I1F-MC-RHBN(c) Protocol

A Phase 1, Single- and Multiple-Dose Study to Assess the Safety and Pharmacokinetics of Ixekizumab (LY2439821) (Anti–IL-17 Humanized Antibody) in Chinese Patients with Psoriasis Vulgaris

NCT03073213

Approval Date: 20-Jun-2017

1. Protocol I1F-MC-RHBN(c)
A Phase 1, Single- and Multiple-Dose Study to Assess the Safety and Pharmacokinetics of Ixekizumab (LY2439821) (Anti–IL-17 Humanized Antibody) in Chinese Patients with Psoriasis Vulgaris

Ixekizumab (LY2439821)

A Phase 1, multicenter, open-label, single- and multiple-dose study of ixekizumab in approximately 45 patients with moderate to severe psoriasis vulgaris. Patients in the single-dose phase will receive ixekizumab 80 mg subcutaneously (SC) followed by a 20-week observation period. Patients in the multiple-dose phase will receive a starting dose of ixekizumab 160 mg SC and will then be randomized to 2 treatment arms (80 mg SC every 2 weeks [Q2W] or every 4 weeks [Q4W]) for an 8-week treatment period, followed by an additional 20-week observation period.

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Indianapolis, Indiana USA 46285

Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly: 10 May 2016
Amendment (a) Electronically Signed and Approved by Lilly: 22 July 2016
Amendment (b) Electronically Signed and Approved by Lilly: 23 November 2016
Amendment (c) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 20-Jun-2017 GMT

2. Synopsis

Clinical Pharmacology Protocol Synopsis: Study I1F-MC-RHBN

Name of Investigational Product: Ixekizumab (LY2439821)	
Title of Study: A Phase 1, Single- and Multiple-Dose Study to Assess the Safety and Pharmacokinetics of Ixekizumab (LY2439821) (Anti–IL-17 Humanized Antibody) in Chinese Patients with Psoriasis Vulgaris	
Number of Planned Patients: Single-dose phase: Enrolled: up to 15 patients Planned to complete: 8 patients Multiple-dose phase: Enrolled: up to 30 patients Planned to complete: every 2 weeks (Q2W) = 10 patients; every 4 weeks (Q4W) = 10 patients	**Phase of Development: 1**
Length of Study: single-dose phase = 20 weeks; multiple-dose phase = 28 weeks	
Objectives: The primary objective of this study is to assess the pharmacokinetics (PK) of ixekizumab after single and multiple subcutaneous (SC) doses in Chinese patients with psoriasis. The secondary objective of this study is as follows: • to assess the safety, tolerability, and immunogenicity of ixekizumab in Chinese patients with psoriasis. The exploratory objective of this study is as follows: • to assess the efficacy endpoints of Psoriasis Area and Severity Index (PASI) and static Physician's Global Assessment (sPGA) of ixekizumab after single and multiple SC doses in Chinese patients with psoriasis.	
Study Design: Study RHBN is an open-label, multiple-site study.	
Diagnosis and Main Criteria for Inclusion and Exclusion: This study will enroll male or female patients aged 18 years or older who have chronic plaque psoriasis based on a confirmed diagnosis of moderate to severe chronic psoriasis vulgaris for at least 6 months before baseline, are candidates for phototherapy and/or systemic therapy, and have ≥10% body surface area (BSA) involvement, an sPGA score ≥3, and a PASI score ≥12 at screening and baseline.	
Dosage and Mode of Administration: Single-dose phase: 80 mg SC Multiple-dose phase: 160 mg SC starting dose for all patients. Patients will then be randomized to receive either 80 mg SC Q2W or 80 mg SC Q4W.	
Planned Duration of Treatment: Single-dose phase: 1 × 80 mg SC Multiple-dose phase: 160 mg SC starting dose followed by 80 mg SC Q2W or 80 mg SC Q4W for 8 weeks.	
Criteria for Evaluation: Safety: Safety endpoints will include adverse events (AEs), clinical laboratory testing (eg, hematology, clinical chemistry, and urinalysis), electrocardiogram (ECG) monitoring, and physical examinations. Bioanalytical: Serum will be collected at selected visits to determine concentration of ixekizumab. Pharmacokinetic: Ixekizumab concentration versus time profile. Pharmacodynamic: PASI, sPGA. Immunogenicity: Anti-ixekizumab antibodies will be assessed at selected visits.	
Evaluation Methods: Safety: Descriptive statistical methods will be employed to analyze clinical safety parameters. Bioanalytical: Serum concentrations of ixekizumab will be assayed using validated enzyme-linked immunosorbent assay. Pharmacokinetic: Pharmacokinetic parameter estimates for ixekizumab will be calculated by standard noncompartmental methods of analysis. The PK parameters for estimation will include maximum observed drug concentration (C_{max}), time to C_{max}, area under the concentration versus time curve (AUC), terminal half-life, apparent clearance, and apparent volume of distribution. Pharmacodynamic: Descriptive statistics of pharmacodynamic (PD) parameters will be presented at each scheduled time point.	

3. Table of Contents

Protocol I1F-MC-RHBN

A Phase 1, Single- and Multiple-Dose Study to Assess the Safety and Pharmacokinetics of Ixekizumab (LY2439821) (Anti–IL-17 Humanized Antibody) in Chinese Patients with Psoriasis Vulgaris

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Attachments

4. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BCG	Bacillus Calmette-Guérin
BMI	body mass index
BP	blood pressure
BSA	body surface area
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CRF/eCRF	case report form/electronic case report form: Sometimes referred to as clinical report form. A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP/CRS	clinical research physician/clinical research scientist: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, CRS, global safety physician, or other medical officer.

CSE	clinically significant event: A moderate to severe adverse event (AE), abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the subject.
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
EMA	European Medicines Agency
end of trial (study)	End of trial is the date of the last visit or last scheduled procedure shown in the study schedule for the last patient.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form (ICF) directly or through their legally acceptable representatives.
ERB/IRB	ethical review board/institutional review board: A board or committee (institutional, regional, or national) composed of medical professionals and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
FSH	follicle-stimulating hormone
GCP	good clinical practice: A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.
ICF	informed consent form
ICH	International Conference on Harmonisation
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form (ICF).
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.

investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IL	interleukin
IV	intravenous
LTBI	latent tuberculosis infection
MAb	monoclonal antibody
MI	myocardial infarction
open-label	A study in which there are no restrictions on knowledge of treatment allocation; therefore, the investigator and the study participant are aware of the drug therapy received during the study.
PASI	Psoriasis Area and Severity Index
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPD	purified protein derivative
PUVA	psoralens and ultraviolet A
Q2W	every 2 weeks
Q4W	every 4 weeks
QIDS-SR$_{16}$	Quick Inventory of Depressive Symptomatology–Self Report, 16 item
QTF	QuantiFERON®-TB Gold test
randomize	The process of assigning subjects to an experimental group according to the randomization schedule for the trial.
rescreen	To screen a subject who was previously declared a screen failure for the same study.
SAE	serious adverse event: Any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.
SC	subcutaneous

screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
sPGA	static Physician's Global Assessment
subject	An individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient.
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TPO	third-party organization
T-SPOT	T-SPOT®.TB test
ULN	upper limit of normal
US-FDA	United States Food and Drug Administration
WBC	white blood cell

Protocol I1F-MC-RHBN: A Phase 1, Single- and Multiple-Dose Study to Assess the Safety and Pharmacokinetics of Ixekizumab (LY2439821) (Anti–IL-17 Humanized Antibody) in Chinese Patients with Psoriasis Vulgaris

5. Introduction

5.1. General Introduction

Psoriasis is a common, lifelong, and life-shortening chronic inflammatory skin disease manifested by prototypic red, thick, and scaly plaques. Psoriasis vulgaris or plaque psoriasis (hereafter psoriasis) is the most common form and has been shown to have a significant impact on the overall health of patients, including an association with inflammatory arthritis in the form of psoriatic arthritis. Psoriasis is associated with increased risk for multiple comorbid conditions, including myocardial infarction (MI) and stroke, metabolic syndrome, diabetes mellitus, chronic renal insufficiency, and liver abnormalities (Yeung et al. 2013).

The worldwide prevalence of psoriasis is 2% to 3% (Christophers 2001; International Federation of Psoriasis Associations [IFPA] 2014 [WWW]), with rates varying across ethnic groups and geographic regions (Chandran and Raychaudhuri 2010; Parisi et al. 2013). A recent population-based and dermatologist-confirmed study showed that the prevalence of psoriasis in China is 0.47%, higher than the incidence of 0.12% observed in a 1987 study, which may mean it is increasing (Ding et al. 2012).

Ixekizumab (LY2439821) was approved in March 2016 for the treatment of moderate-to-severe psoriasis in adults by the United States Food and Drug Administration (US-FDA). Ixekizumab (LY2439821) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (MAb) designed and engineered to selectively inhibit interleukin-17A (IL-17A). Psoriasis is an IL-17A-driven disease (Clark 2015). Ixekizumab binds with high affinity (≤3 pM) and specificity to IL-17A, a proinflammatory cytokine. Neutralization of IL-17A by ixekizumab has been shown to reduce excess keratinocyte proliferation and activation (Krueger et al. 2012). Ixekizumab does not bind to ligands IL-17B, IL-17C, IL-17D, IL-17E, or IL-17F.

The global clinical development program for ixekizumab for treatment of psoriasis included one Phase 1 study I1F-MC-RHAG [RHAG]; one Phase 2 study I1F-MC-RHAJ [RHAJ]; and three pivotal Phase 3 studies (I1F-MC-RHAZ [RHAZ], I1F-MC-RHBA [RHBA], and I1F-MC-RHBC [RHBC]). A Phase 3, randomized, open-label, pharmacokinetics (PK) study (I1F-MC-RHBL; [RHBL]) compared the PK of ixekizumab administered via prefilled syringe and auto-injector device. Additionally, for the purposes of registration in Japan, in addition to participation in the global Phase 3 trial RHAZ, one Phase 3 open-label study (1IF-JE-RHAT; [RHAT]) determined the efficacy and safety of ixekizumab in Japanese patients diagnosed with plaque psoriasis or the more severe psoriasis subtype of erythrodermic and pustular psoriasis. Additional details on each of these studies are located in the Investigator's Brochure (IB).

Results of a population PK analysis of data in patients with psoriasis from global studies show that ixekizumab exhibits linear PK over a dose range of 5 to 160 mg. The mean elimination half-life of ixekizumab after subcutaneous (SC) administration was approximately 13 days, and the time of maximum observed serum drug concentration (C_{max}) occurred at approximately 4 to 7 days. These values are typical for MAbs in humans. Based on PK, efficacy, and safety evaluations, no dose adjustment of ixekizumab is recommended based on body weight, age, sex, and ethnic origin.

From global clinical trials, individual treatment-emergent adverse events (TEAEs) (preferred terms) that were reported at a significantly greater frequency in the total ixekizumab group than in the placebo group were injection site reaction, injection site erythema, nausea, and oropharyngeal pain. Most TEAEs were mild or moderate in severity. Overall, severe TEAEs were similar across the ixekizumab treatment groups compared with those of the placebo group. For the percentage of patients with at least 1 serious adverse event (SAE), there were no significant differences between the ixekizumab treatment groups and the placebo group. Approximately 2% of ixekizumab-treated patients discontinued because of adverse events (AEs), whereas approximately 1% of placebo-treated patients discontinued because of AEs.

More information about the known and expected benefits, risks, and reasonably anticipated AEs may be found in the IB. Information on AEs expected to be related to the investigational product may be found in Section 7 (Development Core Safety Information) of the IB. Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the study may be found in Section 6 (Effects in Humans) of the IB.

The proposed study, Study I1F-MC-RHBN (RHBN), is a Phase 1, multicenter, single- and multiple-dose, open-label study in Chinese patients with moderate to severe psoriasis. This study will assess the PK and safety of ixekizumab for the future development of ixekizumab in China. The sponsor, monitor, and investigators will perform this study in compliance with the protocol, good clinical practice (GCP), International Conference on Harmonisation (ICH) guidelines, and applicable regulatory requirements.

5.2. Rationale and Justification for the Study

The purpose of this study is to assess the PK and safety of ixekizumab in Chinese patients with moderate to severe psoriasis to enable the future development of ixekizumab in China. The PK of ixekizumab in Chinese patients will be compared to the PK observed in non-Chinese patients from global studies.

6. Objectives

6.1. Primary Objective

The primary objective of this study is to assess the PK of ixekizumab after single and multiple SC doses in Chinese patients with psoriasis.

6.2. Secondary Objective

The secondary objective of this study is as follows:

- to assess the safety, tolerability, and immunogenicity of ixekizumab in Chinese patients with psoriasis.

6.3. Exploratory Objective

The exploratory objective of this study is as follows:

- to assess the efficacy endpoints of Psoriasis Area and Severity Index (PASI) and static Physician's Global Assessment (sPGA) of ixekizumab after single and multiple SC doses in Chinese patients with psoriasis.

7. Investigational Plan

7.1. Summary of Study Design

Study RHBN is a Phase 1, multicenter, open-label, single- and multiple-dose outpatient study in up to 45 patients with psoriasis. This study will assess the safety, tolerability, and PK profile of ixekizumab 80 mg SC in Chinese patients since 80 mg SC is the maintenance dose used in Phase 3 global studies and is the planned dose for Phase 3 studies in China. Ixekizumab was evaluated as a 160 mg SC starting dose and as an 80 mg SC maintenance dose every 2 weeks (Q2W) or every 4 weeks (Q4W) in global Phase 3 studies for the treatment of psoriasis; therefore, these dose regimens will be used for the multiple-dose phase in Study RHBN.

For the single-dose phase, patients will receive a single dose of ixekizumab 80 mg SC on Day 1 and will be assessed at regular visits for 20 weeks. Patients completing the single-dose phase have the option of enrolling in the multiple-dose phase after completing the final visit in the single-dose phase. Patients will remain at the site for a minimum of 4 hours postdose.

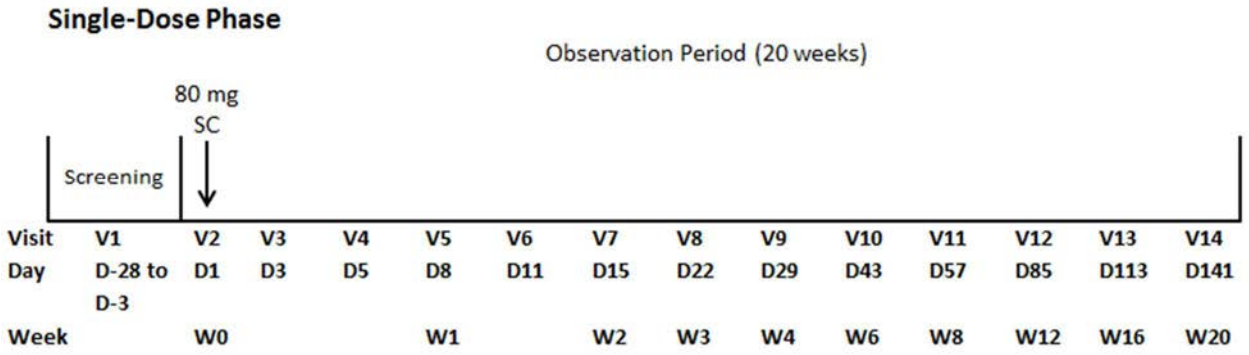
The multiple-dose phase can be initiated once 6 patients have completed the Week 6 (Day 43) visit in the single-dose phase and safety data collected through 6 weeks postdosing from these patients have been reviewed. After review of these safety data, an agreement on initiation of the multiple-dose phase will be made by the investigator and sponsor.

In the multiple-dose phase, patients will be administered a starting dose of ixekizumab 160 mg SC on Day 1 and will then be randomized into 1 of 2 dosing regimens for the 8-week treatment period: (1) 80 mg SC Q2W or (2) 80 mg SC Q4W. Patients will be assessed at regular visits for an additional 20 weeks. Patients will remain at the site for a minimum of 4 hours after the first dose and for 2 hours after subsequent doses.

Figure RHBN.1 and Figure RHBN.2 illustrate the study design for the single-dose phase and multiple-dose phase, respectively. The rationale for dose selection is described in Section 9.3. The Study Schedules (Attachment 1 and Attachment 2) detail the procedures and tests occurring at specific times throughout the study.

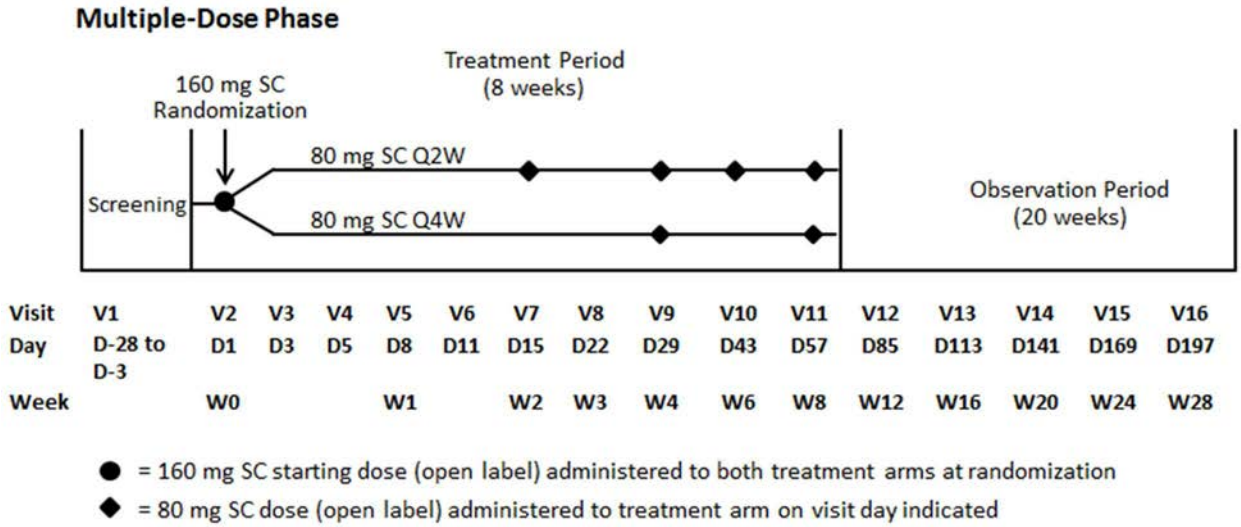
7.2. Discussion of Design and Control

The primary endpoint is the evaluation of PK of ixekizumab in Chinese patients with moderate to severe psoriasis; therefore, an open-label study design is considered appropriate. The psoriasis population for this study will be patients with a minimum body surface area (BSA) involvement of 10%, a total PASI score of at least 12, and an sPGA score of ≥3, representative of the population likely to receive a biologic therapy. Additional patients may be added to a group if several patients discontinue treatment for reasons other than AEs possibly related to study drug. Safety and outcome measures during the follow-up period will allow detection and assessment of delayed effects, if any, that could result from treatment with ixekizumab.



Abbreviations: D = day; SC = subcutaneous; V = visit; W = week.
Note: Patients who complete Visit 14 of the single-dose phase are eligible for participation in the multiple-dose phase.

Figure RHBN.1. Study design for the single-dose phase of Study I1F-MC-RHBN.



Abbreviations: D = day; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; V = visit; W = week.

Figure RHBN.2. Study design for multiple-dose phase of Study I1F-MC-RHBN.

7.3. End of Study

The end of the study is the date of the last visit or last scheduled procedure shown in the Study Schedule (Attachment 2) for the last patient.

8. Study Population

8.1. Criteria for Enrollment

Eligibility of patients for study enrollment will be based on the results of a screening medical history, physical examination, vital signs, clinical laboratory tests, and electrocardiogram (ECG).

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur from 28 days up to 3 days prior to enrollment. Patients who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Individuals may be rescreened once. The interval between rescreening should be at least 2 weeks. If rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

8.1.1. Inclusion Criteria

Patients are eligible for enrollment in the study only if they meet all of the following criteria:

[1] are male or female patients 18 years or older.

[1a] male patients:

will agree to use a reliable method of birth control and will not donate sperm during the study and for at least 3 months following the last dose of ixekizumab, whichever is longer.

Examples of reliable methods of birth control are condoms with spermicide, oral contraceptives, intrauterine device, and male sterilization.

[1b] female patients:

are women of childbearing potential who test negative for pregnancy and agree to use a reliable method of birth control or remain abstinent during the study and for at least 3 months following the last dose of ixekizumab, whichever is longer. Methods of contraception considered acceptable include oral contraceptives, contraceptive patch, intrauterine device, vaginal ring, diaphragm with contraceptive gel, or condom with contraceptive gel.

-or-

are women of nonchildbearing potential, defined as:

women who have had surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation);

-or-

women who are ≥60 years of age;

-or-

women ≥40 and <60 years of age who have had a cessation of menses for ≥12 months and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (≥40 mIU/mL).

[2] have a body mass index (BMI) between 18 and 35, inclusive.

[3] present with chronic plaque psoriasis based on a confirmed diagnosis of chronic psoriasis vulgaris for at least 6 months before baseline (Week 0; Visit 2).

[4] have ≥10% BSA involvement at screening (Visit 1) and baseline (Week 0; Visit 2).

[5] have both an sPGA score of ≥3 and PASI score ≥12 at screening (Visit 1) and baseline (Week 0; Visit 2).

[6] are candidates for phototherapy and/or systemic therapy at the discretion of the investigator.

[7] have given written informed consent approved by Lilly or its designee and by the ethical review board (ERB)/institutional review board (IRB) governing the site.

8.1.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet **any** of the following criteria:

[8] are investigator site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[9] are Lilly employees.

[10] are currently enrolled in a clinical trial involving an investigational product or off-label use of a drug or device, or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[11] have pustular, erythrodermic, and/or guttate forms of psoriasis.

[12] have a history of drug-induced psoriasis.

[13] had a clinically significant flare of psoriasis during the 12 weeks before baseline (Week 0; Visit 2).

[14] have received systemic nonbiologic psoriasis therapy (including but not limited to oral psoralens and ultraviolet A [PUVA] light therapy, cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate mofetil, thioguanine, hydroxyurea, sirolimus, azathioprine, fumaric acid derivatives, or 1, 25 dihydroxy vitamin D3 and analogues) or phototherapy (including either oral or topical PUVA light therapy, ultraviolet B, self-treatment with tanning beds, or therapeutic sunbathing) within 4 weeks prior to baseline (Week 0; Visit 2) or have had topical psoriasis treatment (including but not limited to corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, emollients, and other nonprescription topical products containing urea, >3% salicylic acid, or α- or β-hydroxyl acids), or medicated shampoos [for example those that contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues]) within the previous 2 weeks prior to baseline (Week 0; Visit 2).

Exceptions: mild (for example, desonide) or least potent (for example, hydrocortisone) topical steroids will be permitted for use, limited to the face, axilla, and/or genitalia.

[15] cannot avoid excessive sun exposure or use of tanning booths for at least 4 weeks prior to baseline (Week 0; Visit 2) and during the study.

[16] current or recent use of any biologic agent within the following washout periods: etanercept <28 days; infliximab, adalimumab, or alefacept <60 days; golimumab <90 days; ustekinumab <8 months; rituximab or efalizumab <12 months; or any other biologic agent <5 half-lives prior to baseline (Week 0; Visit 2).

[17] have ever received natalizumab or other agents that target α-4-integrin.

[18] have previously completed or withdrawn from this study, participated in any other study with ixekizumab, or have participated in any study investigating other IL-17 antagonists.

[19] have a known allergy or hypersensitivity to any biologic therapy that would pose an unacceptable risk to the patient if participating in this study.

[20] have had a live vaccination within 12 weeks prior to baseline (Week 0; Visit 2), intend to have a live vaccination during the study or within 12 months of completing treatment in this study, or have participated in a vaccine clinical study within 12 weeks prior to baseline. Investigators should review the vaccination status of their patients and follow the local guidelines for adult vaccination with nonlive vaccines intended to prevent infectious disease prior to therapy.

(Note: Killed/inactive vaccines are expected to be safe.)

[21] had a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months prior to baseline (Week 0; Visit 2) or intend to have this vaccination with BCG during the study or within 12 months of completing treatment in this study.

[22] had any major surgery within 8 weeks prior to baseline (Week 0; Visit 2) or will require such during the study that, in the opinion of the investigator in consultation with Lilly or its designee, would pose an unacceptable risk to the patient.

[23] have current or a history of lymphoproliferative disease; or signs or symptoms of lymphoproliferative disease; or have active or history of malignant disease.

(Note: Patients with successfully treated basal cell carcinoma [no more than 3 treatments for removal of basal cell carcinoma], squamous cell carcinoma of the skin, or cervical carcinoma in situ, with no evidence of recurrence within the 5 years prior to baseline [Week 0; Visit 2] may participate in the study.)

[24] have the presence of significant uncontrolled cerebrocardiovascular disorder (for example, MI, unstable angina, unstable arterial hypertension, moderate to severe [New York Heart Association class III/IV] heart failure, or cerebrovascular accident); respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic, or neuropsychiatric disorder; or abnormal laboratory values at screening that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or risk of interfering with the interpretation of data.

[25] have had fluid overload, MI, or new-onset ischemic heart disease (for example, unstable angina), uncompensated heart failure or, in the opinion of the investigator, other serious cardiac disease within 12 weeks prior to baseline (Week 0; Visit 2).

[26] have the presence of significant uncontrolled neuropsychiatric disorder, have history of a suicide attempt, have a score of 3 on Item 12 (Thoughts of Death or Suicide) of the 16-item Quick Inventory of Depressive Symptomatology–Self Report ($QIDS\text{-}SR_{16}$) at screening (Visit 1), or are clinically judged by the investigator to be at risk for suicide.

[27] had a serious infection (for example, pneumonia, cellulitis), have been hospitalized, or have received intravenous (IV) antibiotics for an infection within 12 weeks prior to baseline (Week 0; Visit 2); had a serious bone or joint infection within 24 weeks prior to baseline; have ever had an infection of an artificial joint; or are immunocompromised to an extent such that participation in the study would pose an unacceptable risk to the patient.

[28] have or have had an infection that is typical of an immunocompromised host and/or that occurs with increased incidence in an immunocompromised host (including, but not limited to, *Pneumocystis jirovecii* pneumonia, histoplasmosis, or coccidioidomycosis) or have a known immunodeficiency.

[29] have a herpes zoster or any other clinically apparent varicella-zoster virus infection or had such within 12 weeks of baseline (Week 0; Visit 2).

[30] have any other active or recent infection within 4 weeks of baseline (Week 0; Visit 2) that, in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study; these patients may be rescreened (1 time) ≥4 weeks after documented resolution of symptoms.

[31] have a body temperature ≥38°C (100.5°F) at baseline (Week 0; Visit 2); these patients may be rescreened (1 time) ≥4 weeks after documented resolution of elevated temperature.

[32] have clinical evidence or suspicion of active TB or have previously had evidence of active TB and did not receive appropriate and documented treatment. (Refer to Section 10.4.3.5 for additional details on determining full TB exclusion criteria.)

a Evidence of active TB is documented by a positive purified protein derivative (PPD) test (≥5-mm induration) which is to be read between 48 and 72 hours after placement, regardless of vaccination history, medical history, clinical symptoms, and abnormal chest x-ray at screening.

b If either the QuantiFERON®-TB Gold test (QTF) or T-SPOT® TB test (T-SPOT) is available, it may be used as an alternative instead of the PPD test, per principal investigator preference or judgment, and may be read locally. Locally read results must be documented in the eCRF.

have evidence of latent TB (as documented by a positive QTF or T-SPOT or PPD [≥5-mm induration] with no clinical symptoms or signs consistent with active TB, and a normal chest x-ray at screening) **unless** patients complete at least 4 weeks of appropriate treatment prior to randomization and agree to complete the remainder of treatment while in the trial (see Section 10.4.3.5 for additional requirements).

a If the QTF or T-SPOT test is indeterminate, the test may be repeated once within approximately 2 weeks of the initial value. If the repeat test is indeterminate, the patient will be excluded from the study. If the retest is positive with no clinical evidence of TB, the patient will be considered to have latent TB.

b If the PPD test is performed and positive (≥5-mm induration) and the patient has no medical history or chest x-ray findings consistent with active TB, a retest can be performed using a QTF or T-SPOT test.

Note: If retest is done with QTF or T-SPOT, this result will be used to determine eligibility in place of the PPD result. Indeterminate results of either test are to be handled as directed above.

c Exceptions include patients with a history of active or latent TB who have documented evidence of appropriate treatment.

[33] have uncontrolled arterial hypertension characterized by a systolic blood pressure (BP) >160 mm Hg or diastolic BP >100 mm Hg.

(Note: This will be determined by 2 consecutive elevated readings. If an initial BP reading exceeds this limit, the BP may be repeated once after the patient has rested sitting for ≥10 minutes. If the repeat value is less than the criterion limits, the second value may be accepted.)

[34] are positive for human immunodeficiency virus (HIV) serology (positive for HIV antibody).

[35] have evidence of active hepatitis B virus (positive for hepatitis B surface antigen) OR are positive for hepatitis B core antibody and negative for hepatitis B surface antibody.

[36] have evidence of or test positive for hepatitis C virus (HCV). A positive test for HCV is defined as: (1) positive for hepatitis C antibody and (2) positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction).

[37] have clinical laboratory test results at screening that are outside the normal reference range for the population and are considered clinically significant and/or have any of the following specific abnormalities:

[37a] neutrophil count <1500 cells/μL (<1.50×10^3 cells/μL or <1.50 GI/L)

[37b] lymphocyte count <500 cells/μL (<0.50×10^3 cells/μL or <0.50 GI/L)

[37c] platelet count <100,000 cells/μL (<100×10^3 cells/μL or <100 GI/L)

[37d] aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (>2.5xULN)

[37e] total white blood cell (WBC) count <3000 cells/μL (<3.00×10^3 cells/μL or <3.00 GI/L)

[37f] hemoglobin <8.5 g/dL (85.0 g/L) for male patients and <8.0 g/dL (80 g/L) for female patients

[37g] serum creatinine >2.0 mg/dL.

(Note: The AST and ALT may be repeated once within a week if the initial response exceeds this limit, and the repeat value may be accepted if it meets this criterion. Other laboratory tests should not be repeated unless there is a technical error or clinical reasons to believe a result may be erroneous.)

[38] have ECG abnormalities that are considered clinically significant and would pose an unacceptable risk to the patient if participating in the study.

[39] have any other condition that precludes the patient from following and completing the protocol, in the opinion of the investigator.

[40] have donated blood >400 mL within the last 4 weeks prior to baseline or intend to donate blood during the course of the study.

[41] are women who are lactating or breastfeeding.

[42] are unwilling to abstain from alcohol beverage intake 24 hours prior to any scheduled visits until the completion of all study visit procedures.

[43] have used any traditional Chinese treatments within 14 days prior to study enrollment or intend to use any traditional Chinese treatment during the study.

[44] Have allergy to rubber or latex.

8.1.3. Rationale for Exclusion of Certain Study Candidates

Exclusion Criteria [8] and [9] reduce the potential bias that may be introduced at the study site. Exclusion Criteria [14] through [18] exclude patients who are taking concomitant medications or receiving treatment or phototherapy that could have a negative safety impact on the patients enrolled or confound the results of the study. Exclusion Criteria [19] through [38] exclude patients who would be at a greater safety risk, including patients at increased risk of infective complications or immunosuppression, if administered investigational product or whose data could confound the results of the study in the analysis of ixekizumab and/or patients. Exclusion Criterion [41] provides protection to offspring.

8.2. Discontinuation

The reason for and date of discontinuation will be collected for all patients. All patients who discontinue, regardless of whether or not they received investigational product, will have procedures performed as shown in the Study Schedule (Attachment 1).

8.2.1. Discontinuation of Patients

8.2.1.1. Patients Inadvertently Enrolled

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the Lilly clinical pharmacologist or clinical research physician (CRP) and the investigator to determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the investigator and Lilly clinical pharmacologist or CRP agree it is medically appropriate for that patient.

The patient may not continue in the study with or without investigational product if the Lilly clinical pharmacologist or CRP does not agree with the investigator's determination that it is medically appropriate for the subject to continue. The investigator must obtain documented approval from the Lilly clinical pharmacologist or CRP to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

8.2.1.2. Discontinuations from Investigational Product or from the Study

In addition, patients will be discontinued from the investigational product or from the study in the following circumstances:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator decision:
    - The investigator decides that the patient should be discontinued from the study.
    - If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the other agent.
- Subject decision:
    - The patient requests to be discontinued from the study.
- Sponsor decision:
    - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.
- AE:
    - If a clinically significant event (CSE) occurs, the investigational product is to be discontinued and appropriate measures taken. Lilly or its designee should be alerted immediately. A CSE will be defined as a moderate to severe AE, abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the subject. Refer to Section 10.4, Safety Evaluations.
    - A clinically significant systemic hypersensitivity reaction occurs following administration of the investigational product (for example, drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension) and requires parenteral medication, does not respond to symptomatic medication, or results in clinical sequelae or an anaphylactic reaction.

After the investigator's determination that CSE criteria have been met and the investigator's judgment of relatedness to the investigational product is documented, a decision will be made between the investigator and Lilly or its designee regarding subject discontinuation.

The nature of any conditions, clinical signs or symptoms, or abnormal laboratory values present at the time of discontinuation and any applicable follow-up procedures will be documented.

Discontinuation procedures are outlined in the Study Schedules (Attachment 1 and Attachment 2).

8.2.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for any reason consistent with applicable laws, regulations, and GCP.

8.2.3. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

9. Treatment

9.1. Treatment Materials and Supplies

All patients will be administered ixekizumab via prefilled syringe.

9.1.1. Packaging, Preparation, Labeling, and Storage

The ixekizumab solution for injection will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practices. Ixekizumab will be supplied as an injectable solution in a 1-mL, single-dose, disposable manual syringe. Each syringe of ixekizumab is designed to deliver 80 mg of ixekizumab. Syringes will be supplied in cartons, with the appropriate quantity of syringes specific to the planned dispensing schedule of the investigational product.

Clinical trial materials will be labeled according to China's regulatory requirements. All investigational products will be supplied with lot numbers, expiry dates, and certificates of analysis and will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

The investigational product should be stored at 2°C to 8°C (36°F to 46°F) in its original carton to protect from light. Investigational product should not be frozen or shaken. Sites will be required to monitor temperature of the on-site storage conditions of the syringes.

9.2. Treatment Administration

This study involves an evaluation of ixekizumab 80 mg administered by prefilled syringe during the treatment period. For the single-dose phase, all patients will receive a single dose of 80 mg given as one 80 mg SC injection at Week 0 (Visit 2) and will then be observed for a 20-week period. For the multiple-dose phase, all patients will receive a 160 mg SC starting dose (2 injections) and will then be randomized at a 1:1 ratio to 1 of 2 dose groups via a computer-generated random sequence using an interactive web-response system (IWRS): one group will receive 80 mg SC Q2W starting on Day 15, and the other group will receive 80 mg SC Q4W starting on Day 29 for the duration of the 8-week treatment period. All patients in the multiple-dose phase will be followed for an additional 20-week observation period after the treatment period completes.

Injections will be administered at the site by the clinical staff.

Administration: A dose of investigational product will consist of SC injection(s) of investigational product. Possible injection sites include the abdomen, thigh, and upper arm. The injection site should not be in a psoriatic lesion and should be rotated to another area for subsequent doses.

Allow the prefilled syringe containing the drug product to equilibrate to room temperature for approximately 30 minutes. Do not return syringe to the refrigerator.

The investigator or designee is responsible for:

- explaining the correct use of the investigational agent to the site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of investigational product dispensing and collection,
- and returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed. See Section 10.4.5 for more details.

All clinical trial material provided to the investigator will be stored in a secure place and allocated and dispensed by appropriately trained persons. The allocation and dispensing of the investigational products will be fully documented and verified by a second person. Detailed records of the amounts of investigational product received, dispensed, and remaining at the end of the study will be maintained.

The doses will be administered at approximately the same times on each planned dosing day, and each patient should have doses administered by the same member of the staff as far as possible.

The actual time of all dose administrations will be recorded in the subject's case report form (CRF).

9.3. Rationale for Selection of Dose

Ixekizumab has been administered to patients with rheumatoid arthritis, psoriatic arthritis, and psoriasis. A 160 mg SC starting dose (Week 0) followed by an 80 mg SC dose Q2W or Q4W was evaluated as an induction dosing regimen over 12 weeks of treatment in global pivotal Phase 3 studies in patients with psoriasis (Studies RHAZ, RHBA, and RHBC). In this study, the PK profile and safety/tolerability of ixekizumab 80 mg will be assessed initially in the single-dose phase. Thereafter, the induction dosing regimens evaluated in the pivotal Phase 3 studies will be evaluated in the multiple-dose phase for this Phase 1 study in China. The doses planned for this study are justified by adequate margins of safety from toxicology studies in cynomolgus monkeys (Table RHBN.1) and the safety and tolerability data from single- and multiple-dose studies in patients with psoriasis.

Table RHBN.1. Margin of Safety for Administration of Ixekizumab to Humans Based on Exposure at the NOAEL and LOAEL in Monkeys

	SC Dose	$AUC_{0\text{-}168hr}$ (mg•hr/mL)	Margin of Safety Based on AUC in Phase 3
Human			
Dose regimen producing highest exposure in Phase 3 studies	80 mg Q2W following 160 mg starting dose	2.366[a]	-
Monkey			
NOAEL	5 mg/kg Q1W	15.3[b]	6.5x
LOAEL	50 mg/kg Q1W	144[c]	61x

Abbreviations: AUC = area under the concentration versus time curve; $AUC_{0\text{-}168hr}$ = AUC from time 0 to 168 hours after dosing; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Q1W = once weekly; Q2W = every 2 weeks; SC = subcutaneous.

[a] Predicted mean steady-state $AUC_{0\text{-}168hr}$ following 80 mg Q2W dosing, using simulations from the integrated population pharmacokinetic model. The model-predicted $AUC_{0\text{-}168hr}$ value for the starting dose of 160 mg was 1.987 mg•hr/mL, and for the proposed maintenance dose of 80 mg every 4 weeks was 1.560 mg•hr/mL.

[b] Estimated mean male and female $AUC_{0\text{-}168hr}$ after 39 weekly SC doses of 5 mg/kg in Study 7608-478; Day 1 AUC was multiplied by 2.5, which was the extent of accumulation observed at 50 mg/kg.

[c] Mean male and female $AUC_{0\text{-}168hr}$ after 39 weekly SC doses of 50 mg/kg in Study 7608-478.

9.4. Specific Restrictions/Requirements

Prior to beginning the study, the patients will complete informed consent and baseline tests.

Patients will be screened for eligibility in the study as described in Sections 8.1 and 8.2 and will be informed of the study-specific restrictions and requirements of the study. Patients who are not willing to comply with the study restrictions and requirements will not be eligible to be enrolled. Patients will reside in the clinical research unit during the infusion visits until completion of all procedures associated with that visit. Patients will adhere to the following study restrictions and/or requirements:

- It is unlikely that there are significant reproductive risks, including risks of harm to the fetus or infant, with ixekizumab treatment. This is based on results from reproductive and developmental toxicity studies in monkeys. However, male patients should use barrier method contraception during intercourse with female partners of childbearing potential during the study and for at least 3 months after the last dose of ixekizumab, whichever is longer. Female patients must use a reliable method of birth control or remain abstinent during the study and for at least 3 months after the last dose of ixekizumab, whichever is longer (additional details are provided in the Inclusion Criteria [Section 8.1.1]).
- Patients must abstain from alcoholic beverages intake for 24 hours prior to any scheduled visit and until completion of the study procedures associated with that visit.
- Patients must refrain from smoking for 30 minutes prior to any study procedure and until completion of that procedure.

9.4.1. Special Treatment Considerations

Patients should be instructed not to donate blood or blood products during participation in the study. All biological agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include but are not limited to:

- skin rash
- pruritus (itching)
- urticaria (hives)
- angioedema (for example, swelling of the lips and/or tongue)
- anaphylactic reaction.

Sometimes, these reactions can be life threatening. Proteins may also cause redness, itching, swelling, or pain locally at the injection site; therefore, all patients should be closely monitored for signs or symptoms that could result from such reactions, educated on the signs or symptoms of these types of reactions, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection. If a patient experiences an acute allergic/hypersensitivity reaction after an injection of investigational product, he or she should be managed appropriately and given instruction to receive relevant supportive care. Additionally, for an event judged by the investigator to be a potential systemic allergic/hypersensitivity reaction, a blood sample should be drawn to test for antidrug antibodies.

For patients who experience a potential allergic or hypersensitivity reaction, consideration for any premedication for future injections will be agreed upon between the investigator and the sponsor and/or its designee. Examples of potential allergic or hypersensitivity reactions that might merit premedication include mild to moderate skin rashes, mild to moderate generalized pruritus and/or urticaria, and mild to moderate injection site reactions (for example, injection site erythema or injection site pruritus). Patients who develop clinically significant systemic allergic or hypersensitivity reactions after administration of investigational product who do not respond to symptomatic medication or have clinical sequelae (for example, hospitalization) should be discontinued from the study and should not receive further doses of investigational product, with or without premedication (see Section 8.2). Medications considered appropriate for premedication include but are not restricted to acetaminophen/paracetamol up to 1000 mg and antihistamines (for example, oral diphenhydramine 50 mg), given 30 to 60 minutes prior to investigational product injection. Patients may self-premedicate at home prior to administration of investigational product as directed by the investigator. All such premedications will be recorded as concomitant therapy. Corticosteroids are not permitted as agents for premedication.

9.5. Blinding

This study is an open-label study.

9.6. Concomitant Therapy

Patients will maintain their usual medication regimen for other concomitant diseases throughout the study unless that regimen is specifically excluded in the protocol. Patients taking concomitant medications should be on stable doses at the time of baseline and should remain at stable doses throughout the study unless changes need to be made for an AE. Additional systemic drugs are to be avoided during the study unless they are required to treat an AE. Other medications may be allowed if approved by the sponsor or its designee.

If the need for concomitant medication arises, inclusion or continuation of the patient may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist or CRP. Any additional medication used during the course of the study must be documented.

All concomitant medication taken during the study must be recorded on the concomitant medication page of the CRF. Treatment with concomitant psoriasis therapies during the study is permitted only as outlined in the Exclusion Criteria (Section 8.1.2) and as described in the following paragraphs. Patients taking permitted medications should be on chronic stable doses at the baseline visit (Week 0; Visit 2) as specified in Section 8.1.2.

The following therapies will not be permitted during the course of the study:

- psoriasis therapy as described in the Inclusion and Exclusion Criteria (Sections 8.1.1 and 8.1.2), except as described in the following paragraphs for topical agents.
- concomitant medications as described in the Inclusion and Exclusion Criteria (Sections 8.1.1 and 8.1.2)
- live vaccines
- phototherapy.

Topical Psoriasis Treatment: Topical psoriasis treatment as indicated below will be permitted after completion of Week 4 (Visit 9) and prior to Week 18 (Day 127) during the single-dose phase and after completion of the Week 12 visit during the multiple-dose phase.

- Topical treatments including, but not limited to corticosteroids, vitamin D analogues, tarzarotene, and tacrolimus are permitted. Only steroids of mild potency (for example, desonide, fluocinolone acetonide, and alclometasone) or low potency (that is, hydrocortisone) are recommended for the face, axilla, and/or genitalia. These topical medications should not be used within approximately 24 hours prior to study visits requiring sPGA and PASI measures.
- **Medicated shampoos and other nonsteroidal topical therapies:** Medicated shampoos, topical moisturizers/emollients, and other nonprescription topical products are permitted. These topical medications should not be used within approximately 12 hours prior to study visits requiring sPGA and PASI measures.

Vaccines: Use of nonlive seasonal vaccinations and/or emergency vaccination (such as rabies or tetanus vaccinations) is allowed.

Other Concomitant Therapies: Acetaminophen or aspirin will also be allowed as needed.

Traditional Chinese Medicine: Patients must stop any traditional Chinese treatments at least 14 days prior to study enrollment and must not resume treatment until after last study visit.

10. Sample Collection and Safety Data Collection

Attachment 1 and Attachment 2 list the schedules for sample collection in this study.

Attachment 3 lists the clinical laboratory tests that will be performed for this study.

Attachment 4 summarizes the blood volumes for all blood sampling during the study.

10.1. Laboratory Samples

Blood and urine samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health. Routine clinical laboratory tests will be analyzed by a central laboratory selected by Lilly.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.2. Samples for Pharmacokinetic and Pharmacodynamic Evaluations

10.2.1. Pharmacokinetic Samples

Samples for the measurement of serum ixekizumab concentrations will be collected from patients enrolled in the study at the time points specified in the PK sampling times in the Study Schedules (Attachment 1 and Attachment 2). An intensive sampling scheme is being implemented to capture the entire ixekizumab concentration profile after single-dose administration and at steady state during a dosing interval.

Venous blood samples (approximately 4 mL) will be collected into tubes, and serum ixekizumab concentrations will be determined. Instructions for collection and handling of blood samples will be provided by Lilly or its designee. The actual date and time (24-hour clock time) of each sampling will be recorded.

10.2.2. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of ixekizumab will be assayed using a validated enzyme-linked immunosorbent assay.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last patient visit for the study.

10.2.3. Pharmacodynamic Clinical Outcome Measures

The clinical outcome measures, PASI and sPGA, are considered the pharmacodynamic (PD) measures in this study.

The PASI is the most commonly used primary endpoint and measure of psoriasis severity in clinical trials (European Medicines Agency [EMA] 2004 WWW; Menter et al. 2008). The PASI combines assessments of the extent of BSA involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque induration/infiltration (thickness) in each region, yielding an overall score of 0 for no psoriasis to 72 for severe disease (Fredriksson and Pettersson 1978).

The static Physician Global Assessment (sPGA) is the physician's global assessment of the patient's psoriasis (Ps) lesions evaluated at a given time point (European Medicines Agency [EMA] 2004 [WWW]). Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).

Data will be collected at the times shown in the Study Schedules (Attachment 1 and Attachment 2).

10.3. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against ixekizumab. Immunogenicity will be assessed by a validated assay designed to detect antidrug antibodies in the presence of ixekizumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of ixekizumab. Immunogenicity samples may also be analyzed for ixekizumab serum concentration to facilitate in the interpretation of the immunogenicity data.

Samples may be stored for a maximum of 15 years following last patient visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to ixekizumab. The duration allows the sponsor to respond to regulatory requests related to ixekizumab.

10.4. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study. Planned safety assessments and measures are detailed in Section 10.4.3, but additional assessments and safety tests may be performed at the investigator's discretion.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

In addition to records of observations made at specific times, unexpected signs and symptoms and concomitant medications will be recorded in the clinical trial records throughout the study.

10.4.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

Cases of pregnancy that occur during maternal or paternal exposures to the investigational product should be reported. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

After the ICF is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or designee.

Any clinically significant findings from ECGs, laboratory test results, vital sign measurements, other procedures, and so on should be reported as AEs to Lilly or its designee.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, or investigational product via CRF, electronic data entry, or designated data transmission methods.

The investigator decides whether he or she interprets the observed AEs as related to disease, study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the investigational product, the following terminologies are defined:

- **Related**: A direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly related**: A cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Unrelated**: Without question, the AE is definitely not associated with the study treatment.

Per Lilly's standard operating procedures, all "related" and "possibly related" AEs and SAEs will be defined as related to the investigational product.

10.4.2. Serious Adverse Events

Serious adverse event collection and reporting will commence after the ICF is signed.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events occurring up to and including the patient's last study visit will be collected, regardless of the investigator's opinion of causation, in the clinical data collection database and the pharmacovigilance system at the sponsor.

If an investigator becomes aware of SAEs occurring to a patient after the patient's participation in the trial has ended, the investigator should report them to the sponsor, regardless of the investigator's opinion of causation, and the SAEs will be entered in the pharmacovigilance system at the sponsor.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

10.4.2.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 Code of Federal Regulations (CFR) 312.32 and European Union Clinical Trial Directive 2001/20/EC, and the associated detailed guidances or national regulatory requirements in participating countries, require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

10.4.3. Other Safety Measures

10.4.3.1. Physical Examination

Physical examinations and routine medical assessments will be conducted as specified in the Study Schedules (Attachment 1 and Attachment 2) and as clinically indicated.

10.4.3.2. Vital Signs

Vital signs (BP, respiratory rate, pulse rate, and body temperature) will be measured in a sitting posture. Any clinically significant findings that result in a diagnosis should be captured on the CRF. Additional measurements of vital signs may be performed at the discretion of the investigator.

10.4.3.3. Body Weight

Body weight will be recorded as specified in the Study Schedules (Attachment 1 and Attachment 2) and as clinically indicated.

10.4.3.4. Electrocardiograms

For each patient, a single 12-lead digital ECG will be collected according to the Study Schedules (Attachment 1 and Attachment 2). Electrocardiograms must be recorded before collecting any blood for safety or PK tests. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times when deemed clinically necessary. Collection of additional ECGs at a particular time point is allowed to ensure high quality records. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, ideally while the patient is still present, to determine whether the patient meets entry criteria at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to changes in QT/QTc interval from baseline) after enrollment, the investigator will determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

10.4.3.5. Chest X-Ray and Tuberculosis Testing

A posterior-anterior view chest x-ray will be obtained, unless the x-ray or results from a chest x-ray obtained within 6 months prior to the study are available. The chest x-ray or results will be reviewed by the investigator or designee to exclude patients with active TB infection.

In addition, patients will be tested at screening as indicated in the Study Schedules (Attachment 1 and Attachment 2) for evidence of active or latent TB (positive PPD [≥5-mm induration] or positive QTF or T-SPOT at screening but no other evidence of active TB). In sites where the QTF or T-SPOT test is available and, in the judgment of the investigator, preferred as an alternative to the PPD skin test for the evaluation of TB infection, it may be used instead of the

PPD test (positive test excluded) and may be read locally. If the QTF or T-SPOT test is indeterminate, 1 retest is allowed. If the retest is indeterminate, the patient will be excluded from the study. If the retest is positive but without clinical evidence of TB, the patient will be considered as latent TB for study purposes.

Patients with documentation of a negative test result within 3 months prior to baseline (Week 0; Visit 2) do not need a TB screen at Visit 1. Documentation of this test result must include a record of the size of the induration response. A PPD test recorded as negative without documenting the size of induration will result in a retest.

However, patients with a positive QTF or T-SPOT at screening, but no other evidence of active TB, may be rescreened 1 time and may be enrolled without repeating the test if the following conditions are met:

- after receiving at least 4 weeks of appropriate latent TB infection (LTBI) therapy, and
- no evidence of hepatotoxicity (ALT/AST must remain ≤2xULN) upon retesting of serum ALT/AST prior to randomization (such patients must complete appropriate LTBI therapy during the course of the study in order to remain eligible), and
- meet all other inclusion and exclusion criteria for participation.

If rescreening occurs within 6 months of the screening chest x-ray, there is no necessity for repeat of chest x-ray for considering enrollment. Patients who have a documented history of completing an appropriate TB treatment regimen with no history of re-exposure to TB since their treatment was completed and no evidence of active TB are eligible to participate in the study. Patients who have had household contact with a person with active TB are excluded, unless appropriate and documented prophylaxis for TB was given.

10.4.3.6. Quick Inventory of Depressive Symptomatology–Self Report, 16 item

The QIDS-SR_{16} is a self-administered, 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (APA 1994). A patient is asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity. The domains assessed by the instrument include: (1) sad mood, (2) concentration, (3) self-criticism, (4) suicidal ideation, (5) interest, (6) energy/fatigue, (7) sleep disturbance (initial, middle, and late insomnia or hypersomnia), (8) decrease/increase in appetite/weight, and (9) psychomotor agitation/retardation. Additional information and the QIDS-SR_{16} questions can be found at the University of Pittsburgh IDS/QIDS internet page (http://www.ids-qids.org).

10.4.3.7. Columbia-Suicide Severity Rating Scale

Consistent with the United States Food and Drug Administration (US-FDA) regulatory guidance (FDA 2012), any occurrence of suicide-related thoughts and behaviors will be assessed as indicated in the Study Schedules (Attachment 1 and Attachment 2) using the Columbia-Suicide Severity Rating Scale (C-SSRS), a scale that captures the occurrence, severity, and frequency of

suicide-related thoughts and behaviors during the corresponding assessment period. The scale includes suggested questions to elicit the type of information needed to determine if a suicide-related thought or behavior occurred.

Terms captured by the use of the C-SSRS can be mapped to Columbia Classification Algorithm for Suicide Assessment (Posner et al. 2007) to facilitate future pooling of data.

The first time the scale is administered in this study, the C-SSRS "Baseline" version will be used, and the findings will constitute the baseline assessment. The C-SSRS "Since Last Visit" scale will be used for all subsequent assessments. If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided. The Lilly Self-Harm Supplement should be completed every time the C-SSRS is administered. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

10.4.4. Safety Monitoring

The Lilly clinical pharmacologist or CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist or research physician will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist (CRS) when appropriate, and periodically review:

- trends in safety data
- laboratory analytes
- AEs including monitoring of infection.

10.4.5. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.5. Appropriateness and Consistency of Measurements

Pharmacokinetic measurements are appropriate for the proposed study design which consists of both single- and multiple-dose treatment groups. Safety measures used in this trial are all well established. The PASI and sPGA, rating measures specific for psoriasis, are well-recognized tools for assessing efficacy in this disease.

10.6. Compliance

Every attempt will be made to select patients who have the ability to understand and comply with instructions. Noncompliant patients may be discontinued from the study. The time and day of drug administration will be recorded. Drug accountability records will be maintained by the study site.

The specifications in this protocol for the timings of safety, PK, and PD sampling are given as targets, to be achieved within reasonable limits. Modifications may be made to the time points based upon the safety information obtained. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF.

Any major modifications that might affect the conduct of the study, patient safety, and/or data integrity will be detailed in a protocol amendment.

11. Sample Size and Analyses Methods

11.1. Determination of Sample Size

Up to 45 patients (15 patients for the single-dose phase and 30 patients for the multiple-dose phase) will be enrolled to target that 8 patients complete the single-dose phase and 20 patients (10 for each dosing regimen) complete the multiple-dose phase.

This study has been designed to meet the primary objective of assessing the PK of a single dose and multiple doses of ixekizumab in Chinese patients with psoriasis. The sample size was chosen to meet Chinese regulatory requirements and to provide sufficient data to evaluate the objectives and is not intended to achieve any prior statistical requirements.

11.2. Data Analysis Plans

11.2.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

PK and PD analyses will be conducted on the full analysis set. This set includes all data from all patients receiving at least 1 dose of the investigational product, and for PK analyses, it includes patients with sufficient PK samples to enable a PK assessment. Safety analyses will be conducted for all enrolled patients, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Analyses will be fully detailed in the statistical analysis plan. Study results may be pooled with the results of other studies for population PK analysis to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

Data will be presented using summary tables and patient data listings.

11.2.2. Study Participant Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

11.2.3. Study Participant Characteristics

The patient's age, sex, weight, BMI, height, race, and ethnicity, or other demographic characteristics (such as geographic region, baseline disease severity, duration of disease, previous systemic therapy, and previous biologic therapy) will be summarized.

Baseline clinical measures (such as sPGA score, PASI total score, and BSA) will be summarized.

11.2.4. Pharmacokinetic Analyses

Pharmacokinetic parameter estimates for ixekizumab will be calculated by standard noncompartmental methods of analysis. The PK parameters for estimation after the single dose will include C_{max}, time to C_{max} (t_{max}), and area under the concentration versus time curve (AUC). Other parameters such as terminal half-life, apparent clearance, and apparent volume of distribution may be determined. The PK parameters for estimation after the last dose of the 8- week treatment will include C_{max}, t_{max}, and AUC. Other parameters such as terminal half-life, apparent clearance, and apparent volume of distribution may be determined.

Descriptive statistics of PK parameters will be presented for each dose regimen (single dose, Q2W multiple dose, and Q4W multiple dose). Data may also be analyzed by population PK methods alone or in combination with other studies as deemed appropriate.

11.2.5. Pharmacodynamic Analyses

11.2.5.1. Pharmacodynamic Parameter Estimation

Clinical outcome measures PASI and sPGA are considered the PD measures in this study (see Section 10.2.3).

11.2.5.2. Pharmacodynamic Statistical Inference

Descriptive statistics will be presented for PASI scores and sPGA scores (for both the single-dose and multiple-dose phases of the study) by dose regimen and study day. Mean percentage change in PASI scores from baseline will be calculated and summarized.

Additional analyses may be conducted as deemed appropriate.

11.2.6. Pharmacokinetic/Pharmacodynamic Analyses

Exploratory exposure-response relationship analyses for PASI scores and sPGA scores may be conducted, if deemed appropriate.

11.2.7. Safety Analyses

11.2.7.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur prior to study enrollment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

The number of SAEs related to the investigational product will be reported.

11.2.7.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include the C-SSRS, safety laboratory test parameters, and vital signs. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

11.2.7.3. Evaluation of Immunogenicity

The frequency of antibody formation to ixekizumab will be determined. If a neutralization assay is performed, the frequency of neutralizing antibodies will be determined. The relationship between the presence (or absence) of antibodies and clinical parameters (for example, AEs and PD measures) will be assessed, as will the relationship between the presence of antibodies and the PK parameters of ixekizumab.

11.3. Interim Analyses

No interim analyses are planned for this study in order to support the primary or secondary objectives. If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, CRP or investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

However, interim access to data may be conducted to support comparisons of PK data from Chinese patients in this study to PK data observed in non-Chinese patients from global studies, to enable planning for future studies. No changes to this study design are planned based on these PK analyses. Additionally, interim access to safety data may occur if deemed necessary or appropriate.

12. Data Management Methods

12.1. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate.
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site.
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- review and evaluate CRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

12.2. Data Capture Systems

12.2.1. Source Data and Case Report Form

A source document is the first record of data. These can be paper (for example, ECG tracing or patient diary), a paper CRF on which the data is initially recorded, or data captured directly on an investigator site electronic system (for example, Holter monitor record data files or electronic health records). The site must retain all source records and must maintain a record of any data where source data are directly entered into the paper CRF.

Data may then be entered into either an electronic (eCRF) or paper CRF, and the process will be documented and communicated by the sponsor to the investigator site before first patient visit.

Some investigator site data may be collected directly in the paper CRF, whereas other data that is collected by the site on paper or electronic records may be transferred to the paper CRF.

Lilly does not allow direct source data entry into Lilly computer systems, with the exception of the investigator site systems at the Lilly clinical research unit.

For data handled by a data management third-party organization (TPO), CRF data and some or all data that are related will be managed and stored electronically in the TPO system. Subsequent to the final database lock, validated data will be transferred to the sponsor.

For data handled internally, CRF data and some or all data that are related will be managed by the sponsor and stored electronically in the sponsor's system.

12.2.2. Ancillary Data

Data managed by a central vendor will be stored electronically in the central laboratory's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse and the TPO's system.

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. Data will subsequently be transferred from the bioanalytical laboratory to the Lilly data warehouse and the TPO's system.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study and to document that the patient is satisfied with his or her understanding of the potential risks and benefits of participating in the study and desires to participate in the study.

The investigator is ultimately responsible for ensuring that informed consent is given by each patient before the study is started. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of the investigational product.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at investigative sites. All ICFs must be compliant with the ICH guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

The study site's ERB(s) should be provided with the following:

- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae.

13.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2) the ICH GCP Guideline [E6]
3) applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of the sponsor will be assigned to a TPO.

An identification code assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Site-specific contact information may be provided in a separate document.

13.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

The final report coordinating investigator or designee will sign the clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most enrolled patients will serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

The sponsor's responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

14. References

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Attachment 1. Protocol RHBN Study Schedule—Single-Dose Phase

Study Schedule Protocol I1F-MC-RHBN—Single-Dose Phase

Period / Procedure	Screening	Dosing	Observation Period											
Visit Number	**V1[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
Day Relative to Start of Study Drug	-28 to -3	1	3	5	8	11	15	22	29	43	57	85	113	141
Week Relative to Start of Study Drug		0			1		2	3	4	6	8	12	16	20
Visit Tolerance Interval (Days)		0	0	0	0	0	±1	±2	±2	±2	±2	±2	±7	±7
Informed consent (before procedures/ tests)	X													
Demographics, height, weight[b]	X													
Inclusion/exclusion review	X	PreD												
History and/or physical examination	X	PreD								X			X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Preexisting conditions/adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X	PreD, 1h, 3 h							X		X	X	X	X
Body temperature	X	PreD												X
Chest x-ray and PPD/QTF or T-SPOT testing for TB[d,e]	X													
ECG[f,g]	X	PreD	X	X						X				X
Study drug dosed		X												
Serum ixekizumab PK sample[h]		PreD	X	X	X	X	X	X	X	X	X	X	X	X
QIDS-SR_{16}	X													
C-SSRS		PreD	X	X	X	X	X	X	X	X	X	X	X	X
PASI	X	PreD					X			X		X	X	X
sPGA	X	PreD					X			X		X	X	X
Clinical chemistry, electrolytes, hematology[i]	X	PreD			X		X		X	X				X
High-sensitivity C-reactive protein		PreD					X			X				X
Urinalysis	X	PreD			X					X				X
Serum for anti-ixekizumab antibody		PreD			X		X		X			X		X
Urine pregnancy test[j]	X	PreD								X				X

Study Schedule Protocol I1F-MC-RHBN—Single-Dose Phase

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; h = hour(s); PASI = Psoriasis Area and Severity Index; PK = pharmacokinetics; PPD = purified protein derivative; PreD = prior to dose; QIDS-SR_{16} = Quick Inventory of Depressive Symptomatology–Self Report, 16 item; QTF = QuantiFERON®-TB Gold test; sPGA = static Physician's Global Assessment; TB = tuberculosis; T-SPOT = T-SPOT®.TB test; V = visit.

Notes: Patients who withdraw from the treatment phase will have an early treatment discontinuation visit with procedures performed as shown for Visit 14.

Each blood draw should be collected at approximately the same time of day as the dose administration at Week 0 (Visit 2).

[a] Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results).

[b] Weight may be recorded at other visits as clinically indicated.

[c] Sitting blood pressure, respiratory rate, and pulse rate are to be obtained at approximately the same time as ECG measurements or plasma ixekizumab blood sampling. When multiple assessments are scheduled for the same time point, the order of completion should be ECG, vital signs, and then blood sampling.

[d] Patients with documentation of a negative test result within 3 months prior to baseline (Week 0; Visit 2) do not need a TB screen at Visit 1.

[e] See Section 10.4.3.5 for detailed description of PPD/QTF or T-SPOT testing.

[f] To account for diurnal variations, ECGs should be performed at approximately the same time of day as the Visit 2 predose ECG (±2 hours).

[g] Additional ECGs may be performed as clinically indicated.

[h] Each blood draw should be collected at approximately the same time of day as the initial sample taken prior to dose administration at Week 0 (Visit 2).

[i] Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator.

[j] Required for all women.

Attachment 2. Protocol RHBN Study Schedule—Multiple-Dose Phase

Study Schedule Protocol I1F-MC-RHBN—Multiple-Dose Phase

Period / Procedure	Screening	Treatment Period																Observation Period					
Visit Number	**V1[a]**	**V2 Randomize**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V11A**	**V11B**	**V11C**	**V11D**	**V11E**	**V11F**	**V12**	**V12A**	**V13**	**V14**	**V15**	**V16**
Day Relative to Start of Study Drug	-28 to -3	1	3	5	8	11	15	22	29	43	57	59	61	64	67	71	78	85	99	113	141	169	197
Week Relative to Start of Study Drug		0			1		2	3	4	6	8	8	8	9	9	10	11	12	14	16	20	24	28
Visit Tolerance Interval (Days)		0	0	0	0	0	±1	±2	±2	±2	±2	±1	±1	±1	±1	±1	±2	±2	±7	±7	±7	±7	±7
Informed consent (before procedures/tests)	X																						
Demographics, height, weight[b]	X																						
Inclusion/exclusion review	X	PreD																					
History and/or physical examination	X	PreD								X										X			X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X							X	X	X	X	X	X
Preexisting conditions/adverse events	X	X	X	X	X	X	X	X	X	X	X							X	X	X	X	X	X
Vital signs[c]	X	PreD, 1h, 3 h							X		X							X		X	X	X	X
Body temperature	X	PreD					X		X	X[d]	X												X
Chest x-ray and PPD/QTF or T-SPOT testing for TB[e,f]	X																						
ECG[g,h]	X	PreD	X	X			X		X		X												X
Study drug dosed																							
Q2W group		X					X		X	X	X												
Q4W group		X							X		X												
Serum ixekizumab PK sample[i,j]		PreD	X	X	X	X	X	X	X	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X
QIDS-SR_{16}	X																						
C-SSRS		PreD	X	X	X	X	X	X	X	X	X							X		X	X	X	X
PASI	X	PreD					X			X	X							X		X	X	X	X

Study Schedule Protocol I1F-MC-RHBN—Multiple-Dose Phase

Period / Procedure	Entry	Treatment Period																Observation Period					
Visit Number	**V1[a]**	**V2 Randomize**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V11A**	**V11B**	**V11C**	**V11D**	**V11E**	**V11F**	**V12**	**V12A**	**V13**	**V14**	**V15**	**V16**
Day Relative to Start of Study Drug	-28 to -3	1	3	5	8	11	15	22	29	43	57	59	61	64	67	71	78	85	99	113	141	169	197
Week Relative to Start of Study Drug		1			2		3	4	5	7	9	9	9	10	10	11	12	13	15	17	21	25	29
Visit Tolerance Interval (Days)		0	0	0	0	0	±1	±2	±2	±2	±2	±1	±1	±1	±1	±1	±2	±2	±7	±7	±7	±7	±7
sPGA	X	PreD					X			X	X							X		X	X	X	X
Clinical chemistry, electrolytes, hematology[l]	X	PreD			X		X		X	X										X			X
High-sensitivity C-reactive protein		PreD					X			X										X			X
Urinalysis	X	PreD			X					X										X			X
Serum for anti-ixekizumab antibody		PreD			X		X		X									X			X		X
Urine pregnancy test[m]	X	PreD								X										X			X

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; h = hour(s); PASI = Psoriasis Area and Severity Index; PK = pharmacokinetics; PPD = purified protein derivative; PreD = prior to dose; Q2W = every 2 weeks; Q4W = every 4 weeks; QIDS-SR_{16} = Quick Inventory of Depressive Symptomatology–Self Report,16 item; QTF = QuantiFERON®-TB Gold test; sPGA = static Physician's Global Assessment; TB = tuberculosis; T-SPOT = T-SPOT®.TB test; V = visit.

Notes: Patients who withdraw from the treatment phase will have an early treatment discontinuation visit with procedures performed as shown for Visit 16.

Visits denoted by a letter after the visit number are visits at which the patient will visit the study site for serum ixekizumab sampling only. No other tests will be performed at these visits.

a Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results).

b Weight may be recorded at other visits as clinically indicated.

c Sitting blood pressure, respiratory rate, and pulse rate are to be obtained at approximately the same time as ECG measurements or plasma ixekizumab blood sampling. When multiple assessments are scheduled for the same time point, the order of completion should be ECG, vital signs, and then blood sampling.

d Body temperature should be taken only for patients in the Q2W group at this visit because patients in the Q4W group do not receive study drug at this visit.

e Patients with documentation of a negative test result within 3 months prior to baseline (Week 0; Visit 2) do not need a TB screen at Visit 1.

f See Section 10.4.3.5 for detailed description of PPD/QTF or T-SPOT testing.

g To account for diurnal variations, ECGs should be performed at approximately the same time of day as the Visit 2 predose ECG (±2 hours).

h Additional ECGs may be performed as clinically indicated.

i Each blood draw should be collected at approximately the same time of day as the initial sample taken prior to dose administration at Week 0 (Visit 2).

[j] When PK samples are scheduled at the same visits as dose administrations, then the PK sample should be taken pre-dose.
[k] Only for the Q2W dosing regimen.
[l] Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator.
[m] Required for all women.

Attachment 3. Protocol RHBN Clinical Laboratory Tests

Laboratory Tests

Hematology[a,b]
Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Mean cell volume (MCV)
Mean cell hemoglobin concentration (MCHC)
Leukocytes (WBC)
Neutrophils, segmented
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets

Urinalysis[a]
Specific gravity
pH
Protein
Glucose
Ketones
Blood
Leukocyte esterase
Urine drug screen (at screening only)

Urine Pregnancy Test[c,d]

Clinical Chemistry[a,b]
Serum Concentrations of:
Sodium
Potassium
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Alanine aminotransferase (ALT/SGPT)
Aspartate aminotransferase (AST/SGOT)
Blood urea nitrogen (BUN)
Creatinine
Calcium
Glucose, nonfasting
Total protein
Albumin
Cholesterol
High-sensitivity C-reactive protein (see Study Schedule for sampling time points)

Other Tests
Follicle-stimulating hormone (FSH)[a,d]
Hepatitis B core antibody, Hepatitis B surface antibody, and Hepatitis B surface antigen[a,e]
Hepatitis C antibody[a,e]
Human immunodeficiency virus (HIV)[a,e]
Purified protein derivative (PPD) skin test[c,f]

Immunogenicity testing (anti-ixekizumab antibody)

[a] Assayed by Lilly-designated laboratory.
[b] Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator.
[c] Performed and read by investigator or investigator's designee.
[d] Required for all women of childbearing potential. Also required at Visit 1 for women ≥40 and <60 years of age who have had a cessation of menses for ≥12 months and an FSH test confirming nonchildbearing potential (≥40 mIU/mL).
[e] Test required only at Visit 1 to determine eligibility of subject for the study. Test may be waived if results are available from a test obtained within the last 6 months.
[f] The QuantiFERON®-TB Gold test or T-SPOT®.TB test may be used instead of the PPD test at Visit 1 to determine eligibility of a subject for the study. Test may be waived if documented negative results are available from a test obtained within the last 3 months and no history of exposure to a case of active tuberculosis (TB) or visit to a TB endemic area since the time of the test.

Attachment 4. Protocol RHBN Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study. Fewer venipunctures and blood draws may actually occur, but this will not require a protocol amendment.

Protocol I1F-MC-RHBN Sampling Summary—Single-Dose Phase

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	45	1	45
Blood chemistry and hematology[a]	12	6	72
High-sensitivity C-reactive protein	2.5	4	10
Anti-ixekizumab antibody	7.5	6	45
Serum ixekizumab PK sample[b]	4	13	52
Total for clinical purposes (rounded up to the nearest 10 mL)			230

[a] Additional samples may be drawn if needed for safety purposes.

[b] With the exception of Visit 12, blood samples that may be analyzed for ixekizumab serum concentration will be collected at the same time as the immunogenicity samples. These results may be used to facilitate the interpretation of the immunogenicity data.

Protocol I1F-MC-RHBN Sampling Summary—Multiple-Dose Phase

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	45	1	45
Blood chemistry and hematology[a]	12	7	84
High-sensitivity C-reactive protein	2.5	5	12.5
Anti-ixekizumab antibody	7.5	7	52.5
Serum ixekizumab PK sample[b]	4	22	88
Total for clinical purposes (rounded up to the nearest 10 mL)			290

[a] Additional samples may be drawn if needed for safety purposes.

[b] With the exception of Visit 12, blood samples that may be analyzed for ixekizumab serum concentration will be collected at the same time as the immunogenicity samples. These results may be used to facilitate the interpretation of the immunogenicity data.

Attachment 5. Protocol Amendment I1F-MC-RHBN(c) Summary
A Phase 1, Single- and Multiple-Dose Study to Assess the Safety and Pharmacokinetics of Ixekizumab (LY2439821) (Anti–IL-17 Humanized Antibody) in Chinese Patients with Psoriasis Vulgaris

Overview

Protocol I1F-MC-RHBN(b), A Phase 1, Single- and Multiple-Dose Study to Assess the Safety and Pharmacokinetics of Ixekizumab (LY2439821) (Anti–IL-17 Humanized Antibody) in Chinese Patients with Psoriasis Vulgaris, has been amended. The new protocol is indicated by Amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Section 9.2 has been amended to allow for warming of the syringes for approximately 30 minutes as opposed to strictly 30 minutes. This will allow more flexibility and ease of operation for the site.
- Section 9.6 has been amended to ensure alignment with exclusion criterion [14] and to include additional topical therapies for patient's use during the study since they will not impact the primary and secondary objectives.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

Section 9.2 Treatment Administration

Allow the prefilled syringe containing the drug product to equilibrate to room temperature for approximately 30 minutes. Do not return syringe to the refrigerator. ~~The prefilled syringes should be taken from the refrigerator and allowed to warm up to room temperature for 30 minutes prior to use.~~

Section 9.6 Concomitant Therapy

The following therapies will not be permitted during the course of the study:

- psoriasis therapy as described in the Inclusion and Exclusion Criteria (Sections 8.1.1 and 8.1.2), except as described in the following paragraphs for topical agents.
- concomitant medications as described in the Inclusion and Exclusion Criteria (Sections 8.1.1 and 8.1.2)
- live vaccines
- phototherapy.

Topical Psoriasis Treatment: Topical psoriasis treatment as indicated below will be permitted after completion of Week 4 (Visit 9) and prior to Week 18 (Day 127) during the single-dose phase and after completion of the Week 12 visit during the multiple-dose phase.

- ~~**Steroids:**~~ Topical treatments including, but not limited to corticosteroids, vitamin D analogues, tarzarotene, and tacrolimus are permitted. ~~Steroids~~Only steroids of mild potency (for example, desonide, fluocinolone acetonide, and alclometasone) or low potency (that is, hydrocortisone) ~~will be permitted~~ ~~for use limited to~~ are recommended for the face, axilla, and/or genitalia ~~as needed~~. These topical medications should not be used within approximately 24 hours prior to study visits requiring sPGA and PASI measures. ~~More potent topical steroids may be used as needed after last study visit.~~
- **Medicated shampoos and other nonsteroidal topical therapies:** Medicated shampoos, topical moisturizers/emollients, and other nonprescription topical products are permitted. These topical medications should not be used within approximately 12 hours prior to study visits requiring sPGA and PASI measures.

Other Concomitant Therapies: ~~The following will be allowed as needed: shampoos that do not contain <3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues; topical moisturizers/emollients and other nonprescription topical products that do not contain urea, >3% salicylic acid, α- or β-hydroxyl acids, corticosteroids, or vitamin D3 analogues; and bath oils and oatmeal bath preparations. (These topical therapies are not to be used within 12 hours prior to a study visit.) Shampoos that contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues may be used as needed after end-of-study assessments are complete.~~ Acetaminophen or aspirin will also be allowed as needed.

Leo Document ID = 0858ddad-8548-4a3f-b56b-8a7517d78796

Approver: PPD
Approval Date & Time: 20-Jun-2017 14:36:57 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 20-Jun-2017 16:05:15 GMT
Signature meaning: Approved