borderline” result in re-testing QuantiFERON or T-spot test, and taking anti-tuberculosis agents (isoniazid, as a general rule) on a regular basis since at least 3 weeks before the start of investigational product administration
- Positive result in QuantiFERON or T-spot test (including retest) or "invalid" result in re-testing QuantiFERON or T-spot test, but no findings in chest CT scan suggestive of active tuberculosis, and taking anti-tuberculosis agents (isoniazid, as a general rule) on a regular basis since at least 3 weeks before the start of investigational product administration

## VII Exclusion Criteria

- 1) Complete ankylosis (fusion) of the spine
- 2) Subject with active ongoing inflammatory diseases other than axSpA that might confound the evaluation of KHK4827 therapy, including reactive arthritis, spondyloarthritis associated with inflammatory bowel disease, SAPHO syndrome (pustulotic arthro-osteitis), fibromyalgia, ankylosing spinal hyperostosis, osteitis condensans ilii, spondylosis deformans, or osteoarthritis sacroiliac joint disease
- 3) Subject has a planned surgical intervention between enrollment and week 16
- 4) Subject has an active infection or history of infections as follows:
  - any active infection for which systemic anti-infectives were used within 4 weeks prior to the first investigational product administration
  - a serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to the first investigational product administration
  - recurrent or chronic infections or other active infection that, in the opinion of the investigators, might cause this study to be detrimental to the subject
- 5) Subject has any systemic disease (e.g., renal failure, heart failure, hypertension, liver disease, diabetes, anemia) considered by the investigators to be clinically significant and uncontrolled.
- 6) Subject has a known history of human immunodeficiency virus infection
- 7) Subject has positive result in any item of infection tests (hepatitis B surface [HBs] antigen, HBs antibody, hepatitis B core [HBc] antibody, hepatitis C virus [HCV] antibody, human immunodeficiency virus [HIV] antigen/antibody, or Human T-lymphotropic virus type 1 [HTLV-1] antibody) with the exception of the following cases:
  - Subjects negative for HBs antigen and positive for HBc antibody and/or HBs antibody, and with a hepatitis B virus DNA (HBV-DNA) level below the detection sensitivity (such subjects are required to undergo the HBV-DNA assay at 4-week intervals). 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.
- 8) Subject had myocardial infarction, unstable angina pectoris or stroke within the past 12 months prior to the first investigational product administration

- 9) Subject has any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma.
- 10) Subject has a history of malignancy within 5 years prior to enrollment EXCEPT treated and considered cured cutaneous basal or squamous cell carcinoma, in situ cervical cancer or in situ breast ductal carcinoma
- 11) Subject has any concurrent medical condition or electrocardiogram (ECG) abnormality that, in the opinion of the investigators, could cause this study to be detrimental to the subject.
- 12) Subject has a history of Crohn's disease
- 13) Subject has any of the following laboratory abnormalities at screening:
  - aspartate aminotransferase (AST) or alanine aminotransferase (ALT)  $> 2 \times$  the upper limit of normal (ULN)
  - serum direct bilirubin  $\geq 1.5$  mg/dL (25.7  $\mu$ mol/L)
  - white blood cell (WBC) count  $< 3000/\mu$ L
  - neutrophil count  $< 2000/\mu$ L
- 14) Subject has any other laboratory abnormality, which, in the opinion of the investigators, will prevent the subject from completing the study or will interfere with the interpretation of the study results
- 15) Subject has used DMARDs other than a stable dose of methotrexate or sulfasalazine, or has received live vaccine (s) within 4 weeks of the first dose of investigational product
- 16) Subject has used any narcotic analgesics (excluding tramadol) or medical marijuana within 1 week prior to enrollment
- 17) Subject has a prior history of  $>1$  anti-TNF therapy
- 18) Subject has used commercially available or investigational biologic therapies as follows:
  - anti-TNF therapy: within 4 weeks prior to investigational product initiation for etanercept, within 8 weeks for infliximab, and within 10 weeks for other anti-TNF agents (e.g., adalimumab, golimumab, certolizumab-pegol).
  - anti-IL-17 biologics (e.g., brodalumab, secukinumab, ixekizumab)
  - within 6 months prior to investigational product initiation for anti-IL-12/IL-23 biologic therapy (e.g., ustekinumab, briakinumab)
- 19) Subject has a history of treatment with any intraarticular/intramuscular corticosteroids or systemic corticosteroids (other than oral corticosteroids) within 4 weeks before the start of investigational product administration.
- 20) Subject has treated in a clinical study with an investigational product other than KHK4827 or with an unapproved medical device within 4 months before investigational product administration in this study
- 21) Subject has planned participation in another clinical study during this study.
- 22) Subject has known sensitivity to any of the products or components to be administered during dosing.

- 23) Subject is not likely to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.
- 24) Subject has a history or evidence of suicidal ideation (severity of 4 or 5) or any suicidal behavior based on an assessment with the Columbia-Suicide Severity Rating Scale (C-SSRS) at enrollment
- 25) Subject has a history or evidence of a psychiatric disorder, alcohol and/or substance abuse.
- 26) Subject has severe depression based on a total score of  $\geq 15$  on the Patient Health Questionnaire-8 (PHQ-8) at enrollment (note: subjects with a total score of 10 to 14 on the PHQ-8 should be referred to a mental health care professional).
- 27) Subject has a history or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigators would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.
- 28) Pregnant or lactating women or women who are willing to have a child within 8 weeks after the last dose of the investigational product.
- 29) Women of child-bearing potential (except for permanently sterilized, postmenopausal [defined as amenorrhea  $\geq 12$  consecutive months without an alternative medical cause] or anatomically not of childbearing potential) with a positive pregnancy test (assessed by a serum pregnancy test during screening and a urine pregnancy test at enrollment).
- 30) Women of child-bearing potential who do not agree to use effective contraception from the day of providing consent through 8 weeks after the last dose of investigational product. Fertile men who do not agree to use effective contraception from the day of first dose of investigational product through 8 weeks after the last dose of investigational product. Effective contraception is defined as using any two of the following methods: condom, oral contraceptives, intrauterine contraceptive device, and diaphragm, or practice true abstinence from sexual intercourse. The investigators will thoroughly explain the risks in pregnancy and the effective contraceptive methods to the subjects.
- 31) Anyone otherwise considered unsuitable for the study by the investigators

### **VIII Planned Number of Subjects**

A total of 120 subjects will be allocated to receive investigational product.

(AS subjects, 90; nr-axSpA subjects, 30)

### **IX Investigational Product**

Investigational Drug

Company code No.: KHK4827

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Non-proprietary name: brodalumab (INN), Brodalumab (genetical recombination) (JAN)

Strength and dosage form: A prefilled syringe (0.5 mL) containing 70 mg of KHK4827

A prefilled syringe (1.0 mL) containing 140 mg of KHK4827

#### Comparator

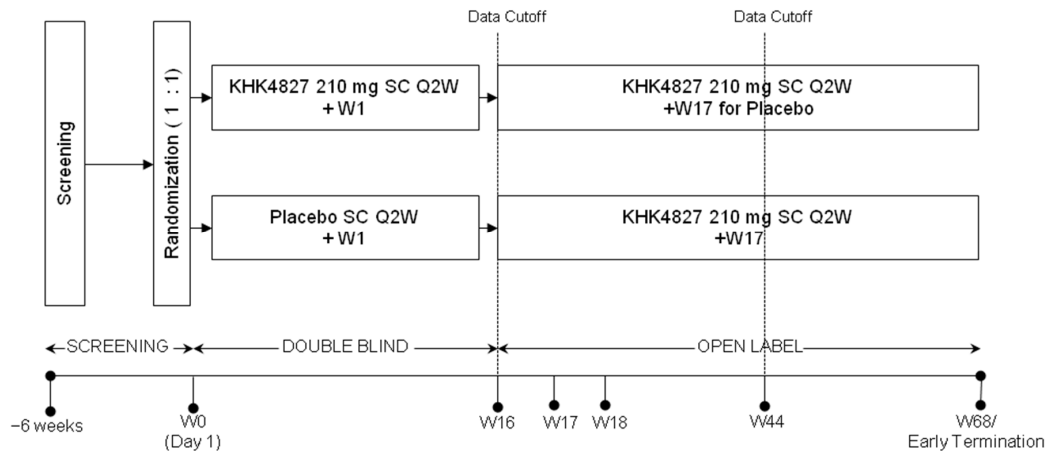
Placebo

Strength and dosage form: A prefilled syringe (0.5 mL) not containing KHK4827

A prefilled syringe (1.0 mL) not containing KHK4827

## X Study Design

The outline of the study design is shown below.



After a screening period from informed consent to enrollment (randomization) (for up to 6 weeks), there is a 16-week, randomized, double-blind, placebo-controlled phase, followed by an open-label extension treatment for 52 weeks. A total of 120 axSpA subjects will be randomized in a 1:1 ratio to subcutaneous (SC) doses of 210 mg KHK4827 or placebo every other week (Q2W) with 1 additional dose at week 1. Randomization will be stratified by CRP level at screening ( $\geq$  ULN and  $<$  ULN), informed consent for PK additional sampling (yes, no), region (Japan, Korea, Taiwan), and disease subpopulations (AS, nr-axSpA). In addition, the prior use of anti-TNF agent will be entered in IWRS. To allow evaluation of the efficacy and safety in subjects without any prior history of anti-TNF therapy, the number of enrolled subjects with prior history of anti-TNF therapy will be up to 60 (AS, 45; nr-axSpA, 15) and at least 50% of the study population will be subjects without any prior history of anti-TNF therapy. At the week 16 visit, all subjects will enter an open label extension and receive 210 mg KHK4827 Q2W for the remainder of the study (including an additional blinded dose at week 17).

The entire study will be 68 weeks in duration for each subject.

The study will also include two additional examinations (both of which are optional and will be conducted in subjects who provide separate informed consent):

- **PK additional sampling (optional):** Additional pharmacokinetic data will be collected from  $\geq 6$  axSpA subjects in each country, with samples at additional time points (Table 1).

**Table 1 Pharmacokinetic additional sampling: schedule**

Study Visit	Week 14 post 3 days*	Week 14 post 7 days*	Week 14 post 10 days*	Week 30 predose	Week 30 post 3 days*	Week 30 post 7 days*	Week 30 post 10 days*
Time window	±1 day	±1 day	±1 day	±3 days**	±1 day	±1 day	±1 day
Date of visit	X	X	X	X	X	X	X
PK additional sampling	X	X	X	X	X	X	X

\*To be counted from the date of dosing at week 14 or week 30.

\*\*Time window for the week 30 visit.

- **Ankylosing Spondylitis longitudinal MRI (optional):** Longitudinal spine MRI will be assessed in AS subjects who have signed separate informed consent. Only subjects with evidence of spinal inflammation on MRI at enrollment (MRI images obtained within 6 weeks before enrollment may be used instead) will be assessed in this optional study. An additional MRI will be obtained for these subjects at week 16 and week 68/early termination (ET). Image will be centrally read.

## XI Dosage, Administration, and Treatment Duration

Subjects will receive investigational product (210 mg KHK4827 or placebo) by SC injection from a prefilled syringe at day 1 (week 0), week 1, 2, then Q2W until week 14. After week 16, subjects will receive 210 mg KHK4827 through week 68. To maintain blindness, subjects who are assigned to the placebo group in the double-blind phase will receive an additional blinded dose of KHK4827 at week 17. Subjects who are assigned to the KHK4827 group in the double-blind phase will receive an additional blinded dose of placebo at week 17. Investigational product will be administered to the anterior upper abdomen, thigh or upper arm. At all visits up to and including week 32, doses of investigational product must be given with  $\pm 3$  days from the scheduled dose date. Starting at week 34, doses of investigational product must be given  $\pm 7$  days from the scheduled dose date.

## XII Planned Study Period

October 2016 to December 2019

After all subjects (except for those who early terminate from the study) complete their week 16 and week 44 visit, data will be cut off and efficacy and safety data until week 16 (or ET) and week 44 (or ET) will be evaluated respectively.

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## 1 INTRODUCTION

### 1.1 Background

Overproduction of cytokines contributes to the development of a number of inflammatory autoimmune diseases including psoriasis (PsO) and psoriatic arthritis (PsA). The Interleukin (IL)-17 family of cytokines is composed of 6 family members with the following nomenclature: IL-17A, IL-17B, IL-17C, IL-17D, IL-25 (also known as IL-17E), and IL-17F. IL-17A, IL-17F, and IL-17A/F heterodimer are hallmark proinflammatory cytokines produced by T helper cells producing IL-17 (Th17 cells) and innate immune cells and have been shown to contribute to an inflammatory response in models of autoimmune disorders (Cua DJ and Tato CM, 2010; Littman DR and Rudensky AY, 2010; Gaffen SL, 2009; Ouyang W et al, 2008; Langrish CL et al, 2005; Park H et al, 2005).

IL-17A, IL-17F, and IL-17A/F heterodimer have pleiotropic activities including the induction of proinflammatory mediators from epithelial cells, endothelial cells, and fibroblasts that promote tissue inflammation and destruction; the proliferation, maturation, and chemotaxis of neutrophils; and the maturation of dendritic cells (Kolls J and Lindén A, 2004; Antonysamy MA et al, 1999). IL-17C is also produced by epithelial cells and the biological activities of this cytokine are being explored but appear to be similar to the activities of IL-17A and IL-17F (Ramirez-Carrozzi V et al, 2011).

IL-17RA is a type I transmembrane receptor that is found on a wide variety of cell types including but not limited to fibroblasts, epithelial cells, and monocytes (Yao Z et al, 1997). IL-17A, IL-17F, IL-17A/F heterodimer, IL-17C, and IL-25 stimulate cellular signaling by binding to IL-17RA. IL-17A, IL-17F, and IL-17A/F heterodimer signal via a heteromeric IL-17RA/IL-17RC complex, IL-17C signals via a heteromeric IL-17RA/IL-17RE complex, and IL-25 signals via a heteromeric IL-17RA/IL-17RB complex (Ramirez-Carrozzi V et al, 2011; Song X et al, 2011; Rickel EA et al, 2008; Wright JF et al, 2008; Toy D et al, 2006).

IL-17RA blockade represents a novel mechanism to inhibit the inflammation and clinical symptoms associated with autoimmune and inflammatory diseases including but not limited to psoriasis and psoriatic arthritis.

### 1.2 KHK4827

KHK4827 (non-proprietary name: brodalumab) is a fully human monoclonal IgG2 antibody directed against human IL-17RA, which is produced in a Chinese hamster ovary (CHO) cell line and blocks the biological activities of IL-17A, IL-17C, IL-17F, IL-17A/F heterodimer, and IL-25.

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### 1.3 Spondyloarthritis

Spondyloarthritis (SpA) encompasses a group of inflammatory diseases with clinical features that include involvement of the axial skeleton (sacroiliac joints and spine), peripheral arthritis, enthesitis, dactylitis, acute anterior uveitis, associated PsO, or inflammatory bowel disease. Depending on the predominant clinical manifestations, SpA can be classified either as axial SpA (characterized by predominant involvement of the spine and/or sacroiliac joints) or as peripheral SpA (peripheral arthritis, enthesitis, and/or dactylitis). The presence of the human leukocyte antigen (HLA)-B27 is strongly associated with SpA. Axial SpA is characterized by chronic inflammatory back pain and can be separated into two groups based on clinical and radiological features. These groups of axial SpA include: i) Ankylosing spondylitis (AS), which requires radiographic evidence of disease; and ii) non-radiographic axial SpA (nr-axSpA), which requires the presence of sacroiliac inflammation as detected by magnetic resonance imaging (MRI) or the presence of HLA-B27 in combination with the presence of  $\geq 2$  features typical of SpA. As noted above, the diagnosis of AS requires evidence of sacroiliitis by standard radiography (i.e., x-ray), and typically radiographic confirmation of sacroiliitis becomes possible late in disease. The diagnostic category of nr-axSpA has recently been advocated in an attempt to identify patients early in disease to enable aggressive treatment and to avoid long-term morbidity.

AS is a chronic inflammatory disease that involves primarily the sacroiliac joints and the axial skeleton with frequent involvement of peripheral joints and joint insertions (entheses). Extra-articular manifestations of AS include acute anterior uveitis, PsO, inflammatory bowel disease, osteoporosis, vertebral fractures, and cardiovascular disease (Stolwijk C et al, 2014). The prevalence of AS has been estimated to be between 0.1% and 1.1% of the population, and it is more common in males (Braun J and Sieper J, 2007). Clinical manifestations usually begin in late adolescence or early adulthood and onset after age 45 is rare. Patients with AS experience diminished physical functioning. Longer disease duration, increasing age, and smoking are associated with greater decreases in function. Radiographic evidence of sacroiliitis is a hallmark of AS. Syndesmophytes (bony growths originating inside a ligament) with bridging of the intervertebral spaces may give the classic bamboo spine appearance and loss of spinal range of motion. Radiographic progression may take many years, making early definitive diagnosis difficult.

Recently newer imaging modalities including MRI have been more employed to detect sacroiliitis earlier in the disease course (Braun J and Sieper J, 2007; Sieper J et al, 2009). A novel diagnostic algorithm has been developed to facilitate earlier recognition of axSpA (Rudwaleit M et al, 2009), making it possible to identify axSpA patients with and without



radiographic sacroiliitis, using X-rays and MRI. A sizable subset of axial spondylitis patients without evidence of definite structural changes in the sacroiliac joints have been classified on radiographs as having non-radiographic axial SpA (nr-axSpA), and this diagnosis requires the presence of sacroiliac inflammation as detected by MRI or the presence of HLA-B27 in combination with the presence of features typical of spondyloarthritis (SpA). The rate of progression from nr-axSpA to AS has been reported to be 10% to 12% over 2 years (Poddubnyy D et al, 2011; McInnes IB et al, 2015) and 24.3% over 5 to 10 years (Sampaio-Barros PD et al, 2010). Thus, nr-axSpA in certain patients may represent a stage before progression to AS. In addition, since pathological conditions are generally similar in nr-axSpA and AS patients, except for the presence of radiographic findings, it has been proposed that nr-axSpA and AS should be considered as one disease, namely, axSpA (Deodhar A et al, 2016; Baraliakos X and Braun J, 2015). Nevertheless, despite evidence of similar burden on daily functions in AS and nr-axSpA patients, delays in the diagnosis of nr-axSpA can postpone administration of suitable treatment by several years.

The IL-17 ligands and cognate receptors have emerged as potential novel therapeutic targets for SpA, including PsA and AS. Multiple animal models of spondyloarthritis are associated with expansion of Th17 cells and expression of IL-17 (Glatigny S et al, 2011; Sherlock JP et al, 2012; DeLay ML et al, 2009). There is a striking increase in IL-17+ cells both in circulation (Shen H et al, 2009) and in inflamed target tissues (Appel H et al, 2011; Noordenbos T et al, 2012) in AS subjects. Finally, trials with anti-IL-17 agents, including KHK4827, have shown significant clinical efficacy in PsO and PsA (Papp KA et al, 2012; Mease PJ et al, 2014), the latter indication being closely related to AS. KHK4827 is approved for use in PsA in Japan. Recently, the anti-IL-17A antibody secukinumab (Cosentyx USPI, 2016) was approved for the indication of AS in Europe and the United States.

Although a long-term treatment with non-steroidal anti-inflammatory drugs (NSAIDs), currently recommended as first line drug, alleviates symptoms in many patients with AS, chronic NSAIDs use are known to have adverse gastrointestinal and possible cardiovascular effects. About half of the patients report insufficient control of symptoms with NSAIDs alone. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate and sulfasalazine have been utilized in AS, but results are disappointing. Other mechanisms of action have been studied in AS without meaningful clinical success, including antagonism of IL-6 signaling, B-cell depletion, and blockade of T-cell co-stimulatory signaling (Mease P, 2013). On the other hand, anti-tumor necrosis factor (TNF) agents have demonstrated meaningful efficacy for axial and peripheral joint inflammation. However, there remains a significant unmet need for drugs with novel mechanisms of action targeting the patients who do not respond to, lose their response to, or do not tolerate anti-TNF agents.

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#### 1.4 Data from Clinical Studies

To date, four Phase 2 clinical studies and eight Phase 3 clinical studies have been conducted in subjects with plaque psoriasis (psoriasis vulgaris and/or PsA) in and outside Japan. These studies include two Phase 2 double-blind comparative studies (Study 4827-002 [Japan] and Study 20090062 [overseas]); three Phase 3, placebo- or ustekinumab-controlled, double-blind comparative studies (Studies 20120102, 20120103, and 20120104 [overseas]); and the long-term extension studies 4827-003 (Japan) and 20090403 (overseas). Study 4827-004, a Phase 3 long-term administration study, was conducted in subjects with pustular psoriasis or psoriatic erythroderma. In addition, Study 4827-005 is ongoing in subjects who completed study treatment in Studies 4827-003 and 4827-004 in Japan. Clinical studies in subjects with PsA include the Phase 2 placebo-controlled, double-blind comparative study 20101227 and the Phase 3 placebo-controlled, double-blind comparative studies 20090406 and 20110144, all of which were conducted outside Japan.

In both Studies 20090062 and 4827-002, which were conducted in subjects with moderate to severe plaque psoriasis, percent improvement in PASI score at week 12 as the primary endpoint was significantly higher in the KHK4827 groups than in the placebo group ( $p < 0.001$ ). No fatal adverse events occurred, and no adverse events that occurred with a markedly higher incidence in the KHK4827 groups than in the placebo group were reported. The placebo-controlled, double-blind, comparative, washout/resumption study 20120102 and the placebo- and ustekinumab-controlled, double-blind comparative studies 20120103 and 20120104 were subsequently conducted in subjects with moderate to severe plaque psoriasis. In all of these studies, the percentage of PASI 75/100 responders at week 12 was higher in the KHK4827 groups than in the placebo group ( $p < 0.001$ ). In Studies 20120103 and 20120104, the percentage of PASI 75/100 responders at week 12 was significantly higher in the KHK4827 210 mg Q2W group than in the ustekinumab group ( $p < 0.001$ ). In addition, the results of Studies 4827-003 and 20090403 demonstrated the safety and efficacy of long-term administration of KHK4827. In Study 4827-004 in subjects with pustular psoriasis (generalized) or psoriatic erythroderma, KHK4827 provided early improvement in symptoms, as assessed by the Clinical Global Impression (remission, improved, no change, worsened) as the primary efficacy endpoint, and the effect was sustained up to week 52. The efficacy and safety of KHK4827 in these subjects were demonstrated. In Study 4827-005, no noteworthy events apart from available data from the previous studies have been reported.

Clinical studies in subjects with PsA conducted to date include Studies 4827-002, 4827-003, 20101227, 20090406, and 20110144. These studies demonstrated the efficacy of KHK4827 for joint symptoms in subjects with PsA. In Studies 20101227, 20090406, and 20110144, the

number and percentage of subjects achieving ACR 20, the primary endpoint, were significantly higher in the KHK4827 groups than in the placebo group in all of the studies.

Clinical studies for rheumatoid arthritis, asthma, and Crohn's disease were also conducted. However, no statistically significant results over placebo were obtained with KHK4827 for these diseases, and no improvement in symptoms was noted.

On the basis of the above study results, Kyowa Kirin Co., Ltd. (formerly Kyowa Hakko Kirin Co., Ltd.) filed an application for marketing authorization of KHK4827 for the following indications and dosage and administration. The drug was approved in Japan in July 2016. Data from Studies 20090406 and 20110144 in PsA subjects were not included in the application data package because they became available after filing the application.

#### [Indications]

The following diseases that respond inadequately to existing therapies:

Psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, psoriatic erythroderma

#### [Dosage and Administration]

Usually, for adults, administer subcutaneously 210 mg as brodalumab (genetical recombination) in the first dose, followed by doses at 1 week later, 2 weeks later, and once every 2 weeks thereafter.

### 1.5 Rationale for Conducting the Study

A Phase 2 study (Study 20101227) and Phase 3 studies (Studies 20090406 and 20110144) were conducted in subjects with PsA to evaluate the effect of KHK4827 on improvement of joint symptoms. Joint symptoms were improved in the KHK4827 210 mg Q2W group in all of the studies. Furthermore, the effect on improvement of joint symptoms was retained with long-term administration of KHK4827 210 mg Q2W in Study 20101227. KHK4827 at 210 mg is approved for use in PsA in Japan. In addition, PsA and axSpA have similar pathophysiology, and the effect of drug therapy on spondyloarthritis symptoms is considered similar in these diseases ([Raychaudhuri SP and Deodhar A, 2014](#)). Thus, the regimen of KHK4827 210 mg Q2W is also expected to be effective in improving joint symptoms in axSpA subjects. Thus, this study is planned to evaluate the efficacy and safety of 210 mg KHK4827 or placebo administered every 2 weeks in subjects with axSpA. The primary endpoint is the proportion of subjects who achieve an ASAS 40 response, based on which the efficacy of KHK4827 compared to placebo will be evaluated in subjects with axSpA (AS and nr-axSpA). Furthermore, a 52-week open-label extension period following a 16-week double-

blind treatment period is included in the study to evaluate the safety and efficacy of long-term administration of KHK4827.

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## **2 COMPLIANCE WITH GCP AND OTHER APPLICABLE REGULATORY REQUIREMENTS**

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH guidelines on GCP and any applicable laws and regulations in each country.

## **3 STUDY OBJECTIVES**

### **3.1 Primary Objective**

To evaluate the efficacy of KHK4827 in axSpA (ankylosing spondylitis [AS] and non-radiographic axial spondyloarthritis [nr-axSpA]) subjects compared to placebo, as measured by the proportion of axSpA subjects achieving an Assessment of SpondyloArthritis international Society (ASAS) 40 response at week 16.

### **3.2 Secondary Objectives**

- To evaluate the efficacy of KHK4827 in axSpA (AS and nr-axSpA) subjects on ASAS 20 at week 16
- To evaluate the efficacy of KHK4827 in AS subjects as measured by ASAS 40 at week 16
- To evaluate the efficacy of KHK4827 in nr-axSpA subjects as measured by ASAS 40 at week 16
- To evaluate the efficacy of KHK4827 in axSpA (AS and nr-axSpA) subjects on Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP) at week 16

### **3.3 Safety Objective**

To assess the safety profile of KHK4827 in axSpA (AS and nr-axSpA) subjects.

### **3.4 Pharmacokinetics Objective**

To characterize the pharmacokinetics (PK) of KHK4827 in axSpA (AS and nr-axSpA) subjects.

## **4 STUDY DESIGN**

### **4.1 Study Design**

The study schema is shown in [Figure 4.1-1](#).

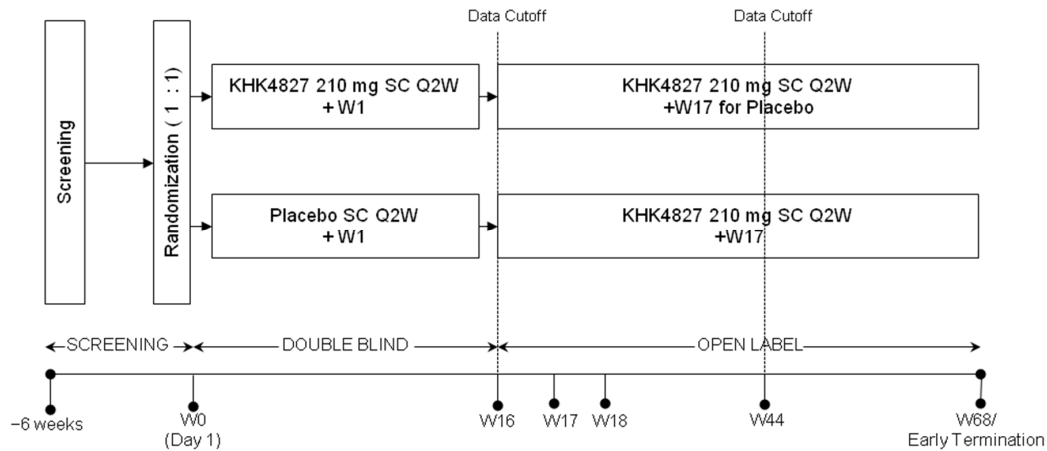
This study consists of a screening period from informed consent to enrollment (randomization) (for up to 6 weeks), a double-blind period of 16 weeks from the first dose of the investigational product, and an open-label extension period of 52 weeks.

Subjects who provide written informed consent will be pre-enrolled in the study and will start to undergo screening. Subjects who are determined to be eligible at the screening will be enrolled and randomized in a 1:1 ratio. Subjects will receive the first injections of the investigational product on the day of enrollment or within 3 days after enrollment (the date of first dose of the investigational product is defined as day 1). Subsequently, subjects will receive KHK4827 210 mg or placebo at week 1, 2, 4, and then Q2W. After week 16, subjects will receive 210 mg KHK4827 through week 68. To maintain blindness, subjects who are assigned to the placebo group in the double-blind phase will receive an additional blinded dose of KHK4827 at week 17. Subjects who are assigned to the KHK4827 group in the double-blind phase will receive an additional blinded dose of placebo at week 17.

After all subjects (except for those who early terminate from the study) complete their week 16 visit and week 44 visit, the data until week 16 (or early termination [ET]) and week 44 (or ET) will be compiled respectively to perform an interim analysis. After all subjects complete their week 16 visit and database is locked, the code for the double-blind period will be unblinded.

The study will also include two additional examinations (both of which are optional and will be conducted in subjects who provide separate informed consent):

- 1) ***PK additional sampling (optional)***: In order to better characterize the pharmacokinetics of KHK4827 in axSpA subjects following subcutaneous administration, additional blood sampling will be conducted 7 times to calculate  $AUC_{0-\tau}$  at steady-state in a small subset of subjects. For  $\geq 6$  axSpA subjects in each country, samples at additional time points for pharmacokinetic analysis will be collected.
- 2) ***Ankylosing Spondylitis longitudinal MRI (optional)***: Longitudinal spine MRI will be conducted in AS subjects who have signed separate informed consent to evaluate the change in spinal inflammation. Only subjects with evidence of spinal inflammation on MRI at enrollment (MRI images obtained within 6 weeks before enrollment may be used instead) will be assessed in this optional study. An additional MRI will be obtained for these subjects at week 16 and week 68/ET. Image will be centrally read.

**Figure 4.1-1 Outline of the Study Design**

## 4.2 Type of Study

Phase 3 clinical study

## 4.3 Endpoints

### 4.3.1 Efficacy

Primary endpoints

- ASAS 40 at week 16 in axSpA (AS and nr-axSpA) subjects

Secondary Endpoints:

- ASAS 20 at week 16 in axSpA (AS and nr-axSpA) subjects
- ASAS 40 at week 16 in AS subjects
- ASAS 40 at week 16 in nr-axSpA subjects
- ASDAS-CRP change from baseline at week 16 in axSpA subjects

Exploratory Endpoints:

- BASFI
- BASDAI
- Patient Global Assessment of Spine Pain and axSpA
- ASQoL
- SF-36v2
- WPAI
- Enthesitis
- BASMI

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- Swollen joint count
- MRI substudy

#### **4.3.2 Safety**

- Adverse events
- Anti-KHK4827 antibodies

#### **4.3.3 Pharmacokinetics**

- Serum KHK4827 concentration
- PK parameters ( $t_{\max}$ ,  $C_{\max}$ ,  $AUC_{0-\tau}$ ) of weeks 14 to 16 and weeks 30 to 32

#### **4.4 Target Number of Subjects**

A total of 120 subjects will be allocated to receive investigational product.

(AS subjects, 90; nr-axSpA subjects, 30)

#### **4.5 Randomization and Blinding**

##### **4.5.1 Randomization**

###### **4.5.1.1 Randomization Method**

Randomization will be performed using an interactive web response system (IWRS). The IWRS will, using dynamic allocation, randomly assign eligible enrolled subjects to the KHK4827 210 mg group or the placebo group in a 1:1 ratio, based on CRP level at screening ( $\geq$  ULN and  $<$  ULN), informed consent for PK additional sampling (yes, no), region (Japan, Korea, Taiwan), and disease subpopulations (AS, nr-axSpA) as stratification factors. In addition, the prior use of anti-TNF agent will be entered in IWRS. To allow evaluation of the efficacy and safety in subjects without any prior history of anti-TNF therapy, the number of enrolled subjects with prior history of anti-TNF therapy will be up to 60 (AS, 45; nr-axSpA, 15) and at least 50% of the study population will be subjects without any prior history of anti-TNF therapy. Detailed procedures for randomization will be specified separately.

###### **4.5.1.2 Timing of Randomization**

After eligibility assessment of the enrolled subjects, eligible subjects will be randomized in the order of enrollment using the IWRS. A subject will be considered enrolled and randomized into the study when a Box no. is assigned. A Box no. will be entered into the electronic Case Report Form (eCRF).



## **4.5.2 Blinding**

### **4.5.2.1 Blinding Method**

Placebo-controlled, double-blind design

### **4.5.2.2 Indistinguishability of Investigational Product**

Amgen Inc., the manufacturer of the investigational product, will confirm the indistinguishability of the investigational product in appearance before allocation of the investigational product.

### **4.5.2.3 Creation and Storage of Master Randomization List and Emergency Key Codes**

PAREXEL International Inc. will create a master randomization list and allocate the investigational product using the IWRS according to the written procedure separately developed. The randomization list will be strictly stored and controlled until the data are locked after the end of the double-blind period and unblinded after the all subjects have completed their week 16 visit. PAREXEL International Inc. will create the emergency key codes to be used in the cases of serious treatment-emergent adverse events or other emergent conditions. In the cases of serious TEAEs or other emergent conditions, the Sponsor will unseal the emergency key codes as necessary in accordance with the written procedure, which is developed separately.

### **4.5.2.4 Unblinding Due to the Known Effects of KHK4827**

The known effects of KHK4827 can make the changes in the results of inflammatory response tests a source of unblinding. Hence the test result of CRP should be kept confidential to those including the investigators or medical staff, and anyone related to the Sponsor until the Sponsor opens the key codes, except at the screening test or in the emergent treatment for adverse events. If the investigators have come to know the results of CRP whatever the reason is, he/she is requested to inform the Sponsor of the fact.

## **5 INVESTIGATIONAL PRODUCT**

### **5.1 Investigational Drug and Comparator**

#### **5.1.1 Investigational Drug**

Company code No.: KHK4827

Non-proprietary name: brodalumab (INN), Brodalumab (genetical recombination) (JAN)

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Strength and dosage form: A prefilled syringe containing 70 mg of KHK4827 (0.5 mL)  
A prefilled syringe containing 140 mg of KHK4827 (1.0 mL)

### **5.1.2 Comparator**

Placebo

Strength and dosage form: A prefilled syringe containing the same ingredients as KHK4827, except the active substance (0.5 mL)  
A prefilled syringe containing the same ingredients as KHK4827, except the active substance (1.0 mL)

## **5.2 Packaging and Labeling**

### **5.2.1 Packaging**

Each box will contain 2 syringes (KHK4827 or placebo).

### **5.2.2 Labeling**

For the information to be included in the label, see the procedures defined separately.

## **5.3 Storage**

To be stored at 2°C to 8°C under protection from light

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

After executing a clinical study agreement, the Sponsor will dispense the investigational product to each investigative site through monitors or carrier companies with which the Sponsor appropriately concludes a contract. The procedure specified separately will be followed for dispensing investigational product. The Sponsor will prepare a written procedure for managing the investigational product and submit it to the investigative site.

The investigational product manager at each site will properly store and manage the investigational product according to the procedure, and will document the use of the investigational product, including inventory and collection. The investigational product manager will properly check the consistency of unused and used supplies of the investigational product against the investigational product management record. After study completion, the investigational product manager will return all unused supplies to the Sponsor.

The investigational product manager will submit a copy of the investigational product management record to the Sponsor after study completion.

## 6 SUBJECT ELIGIBILITY CRITERIA

### 6.1 Target indication

axial spondyloarthritis (axSpA)

### 6.2 Inclusion Criteria

- 1) Personally submitted written voluntary informed consent to participate in the study (if a minor at the time of consent, written informed consent must be obtained from his or her legally acceptable representative as well)
- 2) Aged  $\geq 18$  years at the time of consent (the cut-off age depends on the local law)
- 3) Subject with age at onset  $<45$  years and continuous chronic back pain for  $\geq 3$  months fulfills the ASAS classification criteria of axial spondyloarthritis (with the exception of the Crohn's disease)

*AS subjects:* Subject has radiographic evidence of sacroiliitis grade  $\geq 2$  bilaterally or grade 3 to 4 unilaterally (image obtained within 6 months prior to the time of consent may be used; centrally read) and at least one of the SpA features specified in the ASAS classification criteria of axial spondyloarthritis (with the exception of Crohn's disease)

OR

*nr-axSpA subjects:* Subject does not have radiographic evidence of sacroiliitis grade  $\geq 2$  bilaterally or grade 3 to 4 unilaterally (image obtained within 6 months prior to the time of consent may be used; centrally read)

AND

Subject meets either of the following criteria:

- Presence of inflammatory lesions of sacroiliac joint on MRI of Spondyloarthritis Research Consortium of Canada (SPARCC) level  $\geq 2$  (centrally read) and at least one of the SpA features specified in the ASAS classification criteria of axial spondyloarthritis (with the exception of Crohn's disease)
  - Positive test for HLA-B27\* and the presence of at least 2 of the SpA features specified in the ASAS classification criteria of axial spondyloarthritis (with the exception of Crohn's disease), one of which must be elevated CRP\*\* ( $>$  upper limit of normal [ULN])
- \* Previous positive test result or positive result at screening
- \*\* Limited to the elevation of CRP (centrally measured) that is attributed to axSpA.
- 4) Subject has Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score  $\geq 4$  at screening and enrollment
  - 5) Subject has spinal pain score (BASDAI question #2)  $\geq 4$  at screening and enrollment

- 6) Subject has had adequate therapy with non-steroidal anti-inflammatory drugs (oral NSAIDs) for back pain for at least 3 months with inadequate treatment response before enrollment (however, subjects with contraindication or intolerance to oral NSAIDs may be enrolled even if the subject does not meet the above criterion).
- 7) For subjects receiving non-biologic DMARDs (methotrexate or sulfasalazine): the subject has received treatment for  $\geq 3$  months prior to initiation of investigational product, with a stable dose for  $\geq 4$  weeks prior to initiation of investigational product.
- 8) For subject receiving oral corticosteroids: the subject has received treatment for  $\geq 4$  weeks prior to initiation of investigational product.
- 9) No findings in chest X-ray (or chest computed tomography (CT) scan) suggestive of active tuberculosis, meeting any of the following criteria at screening:
  - Negative QuantiFERON or T-spot test
  - “Borderline” or “invalid” result of QuantiFERON or T-spot test, and negative result in re-testing
  - “Borderline” result in re-testing QuantiFERON or T-spot test, and taking anti-tuberculosis agents (isoniazid, as a general rule) on a regular basis since at least 3 weeks before the start of investigational product administration
  - Positive result in QuantiFERON or T-spot test (including retest) or “invalid” result in re-testing QuantiFERON or T-spot test, but no findings in chest CT scan suggestive of active tuberculosis, and taking anti-tuberculosis agents (isoniazid, as a general rule) on a regular basis since at least 3 weeks before the start of investigational product administration

### 6.3 Exclusion Criteria

- 1) Complete ankylosis (fusion) of the spine
- 2) Subject with active ongoing inflammatory diseases other than axSpA that might confound the evaluation of KHK4827 therapy, including reactive arthritis, spondyloarthritis associated with inflammatory bowel disease, SAPHO syndrome (pustulotic arthro-osteitis), fibromyalgia, ankylosing spinal hyperostosis, osteitis condensans ilii, spondylosis deformans, or osteoarthritis sacroiliac joint disease
- 3) Subject has a planned surgical intervention between enrollment and week 16
- 4) Subject has an active infection or history of infections as follows:
  - any active infection for which systemic anti-infectives were used within 4 weeks prior to the first investigational product administration
  - a serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to the first investigational product administration
  - recurrent or chronic infections or other active infection that, in the opinion of the investigators, might cause this study to be detrimental to the subject
- 5) Subject has any systemic disease (e.g., renal failure, heart failure, hypertension, liver disease, diabetes, anemia) considered by the investigators to be clinically significant and uncontrolled.

- 6) Subject has a known history of human immunodeficiency virus infection
- 7) Subject has positive result in any item of infection tests (hepatitis B surface [HBs] antigen, HBs antibody, hepatitis B core [HBc] antibody, hepatitis C virus [HCV] antibody, human immunodeficiency virus [HIV] antigen/antibody, or Human T-lymphotropic virus type 1 [HTLV-1] antibody) with the exception of the following cases:
  - Subjects negative for HBs antigen and positive for HBc antibody and/or HBs antibody, and with a hepatitis B virus DNA (HBV-DNA) level below the detection sensitivity (such subjects are required to undergo the HBV-DNA assay at 4-week intervals). 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.
- 8) Subject had myocardial infarction, unstable angina pectoris or stroke within the past 12 months prior to the first investigational product administration
- 9) Subject has any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma.
- 10) Subject has a history of malignancy within 5 years prior to enrollment EXCEPT treated and considered cured cutaneous basal or squamous cell carcinoma, in situ cervical cancer or in situ breast ductal carcinoma
- 11) Subject has any concurrent medical condition or electrocardiogram (ECG) abnormality that, in the opinion of the investigators, could cause this study to be detrimental to the subject.
- 12) Subject has a history of Crohn's disease
- 13) Subject has any of the following laboratory abnormalities at screening:
  - aspartate aminotransferase (AST) or alanine aminotransferase (ALT)  $> 2 \times$  the upper limit of normal (ULN)
  - serum direct bilirubin  $\geq 1.5$  mg/dL (25.7  $\mu$ mol/L)
  - white blood cell (WBC) count  $< 3000/\mu$ L
  - neutrophil count  $< 2000/\mu$ L
- 14) Subject has any other laboratory abnormality, which, in the opinion of the investigators, will prevent the subject from completing the study or will interfere with the interpretation of the study results
- 15) Subject has used DMARDs other than a stable dose of methotrexate or sulfasalazine, or has received live vaccine (s) within 4 weeks of the first dose of investigational product
- 16) Subject has used any narcotic analgesics (excluding tramadol) or medical marijuana within 1 week prior to enrollment
- 17) Subject has a prior history of  $>1$  anti-TNF therapy
- 18) Subject has used commercially available or investigational biologic therapies as follows:

- anti-TNF therapy: within 4 weeks prior to investigational product initiation for etanercept, within 8 weeks for infliximab, and within 10 weeks for other anti-TNF agents (e.g., adalimumab, golimumab, certolizumab-pegol).
  - anti-IL-17 biologics (e.g., brodalumab, secukinumab, ixekizumab)
  - within 6 months prior to investigational product initiation for anti-IL-12/IL-23 biologic therapy (e.g., ustekinumab, briakinumab)
- 19) Subject has a history of treatment with any intraarticular/intramuscular corticosteroids or systemic corticosteroids (other than oral corticosteroids) within 4 weeks before the start of investigational product administration.
  - 20) Subject has treated in a clinical study with an investigational product other than KHK4827 or with an unapproved medical device within 4 months before investigational product administration in this study.
  - 21) Subject has planned participation in another clinical study during this study.
  - 22) Subject has known sensitivity to any of the products or components to be administered during dosing.
  - 23) Subject is not likely to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.
  - 24) Subject has a history or evidence of suicidal ideation (severity of 4 or 5) or any suicidal behavior based on an assessment with the Columbia-Suicide Severity Rating Scale (C-SSRS) at enrollment
  - 25) Subject has a history or evidence of a psychiatric disorder, alcohol and/or substance abuse.
  - 26) Subject has severe depression based on a total score of  $\geq 15$  on the Patient Health Questionnaire-8 (PHQ-8) at enrollment (note: subjects with a total score of 10 to 14 on the PHQ-8 should be referred to a mental health care professional).
  - 27) Subject has a history or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigators would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.
  - 28) Pregnant or lactating women or women who are willing to have a child within 8 weeks after the last dose of the investigational product.
  - 29) Women of child-bearing potential (except for permanently sterilized, postmenopausal [defined as amenorrhea  $\geq 12$  consecutive months without an alternative medical cause] or anatomically not of childbearing potential) with a positive pregnancy test (assessed by a serum pregnancy test during screening and a urine pregnancy test at enrollment).
  - 30) Women of child-bearing potential who do not agree to use effective contraception from the day of providing consent through 8 weeks after the last dose of investigational product. Fertile men who do not agree to use effective contraception from the day of first dose of investigational product through 8 weeks after the last dose of investigational product. Effective contraception is defined as using any two of

the following methods: condom, oral contraceptives, intrauterine contraceptive device, and diaphragm, or practice true abstinence from sexual intercourse. The investigators will thoroughly explain the risks in pregnancy and the effective contraceptive methods to the subjects.

31) Anyone otherwise considered unsuitable for the study by the investigators

## 7 TREATMENT PLAN AND CONCOMITANT THERAPY

### 7.1 Dosage, Administration, and Treatment Duration

Dose:

KHK4827 210 mg or placebo

Method of administration:

[Table 7.1-1](#) provides the dosing regimen for the investigational product. The investigators or clinical research coordinator (nurses) will administer a subcutaneous injection to the anterior upper abdomen, thigh, or upper arm. Starting at week 18, subjects who wish “Self-administration” may administer the injection by him/herself or by a trained designated person (relative or caregiver) if judged by the investigators as able to do so.

At all visits up to and including week 32, doses of investigational product must be given with  $\pm 3$  days from the scheduled dose date. Starting at week 34, doses of investigational product must be administered  $\pm 7$  days from the scheduled dose date; however, any 2 consecutive doses must be at least 7 days apart. If the window is missed, that dose will not be administered. The next dose will be administered at the next scheduled dosing date. When an injection is to be administered on the same day as a study visit, it should not be administered until all other study visit procedures have been completed.

Treatment duration:

68 weeks

**Table 7.1-1 Investigational Product Dosing Regimen**

Treatment Group	Dosing regimen
KHK4827 210 mg	1 prefilled syringe of KHK4827 70 mg (0.5 mL) and 1 prefilled syringe of KHK4827 140 mg (1.0 mL)
Placebo	1 prefilled syringe of placebo (0.5 mL) and 1 prefilled syringe of placebo (1.0 mL)

### 7.2 Self-Administration

In this study, subjects are allowed to self-administer investigational product from week 18. Before a subject may begin self-administration, it is the responsibility of the study staff to

ensure that the subject or the subject's designated person (relative or caregiver) is trained to prepare and administer the injection properly. Furthermore, subjects or the subject's designated person (relative or caregiver) who received education on self-administering treatment at home may self-administer the investigational product if judged by the investigators as able to do so properly.

The first self-administered dose must be administered at the site with the investigator, subinvestigator, or clinical research coordinator present. After the first self-administered dose, doses can be administered at home. Subjects are instructed to record their self-administration at home in a patient diary and bring it to the investigative site at the time of next visit.

### 7.3 Rules for Dose Interruption/Resumption

The administration of the investigational product will be interrupted for subjects who meet any of the following criteria:

- An AE such as infection has occurred and the investigator determines that the investigational product treatment should be interrupted.
- Neutrophil count is  $< 1000/\mu\text{L}$ .
- After week 16, the subject has any other abnormality than is described above, which, in the opinion of the investigator, warrant dose interruption.

Duration of dose interruption is permitted at most 4 weeks if it starts during the first 16 weeks of the study. If it starts at week 17 or later, no limitation of duration is defined.

The subject who meets either of the following criteria may resume the scheduled dose:

- The infection has resolved in the opinion of the investigator.
- The subject's neutrophil count is  $\geq 1000/\mu\text{L}$ . If subject has second episode of neutropenia (neutrophil count  $< 1000/\mu\text{L}$ ) following full recovery (neutrophil count  $\geq 1000/\mu\text{L}$ ), treatment with investigational product should be permanently discontinued.

### 7.4 Concomitant Medications

Throughout the study, the investigators may prescribe any concomitant medications deemed necessary to provide adequate supportive care except for those listed in Section 7.4.2 and following the restrictions for use of analgesics, NSAIDs, non-biologic DMARDs and oral corticosteroids in Sections 7.4.1.1 to 7.4.1.4.

If any drug product other than the investigational product is administered from initiation of investigational product administration through the end of study (or ET), the following information will be entered into the eCRF: the name of medication, route of administration, and dosing duration (start date of medication, end date of medication).



## **7.4.1 Concomitant Medications and Therapies Allowed with Restrictions**

### **7.4.1.1 Analgesics**

Except within 12 hours before a scheduled study efficacy evaluation (excluding screening), acetaminophen and tramadol can be used as needed. Tramadol sustained release drugs must not be used within 48 hours before the study efficacy evaluation (excluding screening).

### **7.4.1.2 NSAIDs**

Except within 12 hours before a scheduled study efficacy evaluation (excluding screening), the use of NSAIDs, such as a temporary dose increase or start of NSAIDs at the time of disease flare, will be permitted if necessary. In the case of a temporary dose increase or start of NSAIDs at the time of disease flare, the dose of NSAIDs must be reduced or discontinued with resolution of flare.

### **7.4.1.3 Non-biologic DMARDs**

Subjects taking either methotrexate or sulfasalazine and receiving the same dose thereafter at enrollment must remain on a stable dose during the 16-week double-blind placebo-controlled period.

### **7.4.1.4 Oral Corticosteroids**

Subjects taking oral corticosteroids and receiving the same dose thereafter at enrollment must remain on a stable dose during the 16-week double-blind placebo-controlled period.

## **7.4.2 Prohibited Concomitant Medications**

The following medications are prohibited from initiation of investigational product administration through the end of study:

- Any investigational drug other than KHK4827
- Abatacept
- Azathioprine
- Chronic minocycline or tetracycline (except use for  $\leq 10$  days to treat infection, or for acne)
- Cyclosporine (except external agents)
- Intraarticular or intramuscular corticosteroids, including adrenocorticotrophic hormone
- Systemic corticosteroids other than oral corticosteroids
- Live vaccines
- Medical marijuana

- Narcotic analgesics (e.g., hydrocodone, oxycodone, codeine, and/or propoxyphene, except tramadol [refer to Section 7.4.1.1])
- Tacrolimus (except external agents)
- TNF antagonists (e.g., etanercept, infliximab, adalimumab, golimumab, certolizumab-pegol)
- Tocilizumab
- Other biologic agents
- DMARDs except methotrexate and sulfasalazine

## 8 SUBJECT ENROLLMENT

### 8.1 Procedure for Enrollment

The investigators will provide information about the study to candidate subjects (and legally acceptable representative if he/she is a minor) by giving the subjects the institutional review board (IRB)-approved informed consent form/information for subjects. The investigators will respond to any questions the subjects have on the study. The investigators accept the informed consent form from subjects who intend to participate. Subjects will give informed consent before undergoing screening and any other protocol-specified procedures. For the details of the informed consent form/information for subjects, see “15.5 Information for Subjects/Informed Consent Form.”

#### 8.1.1 Pre-enrollment

The investigators or clinical research coordinator will assign subject identifiers (SIDs) to all subjects who have provided informed consent at his/her investigative site in accordance with the subsequent rules and will register the subjects in the IWRS. The same SID will be used from the time of informed consent through study completion.

SID: 4827-006-Country code-XX-YY

Country code: JP (Japan), KR (Korea), TW (Taiwan)

XX: Investigative site code

YY: Sequential number for each subject who has provided informed consent at the investigative site

For example, the SID of the first subject who provides informed consent at Japanese ●● Hospital (investigative site code: 01) is 4827-006-JP-01-01.

### 8.1.2 Enrollment

The investigators or clinical research coordinator will enroll in the IWRS the subjects who meet all of the criteria required for participating in the study, based on the results of examinations and investigations conducted during the screening period (enrollment). Screening and enrollment of subjects should be completed within 6 weeks from the date of informed consent. The investigators or clinical research coordinator will record the subject's fulfillment of the eligibility criteria in the IWRS. The day on which a subject is enrolled in the IWRS will be regarded as the date of enrollment. The date of enrollment will be entered into the eCRF. Subjects will receive the first injection of the investigational product on the day of enrollment or within 3 days after enrollment.

### 8.1.3 Re-screening

On the discretion of the investigators, subjects who are unable to complete or meet eligibility requirements at the initial screening will be permitted to re-screen twice. Subjects will retain the same SID assigned at the original screening.

Subjects re-screening within the original 6-week screening window need to repeat only the assessment(s) that did not originally meet the eligibility criteria. If a subject fails to meet eligibility requirements at the first re-screening, the second re-screening should be conducted after at least a 6-week interval from the first re-screening and after re-obtaining consent from the subject.

Subjects re-screening after the 6-week screening window has ended must be re-consented and repeat all screening procedures provided in "8.1.2 Enrollment." However, a tuberculosis test or infection test conducted within 2 months prior to the re-consent date, radiography of the sacroiliac joint conducted within 6 months prior to the re-consent date, and HLA-B locus genotyping (regardless of timing) need not to be repeated. If the second re-screening is within 6 weeks following the first re-screening, only the assessment(s) that did not meet eligibility requirements at the first re-screening need to be repeated.

### 8.1.4 Discontinuation of Screening

The investigators will discontinue screening of subjects who are determined to be ineligible for the study based on the tests and investigations conducted during the screening period. In this case, the reason for discontinuation, the date of written informed consent, and gender will be entered in the eCRF. The investigators or clinical research coordinator will also enter the date of discontinuation of the screening period in the IWRS.

## &lt;Steps for Enrollment&gt;

Informed consent

Informed consent is obtained before the start of screening

Pre-enrollment

Pre-enrollment information is recorded in the IWRS during the screening period (if the subject is found to be ineligible for the study, the screening should be discontinued)

Enrollment

Enrollment information is recorded in the IWRS (within 6 weeks from the date of informed consent)

## 9 STUDY PROCEDURES

### 9.1 Overall Schedule

Subjects who provide written informed consent will be pre-enrolled. Screening and enrollment of the subjects should be completed within 6 weeks from the date of informed consent. Subjects will receive the first injection of the investigational product on the day of enrollment or within 3 days after enrollment. The observations, investigations, and examinations in the study will be performed according to the schedule shown in [Table 9.1-1](#). Detailed study procedures are shown in “[9.3 Observations, Assessments and Schedule](#).” Study visits and assessments up to and including week 32 may be completed within  $\pm 3$  days from the scheduled visit date. Starting at week 34, study visits and assessments must be completed  $\pm 7$  days from the scheduled visit date. Examinations and observations must be completed before investigational product administration.

**Table 9.1-1 Study Procedures and Schedule**

Study Visit-Week	Scr	Enr	0	1	2	4	6	8	10	12	14	16	17	18	20	24	28	32	36	40	44	48	52	56	60	64	68/ET	
Date of visit <sup>a</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Informed Consent	X																											
Pre enrollment (IWRS)	X																											
Enrollment, Randomization (IWRS)		X																										
<b>SUBJECT COMPLETED ASSESSMENTS</b>																												
PHQ-8		X				X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	
BASFI		X			X	X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	
BASDAI	X	X			X	X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient Global Assessment of Spine Pain and axSpA		X			X	X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	
ASQoL		X										X										X					X	
SF-36v2		X										X										X					X	
WPAI		X										X										X					X	
<b>GENERAL &amp; SAFETY ASSESSMENTS</b>																												
Demographics	X																											
Medical/Medication History	X																											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination <sup>b</sup>		X										X											X				X	
Vital signs	X	X										X							X				X				X	
Weight	X											X							X				X				X	
Height	X																											
ECG		X										X											X				X	
C-SSRS		X				X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-KHK4827 antibody		X										X						X				X					X	
<b>LABORATORY ASSESSMENTS</b>																												
Tuberculosis test <sup>c</sup>	X																											
Viral infection test <sup>d</sup>	X																											
HBV-DNA assay <sup>d</sup>	X					X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum pregnancy test <sup>e</sup>	X																											
Urine pregnancy test <sup>e</sup>		X				X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	
HLA-B locus genotyping	X																											
Hematology	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X		X	X	X		X		X		X			X	X			X				X				X	
Urinalysis	X	X										X			X								X				X	
CRP	X	X			X	X		X		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	

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**Table 9.1-1 Study Procedures and Schedule (Continued)**

Study Visit-Week	Scr	Enr	0	1	2	4	6	8	10	12	14	16	17	18	20	24	28	32	36	40	44	48	52	56	60	64	68/ET	
<b>PHARMACOKINETIC (PK) ASSESSMENTS</b>																												
PK sample		X		X	X	X		X		X	X	X <sup>f</sup>				X	X	X <sup>g</sup>										
<b>DOSING</b>																												
Investigational product			X <sup>h</sup>	X	X	X	X	X	X	X	X	X	X	X <sup>i</sup>	← § →													
<b>DISEASE ASSESSMENTS</b>																												
ASAS Criteria	X																											
Entheses		X			X	X		X		X		X				X							X					X
BASMI		X			X	X		X		X		X				X							X					X
Joint Count		X										X											X					X
<b>RADIOLOGICAL ASSESSMENTS</b>																												
Radiograph sacroiliac joint <sup>†</sup>	X																											X*
<i>nr-axSpA subjects</i>																												
MRI of sacroiliac joint <sup>†</sup>	X																											X
<i>Additional longitudinal MRI image**</i>																												
MRI of axial spine <sup>†</sup>		X <sup>j</sup>										X																X

Scr, Screening; Enr, Enrollment; ET, Early Termination;

a: Subjects who do not self-administer the investigational product at home will visit the investigative site every 2 weeks at week 20 onwards.

b: includes assessment for peripheral arthritis

c: QuantiFERON or T-spot test and chest imaging (chest X-ray or chest CT scan) will be conducted.

d: HBV-DNA assays will be conducted every 4 weeks in subjects who tested negative for HBs antigen but positive for HBc and/or HBs antibodies and whose HBV-DNA level at screening is below the detection sensitivity.

e: as applicable

f: For subjects who provide consent for the PK additional sampling, blood will be collected after the date of blood sampling at week 14 post 10 days (±1 day).

g: For subjects who provide consent for the PK additional sampling, blood will be collected after the date of blood sampling at week 30 post 10 days (± 1 day).

h: Investigational product administration must be started on the day of enrollment or within 3 days after enrollment.

i: Self-administration will be allowed from week 18. The first self-administered dose must be administered at the investigative site by the trained subjects or designated person (relative or caregiver).

j: MRI images obtained within 6 weeks before enrollment may be used.

§ The investigational product will be administered every 2 weeks. The last dose will be administered at week 66.

† All image(s) will be sent to a central imaging reader for assessment. Radiographic images obtained within 6 months prior to the time of consent may be used for the assessment.

\* Only required for AS subgroup subject population

\*\* Only required for the longitudinal MRI substudy in the AS subject population

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## 9.2 Subjects Characteristics

The following information will be collected:

- The date of written informed consent
- Sex
- Date of birth
- Race
- Medical History (on-going at screening)
- Medical History (before) (during the past 5 years)
- History of anti-TNF therapy use
- Diagnosis date of axSpA
- Medication history of axSpA  
axSpA-specific medication used after obtaining informed consent will be recorded on the eCRF.
- Other items related to inclusion/exclusion criteria

Timing: Screening

## 9.3 Observations, Assessments and Schedule

### 9.3.1 Physical Examination

A physical examination will be performed to assess for any changes in symptoms or findings and for new symptoms or findings after the start of investigational product administration according to the observation schedule.

Timing: Enrollment, weeks 16, 52, and 68/ET

### 9.3.2 Investigational Product Administration Survey

The following items will be recorded on the eCRF:

- Date and time of administration
- Entire dose administration (yes/no)
- Location for administration
- Self-administration (In-Clinic/Non-Clinic)
- Box no.
- Reason for dose interruption

Timing: Week 0 (day 1) to week 66 (at investigational product administration)



## **9.4 Test Items and Assessment Time Points**

### **9.4.1 Laboratory Tests**

Laboratory tests will be performed to confirm the presence of any changes in laboratory values after the start of investigational product administration according to the specified test schedule. Laboratory tests other than hematology, tuberculosis test and urine pregnancy test will be conducted by the central laboratory. Tuberculosis test may also be conducted by the central laboratory as needed. The central laboratory will submit a report on laboratory values to each investigative site, and will also provide the Sponsor with the laboratory results.

It should be noted that CRP except for those measured at screening test are not provided to either the investigative sites or the Sponsor until the Sponsor opens the key codes as described Section 4.5.2.4 because known effects of KHK4827 can make those values a source of unblinding.

#### **9.4.1.1 Hematology**

Parameters: WBC, RBC, hemoglobin, hematocrit, platelets, differential leukocyte count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)

Timing: Screening, enrollment, weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 17, 18, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68/ET

#### **9.4.1.2 Chemistry**

Parameters: Na, K, Cl, TP, ALB, Ca, Mg, P, Glu, BUN, Cr, UA, T-Bil, D-Bil, ALP, AST, ALT

Timing: Screening, enrollment, weeks 1, 2, 4, 8, 12, 16, 20, 24, 36, 52, and 68/ET

#### **9.4.1.3 Urinalysis**

Parameters: Specific gravity, pH, qualitative (blood, protein, glucose, bilirubin, urobilinogen, ketones)

Timing: Screening, enrollment, weeks 16, 24, 52, and 68/ET

#### **9.4.1.4 Viral Infection Test (Blood)**

Parameters: HBs antigen, HBs antibodies, HBc antibodies, HCV antibodies, HIV antigen/antibodies, HTLV-1, HBV-DNA\*

Timing: Screening

\* HBV-DNA assays will be conducted every 4 weeks in subjects who tested negative for HBs antigen but positive for HBc and/or HBs antibodies and whose HBV-DNA level at screening is below the detection sensitivity. HBV-DNA measurement will not be required for subjects who are positive for antibodies produced after HB vaccination and who do not suffer from hepatitis B at screening.

#### **9.4.1.5 Tuberculosis Test**

Tests: Interferon-Gamma release assay (QuantiFERON or T-spot test), and Chest X-ray or chest CT scan

Timing: Screening

#### **9.4.1.6 Pregnancy Test (Blood/ Urine)**

The presence/absence and cycle of menstruation, surgical history, and other relevant information will be collected through medical interview during screening assessments, and those female subjects considered to be of childbearing potential will undergo the pregnancy test. Women of childbearing potential are defined as women other than those who are permanently sterilized, amenorrhea  $\geq 12$  consecutive months without an alternative medical cause, or anatomically not capable of becoming pregnant. Blood tests, with measurement by the central laboratory, are performed only at screening, and urinalysis is conducted at each investigative site at other scheduled visits. For those female subjects excluded from the test, the reason for exclusion should be documented.

Parameters: Serum human chorionic gonadotropin (hCG) or urine hCG

Timing: Blood tests: Screening

Urinalysis: Enrollment, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, and 68/ET

#### **9.4.1.7 CRP**

Test results must not be known by the investigators, subinvestigators, or investigative site staff, who are involved in treatment or clinical assessment of subjects, or the Sponsor until data up to week 16 are unblinded by the Sponsor.

Parameters: CRP

Timing: Screening, enrollment, weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68/ET

#### **9.4.1.8 HLA-B Locus Genotyping**

Results of HLA-B locus genotyping will be disclosed to subjects upon request, with an adequate explanation by the investigators to the subject.

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Measurement results will be entered in the eCRF.

Parameters: HLA-B locus genotyping

Timing: Screening

#### **9.4.2 Vital Signs and Other Tests**

##### **9.4.2.1 Vital Signs**

Parameters\*: Systolic/diastolic blood pressure, pulse rate, respiratory rate, temperature

\*Subject must be seated in a rested and calm state for at least 5 minutes before measurement.

Timing: Screening, enrollment, weeks 16, 36, 52, and 68/ET

##### **9.4.2.2 Height**

Height should be measured without shoes.

Parameters: Height

Timing: Screening

##### **9.4.2.3 Weight**

Weight should be measured without shoes and with light clothing on.

Parameters: Weight

Timing: Screening, weeks 16, 36, 52, and 68/ET

#### **9.4.3 ECG**

12-lead ECG will be recorded after the subject has been supine for at least 5 minutes. However, for subjects who cannot tolerate being supine, any other body positions can be used for measurement to ensure proper safety evaluation. The investigators will review the results for any clinically significant abnormal findings. If a clinically significant abnormal finding is detected, the investigators will record the determination (Interpretation: Normal or Abnormal, not clinically significant/Abnormal, clinically significant) in the eCRF.

Timing: Enrollment, weeks 16, 52, and 68/ET

## 9.4.4 Axial Spondyloarthritis Disease Assessments

### 9.4.4.1 Assessment of SpondyloArthritis International Society Criteria

ASAS criteria for classification of axial spondyloarthritis (Rudwaleit M et al, 2009) (Figure 9.4.4.1-1) should be applied to subjects with  $\geq 3$  months chronic back pain and age at onset  $< 45$  years.

Timing: Screening

**Figure 9.4.4.1-1 ASAS criteria for classification of axSpA**

Sacroiliitis on imaging* plus $\geq 1$ SpA feature**	or	HLA-B27 (positive) plus $\geq 2$ other SpA features** (One of the 2 SpA features must be elevated CRP)
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\* Sacroiliitis on imaging:

- Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- or
- Definite radiographic sacroiliitis according to modified New York criteria

\*\*SpA features:

- inflammatory back pain
- arthritis
- enthesitis (heel)
- uveitis
- dactylitis
- psoriasis
- #colitis (however subjects with Crohn's disease are excluded from this study)
- good response to NSAIDs
- family history for SpA
- HLA-B27
- elevated CRP

#For this study, the clinical feature of Crohn's disease is excluded.

Record all ASAS criteria met by the subject in the eCRF.

### 9.4.4.2 Sacroiliac Joint Radiographs

A standardized procedure for obtaining sacroiliac joint radiographs or historical films will be used by all sites. This procedure and instructions on sending radiographs will be provided in a

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separate manual provided by the central imaging center. All original radiographs will be sent to the central image processing vendor for analysis.

Screening radiographs will be used to determine radiographic evidence of sacroiliitis grade  $\geq 2$  bilaterally or grade 3–4 unilaterally (modified New York criteria; [van der Linden S et al, 1984](#)). Radiographs will be read centrally by the image processing vendor.

Refer to the applicable supplemental imaging manuals for detailed collection and handling procedures.

Timing: Screening and 68/ET\*

\*Only required for AS subgroup subject population

#### **9.4.4.3 Magnetic Resonance Images (MRI)**

##### **9.4.4.3.1 Non-radiographic Axial Spondyloarthritis Subjects**

Approximately 30 subjects with nr-axSpA will be enrolled.

Refer to the applicable supplemental imaging manuals for detailed collection and handling procedures.

Radiographs and MRIs will be centrally read.

Timing: Screening and 68/ET

##### **9.4.4.3.2 Ankylosing Spondylitis Longitudinal MRI (Optional)**

AS subjects who sign the optional consent for the longitudinal MRI will undergo longitudinal spine MRI at enrollment. Only subjects with evidence of spinal inflammation on MRI at enrollment will be assessed in this optional study.

Refer to the applicable supplemental imaging manuals for detailed collection and handling procedures.

MRI scans will be centrally read.

Timing: Enrollment\*, weeks 16 and 68/ET

\* MRI images obtained within 6 weeks before enrollment may be used.

##### **9.4.4.4 Spinal Mobility Testing / Bath Ankylosing Spondylitis Metrology Index**

The BASMI is a validated instrument used to define clinically significant changes in spinal movement by assessing the severity of the subject's limitation of movement due to their axSpA ([Jenkinson TR et al, 1994](#)). As a general rule, each subject should have their

assessments done by the same assessor throughout the study. Extra care should be taken to ensure that the same assessor performs the assessments at enrollment and week 16.

BASMI includes the following 5 indices: (i) cervical rotation, (ii) tragus to wall, (iii) lumbar side flexion, (iv) lumbar flexion (via modified Schober test), and (v) intermalleolar distance. Each index is scored on the basis of observed values, and the total score (0 to 10) is used to assess spinal and hip joint mobility and leg position.

Data are to be entered in the eCRF.

Timing: Enrollment, weeks 2, 4, 8, 12, 16, 24, 52, and 68/ET

#### **9.4.4.5 Enthesitis Count**

The presence of enthesitis will be assessed on 13 entheses using the Maastricht Ankylosing Spondylitis Enthesitis Score (MASSES). As a general rule, assessment will be performed by the same assessor throughout the study. Data are to be entered in the eCRF.

Timing: Enrollment, weeks 2, 4, 8, 12, 16, 24, 52, and 68/ET

#### **9.4.4.6 Swollen Joint Count**

As a general rule, a 44 swollen joint count assessment will be performed by the same assessor throughout the study. The data will be entered in the eCRF.

Joints that have been replaced are considered not evaluable.

Timing: Enrollment, weeks 16, 52, and 68/ET

#### **9.4.4.7 Patient Reported Outcomes**

The following assessments will be completed by the subject. The data will be entered in the eCRF. The assessments should be completed before medical examination at the applicable visit.

##### **9.4.4.7.1 Patient Global Assessment**

###### **9.4.4.7.1.1 Patient Assessment of Spinal Pain**

The severity of the subject's spinal pain will be assessed by completion of a patient-reported assessment of spinal pain in axSpA. This is a two-item questionnaire using an 11-point numerical rating scale labeled from "0 = no pain" to "10 = most severe pain". One item asks the patient to rate his or her pain of the spine due to axSpA, and the other item is specific to pain of the spine due to axSpA at night.

Timing: Enrollment, weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68/ET

#### **9.4.4.7.1.2 Patient Global Assessment of axSpA**

The subject's global assessment of his or her disease activity will be assessed using a single item global measure asking about disease activity on average during the last week. This measure uses an 11-point numerical rating scale labeled from "0 = not active" to "10 = very active."

Timing: Enrollment, weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68/ET

#### **9.4.4.7.2 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)**

The BASDAI is a self-administered patient-reported questionnaire measuring disease activity on average during the last week in axSpA ([Garrett S et al, 1994](#)). It is composed of six items using an 11-point numerical rating scale labeled from "0 = none" to "10 = very severe" for the first five items, and "0 = 0 hours" to "10 = 2 or more hours" for the sixth item that asks about the duration of morning stiffness. A mean score is yielded for the stiffness items (fifth and sixth items), which is then added to the first four items' scores and divided by 5 to yield BASDAI score ranging from 0 to 10. The BASDAI assesses the severity of fatigue, spinal and peripheral joint pain, localized tenderness, and morning stiffness.

Timing: Screening, enrollment, weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68/ET

#### **9.4.4.7.3 Bath Ankylosing Spondylitis Functional Index (BASFI)**

The BASFI is a self-administered patient-reported questionnaire measuring perceptions of physical functional ability in everyday life on average during the last week for patients with axSpA ([Calin A et al, 2004](#)). It is composed of 10 items using an 11-point numerical rating scale labeled from "0 = easy" to "10 = impossible." A mean score is computed from the 10 item scores to yield a BASFI score ranging from 0 to 10.

Timing: Enrollment, weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68/ET

#### **9.4.4.7.4 Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL)**

The ASQoL assesses the patient-reported impact of axSpA on the quality of life, with an emphasis on one's current ability to fulfil one's needs ([Doward LC et al, 2003](#)). The measure comprises 18 items related to the impact of pain on sleep, mood, motivation, ability to cope, activities of daily living, independence, relationships, and social life. The ASQoL uses a

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dichotomous response scale (yes = 1 or no = 0) for each of the items where yes indicates axSpA has an adverse effect on quality of life. The item scores sum up to an ASQoL total score ranging from 0 to 18 with higher scores indicating worse quality of life.

Timing: Enrollment, weeks 16, 48, and 68/ET

#### **9.4.4.7.5 SF-36v2 Health Survey**

The SF-36v2 Health Survey ([Ware JE et al, 2001](#)) contains 36 items and is a revised version of the SF-36 Health Survey. The SF-36v2 is a patient-reported generic measure of health status. This survey yields assessments of 8 domains of health-related quality of life: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The scores from the 8 domains can further be aggregated into 3 norm-based summary component measures of physical, mental, and social health. The SF-36v2 has either a 7-day recall (acute) or 4-week recall (standard), and the 4-week recall will be used in this study.

Timing: Enrollment, weeks 16, 48, and 68/ET

#### **9.4.4.7.6 Work Productivity and Activity Impairment Questionnaire (WPAI)**

The WPAI ([Reilly MC et al, 2010](#)) is a self-administered patient-reported questionnaire to assess the impact of health problems (physical and mental problems or symptoms) on work and daily activities during the last 7 days. The questionnaire comprises 6 items. The first 4 items are fill-in-the-blank questions to be completed according to instructions for each item, and the remaining 2 items are questions measuring the impact of health problems using an 11-point numerical rating scale labeled from “0 = no effect” to “10 = completely prevented.”

Timing: Enrollment, weeks 16, 48, and 68/ET

#### **9.4.4.7.7 Patient Health Questionnaire-8 (PHQ-8)**

The PHQ-8 is a validated and widely used eight-item version of the Patient Health Questionnaire depression scale designed to evaluate the severity of depression ([Kroenke K and Spitzer RL, 2002](#); [Kroenke K et al, 2009](#); [Muramatsu K et al, 2007](#)). In this questionnaire, a subject will be asked to rate the frequency of experiencing any depressive symptom over the last 2 weeks on a 4-point scale: “not at all (0)”, “several days (1)”, “more than half the days (2)”, and “nearly every day (3).” The total score will then be calculated as the PHQ-8 score (0-24 points).

Timing: Enrollment, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, and 68/ET



### 9.4.5 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a standardized and validated instrument developed for the assessment of the severity and frequency of suicidal ideation and behavior (Mundt JC et al, 2010; Posner K et al, 2011). The “suicidal ideation” section is designed to evaluate the severity, frequency, and other characteristics of suicidal ideation, while the “suicidal behavior” section is designed to determine the type of suicidal behavior. C-SSRS assessment should be performed by trained investigators or a trained clinical research coordinator using a pre-specified questionnaire through interview with a subject. The “C-SSRS Baseline Screening” form will be used at the first assessment for each subject, and the “C-SSRS Since Last Visit” form will be used in the subsequent assessments.

Timing: Enrollment, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, and 68/ET

## 9.5 Pharmacokinetic Concentrations

### 9.5.1 Serum KHK4827 Concentrations

#### 9.5.1.1 Blood Sampling

A total of 5 mL of venous blood per sampling will be collected into a prescribed tube. Date and time of blood collection will be entered in the eCRF.

#### 9.5.1.2 Time Points for Blood Sampling

Blood for pharmacokinetic concentration analysis will be collected at the following time points.

Blood sampling points: Enrollment, weeks 1, 2, 4, 8, 12, 14, 16, 24, 28, and 32

Subjects who provide consent for the pharmacokinetic additional sampling will undergo additional blood collection at the time points shown in Table 9.5-1. At least 6 subjects with axSpA per country will be included in the pharmacokinetic additional sampling.

**Table 9.5-1 Pharmacokinetic additional sampling: schedule**

Study Visit	Week 14 post 3 days*	Week 14 post 7 days*	Week 14 post 10 days*	Week 30 predose	Week 30 post 3 days*	Week 30 post 7 days*	Week 30 post 10 days*
Time window	±1 day	±1 day	±1 day	±3 days**	±1 day	±1 day	±1 day
Date of visit	X	X	X	X	X	X	X
PK additional sampling	X	X	X	X	X	X	X

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\*To be counted from the date of dosing at week 14 or week 30.

\*\*Time window for the week 30 visit.

### **9.5.1.3 Blood Sample Processing**

The blood will be allowed to stand still at room temperature after sampling and then centrifuged. The resulting serum will be dispensed into sample tubes. The serum samples should be frozen immediately and stored at  $-20^{\circ}\text{C}$  or lower in the frozen state until the start of measurement.

### **9.5.1.4 Analytical Procedure and Protocol**

Serum concentrations of KHK4827 will be measured using ELISA at Covance Inc. Covance will develop an analytical protocol prior to the measurement.

### **9.5.1.5 Transport of Serum Samples**

The central laboratory will collect serum sample tubes from the investigative site and will send them to Covance Inc. in the frozen state together with a check sheet for each tube. Investigative site, the central laboratory, and Covance Inc. will retain records on transfer of the samples and the related information.

## **9.5.2 Reporting of Analytical Results**

Covance Inc. will develop a final report describing analytical results on the serum concentrations and will submit it to the Sponsor.

## **9.6 Antibody Testing**

### **9.6.1 Anti-KHK4827 Antibody Sampling**

#### **9.6.1.1 Blood Sampling**

A total of 5 mL of venous blood per sampling will be collected into a prescribed tube. Date of blood collection will be entered in the eCRF.

#### **9.6.1.2 Time Points for Blood Sampling**

Blood sampling points: Enrollment, weeks 16, 32, 48, and 68/ET

#### **9.6.1.3 Blood Sample Processing**

The blood will be allowed to stand still at room temperature after sampling and then centrifuged. The resulting serum will be dispensed into sample tubes. The serum samples

should be frozen immediately and stored at  $-20^{\circ}\text{C}$  or lower in the frozen state until the start of measurement.

#### **9.6.1.4 Analytical Procedure and Protocol**

Anti-KHK4827 antibodies will be measured by PPD, Inc. using an electrochemiluminescent immunoassay. The positive samples in the immunoassay will be further analyzed for the presence of neutralizing antibodies using a cell based bioassay. An analytical protocol will be developed by PPD, Inc. prior to the measurement.

#### **9.6.1.5 Transport of Serum Samples**

The central laboratory will collect serum sample tubes from the investigative site and will send them to PPD, Inc. in the frozen state together with a check sheet for each tube. Investigative site, the central laboratory, and PPD, Inc. will retain records on transfer of the samples and the related information.

#### **9.6.1.6 Reporting of Analytical Results**

PPD, Inc. will develop a final report describing analytical results on the anti-KHK4827 antibodies and will submit it to the Sponsor.

### **9.7 Adverse Events**

#### **9.7.1 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 investigational product. A TEAE can therefore be any unfavorable or unintended signs (including any abnormal laboratory findings), symptoms, or disease that occurred after treatment with the investigational product, whether or not considered related to the investigational product. A drug-related TEAE is defined as a sign (including an abnormal laboratory finding), symptom, or disease whose relationship to the investigational product is assessed as “related” or “unknown.”

Results of laboratory tests (hematology, chemistry, urinalysis) will be checked against the normal range at the investigative site for any deviations (abnormal test results) and any abnormal test results will be compared with those obtained prior to treatment with the investigational product to determine whether such a change is clinically significant (abnormal change).

Any abnormal changes in signs, symptoms, and laboratory data associated with a disease (name of diagnosis) are considered a TEAE under the name of diagnosis. However, any

individual atypical or extremely severe signs or symptoms of the disease will also be considered TEAEs along with the name of diagnosis.

If the device (prefilled syringe) malfunction accompanied by serious TEAE (including potential serious TEAE) occurs, this information must be reported according to the rules in Section [11.1.2.2.2](#).

#### **9.7.1.1 Definition of Serious Treatment-Emergent Adverse Events**

A serious TEAE is any event defined as below.

- 1) Death
- 2) Life-threatening
- 3) Hospitalization or prolongation of existing hospitalization
- 4) Persistent or significant disability (as assessed by the reporter of the event)
- 5) Congenital anomaly
- 6) Other clinically critical conditions

In the C-SSRS assessment, suicidal ideation of severity 4 or 5 or any suicidal behavior will be regarded as a serious TEAE.

#### **9.7.1.2 Definition of Other Significant Treatment-Emergent Adverse Events**

Other significant TEAEs are defined as any non-serious TEAEs that lead to discontinuation of investigational product administration or dose suspension.

#### **9.7.2 Assessments**

The following information will be recorded on the eCRF.

TEAEs will be followed up until the subject recovers to the baseline status or until the investigators judge that no further follow-up is necessary based on symptoms, findings, and laboratory data, among other conditions. Information collected from the time of investigational product administration to study completion will be entered on the eCRF.

- 1) Term of Adverse Event
- 2) Date of onset: The date of TEAE onset will be entered.
- 3) Severity (based on CTCAE v4.0)
  - 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) (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

- Grade 3: Severe or medically significant but not immediately life-threatening (Severe); 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 (Life-threatening); urgent intervention indicated.
  - Grade 5: Death related to a TEAE (Fatal)
- 4) Seriousness
    - Serious: TEAEs defined in [9.7.1.1](#)
    - Non-serious: TEAEs other than those defined in [9.7.1.1](#)
  - 5) Actions taken for the investigational product
    - Dose not changed
    - Drug interrupted
    - Drug withdrawn
    - Not applicable
  - 6) Other actions taken: Actions taken for other than investigational product
    - None
    - Other Drug Taken
    - Any Treatments Taken
  - 7) Outcome of event
    - Recovered/resolved
    - Recovering/resolving
    - Not recovered/not resolved
    - Recovered/resolved with sequelae
    - Fatal
    - Unknown
  - 8) Date of outcome identification
  - 9) Causal relationship to the investigational product

Causal relationships to the investigational product will be classified into 3 categories below. For any AE determined as “not related,” the rationale will be recorded in the eCRF.

- Not related
- Unknown
- Related

## **10 SUBJECT CARE**

### **10.1 Notification to Other Departments or Hospitals**

The investigators will check with the subject if he/she is scheduled to receive medical care or medications at any other department or hospital before the start of treatment with the investigational product. If the subject is receiving medical care or medications at other department or hospital, the treating physician will be notified that the subject is participating in the clinical study. The investigators will identify the name of any medication that the subject has received other than those prescribed by the investigators as well as how it has been used.

If the subject newly receives medical care or medications at any other department/hospital during the study, the investigators will take similar steps.

### **10.2 Instructions for Subjects**

The investigators or clinical research coordinator will provide with the following information to each subject.

#### **10.2.1 Study Visits**

Subjects will visit the investigative site for screening within 6 weeks after the date of giving informed consent and be enrolled. Thereafter, subjects will come back to scheduled study visits between day 1 (week 0) and week 68 to undergo the specified observations and examinations.

#### **10.2.2 Patient Diary**

The investigators or clinical research coordinators will provide a patient diary to subjects who self-administer the investigational product at home after fully explaining how to complete and handle the diary and instructing the subjects to bring it to the investigative site at the time of next visit. The investigators or clinical research coordinators will also instruct the subjects to complete the patient diary by themselves.

The investigators or clinical research coordinators will review records in the diary submitted by the subjects and fully explain how to complete or handle the diary again in the case of any incompleteness.

### **10.2.3 Contraception**

The investigators will instruct the subjects to use effective contraception from the day of providing informed consent up to 8 weeks after the last dose of investigational product administration for women of child-bearing potential, and from the day of the first investigational product administration up to 8 weeks after the last dose of investigational product administration for men with reproductive capability. Effective contraception is defined as using any two of the following methods or practicing true abstinence from sexual intercourse: condom, oral contraceptives, intrauterine contraceptive device, or diaphragm. The investigators will thoroughly explain the risks in pregnancy and the effective contraceptive methods to the subjects.

### **10.2.4 Action Taken in Case of Pregnancy**

The investigators will instruct that, if a female subject or the partner of a male subject became pregnant, the subject should immediately inform the investigators of such information. In case of necessity, the investigators will take on appropriate action such as withdrawal from the study to secure her safety and will follow her until no further follow-up is judged to be necessary.

### **10.2.5 Physical and Mental Evaluation**

The investigators will recommend consultation with a psychiatrist, clinical psychologist, or mental healthcare professional to the subjects with the evidence of suicidal ideation (severity of 4 or 5) or any suicidal behavior based on an assessment with the C-SSRS and the subjects with a total score of  $\geq 10$  on the PHQ-8.

## **11 REPORTING OF TREATMENT-EMERGENT ADVERSE EVENTS**

### **11.1 Reportable Treatment-Emergent Adverse Events**

#### **11.1.1 Definition of Serious Treatment-Emergent Adverse Events**

Refer to “[9.7.1.1 Definition of Serious Treatment-Emergent Adverse Events](#).”

#### **11.1.2 Actions to be Taken for Treatment-Emergent Adverse Events and Follow-up**

##### **11.1.2.1 Actions for Subjects**

If a TEAE occurs, the investigators 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 investigational product (drug) received by the subject, the emergency key code for the subject will be broken as described in Sections 4.5.2.3.

### **11.1.2.2 Reporting to Personnel Concerned**

#### **11.1.2.2.1 Serious Treatment-Emergent Adverse Events**

- 1) If a serious TEAE occurs, regardless of whether it is related to investigational product or not, the investigators will immediately (within 24 hours of acknowledgement of event) notify the emergency safety information center or the Sponsor orally in person, or by phone, e-mail, or fax (using the Serious Adverse Event Report Form provided by KHK or a form prescribed by the investigative site).
- 2) Within 7 days of acknowledgement of event, a detailed written report by the investigator using the Serious Adverse Event Report Form (Detailed Report) will be submitted to the Sponsor.
- 3) The investigator will handle serious TEAEs that occurred at their investigative site in accordance with procedures at each investigative site and any applicable laws and regulations.

#### **11.1.2.2.2 Malfunctions of Medical Devices Accompanied by Serious Treatment-Emergent Adverse Events (Including Potential Serious Treatment-Emergent Adverse Events)**

- 1) If the device malfunction (prefilled syringe) accompanied by a serious TEAE occurs during the study, regardless of whether it is related to investigational product or not, the investigators will immediately (within 24 hours of acknowledgement of event) notify the emergency safety information center or the Sponsor using the Serious Adverse Event Report (Initial Report) Form and Device Malfunction Report (Initial Report) Form. If the SAE occurred in a person other than the subject, the event should be reported using only the Device Malfunction Report (Initial Report) Form.
- 2) If a device malfunction occurs, a case where there is potential of a SAE in a subject and/or in a person other than the subject, the investigator will notify the emergency safety information center or the Sponsor using only the Device Malfunction Report (Initial Report) Form.
- 3) Within 7 days of acknowledgement of event, a following report will be submitted by the investigator to the Sponsor.
  - If the SAE occurred in a subject; the Serious Adverse Event Report Form (Detailed Report) and the Device Malfunction Report (Detailed Report) Form
  - If the SAE occurred in a person other than the subject, a case where there is potential of a SAE in a subject and/or in a person other than the subject; the Device Malfunction Report (Detailed Report) Form only
- 4) The investigator will handle device malfunctions accompanied by serious TEAEs (including potential serious TEAEs) that occurred at their investigative site in accordance with procedures and any applicable laws and regulations in each region.



### **11.1.2.2.3 Non-Serious Treatment-Emergent Adverse Events**

If a noteworthy but non-serious TEAE occurs, the investigators will promptly provide the Sponsor with a description of the event and the action taken. Any other TEAE will be reported to the Sponsor at appropriate times.

### **11.1.2.3 Follow-Up of Treatment-Emergent Adverse Events**

TEAEs are to be followed up until the subject returns to the baseline status or until the investigators judge that no further follow-ups are necessary based on symptoms, findings, and laboratory data, among other conditions. Information collected from the time of investigational product administration to study completion will be entered on the eCRF.

## **12 CRITERIA AND PROCEDURE FOR REMOVAL FROM STUDY**

### **12.1 Subject Removal (Early Termination)**

#### **12.1.1 Subject Removal Criteria**

Any of the following circumstances will result in the subject being withdrawn from the study:

- 1) The subject is found to be ineligible for participation in this study after the start of the study.
- 2) The subject (or his or her legally acceptable representative) wishes to withdraw the consent for the study.
- 3) It is found not feasible to conduct the necessary observations and examinations due to the subject's private reasons.
- 4) The subject experiences an adverse event, and the investigators determine that the subject should be withdrawn from the study.
- 5) Duration of dose interruption that occurs before completion of week 16 in the subject exceeds 4 weeks.
- 6) The subject experiences a neutrophil count reduction in one of the following manners:
  - Episode of neutropenia (neutrophil count < 1000/ $\mu$ L) that occurs before completion of week 16 is sustained for  $\geq$  4 weeks.
  - Second episode of neutropenia (neutrophil count < 1000/ $\mu$ L), following full recovery (neutrophil count  $\geq$  1000/ $\mu$ L)
  - The neutrophil count decreased to < 500/ $\mu$ L
- 7) The subject is found to be pregnant, or intends to become pregnant.
- 8) Suicidal ideation of a severity level of 4 or 5 or exhibiting a suicidal behavior of any type, as determined by the C-SSRS
- 9) A PHQ-8 score of  $\geq$  15
- 10) The investigators determine that the subject should be withdrawn from the study.

### **12.1.2 Subject Removal Procedure**

If a subject is withdrawn from the study due to safety concerns such as TEAEs, the investigators will take appropriate actions for the subject. The investigators will examine the safety of each withdrawn subject, followed by prompt early termination study assessments.

A subject who stops visiting the investigative site after exposure to investigational product will be followed to up for specified evaluation the extent possible, in a way that will protect the subject's human rights.

The investigators will identify the date and reasons for withdrawal and enter the information on the eCRF. The investigators or clinical research coordinators will also enter the date of withdrawal in the IWRS.

### **12.2 Premature Termination or Suspension of the Study at a Specific Investigative Site**

If the investigator prematurely terminates or discontinues the study at his/her institution due to concerns over the safety of the investigational product or any other reasons, the relevant investigator will immediately provide a written notification to the Sponsor and the IRB in accordance with the local procedures and any applicable laws and regulations.

Any of the following circumstances will also result in the premature termination of the study at the site. In such an event, appropriate steps will be taken in a similar manner to the above.

- 1) There is a request to revise the protocol based on the IRB's recommendation that the Sponsor cannot accept;
- 2) The IRB considers that the study should not be continued; or
- 3) The investigative site has major or continuous violations of GCP, the protocol, or the clinical study agreement.

### **12.3 Premature Termination or Suspension of the Entire Study**

If the entire study needs to be prematurely terminated or suspended, the Sponsor will promptly inform all investigators, the IRB and the regulatory agency with the decision and the reason in writing in accordance with any applicable laws and regulations in each region. If the study is prematurely terminated or suspended, the investigator will promptly notify subjects (and their legally acceptable representatives) of the termination or suspension and take necessary measures such as providing appropriate medical care.

If the interim analysis after data cutoff at week 16 does not demonstrate the efficacy of KHK4827 over placebo, termination of the entire study will be considered.

## 13 ENDPOINTS

### 13.1 Efficacy

#### 13.1.1 Primary endpoint

- 1) ASAS 40 at week 16 in axSpA (AS and nr-axSpA) subjects

#### 13.1.2 Secondary Endpoints

- 1) ASAS 20 at week 16 in axSpA (AS and nr-axSpA) subjects
- 2) ASAS 40 at week 16 in AS subjects
- 3) ASAS 40 at week 16 in nr-axSpA subjects
- 4) ASDAS-CRP change from baseline at week 16 in axSpA (AS and nr-axSpA) subjects

#### 13.1.3 Exploratory Endpoints

- BASFI
- BASDAI
- Patient Global Assessment of Spine Pain and axSpA
- ASQoL
- SF-36v2
- WPAI
- Enthesitis
- BASMI
- Swollen joint count
- MRI substudy

### 13.2 Safety

- Adverse events
- Anti-KHK4827 antibodies

### 13.3 Pharmacokinetics

- Serum KHK4827 concentration
- KHK4827 PK parameters ( $t_{\max}$ ,  $C_{\max}$ ,  $AUC_{0-\tau}$ ) from week 14 through 16 and from week 30 through 32

## 14 STATISTICAL ANALYSIS

### 14.1 Statistical Methods

The major variables for efficacy, safety, and pharmacokinetics and their analytical methods are described below.

Unless otherwise indicated, categorical data will be summarized by treatment group using frequencies and percentages, and continuous variables will be summarized by treatment group using descriptive statistics (the number of subjects, mean, standard deviation, minimum, median, and maximum). Selected data will be also summarized by region.

#### 14.1.1 Efficacy

##### 14.1.1.1 Primary Endpoint

ASAS 40 at week 16 in axSpA (AS and nr-axSpA) subjects will be compared between the KHK4827 210 mg group and the placebo group using Cochran-Mantel-Haenszel (CMH) test adjusted with the stratification factors used for randomization except for the informed consent for PK additional sampling (yes, no). The point estimate and 95% CI of ASAS 40 will be calculated for each treatment group.

##### 14.1.1.2 Secondary Endpoints

The point estimate and 95% CI of ASAS 20 at week 16 in axSpA (AS and nr-axSpA) subjects will be calculated for each treatment group.

The point estimate and 95% CI of ASAS 40 at week 16 in AS subjects will be calculated for each treatment group.

The point estimate and 95% CI of ASAS 40 at week 16 in nr-axSpA subjects will be calculated for each treatment group.

The point estimate and 95% CI of ASDAS-CRP change from baseline at week 16 in axSpA (AS and nr-axSpA) subjects will be calculated for each treatment group using ANCOVA model adjusted with the ASDAS-CRP baseline level and the stratification factors used for randomization except for the informed consent for PK additional sampling (yes, no).

#### 14.1.2 Safety

For all TEAEs and drug-related TEAEs which occur or worsen after the first administration of investigational product, the frequency will be analyzed, and this analysis will be conducted by PT and SOC in MedDRA. The summary of TEAEs which occur at or before week 16 will

be provided by treatment group. TEAEs which occur after the first administration of KHK4827 through week 44 or week 68 will be pooled in the summary tables.

Descriptive statistics of continuous laboratory data (except urinalysis) and quantitative vital sign will be calculated at each time point by treatment group.

The percentage of subjects who developed anti-KHK4827 antibodies will be summarized for each time point.

### **14.1.3 Pharmacokinetics**

Descriptive statistics of serum KHK4827 concentration data at each blood sampling time point will be presented by treatment group. For the subject who signs the optional consent for the PK additional sampling pharmacokinetic parameters ( $t_{max}$ ,  $C_{max}$ ,  $AUC_{0-\tau}$ ) from week 14 through 16 and from week 30 through 32 will be calculated for each subject, and descriptive statistics will be shown by treatment group.

## **14.2 Target Number of Subjects**

A total of 120 subjects will be allocated to receive investigational product.

(AS subjects, 90; nr-axSpA subjects, 30)

For rationale, see “[25.7 Rationale for Target Number of Subjects.](#)”

## **14.3 Level of Significance**

For the analyses of primary endpoint, two-sided p-values of  $< 0.05$  will be deemed statistically significant.

## **14.4 Criteria for Premature Termination of the Study**

No criteria for early termination based on statistical evidence are specified.

## **14.5 Handling of Missing, Unused, and Abnormal Data**

In the analyses shown in Section [14.1.1](#), data will be handled as described below:

- 1) Any missing data of binary response variables at week 16, such as ASAS 20/40, will be treated as non-responder.
- 2) If post-dosing data in continuous variables, such as ASDAS-CRP level, are missing at week 16, the missing value will be imputed with the baseline value. That is, the change from baseline will be treated as 0.

## **14.6 Development of the Statistical Analysis Plan and Procedure for Reporting Deviations from the Original Statistical Analysis Plan**

The statistical analysis plan, including the analyses shown in Section 14.1, is to be finalized prior to the database lock at week 16. Major changes to the statistical analysis plan will be included in the Clinical Study Report.

## **14.7 Selection of Subjects to be Included in the Analyses**

Analysis sets are defined as the following populations. The decision on whether to include each individual subject in an analysis set (except the pharmacokinetic analysis set) will be made prior to the database lock at week 16.

### **14.7.1 Full Analysis Set**

The full analysis set (FAS) will consist of all randomized subjects associated with the assigned treatment and exclude the subjects meeting any of the criteria below. Primary analyses will be performed in the FAS.

- Subjects who received no administration of investigational product
- Subjects with no post-dosing primary efficacy data available

### **14.7.2 Per Protocol Set**

The per protocol set (PPS) will consist of all the FAS subjects associated with the assigned treatment and exclude the subjects meeting any of the criteria below. PPS will be used to assess the robustness of results in the primary analyses.

- Subjects who failed to meet any major eligibility criteria
- Subjects who had any major protocol deviation

### **14.7.3 Safety Analysis Set**

The safety analysis set will consist of all randomized subjects associated with the actual treatment and exclude the subjects meeting the criteria below.

- Subjects who received no administration of investigational product

### **14.7.4 Pharmacokinetic Analysis Set**

The pharmacokinetic analysis set will consist of all randomized subjects and exclude the subjects meeting any of the criteria below.

- Subjects who were not exposed to KHK4827

- Subjects who had no blood collection for pharmacokinetics after the dosing of KHK4827

## **15 ETHICAL CONSIDERATIONS**

### **15.1 Institutional Review Board**

#### **15.1.1 Review of the Propriety of Conducting the Study**

The study will not be initiated without ethical, scientific, and medical review and approval of the study protocol, informed consent form information, and propriety of conducting the study by the IRB.

#### **15.1.2 Follow-up Review**

The investigator will submit a brief summary of the actual status of the study in writing for follow-up review at least once a year or upon request from the IRB.

### **15.2 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 investigators 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 investigators will determine whether each subject is eligible for enrollment based on the inclusion and exclusion criteria to ensure that the study will not include any subjects whose safety cannot be secured.

Throughout the study, the investigators 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 the investigational product. If a TEAE occurs, the investigators will ensure the safety of the subject by taking such measures as providing appropriate treatment to the subject and discontinuing investigational product administration, if necessary.

### **15.3 Protection of the Subject's Personal Information and Privacy**

In filling out the eCRF, the investigators will identify each subject with his/her SID 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.

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## **15.4 Timing and Procedure of Obtaining Informed Consent**

### **15.4.1 Subject Informed Consent**

#### **15.4.1.1 Information for and Informed Consent of Subjects (Legally Acceptable Representatives)**

The investigators will fully inform each subject (and legally acceptable representative if he/she is a minor) before enrollment who is considered appropriate for the study about the description of the study based on the Informed Consent Form (ICF)/Information for Subjects as provided separately. The subject (and legally acceptable representative if he/she is a minor) will be given sufficient time to decide whether or not to participate in the study, and the investigators will obtain written consent (using the ICF provided separately) from the subject (and legally acceptable representative if he/she is a minor) on a voluntary basis before the screening examinations.

The ICF will be personally sealed or signed and dated by the investigators who have conducted the informed consent discussion as well as by the subject (and legally acceptable representative if he/she is a minor).

### **15.4.2 Retention of Informed Consent Forms**

The investigators will provide the subject with a copy of the signed informed consent form and the Information for Subjects. The investigators will retain the original for the investigator's record in accordance with the policy at each investigative site.

## **15.5 Information for Subjects/Informed Consent Form**

Information for Subjects/Informed Consent Form must contain the information specified by the ICH guidelines on GCP, any applicable laws and regulations in the region.

## **15.6 Providing Information to Subjects, Revising the Information for Subjects/Informed Consent Form, and Obtaining the Second Consent**

When any new information that may influence the subject's willingness to continue participation in the study becomes available, the investigators 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 confirms the subject's decision, and the content of the subject's decision in the medical records.



If the investigator determines that the Information for Subjects/ICF needs revising in terms of the explanation given to the subject, the investigator will promptly update it and obtain the IRB's approval. The investigators 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.

## **16 PAYMENTS AND COMPENSATION/INDEMNIFICATION FOR HEALTH INJURY**

### **16.1 Expenses Related to the Study**

The terms related to the expenses during the administration period for examinations, imaging tests, and administration or injection of pharmaceutical products with similar indications or therapeutic effects to those of the investigational product are specified in the clinical study agreement.

### **16.2 Expenses for Reducing the Burden to Subjects Resulting from Participation in the Study**

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 sites, in accordance with the applicable rules of each investigative site.

### **16.3 Compensation for Health Injury**

In the event of any study-related disease or health injury in a subject, necessary therapeutic measures will be taken in accordance with the clauses on compensation in Information for Subjects/Informed Consent Form or the clinical study agreement.

## **17 PROTOCOL COMPLIANCE, DEVIATIONS/CHANGES AND AMENDMENTS**

### **17.1 Compliance with the Protocol**

The investigators will comply with the protocol on which the investigator and the Sponsor have agreed and to which the IRB has given a written approval.

### **17.2 Deviations from or Changes to the Protocol**

The investigators must not deviate from or change the protocol without obtaining the Sponsor's prior written agreement and the IRB's written approval based on its prior review.

In the event of deviations from or changes to the protocol, the investigators will make a record of all of the relevant actions regardless of the reason.

For medical reasons such as a need to eliminate immediate hazards from the subject, the investigators may deviate from or change the protocol without the Sponsor's prior written agreement or the IRB's prior written approval. In such a case, the investigator should immediately report to the Sponsor and the IRB in writing and take necessary measures in accordance with local procedures and any applicable laws and regulations.

### **17.3 Protocol Amendments**

When the Sponsor amends the protocol, the Sponsor will fully explain to each investigator about the revision using the amended protocol or the document describing the amendments to obtain his/her agreement. The investigator will conduct the study according to the amended protocol after receiving a written approval from the IRB based on their prior review. However, this does not apply to amendments that consist of only administrative issues (e.g., changes of affiliation, job title, address, or telephone number).

## **18 INSTRUCTIONS ON THE ELECTRONIC CASE REPORT FORM**

After each subject has completed their week 16 visit (or ET), the efficacy data until week 16 will be entered into the eCRF by the start of investigational product administration at week 18. The investigators will submit data until week 16 (or ET) and week 44 (or ET) to the Sponsor when all subjects complete their week 16 (or ET) and week 44 (or ET), respectively.

### **18.1 Filling out Electronic Case Report Forms and Reporting**

In this study, Electronic Data Capture (EDC) system will be used for collecting data. The EDC system provides each investigative site with the functions of data entry in the eCRF, checking the input data, and responding to the Sponsor's inquiries on the input data, besides the function of electronic signature. The entered data will be encrypted and transferred to the EDC server via the Internet. The EDC system is verified in advance by the Sponsor to comply with the requirements of "Standards for the Implementation of Clinical Trials on Pharmaceutical Products" (Ministry of Health and Welfare Ordinance No. 28, 27 Mar, 1997) and the partial revision of the Ordinance, and "Guidelines for Electronic Record/Electronic Signature Use for Application etc. Involved in Drug Approval or Permission" (Pharmaceutical and Food Safety Bureau Notification No. 0401022, Ministry of Health, Labour and Welfare; April 1, 2005).

The 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 subinvestigator or clinical research coordinator, the investigator will check the accuracy and completeness of data prior to appending his/her electronic signature. "Guide for Changes or Corrections to an Electronic Case Report Form," 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 handled 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. The procedure which is developed separately is to be followed when migrating the data to the electronic document control system.

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

## **18.2 Changes or Corrections to Electronic Case Report Form**

The investigators or clinical research coordinator will change or correct entries in the eCRF according to the above procedure provided by the Sponsor. The change or correction history to eCRF is automatically recorded on the EDC system.

## **18.3 Items that Allow Handling of Electronic Case Report Form Entries as Source Documents (Source Data)**

The following items may be recorded directly in the eCRF and their description may be handled as source documents (source data). If similar information is included in the medical record, the description in the medical record will be regarded as source documents (source data):

- 1) Name of adverse event, severity, seriousness, actions taken, outcome, date of outcome identification, causal relationship to investigational product, and comments
- 2) Date of and reason for the early termination
- 3) Special notes other than those described above and comments from the investigators

## **19 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

During the Sponsor's monitoring and auditing, the IRB's review, and regulatory inspections, the investigators and the investigative site should allow them direct access to all study-related records including source documents.

## **20 QUALITY CONTROL AND QUALITY ASSURANCE OF THE STUDY**

Through monitoring and auditing, the Sponsor will verify that the study, data generation, recording, and reporting are conducted in compliance with the protocol, the ICH guidelines on GCP and any applicable laws and regulations in each region.

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

Study monitors will check and ensure that the study has been conducted in compliance with the GCP Ordinance, the protocol, and the written procedure for investigational product accountability and that the entries of eCRF coincide with the source data. Detailed procedures will be given in a monitoring plan document developed separately or an alternative written procedure.

## **21 EXPECTED DURATION OF THE STUDY**

October 2016 to December 2019 (after all subjects [except for those who early terminate from the study] complete their week 16 and week 44 visit, data will be cut off, and data until week 16 (or ET) and week 44 (or ET), respectively, will be compiled.)

## **22 STUDY COMPLETION**

Upon completion of the protocol-specified dosing and observation in all the subjects at an investigative site, the investigator will promptly notify the IRB and the Sponsor of the completion of the study in writing in accordance with local procedures and any applicable laws and regulations.

## **23 RECORD KEEPING**

### **23.1 Keeping at IRB**

#### **1) Materials to be retained**

The IRB provider will retain all relevant records such as written standard operating procedures, membership list (including the status of each member), list of occupations (job title)/affiliations of members, submitted documents, minutes of meetings and its summary, and correspondence.

## 2) Retention period

The IRB provider will retain the above-mentioned materials for the period determined based on the ICH guidelines on GCP and any applicable laws and regulations in each region.

### **23.2 Keeping at Investigative Sites**

The necessary documents and records will be retained for the period determined based on the clinical study agreement, the ICH guidelines on GCP and any applicable laws and regulations in each region.

### **23.3 Keeping by Sponsor**

#### 1) Materials to be retained

The Sponsor will retain the necessary study-related documents or records.

#### 2) Retention period

The Sponsor will retain the above-mentioned materials until either of the days listed below, whichever comes later.

- The day when 5 years have elapsed since the day of the marketing authorization granted for the investigational product (or, in the case of development discontinued, the day when 3 years have elapsed since the date of the decision). In this regard, however, the day of re-examination completion will apply to the drug that, in accordance with the provisions of the Pharmaceutical and Medical Device Act, is subject to post-approval re-examination whose period is more than 5 years.
- The day when 3 years have elapsed since the study discontinuation or completion.

### **23.4 Retention of Source Documents about Measurement of KHK4827 Concentrations**

The source documents related to the measurement of serum KHK4827 concentrations will be retained at Covance Inc. The retention period will be until either of the days listed below, whichever comes later. The measurement facility (Covance Inc.) and the Sponsor will discuss further retention separately.

- The day when 5 years have elapsed since the day of the marketing authorization granted for the investigational product (or, in the case of development discontinued, the day when 3 years have elapsed since the date of the decision). In this regard, however, the day of re-examination completion will apply to the drug that, in accordance with the provisions of the Pharmaceutical and Medical Device Act, is subject to post-approval re-examination whose period is more than 5 years.
- The day when 3 years have elapsed since the study discontinuation or completion.

### **23.5 Retention of Source Documents about Measurement of Anti-KHK4827 Antibody**

The source documents related to the measurement of anti-KHK4827 antibody will be retained at PPD, Inc. The retention period will be until either of the days listed below, whichever comes later. The measurement facility (PPD, Inc.) and the Sponsor will discuss further retention separately.

- The day when 5 years have elapsed since the day of the marketing authorization granted for the investigational product (or, in the case of development discontinued, the day when 3 years have elapsed since the date of the decision). In this regard, however, the day of re-examination completion will apply to the drug that, in accordance with the provisions of the Pharmaceutical and Medical Device Act, is subject to post-approval re-examination whose period is more than 5 years.
- The day when 3 years have elapsed since the study discontinuation or completion.

### **23.6 Retention of Source Documents about Laboratory Tests**

The source documents related to laboratory tests will be retained at the relevant measurement organization until either of the dates described below, whichever comes later. The study director and the Sponsor will discuss further retention separately.

- The day when 5 years have elapsed since the day of the marketing authorization granted for the investigational product (or, in the case of development discontinued, the day when 3 years have elapsed since the date of the decision). In this regard, however, the day of re-examination completion will apply to the drug that, in accordance with the provisions of the Pharmaceutical and Medical Device Act, is subject to post-approval re-examination whose period is more than 5 years.
- The day when 3 years have elapsed since the study discontinuation or completion.

## **24 PUBLICATION POLICY**

For publications of data derived from this study, for instance, in a conference or journal, the investigators must obtain prior agreement from the Sponsor.

## **25 RATIONALE**

### **25.1 Rationale for Study Design**

This is a Phase 3 clinical study to evaluate the efficacy and safety of SC doses of 210 mg KHK4827 administered every 2 weeks to axSpA subjects. The study is designed as a randomized, placebo-controlled, double-blind comparative study to minimize bias.

The primary efficacy endpoint in this study is defined as the proportion of axSpA subjects achieving an ASAS 40 response at week 16, in view of assessing improvement in level of satisfaction with treatment. Based on this primary endpoint, the efficacy of KHK4827 compared to placebo will be evaluated in axSpA subjects. In addition, a 52-week open-label extension period after week 16 is included in the study to evaluate the safety and efficacy of long-term administration of KHK4827 in axSpA subjects. In order to evaluate the efficacy of KHK4827 compared to placebo in axSpA subjects, data will be cut off after all subjects complete their week 16 examination (or examination at ET), and an interim analysis will be performed using the data until week 16 (or ET) of each subject. Furthermore, since an application for partial changes in approved items for the indication of axSpA will be submitted depending on data obtained at 6 months after transition to treatment with KHK4827 from all subjects, data will also be cut off after all subjects complete their week 44 examination (or examination at ET), and a clinical study report will be prepared using the data until week 44 (or ET) of each subject.

## **25.2 Rationale for Inclusion Criteria**

- 1) This study will be conducted in compliance with the GCP.
- 2) The age is set in view of peak age of onset for the disease.
- 3) The study population in the study is subjects with axSpA.
- 4 to 8) These criteria were established to select appropriate patients for receiving biologic agent.
- 9) This criterion was established to ensure safety for subjects because KHK4827 has immunological effect.

## **25.3 Rationale for Exclusion Criteria**

- 1 to 3, 23) These subjects are inappropriate for the evaluation of KHK4827.
- 15 to 17, 19) Inclusion of these subjects in the study affects the efficacy evaluation of KHK4827.
- 4 to 11, 13, 14, 22, 24 to 30) These criteria were selected to ensure safety for subjects and to evaluate the safety of the investigational product properly.
- 12) This criterion was selected to ensure safety for subjects because KHK4827 has immunological effect.

20) The period of 4 months is based on the guidelines of the Japan Association of Contract Institutes for Clinical Pharmacology.

18, 21) These criteria were selected to evaluate the safety and efficacy of the investigational product properly.

31) This criterion was selected to exclude subjects who are considered inappropriate to participate in the study by the investigators for reasons other than those described above.

#### **25.4 Rationale for Prohibited Concomitant Medications/Therapies and Concomitant Medications and Therapies Allowed with Restrictions**

The prohibition was established because such drugs and therapies affect the efficacy and safety evaluations of the investigational product.

#### **25.5 Rationale for Measurements of Serum KHK4827 Concentration**

In view of the serum KHK4827 concentration-time profile after repeated SC doses in patients with plaque psoriasis, sampling time points were set at enrollment, weeks 1, 2, 4, 8, 12, 14, 16, 24, 28, and 32 to assess the trough concentration-time profile. In addition, in order to assess PK parameters from week 14 through 16 and from week 30 through 32, blood sampling for additional analysis of KHK4827 pharmacokinetics will be performed for those subjects who have consented at week 14 post 3 days, week 14 post 7 days, week 14 post 10 days, week 30 predose, week 30 post 3 days, week 30 post 7 days, and week 30 post 10 days.

#### **25.6 Rationale for Criteria for Early Termination**

- 1) This criterion was selected to withdraw ineligible subjects from the study as early as possible.
- 2) This criterion is intended to protect human rights in accordance with the Declaration of Helsinki.
- 3) This criterion is intended to withdraw subjects who are unable to undergo the required observations, investigations, or examinations from the study as early as possible.
- 4) This criterion was selected to ensure safety for subjects.
- 5) This criterion was selected because dose interruption for more than 4 weeks may preclude efficacy evaluation in the double-blind phase.
- 6) This criterion was selected to ensure safety for subjects because “neutrophil count decreased” has been identified as an important risk associated with KHK4827.
- 7) This criterion was selected to withdraw subjects who are pregnant or intends to become pregnant from the study as early as possible because the safety of KHK4827 in pregnant women has not been established and safety for the offspring of the subjects was considered.



- 8, 9) These criteria were selected to ensure safety for subjects because “events related to suicide/self-injury” have been identified as a potential risk associated with KHK4827.
- 10) This criterion was selected to withdraw subjects deemed by the investigators to be unsuitable for the study due to any reason other than those described above as early as possible.

## 25.7 Rationale for Target Number of Subjects

The number of axSpA subjects was determined as below to confirm the treatment difference in ASAS 40.

The results pooled from two pivotal studies of secukinumab (MEASURE1 and MEASURE2) were referred as the clinically significant difference in ASAS 40 of AS subjects. ASAS 40 of secukinumab 150 mg treatment arm was 40% (52 out of 125 subjects in MEASURE1; and 26 out of 72 subjects in MEASURE2), and ASAS 40 of placebo arm was 12% (16 out of 122 subjects in MEASURE1; and 8 out of 74 subjects in MEASURE2) ([Baeten D et al, 2015](#)).

The results pooled from five clinical studies of four anti-TNF agents were referred as the clinically significant difference in ASAS 40 of nr-axSpA subjects. ASAS 40 of anti-TNF treatment arm was 43% (12 out of 22 subjects and 28 out of 69 subjects in the two adalimumab studies; 22 out of 46 subjects and 24 out of 51 subjects in the certolizumab pegol study with two types of administrations; 33 out of 94 subjects in the etanercept study; and 11 out of 20 subjects in the infliximab study), and ASAS 40 of placebo arm was 15% (3 out of 24 subjects and 10 out of 73 subjects in the two adalimumab studies; 8 out of 50 subjects in the certolizumab pegol study; 16 out of 95 subjects in the etanercept study; and 3 out of 20 subjects in the infliximab study) ([Corbett M et al, 2016](#)).

At least 59 axSpA subjects per treatment group need to be enrolled to achieve 90% power with two-sided 5% significance level under the assumed ASAS 40 (i.e. 40.5% in KHK4827; and 13.0% in placebo), which was pooled in proportion to the number of AS subjects and nr-axSpA subjects based on the above data along with the fact that at most 30 nr-axSpA subjects can be enrolled.

## 26 STUDY ADMINISTRATIVE STRUCTURE

### 26.1 Sponsor

Masashi Miyamoto  
Chief Executive Officer and President  
Kyowa Kirin Co., Ltd.  
1-9-2, Otemachi, Chiyoda-ku, Tokyo, 100-0004, Japan

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**26.2 Clinical Leader (Sponsor Signatory)**

Takuya Morishige

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

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