Protocol I1F-MC-RHBH(b)

A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Maintenance Dosing Period to Evaluate the Efficacy and Safety of LY2439821 in Chinese Patients with Moderate-to-Severe Plaque Psoriasis

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1. Protocol I1F-MC-RHBH(b)

A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Maintenance Dosing Period to Evaluate the Efficacy and Safety of LY2439821 in Chinese Patients with Moderate-to-Severe Plaque Psoriasis

Ixekizumab (LY2439821)

Study I1F-MC-RHBH is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study examining the effect of 2 dose regimens of ixekizumab (80 mg every 2 weeks [Q2W] or every 4 weeks [Q4W]; each with a starting dose of 160 mg) versus placebo in patients with moderate-to-severe plaque psoriasis (Ps) during an Induction Dosing Period with dosing for 12 weeks and the primary endpoint measured at 12 weeks, followed by a randomized, 48-week Maintenance Dosing Period. During the Maintenance Dosing Period, the study will evaluate the maintenance of response/remission with dosing interval of Q4W, as well as relapse or rebound following treatment withdrawal, and response to retreatment following relapse.

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Approval Date: 14-Jun-2019 GMT

2. Synopsis

Study Rationale

Ixekizumab (LY2439821) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (MAb) that neutralizes the cytokine interleukin-17A (IL-17A, also known as IL-17). It has a high affinity for and neutralizes the activity of both human and monkey IL-17. It has high specificity to IL-17A (IL-17) and has no cross-reactivity to other IL-17 family members (IL-17B-F). Ixekizumab blocks IL-17 binding to the IL-17 receptor (IL-17R). Specific inhibition of IL-17 represents a targeted approach to the management of psoriasis (Ps) and a novel mechanism of action compared to other Ps therapies. As such, ixekizumab may provide a therapeutic option for patients who are candidates for initial systemic treatment as well as those patients who have lost response, failed to respond, or are intolerant to current marketed drugs. Ixekizumab may provide an alternative therapy providing a favorable benefit/risk profile. Specifically, targeting IL-17 with ixekizumab is hypothesized to provide optimal therapeutic benefit while reducing the risk of impacting host defenses, which may be inherent with some other biologic-based immunomodulatory treatments.

Clinical Protocol Synopsis: Study I1F-MC-RHBH

Name of Investigational Product: Ixekizumab (LY2439821)

Title of Study: A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Maintenance Dosing Period to Evaluate the Efficacy and Safety of LY2439821 in Patients with Moderate-to-Severe Plaque Psoriasis

Number of Planned Patients:	**Phase of Development:** 3
Entered: 525 Enrolled/Randomized: 420 Planned to Complete: 336	

Length of Study:
Planned first patient visit: Apr 2018 Planned last patient visit: Jun 2020

Objectives: The co-primary objectives of the study are to assess whether ixekizumab 80 mg every 2 weeks (Q2W) or 80 mg every 4 weeks (Q4W) is superior to placebo at Week 12 in the treatment of patients with moderate-to-severe plaque Ps as measured by:

- Proportion of patients with a static Physician Global Assessment (sPGA) (0, 1) with at least a 2-point improvement from baseline
- Proportion of patients achieving a ≥75% improvement in Psoriasis Area and Severity Index (PASI 75) from baseline

The major secondary objectives of the study are to assess whether ixekizumab 80 mg Q2W or 80 mg Q4W induction dosing and 80 mg Q4W maintenance dosing are superior to placebo in the treatment of patients with moderate-to-severe plaque Ps as measured by:

- Proportion of patients achieving an sPGA (0) (remission) at Week 12
- Proportion of patients achieving a ≥90% improvement in PASI (PASI 90) at Week 12
- Proportion of patients achieving a 100% improvement in PASI (PASI 100) at Week 12
- Proportion of patients maintaining an sPGA (0, 1) from Week 12 after re-randomization at start of the Maintenance Dosing Period to Week 60
- Proportion of patients who maintain or achieve an sPGA (0) from Week 12 after re-randomization to Week 60
- Proportion of patients achieving an Itch Numeric Rating Scale (NRS) ≥4 point reduction from baseline at Week 12 for patients who had baseline Itch NRS ≥4

- Change from baseline in dermatology-specific quality of life (Dermatology Life Quality Index [DLQI]) at Week 12
- Change from baseline in Nail Ps Severity Index (NAPSI) score at Week 12 in patients with baseline fingernail involvement

The other secondary objectives of the study are as follows:

- To assess the efficacy of ixekizumab 80 mg Q2W or 80 mg Q4W compared to placebo at Week 12 and over the Induction Dosing Period by evaluating:
    - Time course of response to treatment as measured by the proportion of patients with an sPGA (0, 1) with at least a 2-point improvement from baseline
    - Time course of response to treatment as measured by the proportion of patients with an sPGA (0)
    - Time course of response to treatment as measured by the proportion of patients achieving ≥50% improvement in PASI score from baseline (PASI 50), PASI 75, PASI 90, and PASI 100
    - Time course of response to treatment as measured by change and percent improvement of PASI from baseline
    - Time to sPGA response as measured by an sPGA (0, 1)
    - Time to PASI 75 response
    - Change from baseline in percent of body surface area (BSA) involvement of Ps
    - Change from baseline in NAPSI score in patients with baseline fingernail involvement
    - Change from baseline in Ps Scalp Severity Index (PSSI) score in patients with baseline scalp involvement
    - Change from baseline in other health outcome endpoints: Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, and patient's global assessment of disease severity
    - Change from baseline in itching severity (Itch NRS) score
    - Change from baseline on dermatology-specific quality of life (DLQI)
    - Change from baseline in Palmoplantar PASI (PPASI) and proportion of patients achieving ≥50% improvement in PPASI score from baseline (PPASI 50), ≥75% improvement in PPASI score from baseline (PPASI 75), and a 100% improvement in PPASI score from baseline (PPASI 100) in patients with baseline palmoplantar involvement
- To assess maintenance of efficacy of ixekizumab Q4W compared to placebo at Week 60 and during the Maintenance Dosing Period among ixekizumab-treated patients who had an sPGA (0, 1) at Week 12 and were re-randomized by evaluating:
    - Time to relapse (sPGA ≥3)
    - Time course of the loss of response (relapse) to treatment as measured by an sPGA ≥3
    - Time course of response to treatment as measured by the proportion of patients who maintain an sPGA (0, 1), and by the proportion of patients who maintain or achieve an sPGA (0)
    - Time course of response to treatment as measured by change from baseline and percent improvement from baseline of PASI
    - Change from baseline in percent of BSA involvement of Ps
    - Incidence of disease rebound within 8 weeks (worsening of Ps severity over baseline sPGA score, ***or*** worsening of Ps severity over baseline PASI score by 125%, ***or*** change in Ps phenotype [for example, from plaque to pustular]) after re-randomization to placebo at Week 12
    - Time course of response to treatment as measured by the proportion of patients who maintain or achieve a PASI 75, PASI 90, and PASI 100
    - Change from baseline in NAPSI score in patients with baseline fingernail involvement
    - Change from baseline in PSSI score in patients with baseline scalp involvement
    - Change from baseline in itching severity (Itch NRS) score
    - Change from baseline on dermatology-specific quality of life (DLQI)

- Change from baseline in other health outcome endpoints: SF-36 PCS and MCS scores, and patient's global assessment of disease severity
- Change from baseline in PPASI and proportion of patients achieving PPASI 50, PPASI 75, and a PPASI 100 in patients with baseline palmoplantar involvement

- To assess the efficacy of ixekizumab 80 mg Q4W following disease relapse after re-randomization to placebo treatment in the Maintenance Dosing Period by evaluating:
  - Proportion of patients who regain an sPGA (0, 1) within 12 weeks after ixekizumab retreatment
  - Proportion of patients who achieve a PASI 75, PASI 90, PASI 100 within 12 weeks after ixekizumab retreatment
- To assess the efficacy of ixekizumab 80 mg Q2W or 80 mg Q4W compared to placebo on joint pain at Week 12 and over the Induction Dosing Period, as well as at Week 60 and during the Maintenance Dosing Period in patients who had an sPGA (0, 1) at Week 12 and were re-randomized, by evaluating change from baseline in joint pain (Joint Pain visual analog scale [VAS]) score in patients with psoriatic arthritis (PsA) at baseline
- To evaluate the potential development of anti-ixekizumab antibodies and their impact on patient safety and efficacy
- To measure ixekizumab exposure and assess the relationship between exposure and efficacy, and exposure and immunogenicity

Study Design: Study I1F-MC-RHBH (RHBH) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study examining the effect of ixekizumab versus placebo in patients with moderate-to-severe plaque Ps during an Induction Dosing Period with the primary endpoint at 12 weeks, followed by a randomized Maintenance Dosing Period to Week 60. During the Induction Dosing Period, the study will evaluate the efficacy and safety of 2 dose regimens of ixekizumab (80 mg Q2W or Q4W) compared with placebo. During the Maintenance Dosing Period, the study will evaluate the maintenance of response/remission with the dose regimen of 80 mg Q4W ixekizumab, the safety of this regimen, as well as relapse or rebound following treatment withdrawal, and response to retreatment following relapse.

The study consists of 4 periods:

- **Period 1:** Screening Period (Visits 1 and 1A) lasting from 4 to 30 days prior to Period 2 (baseline; Week 0; Visit 2)
- **Period 2:** Induction Dosing Period will be a double-blind treatment period that will occur from Week 0 (baseline; Visit 2) to Week 12 (Visit 7); dosing will occur Q2W from Weeks 0 to 10 and evaluation of primary endpoints will occur at Week 12 prior to the Week 12 dose.
- **Period 3:** Maintenance Dosing Period will be a double-blind treatment period that will occur from Week 12 (Visit 7) to Week 60 (Visit 19). Two treatment groups (80 mg Q4W and placebo) will be evaluated to determine the maintenance of response/remission, the relapse or rebound following treatment withdrawal, and the response to retreatment following relapse. At Week 12 (Visit 7), patients who enter Period 3 will be classified as a responder or non-responder according to the following criteria:
  - **Responder** = sPGA score of "0" or "1"
  - **Non-responder** = sPGA score of >1
- **Period 4:** Post-Treatment Follow-Up Period occurring from last treatment period visit or Early Termination Visit (ETV) up to a minimum of 12 weeks following that visit

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 Ps based on a confirmed diagnosis of chronic Ps vulgaris for at least 6 months, who are candidates for phototherapy and/or systemic therapy, and who have ≥10% BSA involvement, an sPGA score of ≥3, and a PASI score ≥12 at screening and baseline.

Investigational Product, Dosage, and Mode of Administration or Intervention:

Induction Dosing Period

- **80 mg Q2W** = A starting dose of 160 mg (Week 0) given as 2 subcutaneous (SC) injections followed by 80 mg given as 1 SC injection Q2W (Weeks 2, 4, 6, 8, and 10).
- **80 mg Q4W** = A starting dose of 160 mg (Week 0) given as 2 SC injections followed by 80 mg given as 1 SC injection Q4W (Weeks 4 and 8). To maintain blinding, placebo is given as 1 SC injection at Weeks 2, 6, and 10.

Maintenance Dosing Period

80 mg Q4W = A dose of 80 mg given as 1 SC injection + placebo as 1 SC injection at Week 12; 80 mg given as 1 SC injection Q4W thereafter.

Planned Duration of Treatment: Up to approximately 2 years for study participation (Screening Period: 4 to 30 days; Induction Dosing Period: 12 Weeks; Maintenance Dosing Period: 48 weeks; Post-Treatment Follow-Up Period: 12 to 24 weeks after the date of the patient's ETV or last regularly scheduled visit).

Reference Therapy, Dose, and Mode of Administration or Comparative Intervention:

Induction Dosing Period

- **Placebo** = Placebo (Week 0) given as 2 SC injections followed by placebo given as 1 SC injection Q2W (Weeks 2, 4, 6, 8, and 10).

Maintenance Dosing Period

- **Placebo** = Placebo given as 2 SC injections at Week 12 followed by placebo given as 1 SC injection Q4W thereafter.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoints are sPGA (0, 1) and PASI 75 response at Week 12 (Visit 7). The following secondary efficacy endpoints will be assessed in this study: sPGA (0), PASI 50, PASI 90, PASI 100, NAPSI, PSSI, PPASI 50, PPASI 75, PPASI 100, and BSA.

Safety: The following safety measures will be assessed in this study: serious adverse events (SAEs), adverse events (AEs), AEs of special interest (AESI), suspected unexpected serious adverse reactions (SUSARs), concomitant medications, physical evaluations, chest x-ray and tuberculosis (TB) testing, vital signs, electrocardiograms (ECGs), blood pressure, and laboratory evaluations (including immunogenicity testing [anti-drug antibodies (ADAs)] and safety-related immune markers such as neutrophil counts).

Health Outcomes: The following health outcome measures will be assessed in this study: Itch NRS, DLQI, SF-36 PCS and MCS scores, patient's global assessment of disease severity, and joint pain VAS.

Immunogenicity: Immunogenicity will be assessed by a validated assay designed to perform in the presence of ixekizumab.

Pharmacokinetics: Blood samples will be analyzed for ixekizumab concentrations in serum using a validated method.

Analysis Methods:

Sample size: The total sample size for the study is 420 patients randomized at a 2:2:1 ratio in the blinded Induction Dosing Period to 80 mg Q2W, 80 mg Q4W, and placebo, respectively. In order to account for multiple testing for the 2 ixekizumab groups, a 2-sided Fisher's exact test at the 0.025 level is assumed. Assuming the response rates for both sPGA (0, 1) and PASI 75 at Week 12 (Visit 7) are 75% for each ixekizumab treatment group and 5% for the placebo group, 168 patients in 80 mg Q2W (or 80 mg Q4W) versus 84 patients in placebo group will provide >99% power to test the superiority of each ixekizumab dose regimen to placebo for sPGA (0, 1) and for PASI 75. These assumptions are based on the integrated results from the pivotal Phase 3 psoriasis studies I1F-MC-RHAZ (RHAZ), I1F-MC-RHBA (RHBA), and I1F-MC-RHBC (RHBC).

Analysis population: Unless otherwise specified, efficacy and health outcomes analyses for Period 2 (Induction Dosing Period) will be conducted on the intent-to-treat population (ITT), defined as all randomized patients, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment to which they were assigned. In addition, the primary analyses will be repeated using the per protocol set (PPS), which is defined as all randomized patients who are compliant with therapy, who do not have a subset of important protocol deviations that impact the primary efficacy endpoints, and whose investigator site does not have significant Good Clinical Practice (GCP) issues that require a report to the regulatory agencies prior to Week 12 (Visit 7). Safety analyses for Period 2 will be conducted on the safety population, defined as all randomized patients who received at least 1 dose of study treatment. Patients will be analyzed according to the treatment to which they were assigned. Efficacy, health outcomes, and safety analyses for Period 3 (Maintenance Dosing Period) will be conducted on the Maintenance Dosing Period Primary population, defined as all re-randomized patients (that is, patients randomized to ixekizumab in Period 2 who achieved an sPGA (0, 1) and were re-randomized at Week 12) who received at least 1 dose of study treatment during Period 3 (Maintenance Dosing Period). Patients will be analyzed according to the treatment to which they were re-randomized.

Primary and secondary analyses: Continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, median and number of observations. Categorical data will be summarized as frequency counts and percentages. A gatekeeping testing strategy for the primary and major secondary analyses will be implemented to control the overall type I error rate at a 2-sided alpha level of 0.05. Treatment comparisons of categorical efficacy variables will be conducted using a logistic regression analysis with treatment in the model. The proportions, 95% confidence intervals (CIs), the difference in proportions, and the 95% CI of the difference will be reported. Secondary analysis on the categorical efficacy variables may be conducted using a Fisher’s exact test. The primary analyses for all continuous efficacy and health outcome variables will be made using mixed effects for repeated measures (MMRM) analysis. Type III tests for the LS means will be used for the statistical comparison; the 95% CI will also be reported. In addition, treatment comparisons for continuous efficacy and health outcomes variables may also be made using analysis of covariance (ANCOVA). For the ANCOVA analysis, missing data will be imputed by the last observation carried forward (LOCF) method. Type III sums of squares for the least-squares (LS) means will be used for the statistical comparison; the 95% CI will also be reported. The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to event and time-to relapse (loss of response). Treatment comparisons will be performed using the log-rank test. Other continuous variables will be analyzed by t-tests, unless otherwise stated. All AE, baseline, discontinuation and other categorical data will be summarized and may be tested using Fisher’s exact test. Efficacy, health outcomes, and safety variables will also be summarized for the Maintenance Dosing Period and Post-Treatment Follow-Up Period.

Safety: Fisher's exact test may be used for all AE, baseline, discontinuation, and other categorical data. Continuous vital signs and laboratory values will be analyzed by an ANCOVA model where appropriate. Other continuous variables will be analyzed by t-tests, unless otherwise stated. For patients originally randomized to placebo during Period 2 and enter Period 3, efficacy, health outcomes and safety variables will be summarized.

Pharmacokinetics: Observed ixekizumab serum concentrations will be summarized by treatment regimen, visit and corresponding time when sampling occurred.

Pharmacokinetics/Pharmacodynamics: The exposure-response relationship between steady state ixekizumab trough concentrations and clinically important efficacy measures (for example, sPGA and PASI endpoints) may be explored using graphical methods and/or a modeling approach. The potential impact of immunogenicity on ixekizumab exposure may be evaluated by graphical assessments.

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4. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibody
adverse event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event 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.
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some institutional review boards [IRBs]).
AST	aspartate aminotransferase
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, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BCG	Bacillus Calmette-Guérin
blinding/masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BP	blood pressure
BSA	body surface area
case report form (CRF) and electronic	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.

case report form (eCRF)	
CD	Crohn's disease
CEC	Clinical Events Committee
cGMP	current Good Manufacturing Practices
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
clinical research physician (CRP)	Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CLRM	Clinical Laboratory Results Modernization
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.
consent	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
CRS	clinical research scientist
C-CASA	Columbia Classification Algorithm of Suicide Assessment
C-SSRS	Columbia-Suicide Severity Rating Scale
CVA	cerebrovascular accident
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram

efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result.
end of study (trial)	End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active subject in the study.
ETV	early termination visit
FSH	follicle-stimulating hormone
GCP	good clinical practice
Gro	growth-related oncogene
HBcAb+	positive for anti-hepatitis B core antibody
HBsAg+	positive for hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIVAb	human immunodeficiency virus antibody
HRQoL	health-related quality of life
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Conference on Harmonisation
IgA	immunoglobulin A
IgG	immunoglobulin G
IgG4	immunoglobulin G subclass 4
IgM	immunoglobulin M
IL	interleukin (eg, IL-17, a proinflammatory cytokine produced by Th17 cells)
ILD	interstitial lung disease
INR	International Normalized Ratio
institutional review board/ethical review board (IRB/ERB)	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.

investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
Intent-to-treat (ITT)	The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment
IV	intravenous
IWRS	interactive web-response system
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical study.
LS	least squares
LTBI	latent tuberculosis infection
MAb	monoclonal antibody
LOCF	last observation carried forward
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMRM	mixed-effects model repeated measures
MTX	methotrexate
NAPSI	Nail Ps Severity Index
NK	natural killer
NMSC	non-melanoma skin cancers
NRI	non-responder imputation
NRS	numeric rating scale
NYHA	New York Heart Association
PASI	Psoriasis Area and Severity Index
PASI 50	at least a 50% improvement in PASI score from baseline
PASI 75	at least a 75% improvement in PASI score from baseline
PASI 90	at least a 90% improvement in PASI score from baseline

PASI 100	a 100% improvement in PASI score from baseline
PCP	pneumocystis pneumonia
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PCS	Physical Component Summary
PD	pharmacodynamics
per-protocol set (PPS)	The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PGA	Physician Global Assessment
PK	pharmacokinetics
PPASI	Palmoplantar PASI
PPASI 50	at least a 50% improvement in PPASI score from baseline
PPASI 75	at least a 75% improvement in PPASI score from baseline
PPASI 100	a 100% improvement in PPASI score from baseline
PPD	purified protein derivative
PRO	patient-reported outcome
Ps	psoriasis
PsA	psoriatic arthritis
PSSI	Psoriasis Scalp Severity Index
PT	preferred term
PUVA	psoralen and ultraviolet A
Q2W	every 2 weeks
Q4W	every 4 weeks
Q12W	every 12 weeks
QIDS-SR16	Quick Inventory of Depressive Symptomatology-Self Report (16 items)
randomize	The act of assigning a patient to a treatment. Patients who are randomized in the trial are those who have been assigned to a treatment.
registration	The act of assigning a registration number to the subject indicating that the registration center/sponsor/principal investigator or subinvestigator has verified that the subject

	meets the inclusion criteria and none of the exclusion criteria.
SAE	serious adverse event
SAP	statistical analysis plan
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 study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, 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.
SF-36	Short form (36-item) Health Survey
SOC	system organ class
sPGA	Static Physician Global Assessment: physician's determination of the patient's psoriasis lesions overall at a given time point on a 6 point scale (0 = cleared, 1 = minimal, 2 = mild, 3 = moderate; 4 = marked, 5 = severe).
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
TBL	total bilirubin
TNF	tumor necrosis factor
TPO	third-party organization
treatment-emergent adverse event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
UC	ulcerative colitis
ULN	upper limit of normal
UVB	ultraviolet B
VAS	visual analog scale
WBC	white blood cells
WHOATC	World Health Organization Anatomic Therapeutic Class

A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Maintenance Dosing Period to Evaluate the Efficacy and Safety of LY2439821 in Patients with Moderate-to-Severe Plaque Psoriasis

5. Introduction

Psoriasis (Ps) vulgaris, commonly known as plaque Ps, is a common chronic skin disorder with an estimated prevalence in populations of approximately 3% (Greaves and Weinstein 1995). One recent population-based and dermatologist-confirmed study showed that the prevalence of psoriasis in China is 0.47% in 2012 (Ding et al. 2012), which is higher than that reported (0.12%) in 1987 (Shao et al. 1987). Histologically, the hallmark of Ps is the presence of a greatly thickened, nucleated keratinocyte layer, with exaggeration of the rete pegs, and dermal infiltration by activated T cells and dendritic cells (Lowes et al. 2007). Activated T cells, monocytes, neutrophils, and dendritic cells produce inflammatory cytokines that drive the additional recruitment of inflammatory cells, further elaboration of proinflammatory mediators, and the proliferation of keratinocytes (Bowcock and Krueger 2005; Lowes et al. 2007). The occurrence of Ps is thought to be the pathological consequence of a T-cell-mediated immune response to an as-yet, unidentified autoantigen.

Clinical features include sharply demarcated, scaly erythematous plaques as well as pain, itching, and cracking of the skin. These lesions most typically affect the elbows, knees, scalp, lumbar area, umbilical area, and gluteal cleft.

Approximately 1/4 to 1/3 of patients have moderate-to-severe Ps, corresponding to involvement of over 5% of their body surface area (BSA) (Dubin et al. 2003; Menter and Griffiths 2007). Disease of this extent is frequently painful and physically and/or socially debilitating to a degree comparable with other chronic medical conditions (Rapp et al. 1999).

Current treatments for moderate-to-severe plaque Ps include phototherapy and systemic immune modulators, including biotherapeutics that target cytokines and aspects of T cell function (Menter et al. 2008; Canadian Psoriasis Guidelines Committee 2009 [WWW]; Smith et al. 2009); however, there are limitations to their effectiveness and use. Phototherapy is associated with photoaging, erythema, and a concern around skin cancer induction, and in many geographies, there is limited access to phototherapy. Agents that inhibit T cell function and/or skin cell hyperproliferation, such as cyclosporin A, methotrexate (MTX), or acitretin, may effectively suppress psoriatic disease, but their use is limited due to their potential to cause adverse systemic effects (Cather and Menter 2002). Biologic therapies that inhibit the activity of tumor necrosis factor (TNF) and other proinflammatory cytokines, such as interleukin (IL)-12/23, implicated in psoriatic immunopathogenesis are also efficacious for plaque Ps (Chaudhari et al. 2001; Leonardi et al. 2008). However, the use of these biologic therapies in various indications is associated with safety concerns, such as an increased risk of serious infection, infusion-related events, hematologic/lymphoproliferative disorders, demyelinating disorders,

small vessel vasculitis, immunogenicity, potential congestive heart failure, and on rare occasions, paradoxically, with new-onset Ps or exacerbation of existing Ps (Smith et al. 2009). Therefore, there remains a significant unmet medical need for safer, more effective treatments for patients with Ps.

The development of new biologic therapies that selectively target key inflammatory molecules rather than inducing generalized immunosuppression offer appealing means to address these unmet needs (Chaudhari et al. 2001; Krueger 2002). The classical IL-12/Th1 cytokine pathway was thought to be the dominant immunologic pathway mediating human T-cell-dependent autoimmunity. However, a subset of CD4+ T cells, called Th17, is now thought to play a specific pathological role in Ps and other autoimmune diseases (reviewed by Kikly et al. 2006). Th17 cells secrete many proinflammatory cytokines including interleukin-17A (IL-17A, also known as IL-17), IL-17F, IL-6, and TNF-α that can trigger an inflammatory cascade. IL-17A is 1 of 6 members of the family of proinflammatory IL-17 cytokines (IL-17A-F) and has been implicated in a variety of human autoimmune diseases, including Ps (Arican et al. 2005; Li et al. 2007). Th17 cells are also a source of IL-22, a cytokine implicated in the keratinocyte hyperproliferation characteristic of Ps (Zaba et al. 2007; Zheng et al. 2007), which synergizes with IL-17A to induce the proinflammatory/antimicrobial proteins, S100A7, S100A8, S100A9, and β-defensin, in primary keratinocytes (Liang et al. 2006). IL-17A synergizes with TNF-α (also produced by Th17 cells) to induce the production of neutrophil attracting chemokines, CXCL1 (growth-related oncogene [Gro]-α) and CXCL8 (IL-8) (Laan et al. 1999; Hellings et al. 2003).

Ixekizumab (LY2439821) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (MAb) that neutralizes the cytokine IL-17A (also known as IL-17). Ixekizumab was developed by humanization and optimization of a mouse anti-human IL-17 antibody. It has a high affinity for and neutralizes the activity of both human and monkey IL-17. It has high specificity to IL-17A and has no cross-reactivity to other IL-17 family members (IL-17B-F). Ixekizumab blocks IL-17 binding to the IL-17 receptor (IL-17R).

Results from Phase 1 (Study I1F-MC-RHAG [RHAG]) and Phase 2 (Study I1F-MC-RHAJ [RHAJ]) studies in patients with Ps support the potential efficacy of ixekizumab in Ps. Both studies, although based on relatively small numbers of patients, showed a favorable benefit/risk profile of ixekizumab in this disease.

In Study RHAG, ixekizumab demonstrated a dose-related improvement in Ps over the dose range tested, as measured by the Psoriasis Area and Severity Index (PASI) and Physician Global Assessment (PGA). At the 50- and 150-mg doses, a statistically and clinically significant improvement in PASI was demonstrated, which was sustained after completion of dosing until the end of the study.

Larger Phase 3 pivotal studies have been conducted (Studies I1F-MC-RHAZ [RHAZ], I1F-MC-RHBA [RHBA], and I1F-MC-RHBC [RHBC]) that have further demonstrated the efficacy of ixekizumab 80 mg Q2W and ixekizumab 80 mg Q4W for the treatment of patients with moderate-to-severe plaque psoriasis. In each of these studies, the primary and secondary

outcomes for disease severity, health outcomes, and associated symptoms were superior with ixekizumab compared to placebo. Two of the 3 studies included an active comparator of etanercept 50 mg twice weekly (Studies RHBA and RHBC), and both doses of ixekizumab were demonstrated to be superior in efficacy compared to etanercept. While each of these studies has been concluded for their primary endpoints, the duration of them may extend up to 5 years to study long-term treatment with ixekizumab in patients with moderate to severe plaque psoriasis. Current results indicated that patients had benefits from treatment with ixekizumab. Upon re-randomization at Week 12, patients who were treated with ixekizumab 80 mg every 4 weeks (Q4W) had clearly superior responses than patients who were randomized to receive placebo or ixekizumab 80 mg every 12 weeks (Q12W) dosing.

Study I1F-MC-RHBH (RHBH) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study to evaluate the efficacy and safety profile of ixekizumab in Chinese patients with moderate to severe plaque Ps compared to placebo. There will be an induction dosing period with primary endpoint at Week 12 followed by a randomized maintenance dosing period to Week 60. The dosing regimens are based on Study RHAZ (80 mg Q2W or Q4W for induction period, 80 mg Q4W or 80 mg Q12W for maintenance period). The results of global large pivotal studies demonstrated significant greater efficacy in maintenance of treatment benefits of 80 mg Q4W versus Q12W with comparable safety profiles. Therefore, only 80 mg Q4W dosing regimen will be selected in maintenance period.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of ixekizumab can be found in the Investigator's Brochure (IB). Information on AEs expected to be related to the study drug 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 will be assessed by the sponsor in aggregate periodically during the course of the study and may be found in Section 6 (Effects in Humans) of the IB.

The sponsor, monitor, and investigators will perform this study in compliance with the protocol, good clinical practice (GCP), and International Conference on Harmonisation (ICH) guidelines, and applicable regulatory requirements.

6. Objectives

6.1. Primary Objectives

The co-primary objectives of the study are to assess whether ixekizumab 80 mg Q2W or 80 mg Q4W is superior to placebo at Week 12 in the treatment of patients with moderate-to-severe plaque Ps as measured by:

- Proportion of patients with a static Physician Global Assessment (sPGA) (0, 1) with at least a 2-point improvement from baseline
- Proportion of patients achieving a ≥75% improvement in PASI (PASI 75) from baseline

6.2. Secondary Objectives

6.2.1. Major Secondary Objectives

The major secondary objectives of the study are to assess whether ixekizumab 80 mg Q2W or 80 mg Q4W induction dosing and 80 mg Q4W maintenance dosing are superior to placebo in the treatment of patients with moderate-to-severe plaque Ps as measured by:

- Proportion of patients achieving an sPGA (0) (remission) at Week 12
- Proportion of patients achieving a ≥90% improvement in PASI (PASI 90) at Week 12
- Proportion of patients achieving a 100% improvement in PASI (PASI 100) at Week 12
- Proportion of patients maintaining an sPGA (0, 1) from Week 12 after re-randomization at start of the Maintenance Dosing Period to Week 60
- Proportion of patients who maintain or achieve an sPGA (0) from Week 12 after re-randomization to Week 60
- Proportion of patients achieving an Itch Numeric Rating Scale (NRS) ≥4 point reduction from baseline at Week 12 for patients who had baseline Itch NRS ≥4
- Change from baseline in dermatology-specific quality of life (Dermatology Life Quality Index [DLQI]) at Week 12
- Change from baseline in Nail Ps Severity Index (NAPSI) score at Week 12 in patients with baseline fingernail involvement

6.2.2. Other Secondary Objectives

The other secondary objectives of the study are as follows:

- To assess the efficacy of ixekizumab 80 mg Q2W or 80 mg Q4W compared to placebo at Week 12 and over the Induction Dosing Period by evaluating:
    - Time course of response to treatment as measured by the proportion of patients with an sPGA (0, 1) with at least a 2-point improvement from baseline
    - Time course of response to treatment as measured by the proportion of patients with an sPGA (0)
    - Time course of response to treatment as measured by the proportion of patients achieving at least a 50% improvement in PASI score from baseline (PASI 50), PASI 75, PASI 90, and PASI 100

  - Time course of response to treatment as measured by change and percent improvement of PASI from baseline
  - Time to sPGA response as measured by an sPGA (0, 1)
  - Time to PASI 75 response
  - Change from baseline in percent of BSA involvement of Ps
  - Change from baseline in NAPSI score in patients with baseline fingernail involvement
  - Change from baseline in Ps Scalp Severity Index (PSSI) score in patients with baseline scalp involvement
  - Change from baseline in other health outcomes: Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, patient's global assessment of disease severity
  - Change from baseline in itching severity (Itch NRS) score
  - Change from baseline on DLQI
  - Change from baseline in Palmoplantar PASI (PPASI) and proportion of patients achieving at least a 50% improvement in PPASI score from baseline (PPASI 50), at least a 75% improvement in PPASI score from baseline (PPASI 75), and a 100% improvement in PPASI score from baseline (PPASI 100) in patients with baseline palmoplantar involvement
- To assess maintenance of efficacy of ixekizumab Q4W compared to placebo at Week 60 and during the Maintenance Dosing Period among ixekizumab-treated patients who had an sPGA (0, 1) at Week 12 and were re-randomized by evaluating:
  - Time to relapse (sPGA ≥3)
  - Time course of the loss of response (relapse) to treatment until relapse as measured by an sPGA ≥3
  - Proportion of patients who maintain or achieve an sPGA (0)
  - Time course of response to treatment as measured by the proportion of patients who maintain an sPGA (0, 1), and by the proportion of patients who maintain or achieve an sPGA (0)
  - Time course of response to treatment as measured by change from baseline and percent improvement from baseline of PASI
  - Change from baseline in percent of BSA involvement of Ps
  - Incidence of disease rebound within 8 weeks (worsening of Ps severity over baseline sPGA score, ***or*** worsening of Ps severity over baseline PASI score by 125%, ***or*** change in Ps phenotype [for example, from plaque to pustular]) after re-randomization to placebo at Week 12
  - Time course of response to treatment as measured by the proportion of patients who maintain a PASI 75, PASI 90, and PASI 100
  - Change from baseline in NAPSI score in patients with baseline fingernail involvement
  - Change from baseline in PSSI score in patients with baseline scalp involvement

  - Change from baseline in other health outcome endpoints: SF-36 PCS and MCS scores and patient's global assessment of disease severity
  - Change from baseline in itching severity (Itch NRS) score
  - Change from baseline on DLQI
  - Change from baseline in PPASI and proportion of patients achieving at least a 50% improvement in PPASI score from baseline (PPASI 50), at least a 75% improvement in PPASI score from baseline (PPASI 75), and a 100% improvement in PPASI score from baseline (PPASI 100) in patients with baseline palmoplantar involvement
- To assess the efficacy of ixekizumab 80 mg Q4W following disease relapse after re-randomization to placebo treatment in the Maintenance Dosing Period by evaluating:
  - Proportion of patients who regain an sPGA (0, 1) within 12 weeks after ixekizumab retreatment
  - Proportion of patients who achieve a PASI 75, PASI 90, PASI 100 within 12 weeks after ixekizumab retreatment
- To assess the efficacy of ixekizumab 80 mg Q2W or 80 mg Q4W compared to placebo on joint pain at Week 12 and over the Induction Dosing Period, as well as at Week 60 and during the Maintenance Dosing Period in patients with an sPGA (0, 1) at Week 12 and were re-randomized, by evaluating change from baseline in joint pain (Joint Pain visual analog scale [VAS]) score in patients with psoriatic arthritis (PsA) at baseline
- To evaluate the potential development of anti-ixekizumab antibodies and its impact on patient safety and efficacy
- To measure ixekizumab exposure and assess the relationship between exposure and efficacy, and exposure and immunogenicity

7. Investigational Plan

7.1. Summary of Study Design

Study RHBH is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study examining the effect of ixekizumab versus placebo in patients with moderate-to-severe plaque Ps during an Induction Dosing Period with the primary endpoint at 12 weeks, followed by a re-randomized Maintenance Dosing Period to Week 60. During the Induction Dosing Period, the study will evaluate the efficacy and safety of 2 dose regimens of ixekizumab (80 mg Q2W or Q4W). During the Maintenance Dosing Period, the study will evaluate the maintenance of response/remission with the dose regimen of 80 mg Q4W ixekizumab, the safety of the regimen, as well as relapse or rebound following treatment withdrawal, and response to retreatment following relapse.

The study consists of 4 periods:

- **Period 1 (Section 7.1.1):** Screening Period (Visits 1 and 1A) lasting from 4 to 30 days prior to Period 2 (baseline; Week 0; Visit 2)
- **Period 2 (Section 7.1.2):** Induction Dosing Period will be a double-blind treatment period that will occur from Week 0 (baseline; Visit 2) to Week 12 (Visit 7);
- **Period 3 (Section 7.1.3):** Maintenance Dosing Period will be a double-blind treatment period that will occur from Week 12 (Visit 7) to Week 60 (Visit 19).
- **Period 4 (Section 7.1.4):** Post-Treatment Follow-Up Period occurring from last treatment period visit or Early Termination Visit (ETV) up to a minimum of 12 weeks following that visit.

Figure 7.1 illustrates the study design.

All procedures to be conducted during the study, including timing of all procedures, are indicated in the Study Schedule (Attachment 1). Selected study procedures should be performed prior to administration of the investigational product, as applicable. Attachment 2 lists the specific laboratory tests that will be performed in this study.

Patients discontinuing from the study who have received at least 1 dose of investigational product will continue to the ETV prior to proceeding to the Post-Treatment Follow-Up Period (Period 4). For the management of patient safety, all patients should be monitored through the Post-Treatment Follow-Up Period at least as frequently as indicated on the Study Schedule (Attachment 1).

All treatment groups are described in Section 9.1, and administration of the investigational product is described in Section 9.1.1.

Excluded and restricted therapies are detailed in Section 9.8.

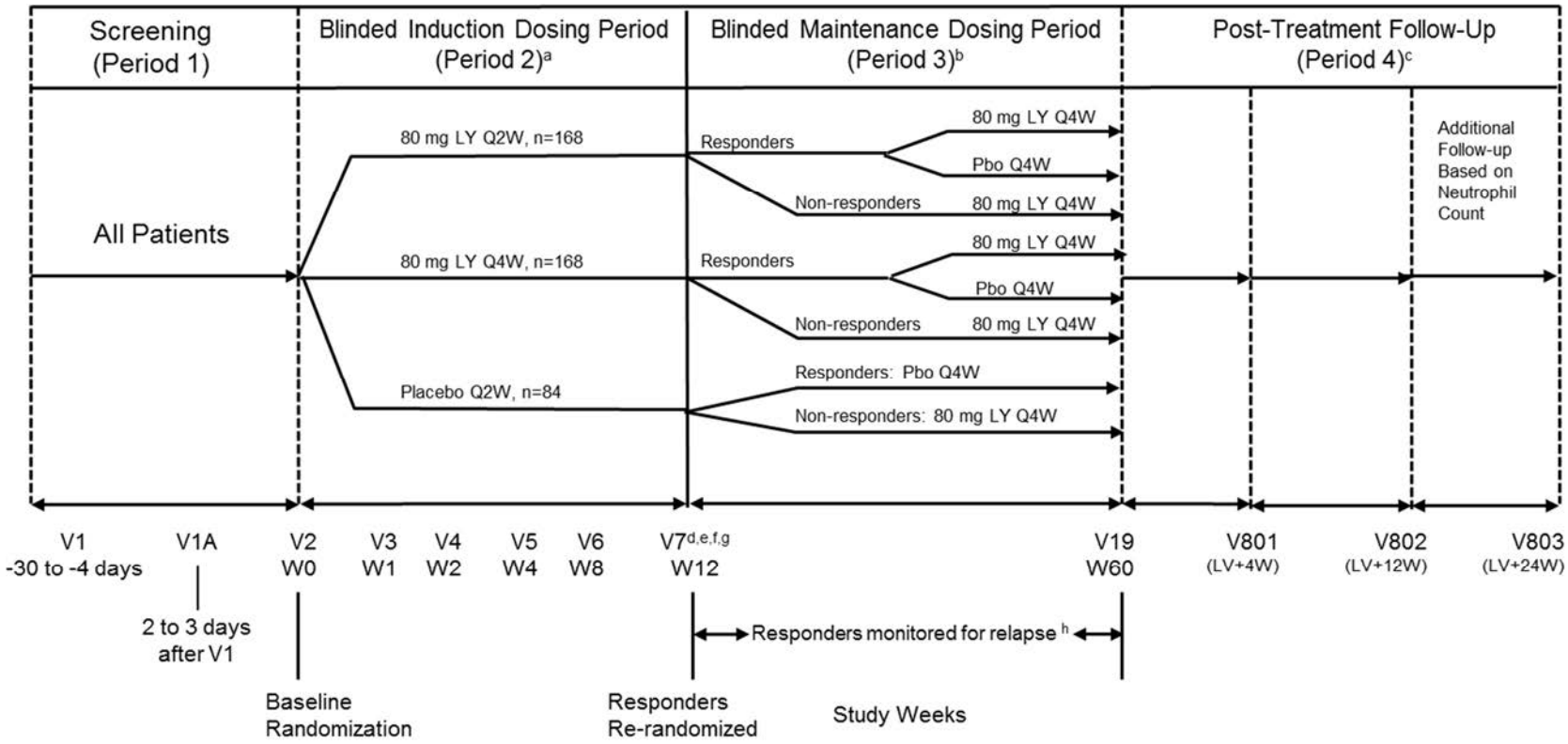

Figure 7.1. Illustration of study design for Clinical Protocol I1F-MC-RHBH (not to scale).

Illustration of study design for Clinical Protocol I1F-MC-RHBH (not to scale) (Abbreviations and footnotes)

Abbreviations: LV = date of last visit; LY = ixekizumab (LY2439821); n = number of patients; Pbo = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; V = study visit; W = study week.

a All patients will receive 2 SC doses of investigational product (ixekizumab 80 mg, placebo) starting at Week 0 (Visit 2) and 1 SC dose Q2W from Week 2 (Visit 4) through Week 10.

b All patients will receive 2 SC doses of investigational product (ixekizumab or placebo) at Week 12 (Visit 7) and 1 SC dose Q4W from Week 16 (Visit 8) through Week 56 (Week 60, no investigational product administration).

c All patients receiving investigational product must enter into Period 4 and complete through Visit 802. Patients may be followed beyond Visit 802 for continued monitoring of their neutrophil count if needed, or if determined by the sponsor/investigator that additional monitoring is needed.

d Responders to ixekizumab at Week 12 (Visit 7; responders are defined as achieving an sPGA score of 0 or 1) will be randomly assigned at a 2:1 ratio to ixekizumab Q4W or placebo.

e Nonresponders to ixekizumab at Week 12 (Visit 7; nonresponders are defined as having an sPGA score of >1) will receive ixekizumab 80 mg Q4W.

f Responders to placebo at Week 12 (Visit 7) will receive 2 injections of placebo at Week 12 and will remain on placebo Q4W until relapse, then they will be switched to 80 mg ixekizumab Q4W.

g Nonresponders to placebo at Week 12 (Visit 7) will receive 2 injections of ixekizumab (starting dose) at Week 12 followed by ixekizumab 80 mg Q4W

h Relapse (loss of response) occurring after Week 12 (Visit 7) is defined as an sPGA score of ≥3.

7.1.1. Screening Period (Period 1)

The duration of the Screening Period is between 4 and 30 days and consists of 1 or 2 screening visits (Visits 1 and 1A, where applicable) to assess patient eligibility. The patient will sign the informed consent form (ICF) prior to any study assessments, examinations, or procedures being performed.

All inclusion and exclusion criteria are provided in Sections 8.1 and 8.2, respectively. Screening procedures will be performed according to the Study Schedule (Attachment 1). At Visit 1, either a QuantiFERON®-TB Gold test assay or T-SPOT®.TB will be performed, or patients will be administered a purified protein derivative (PPD) test for tuberculosis (TB) (Section 10.3.2.2). For those patients administered a PPD test at Visit 1, the test results will be read between 48 to 72 hours after administration, at Visit 1A.

Patients who test positive for latent TB at screening may be rescreened following appropriate treatment as described in Section 10.3.2.2. Additionally, patients who do not qualify at screening under Exclusion Criteria [28] or [29] may be rescreened (1 time) at least 4 weeks after documented resolution of symptoms.

7.1.2. Induction Dosing Period (Period 2)

The Induction Dosing Period (Period 2) will be a double-blind treatment period that will occur from Week 0 (baseline; Visit 2) to Week 12 (Visit 7); dosing will occur Q2W from Weeks 0 to 10 and evaluation of primary endpoints will occur at Week 12 prior to the Week 12 dose.

At Week 0 (baseline; Visit 2), routine safety assessments, laboratory tests, and clinical efficacy assessments will be performed on eligible patients according to the Study Schedule (Attachment 1).

Patients will be randomized at a 2:2:1 ratio to 1 of 3 treatment groups: 80 mg ixekizumab Q2W, 80 mg ixekizumab Q4W, or placebo. Each patient assigned to an ixekizumab dose regimen will receive a starting dose of 160 mg ixekizumab as 2 SC injections at Week 0 (Visit 2).

Blinded dosing will occur at 2-week intervals throughout Period 2. See Section 9.1 and Table RHBH.9.1 for a full description of all treatment groups. To maintain blinding, each patient will be administered 2 injections of blinded investigational product subcutaneously at Week 0, and each patient will be administered 1 injection of blinded investigational product subcutaneously Q2W from Weeks 2 through 10 regardless of his/her assigned dose regimen (that is, placebo will be given as necessary to maintain the blind).

Patients who discontinue the study for any reason during this period will stop treatment and continue to the ETV prior to entering the Post-Treatment Follow-Up Period (Period 4; Section 7.1.4).

7.1.3. Maintenance Dosing Period (Period 3)

The Maintenance Dosing Period (Period 3) will be a double-blind treatment period that will occur from Week 12 (Visit 7) to Week 60 (Visit 19).

In Period 3, safety and efficacy parameters in participating patients will continue to be evaluated according to the Study Schedule (Attachment 1).

Two treatment groups (80 mg Q4W and placebo) will be evaluated to determine the maintenance of response/remission, the relapse or rebound following treatment withdrawal, and the response to retreatment following relapse (see "Treatment Assignment for Responders" and "Non-responders" below).

Blinded dosing will occur at 4-week intervals throughout Period 3. See Section 9.1 and Table RHBH.9.1 for a full description of all treatment groups. To maintain blinding, each patient will be administered 2 injections of blinded investigational product subcutaneously at Week 12, and each patient will be administered 1 injection of blinded investigational product subcutaneously Q4W from Weeks 16 through 56 (Week 60, no investigational product administration) regardless of his/her assigned treatment group (that is, placebo will be given as necessary to maintain the blind).

At Week 12 (Visit 7), patients who enter Period 3 will be classified as a responder or non-responder according to the following criteria:

- **Responder = sPGA score of "0" or "1"**
- **Non-responder = sPGA score of > 1**

Treatment Assignment for Responders: Patients receiving ixekizumab who are responders at Week 12 (Visit 7), will be re-randomized (2:1) to 2 treatment groups (80 mg ixekizumab Q4W or placebo). Patients will be stratified by ixekizumab induction dosing regimen (80 mg Q2W or 80 mg Q4W).

Patients randomized to placebo at Week 0 (Period 2) who are responders at Week 12 (Visit 7) will continue to receive placebo at 4-week intervals during Period 3 until relapse; these patients will receive 2 SC injections of placebo at Week 12 (Visit 7) in order to maintain the study blind.

All treatments will remain in effect until relapse. Relapse (loss of response) is defined as an sPGA score of ≥ 3.

Treatment Following Relapse: Patients who are responders at Week 12 will be monitored and assessed for relapse at each visit after re-randomization. Patients who relapse will be treated as follows:

- Patients receiving 80 mg ixekizumab Q4W, who relapse, will continue on 80 mg ixekizumab Q4W in order to maintain the study blind and to evaluate the long term efficacy of ixekizumab treatment.
- Patients receiving placebo who relapse will be switched to 80 mg ixekizumab Q4W.

Continued treatment for patients who relapse is provided to understand the longer-term efficacy of ixekizumab when treating patients who experience relapse and to maintain study blinding. See Section 8.3.1 for discontinuation criteria.

Treatment Assignment for Non-Responders: Patients randomized to ixekizumab at Week 0 (Period 2) who are non-responders at Week 12 (Visit 7) will receive treatment with 80 mg ixekizumab Q4W during Period 3.

Patients randomized to placebo at Week 0 (Period 2) who are non-responders at Week 12 (Visit 7) will receive treatment with 80 mg ixekizumab Q4W during Period 3. These patients will receive a starting dose of 160 mg ixekizumab as 2 SC injections at Week 12 (Visit 7).

Continued treatment for non-responders is provided so that partial or slow responders to ixekizumab and non-responders to placebo may remain in the study and receive treatment with ixekizumab while maintaining the study blind. Some patients may be deriving benefit from treatment with ixekizumab but will be slow responders or partial responders thereby not meeting the "responder" criteria at Week 12. A discontinuation criterion for patients who remain at or above their baseline sPGA score at both Week 12 and Week 24 is included (see Section 8.3.1) to ensure that patients who have not shown any benefit from treatment with ixekizumab can be treated with any other psoriasis therapy as determined appropriate by the investigator.

Once a patient has switched to 80 mg Q4W, regardless of original treatment in Period 2, re-randomization in Period 3, or any assessments of response/relapse, the patient will remain on 80 mg Q4W.

Patients who discontinue the study for any reason during Period 3 will stop treatment and continue to the ETV prior to entering the Post-Treatment Follow-Up Period (Period 4; Section 7.1.4).

7.1.4. Post-Treatment Follow-Up Period (Period 4)

All patients receiving at least 1 dose of investigational product will enter the Post-Treatment Follow-up Period (Period 4) for a minimum of 12 weeks after their last regularly scheduled visit (or the date of their ETV). Required study visits should occur at 4 weeks (Visit 801) and at 12 weeks (Visit 802) after the last regularly scheduled visit (or the date of the patient's ETV), except for patients with a concurrent infection that requires systemic anti-infective therapy (described in Section 7.1.4.1).

If, at Visit 802, a patient's neutrophil count is ≥1500 cells/μL or greater than or equal to the patient's baseline neutrophil count, the patient's participation in the study will be considered complete unless the investigator deems additional follow-up may be necessary. An additional study visit (Visit 803) at 12 weeks after Visit 802 may be required. Additional visits prior to Visit 803 may be required for appropriate patient management.

7.1.4.1. Neutropenia Follow-Up

If, at the last scheduled visit or ETV, the patient's neutrophil count is <1500 cells/μL and less than the patient's baseline neutrophil count, the following measures should be taken:

- Patients with Concurrent Infection: If there is a concurrent infection that requires systemic anti-infective therapy, the patient should receive appropriate medical care and a repeat test for neutrophil count should be performed at least Q4W (or sooner as appropriate) until resolution of infection. Upon resolution of infection, the neutrophil count should be monitored using the required study visits in the Post-Treatment Follow-Up Period (Period 4) design at Visits 801 (4 weeks post resolution of infection), 802 (8 weeks after Visit 801), and 803 (if necessary; 12 weeks after Visit 802); additional visits may be required depending on the degree of neutropenia.
- Patients without Concurrent Infection: If there is no concurrent infection that requires systemic anti-infective therapy, the neutrophil count should be monitored using the required study visits in the Post-Treatment Follow-Up Period (Period 4) design, Visits 801 (4 weeks post ETV or last regularly scheduled visit), 802, and 803 (if necessary); additional visits may be required depending on the degree of neutropenia.
- For Visit 801 and subsequent visits, the following monitoring applies:
  - As long as a patient's neutrophil count is <1000 cells/μL at any follow up visit, the patient should return for visits at least Q4W (may require unscheduled visits).
  - As long as a patient's neutrophil count is ≥1000 cells/μL and <1500 cells/μL at any follow up visit, the patient should return for additional visit(s) at least every 4 to 8 weeks (may require unscheduled visits).
  - If at Visit 802 or Visit 803, the patient's neutrophil count is ≥1500 cells/μL or greater than or equal to the patient's baseline neutrophil count (whichever is lower), the patient's participation in the study will be considered complete unless the investigator deems additional follow-up may be necessary.
  - If, at Visit 803, the patient's neutrophil count remains <1500 cells/μL and less than the patient's baseline neutrophil count, or if the investigator deems additional follow-up may be necessary, the investigator in consultation with Lilly, or qualified designee, will determine the appropriate management of the patient and the appropriate timing of additional contact(s) or visit(s).

7.2. Discussion of Design and Control

During the Induction Dosing Period (Period 2), 2 dose regimens of ixekizumab will be studied: 80 mg Q2W and 80 mg Q4W. During the Maintenance Dosing Period (Period 3), 1 dose regimen of 80 mg Q4W ixekizumab will be studied. All treatment groups are detailed in Section 9.1, with the dose justification as outlined in Section 9.4.

The study blind is maintained as described in Section 9.7.

The Induction Dosing Period (Period 2) is designed to minimize bias in the evaluation of ixekizumab in patients with Ps. The selection of placebo as a comparator is justified on the basis that the most robust evaluation of efficacy can be made versus placebo treatment, and the duration of the 12-week primary evaluation is sufficiently short that patients will receive placebo without lasting adverse effects.

Following the Induction Dosing Period (Period 2), patients who are non-responders are all assigned to 80 mg ixekizumab Q4W.

The efficacy of ixekizumab in treating Ps will be measured by the sPGA and PASI response scales, with the primary efficacy endpoint at 12 weeks. These measures and the 12-week endpoint are in alignment with efficacy endpoints for currently approved Ps therapies and with regulatory guidance (EMEA 2004 [WWW]). Steady-state exposure is expected to be reached by the 12-week time point (the mean [geometric CV%] half-life was 13 days [40%] in subjects with plaque psoriasis), and it is anticipated that a significant clinical effect will be observed within this timeframe based on previous studies with ixekizumab in patients with Ps.

The Maintenance Dosing Period (Period 3) is designed to evaluate the maintenance of response/remission with the dose regimen of ixekizumab 80 mg Q4W, as well as relapse or rebound following treatment withdrawal, and response to retreatment following relapse.

The Post-Treatment Follow-Up Period (Period 4) is for safety monitoring following last treatment period and study visit.

8. Study Population

This study will include adult patients with chronic moderate-to-severe plaque Ps who have given written informed consent approved by Lilly, or its designee, and the ethical review board (ERB) governing the site.

Study investigator(s) will review patient records and screening test results from Visit 1 (all criteria), Visit 1A (as applicable for PPD read), and Visit 2 to determine if the patient meets all inclusion and exclusion criteria to qualify for participation in the study. All screening activities must be completed and reviewed before the patient is randomized.

Individuals who do not meet the criteria for participation in this study (not qualify at screening under exclusion criteria [28] or [29] and latent TB patients after receiving at least 4 weeks of appropriate treatment [see section for 10.3.2.2 for additional requirements]) may be rescreened (1 time) at least 4 weeks after documented resolution of symptoms or appropriate treatment of latent TB. Each time re-screening is performed, the individual must sign a new 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. Inclusion Criteria

Patients are eligible to be included 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 agree to use a reliable method of birth control during the study and for at least 12 weeks following the last dose of investigational product. Examples of reliable methods include abstinence, vasectomy, and male condom with spermicide.

[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 12 weeks following the last dose of investigational product, 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 non-childbearing 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 non-childbearing potential (≥40 mIU/mL)

[2] Present with chronic plaque Ps based on a confirmed diagnosis of chronic Ps vulgaris for at least 6 months prior to baseline (Week 0; Visit 2)

[3] Have ≥10% BSA involvement at screening (Visit 1) and baseline (Week 0; Visit 2)

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

[5] Are candidate for phototherapy and/or systemic therapy

[6] Have given written informed consent approved by Lilly, or its designee, and the Investigational Review Board (IRB)/ERB governing the site

8.2. Exclusion Criteria

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

[7] Have pustular, erythrodermic, and/or guttate forms of Ps

[8] Have a history of drug-induced Ps

[9] Had a clinically significant flare of Ps during the 12 weeks prior to baseline (Week 0; Visit 2)

[10] Have received systemic non-biologic Ps therapy (including, but not limited to, oral psoralens and ultraviolet A [PUVA] light therapy; cyclosporine; corticosteroids; MTX; oral retinoids; mycophenolate mofetil; thioguanine; hydroxyurea; sirolimus; azathioprine; fumaric acid derivatives; or 1, 25 dihydroxy vitamin D3 and analogues) or phototherapy (including either oral and topical PUVA light therapy, ultraviolet B [UVB] or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to baseline (Week 0; Visit 2);

or had topical Ps treatment (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, emollients and other non-prescription topical products containing urea, > 3% salicylic acid, or alpha- or beta-hydroxyl acids, and 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 and least potent topical steroids [such as desonide, fluocinolone acetonide, and hydrocortisone] will be permitted for use limited to the face, axilla, and/or genitalia

[11] 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

[12] Have concurrent 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)

[13] Have received oral herbal therapy within 4 weeks of baseline (Week 0; Visit 2) but topical herbal therapy is permitted;

[14] Have ever received natalizumab or other agents that target alpha-4-integrin.

[15] Have previously completed or withdrawn from this study, or have previously exposed to ixekizumab or any other biologic drug directly targeting IL-17 (such as secukinumab) or the IL-17 receptor.

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

[17] Had a live vaccination within 12 weeks prior to baseline (Week 0; Visit 2), or intend to have a live vaccination during the course of 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 non-live vaccines intended to prevent infectious disease prior to therapy.

Note: Killed/Inactive or subunit vaccines are expected to be safe; however, their efficacy with concomitant ixekizumab treatment is unknown.

[18] 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 course of the study, or within 12 months of completing treatment in this study.

[19] 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.

[20] Have active Crohn's disease (CD) or active ulcerative colitis (UC).

Note: Patients may be enrolled if they have had a history of inflammatory bowel disease (IBD), including CD and UC, but have had no exacerbation for ≥6 months prior to baseline randomization and, if currently on treatment, must be on stable treatment for ≥6 months prior to baseline randomization.

[21] Have current or a history of lymphoproliferative disease, signs or symptoms of lymphoproliferative disease within 5 years prior to baseline (Week 0; Visit 2); or have active or history of malignant disease within 5 years prior to baseline (week 0; Visit 2)

Note: Patients with history of malignancy with no evidence of recurrence or active disease within 5 years prior to baseline may participate in the study.

[22] Presence of significant uncontrolled cerebro-cardiovascular condition (for example, myocardial infarction [MI], unstable angina, unstable arterial hypertension, moderate-to-severe [New York Heart Association (NYHA) class III/IV] heart failure, or cerebrovascular accident [CVA]), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic disorders, 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 of interfering with the interpretation of data.

[23] 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).

[24] Presence of significant uncontrolled neuropsychiatric disorder, have history of a suicide attempt within 30 days of visit 1, have a score of 3 on Item 12 (Thoughts of Death or Suicide) of the Quick Inventory of Depressive Symptomatology-Self Report (16 items) (QIDS-SR16) at screening (Visit 1) or baseline (Week 0; Visit 2), or are clinically judged by the investigator to be at risk for suicide.

[25] 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), or had a serious bone or joint infection within 24 weeks prior to baseline, or 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.

[26] Have or had an infection 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.

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

[28] 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 or more weeks after documented resolution of symptoms.

[29] 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.

[30] 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 10.3.2.2 for additional details on determining full TB exclusion criteria).

a. Evidence of active TB is documented by a positive PPD test (≥5-mm induration) which is to be read between 48 and 72 hours after placement, regardless of BCG vaccination history.

b. If the QuantiFERON®-TB Gold or T-SPOT®.TB test is available and may be used instead of the PPD test per primary investigator preference or judgment as an alternative. Detailed instruction please refer to Section 10.3.3.2.

[31] Have evidence of latent TB (as documented by a positive QuantiFERON®-TB Gold or T-SPOT®.TB 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 for 10.3.2.2 for additional requirements)

[31a] If the QuantiFERON®-TB Gold 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.

[31b] 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 QuantiFERON®-TB Gold (QTF) or T-SPOT®.TB (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.

[31c] Exceptions include patients with a history of active or latent TB who have documented evidence of appropriate treatment.

[32] Have uncontrolled arterial hypertension characterized by a systolic blood pressure (BP) >160 mmHg or diastolic BP >100 mmHg.

Note: 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.

[33] Are positive for human immunodeficiency virus serology (HIV; positive for human immunodeficiency virus antibody [HIVAb]).

[34] Have evidence of or test positive for hepatitis B virus (HBV) by testing 1) positive for hepatitis B surface antigen (HBsAg+), OR 2) positive for anti-hepatitis B core antibody (HBcAb+) and are HBV deoxyribonucleic acid (DNA) positive.

Note: Patients who are HBcAb+ and HBV DNA negative may be enrolled in the study. Patients who meet these criteria at screening will be identified by the central laboratory as detailed in Section 10.3.3.3.

[35] 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 (anti-HCV Ab), and 2) positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction).

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

[36a] Neutrophil count < 1500 cells/μL (<1.50 × 10^3/μL or <1.50 GI/L)

[36b] Lymphocyte count < 500 cells/μL (<0.50 × 10^3/μL or <0.50 GI/L)

[36c] Platelet count < 100,000 cells/μL (<100 × 10^3/μL or <100 GI/L)

[36d] Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 times the upper limit of normal (ULN)

[36e] Total white blood cell (WBC) count <3000 cells/μL (<3.00×10^3/μL or <3.00 GI/L)

[36f] Hemoglobin <8.5 g/dL (85.0 g/L) for male patients and <8.0 g/dL (80 g/L) for female patients

[36g] 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 is less than the criterion limits. Other laboratory tests should not be repeated unless there is a technical error or clinical reasons to believe a result may be erroneous.

[37] Have electrocardiogram (ECG) abnormalities that are considered clinically significant and would pose an unacceptable risk to the patient if participating in the study.

[38] Have allergy to rubber or latex.

[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 of more than 500 mL within the last 4 weeks, or intend to donate blood during the course of the study.

[41] Are women who are lactating or breastfeeding.

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

[43] Are Lilly employees or its designee or are employees of third-party organizations (TPOs) involved in the study.

[44] Are currently enrolled in, or discontinued from a clinical trial involving an investigational product or nonapproved use of a drug or device within the last 4 weeks or a period of 5 half-lives of the last administration of the drug, whichever is longer, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

8.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criteria [10] through [14] 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 [16] 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. Exclusion Criteria [42] and [43] reduce the potential bias that may be introduced at the study site.

The majority of the exclusion criteria are applied to reduce risks to patients by enrolling medically stable, relatively healthy (aside from the disease being studied) patients who are not receiving concomitant therapies that may impact their safety and/or confound effects when combined with the investigational product being studied.

8.3. Discontinuation Criteria

The reason for and date of discontinuation from study treatment (investigational product) and reason for and date of discontinuation from study participation will be collected for all randomized patients. For patients who discontinue because of death and lost to follow up, only the reason for and date of discontinuation from study participation will be collected.

For any patient discontinued from the study treatment, the investigational product will be withheld, and the patient will complete the ETV and the Post-Treatment Follow-up Period (Period 4), as shown in the Study Schedule (Attachment 1).

Missing data may compromise the integrity of the study. Complete information from each patient is critical to achieving the fullest understanding of the potential benefits and risks of

ixekizumab. All efforts should be made to keep patients in the study, to attend scheduled visits and procedures, and to take investigational product as medically appropriate.

Patients who meet any of the criteria described in Section 8.3.1.1 will be discontinued from study treatment.

8.3.1. Discontinuation from Study Treatment

8.3.1.1. Permanent Discontinuation from Study Treatment

- **Subject Decision**
  - The patient or the patient's designee, for example, parents or legal guardian requests to discontinue investigational product for any reason.
- Neutrophil (segmented) counts (see safety monitoring for neutropenia Section 10.3.3.1):
  - <500 cells/μL (<0.50 × 10^3/μL or <0.50 GI/L)
  - ≥500 and <1000 cells/μL (≥0.50 × 10^3/μL and <1.00 × 10^3/μL or ≥0.50 GI/L and <1.00 GI/L) (based on 2 test results; the second test performed within 1 week from knowledge of the initial result).
  - ≥1000 and <1500 cells/μL (≥1.00 × 10^3/μL and <1.50 × 10^3/μL or ≥1.00 GI/L and <1.50 GI/L) (based on 3 test results as specified in Section 10.3.3.1) - AND - an infection that is not fully resolved.
- Total WBC count <2000 cells/μL (<2.00 × 10^3/μL or <2.00 GI/L).
- Lymphocyte count <200 cells/μL (<0.20 × 10^3/μL or <0.20 GI/L).
- Platelet count <50,000 cells/μL (<50 × 10^3/μL or <50 GI/L).
- Discontinuation due to a hepatic event or liver test abnormality: discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a study patient meets one of the following conditions, after consultation with the Lilly designated medical monitor (clinical research physician [CRP] or clinical research scientist [CRS]):
  - ALT or AST >8X ULN
  - ALT or AST >5X ULN for more than 2 weeks
  - ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or international normalized ratio (INR) >1.5
  - ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - Alkaline phosphatase (ALP) >3X ULN
  - ALP >2.5X ULN and TBL >2X ULN
  - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - Patients who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via electronic case report form (eCRF).
- Changes in BP (systolic BP at ≥160 mmHg plus ≥20 mmHg increase from baseline [Week 0; Visit 2]; and/or diastolic BP at ≥100 mmHg plus ≥10 mmHg increase from

baseline) that do not respond following maximal allowed intervention (Section 10.3.3.4).

- The patient experiences a severe AE, an SAE, or a clinically significant change in a laboratory value occurs that, in the opinion of the investigator, merits the discontinuation of the investigational product and appropriate measures being taken. In this case, Lilly or its designee is to be notified immediately.
- Clinically significant systemic hypersensitivity reaction following SC administration of investigational product that does not respond to symptomatic medication or results in clinical sequelae.
- The patient becomes pregnant.
- The patient develops a malignancy. (Note: Patients may be allowed to continue if they develop no more than 2 non-melanoma skin cancers (NMSC) during the study.)
- Any patient who has a change in disease phenotype at any time (for example, a change to pustular psoriasis).
- If the patient remains at or above their baseline sPGA score at both Week 12 (Visit 7) and Week 24 (Visit 10).
- If the patient scores a 3 for Item 12 (Thoughts of Death or Suicide) on the QIDS-SR16 at any time in the study,
  -OR-
  If the patient develops active suicidal ideation with some intent to act with or without a specific plan (yes to question 4 or 5 on the "Suicidal Ideation" portion of the Columbia-Suicide Severity Rating Scale [C-SSRS]),
  -OR-
  If the patient develops suicide-related behaviors as recorded on the C-SSRS, then it is recommended that the patient be assessed by a psychiatrist or appropriately trained professional to assist in deciding whether the patient is to be discontinued from the study treatment.
- The investigator or attending physician decides that the patient should be withdrawn from the study treatment.
- The patient becomes HBV DNA positive. The patient should be referred to a specialist physician. Discussion of discontinuation from study treatment and from the study is provided in Section 10.3.3.3.

If a patient is noncompliant with study procedures and/or study drug administration, the investigator should assess the patient to determine the reason for noncompliance and educate and/or manage the patient as appropriate to improve compliance.

Any patient who discontinues the study treatment for any reason will stop treatment and continue to the ETV prior to entering the Post-Treatment Follow-Up Period (Period 4).

8.3.1.2. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is identified and is inadvertently enrolled in the study, a discussion must

occur between the sponsor CRP/CRS and investigator to determine whether it is medically appropriate for the patient to continue in the study with or without investigational product.

Safety follow up is as outlined in Attachment 1 (Study Schedule) and Section 10.3 (Safety Evaluations) of the protocol.

8.3.2. Permanent Discontinuation from the Study

Some possible reasons that may lead to permanent discontinuation from the study include:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- Investigator decision
    - The investigator decides that the patient should be discontinued from the study
    - If the patient requires long-term treatment with a therapeutic agent that has been demonstrated to be effective for the treatment of Ps, discontinuation from the study occurs prior to introduction of the new agent.
- Patient decision
    - The patient requests to be withdrawn from the study

Patients discontinuing from the study prematurely for any reason should complete adverse event and other safety follow-up per Attachment 1 (Study Schedule) and Section 10.3 (Safety Evaluations) of this protocol.

8.3.3. Lost to Follow-up

A patient will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Treatment

9.1. Treatments Administered

The investigator (or his/her designee) is responsible for explaining the correct use of the investigational agent(s) to the patient and/or an authorized adult who has been trained, 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. Further instructions regarding administration of the investigational product are provided in Section 9.1.1.

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.

The Induction Dosing Period (Period 2) involves a comparison of ixekizumab at 2 dose regimens, 80 mg Q2W and 80 mg Q4W versus placebo (Table RHBH.9.1). The Maintenance Dosing Period (Period 3) involves a comparison of ixekizumab 80 mg Q4W versus placebo (Table RHBH.9.2). At Week 0 (baseline; Visit 2), any patient assigned to ixekizumab will receive a starting dose of 160 mg ixekizumab as 2 SC injections. At Week 12, patients randomized to placebo at Week 0 (baseline; Visit 2) and who are classified as non-responders will receive a 160-mg ixekizumab dose as 2 SC injections. In order to maintain the study blind at Week 0 and Week 12, all patients, regardless of their assigned treatment group, will receive 2 doses of investigational product at Week 0 and Week 12. All doses are administered as SC injections. Table RHBH.9.3 presents the number of injections administered each study week during each dosing period.

Table RHBH.9.1. Induction Dosing Period (Period 2) Treatment Groups (Weeks 0 to 10)

Treatment Group	Description [a]
ixekizumab-80 mg Q2W	A starting dose of 160 mg (Week 0) given as 2 SC injections followed by 80 mg given as 1 SC injection Q2W (Weeks 2, 4, 6, 8, and 10).
ixekizumab-80 mg Q4W	A starting dose of 160 mg (Week 0) given as 2 SC injections followed by 80 mg given as 1 SC injection Q4W (Weeks 4 and 8). To maintain blinding, placebo is given as 1 SC injection at Weeks 2, 6, and 10.
Placebo	Placebo (Week 0) given as 2 SC injections followed by placebo Q2W (Weeks 2, 4, 6, 8, and 10).

Abbreviations: Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

[a] To maintain the study blind, all patients will receive 2 SC doses of investigational product at Week 0 (Visit 2) and 1 SC dose Q2W from Week 2 (Visit 4) through Week 10.

Table RHBH.9.2. Maintenance Dosing Period (Period 3) Treatment Groups (Weeks 12 to 56)

Treatment Group	Description [b]
ixekizumab-80 mg Q4W[a]	For patients randomized either to 80 mg Q2W or Q4W at Week 0, a dose of 80 mg will be given as 1 SC injection + a placebo injection at (Week 12); 80 mg ixekizumab will be given as 1 SC injection Q4W thereafter. For patients randomized to placebo at Week 0, a starting dose of 160 mg of ixekizumab will be given as 2 SC injections at Week 12; 80 mg ixekizumab will be given as 1 SC injection Q4W thereafter.
Placebo[a]	Placebo given as 2 SC injections at Week 12 followed by placebo given as 1 SC injection Q4W thereafter.

Abbreviations: Q4W = every 4 weeks; SC = subcutaneous.

[a] Refer to Section 7.1.3 for the treatment assignments for Responders, Non-Responders, and patients who relapse in Period 3

[b] To maintain the study blind, all patients will receive 2 SC doses of investigational product at Week 12 (Visit 7) and 1 SC dose Q4W from Week 16 (Visit 8) through Week 56 (Week 60, no investigational product administration). Study visits will occur at least Q4W during Period 3.

Table RHBH.9.3. Number of Injections Administered Each Study Week during Each Dosing Period

Dosing Period	Study Week	Number of Injections
Induction (Period 2)	0	2
	2	1
	4	1
	6	1
	8	1
	10	1
Maintenance (Period 3)	12	2
	16-56	1[a]

[a] Patients will receive 1 injection every 4 weeks, no investigational product administration at Week 60.

9.1.1. Administration of Investigational Product

Injections will be administered by the patient or clinical site staff or an authorized adult who has been trained by the clinical site staff.

Training: For training purposes, the proper procedures for administration of the investigational product and administration of the initial injection will be performed by clinical site staff at Week 0 (Visit 2), and the second injection of investigational product will be administered by the patient under the supervision of clinical site staff at Week 0 (Visit 2). If additional training is necessary, an injection may be administered by the patient under the supervision of clinical site staff at Week 2 (Visit 4).

Administration: If the patient is unable to perform the injection, clinical site staff or an authorized adult who has been trained may inject the investigational product. For these subsequent injections, the investigational product may be administered either at the trial site for safety concerns of the patient or outside the trial site, preferably at the patient's home, except for the Week 12 visit when the injections are to be given at the trial site for post-dose monitoring.

A dose of investigational product will consist of 1 SC injection of ixekizumab or placebo. 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.

Syringes should be at room temperature prior to injection (refer to Manual Syringe Directions for Use provided by the sponsor).

Throughout their participation in the study, randomized patients will record information in a Study Drug Administration Log, including the date, time, and anatomical location of administration of investigational product (for treatment compliance); syringe number; who administered the investigational product; and the reason if investigational product was not fully administered or not administered at all.

Observation: Patients should remain under observation for at least 1 hour after dosing at Week 0 (Visit 2) and Week 12 (Visit 7) to monitor for safety. At Week 12 (Visit 7), injections of the investigational product will be administered at the clinical site by the patient or a clinical site staff or an authorized adult who has been trained at the clinical site to allow for observation for any AEs and collection of post-injection BP and pulse measurements (Section 10.3.2.3 and Attachment 1).

9.2. Materials and Supplies

The ixekizumab solution for injection will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practices (cGMP). Ixekizumab and placebo (excipients only) will be supplied as an injectable solution in 1-mL, single-dose, disposable manual syringe. Each syringe of ixekizumab is designed to deliver 80 mg ixekizumab. The syringes (and contents) containing either ixekizumab or placebo will be visibly indistinguishable from each other. 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 the country's regulatory requirements. All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations. Investigational products will be supplied by Lilly or its representative, in accordance with cGMP, and will be supplied with lot numbers, expiry dates, and certificates of analysis, as applicable.

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.

9.3. Method of Assignment to Treatment

At Week 0 (Visit 2), patients who meet all criteria for enrollment at Visits 1/1A and 2 will be randomized at a 2:2:1 ratio to ixekizumab 80 mg Q2W, ixekizumab 80 mg Q4W, or placebo. Assignment to double-blind treatment groups will be determined by a computer-generated random sequence using an interactive web response system (IWRS). The IWRS will be used to assign double-blind investigational product to each patient. Site personnel will confirm that they have located the correct assigned investigational product package by entering a confirmation number found on the package into the IWRS.

At Week 12 (Visit 7), patients who enter Period 3 will be classified as a responder or non-responder (Section 7.1.3). Patients who received ixekizumab during Period 2 and who are responders will be re-randomized at a 2:1 ratio to 80 mg Q4W or placebo using the IWRS. Patients will be stratified by ixekizumab induction dosing regimen (80 mg Q2W or 80 mg Q4W). Patients who received placebo during Period 2 and who are responders will be assigned to continue to receive placebo until relapse occurs (Section 7.1.3). Non-responders who received any investigational product (assigned to any treatment group) during Period 2 will be assigned to receive treatment with 80 mg ixekizumab Q4W. Assignment to treatment will be determined by the IWRS.

9.4. Rationale for Selection of Doses in the Study

The treatment regimens of a 160 mg starting dose of subcutaneously administered ixekizumab followed by 80 mg Q2W or 80 mg Q4W up to week 12 then 80 mg Q4W thereafter have been selected for evaluation of the relative benefit/risk associated with continuous ixekizumab therapy in Chinese patients with psoriasis. Doses were selected based on efficacy, safety and pharmacokinetics/pharmacodynamics (PK/PD) data from a dose ranging Phase 2 and Phase 3 studies in psoriasis. More details of the efficacy, safety and PK/PD of ixekizumab can be found in the IB.

9.4.1. Dose Rationale for the Induction Dosing Period (Period 2; Weeks 0 to 12)

During the Induction Dosing Period (Period 2), 2 dose regimens of ixekizumab and a placebo group will be investigated:

80 mg Q2W: A starting dose of 160 mg given as 2 SC injections at Week 0 and 80 mg given as 1 SC injection Q2W for 5 doses at Weeks 2, 4, 6, 8, and 10.

80 mg Q4W: A starting dose of 160 mg given as 2 SC injections at Week 0 and 80 mg given as 1 SC injection Q4W for 2 doses at Weeks 4 and 8. To maintain the study treatment blind, placebo will be given at Weeks 2, 6, and 10.

The starting dose of 160 mg is used to shorten the time to achieve steady-state serum concentrations of ixekizumab and obtain a more rapid onset of action. The exposure of ixekizumab following the initial dose at 160 mg was more than 80% of the steady-state exposure

under the 80 mg Q2W regimen, and the severity of psoriasis (PASI and sPGA scores) improved as early as Week 1 in the pivotal Phase 3 studies.

Induction dosing regimens of 80 mg Q2W and 80 mg Q4W were evaluated in the pivotal Phase 3 studies and demonstrated overall efficacy for both doses (vs placebo and active comparator, etanercept) but a more favorable benefit/risk profile with Q2 - differential effects on efficacy but similar safety profiles. In the integrated analysis of data in the Induction Dosing Period from three Phase 3 controlled studies, the PASI 75, sPGA (0 or 1), and sPGA (0) response rates as well as improvements in Itch NRS and DLQI were consistently greater in the ixekizumab 80 mg Q2W group than in the 80 mg Q4W group. In addition, the PASI 75, PASI 90, and PASI 100 response rates as well as the sPGA (0 or 1) and sPGA (0) response rates at Week 12 were significantly higher in the ixekizumab 80 mg Q2W group than in the 80 mg Q4W group.

In the Induction Dosing Period in the Phase 3 studies, the safety profile was similar between the ixekizumab 80 mg Q2W group and 80 mg Q4W group. The frequency of Candida infection-related treatment-emergent adverse events (TEAEs) was higher in the ixekizumab 80 mg Q2W group than in the 80 mg Q4W group, but the differences in the frequencies of oral candidiasis and oral fungal infection between the ixekizumab 80 mg Q2W group and 80 mg Q4W group were less than 1%.

The results from PK and exposure-response analyses were consistent with the results from the efficacy and safety results, with high predictability for more rapid achievement of PASI 75 and sPGA (0 or 1) in the ixekizumab 80 mg Q2W group than in the 80 mg Q4W group during the Induction Dosing Period as well as the PASI 75 and sPGA (0 or 1) response rates at Week 12. In addition, for the adverse events investigated, an exposure-response relationship was generally not observed.

9.4.2. Maintenance Dosing Period (Period 3) Dose Rationale (Weeks 12 to 60)

During the Maintenance Dosing Period (Period 3), one ixekizumab dose regimen will be investigated:

80 mg Q4W: given as 1 SC injection of 80 mg Q4W starting from week 12.

This dosing regimen will be evaluated to establish the sustained response with continuous dosing, to assess durability of response following treatment withdrawal, and to allow evaluation of response to retreatment following disease relapse.

Maintenance dosing regimens of 80 mg Q4W and 80 mg Q12W were evaluated in the pivotal Phase 3 studies. Patients who were treated with ixekizumab 80 mg every 4 weeks (Q4W) had clearly superior responses than patients who were randomized to receive placebo or ixekizumab 80 mg every 12 weeks (Q12W) dosing. For sPGA (0,1) responders at Week 12, the proportion of patients who maintained this response at Week 60 in the integrated maintenance set was higher for ixekizumab 80 mg Q4W (71%) compared with 80 mg Q12W (35.5%) or placebo (7%). Due to the superior efficacy of the Q4W regimen over the Q12W regimen and no

clinically meaningful differences in safety profile for both doses, only the Q4W regimen will be evaluated in Study RHBH. The exposure-adjusted incidence rate of ixekizumab-treated patients reporting at least 1 TEAE was lower in the Maintenance Dosing Period than in the Induction Dosing Period. The exposure-adjusted incidence rate of patients reporting at least 1 TEAE for the Q4W maintenance dosing regimen was generally similar to, or lower than, the rate for the Q12W maintenance dosing regimen.

The results from PK and exposure-response analyses were consistent with the results from the efficacy and safety results. Results from an sPGA time course PK/PD model demonstrated sustainability of response at Week 60 (end of the maintenance dosing period), for the Q4W dose regimen with 25% to 27% higher predicted sPGA (0,1) and sPGA (0) response rates as compared to Q12W. In addition, for the adverse events investigated, an exposure-response relationship was generally not observed.

Additional Supporting Information

Sub-group analyses examining potential differences in response across the endpoints at Week 12 and Week 60 were conducted. Subgroup variables included: patient demographics (age, sex, race, ethnicity, weight), disease-related (previous psoriasis therapy type and frequency, baseline disease severity, age of psoriasis onset, and concomitant topical therapy), and disease location (fingernails, scalp, palmoplantar). Ixekizumab was superior to placebo in all subpopulations on all efficacy endpoints during both the Induction and Maintenance Dosing Periods. The Q2W dosing regimen yielded better outcomes than Q4W for almost every subgroup.

Further details on the efficacy and safety of these ixekizumab dosing regimens can be found in the IIB.

9.5. Selection and Timing of Doses

Patients are assigned to treatment and will receive their assigned treatment as outlined in Sections 9.3 and 9.1, respectively.

Investigational product should be administered at approximately the same time on injection days, as much as possible. For injections not administered on the scheduled day of the week from Week 0 to Week 12, the missed dose should be administered within 3 days of the scheduled day; after Week 12, the missed dose should be administered within 5 days of the scheduled day. Dates of subsequent study visits and injections should not be modified according to this delay.

9.5.1. Special Treatment Considerations

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 of the study will not be eligible for enrollment.

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 reactions/hypersensitivity. 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 reaction/hypersensitivity 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 reaction/hypersensitivity, a blood sample should be drawn to test for anti-drug antibodies (ADAs).

For patients who experience a potential allergic reaction/hypersensitivity, consideration for any premedication for future injections will be agreed upon between the investigator and sponsor and/or its designee. Examples of potential allergic reactions/hypersensitivities 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, injection-site pruritus). Patients who develop clinically significant systemic allergic reactions/hypersensitivities following administration of investigational product who do not respond to symptomatic medication or result in clinical sequelae (for example, hospitalization) should be discontinued from the study and not receive further doses of investigational product, with or without premedication (See Section 8.3.1.1). 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.

9.6. Continued Access to Investigational Product

Investigational product will not be made available at the conclusion of the study.

9.7. Blinding

This is a double-blind study; patients and study site personnel will be blinded to study treatment until all patients reach Week 60 (Visit 19) or have discontinued from the study (moved into Period 4). To preserve the blinding of the study, a minimum number of sponsor personnel not in direct contact with study sites will see the randomization table and treatment assignments before the study is unblinded. Section 9.1 provides the dosing details pertinent to maintenance of the study blind.

The investigator should make every effort to contact the Lilly CRP/CRS prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately by telephone. Unblinding will be performed through IWRS. Emergency unblinding for AEs may be performed through an IWRS. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is prematurely unblinded, the patient must be discontinued from the investigational product and should continue in the Post-Treatment Follow-Up Period (Period 4). In cases where there are ethical reasons to have the patient remain on the investigational product, the investigator must obtain specific approval from a Lilly study physician or representative for the patient to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. Patient safety must always be the first consideration in making such a determination.

9.8. Concomitant Therapy

All concomitant medication taken during the study must be recorded on the Concomitant Medication case report form (CRF). Treatment with concomitant Ps therapies during the study is permitted only as outlined in the inclusion/exclusion criteria (Sections 8.1 and 8.2) and as described in the paragraphs below. Patients taking permitted medications should be on chronic stable doses at the baseline visit (Week 0; Visit 2) as specified in Sections 8.1 and 8.2.

The following therapies will not be permitted during the course of the study Periods 1 through 3:

- Psoriasis therapy as described in the inclusion/exclusion criteria (Sections 8.1 and 8.2) except as noted below for other concomitant therapies.
- Any biologic therapy within the washout periods specified in Section 8.2.
- Concomitant medications as described in the inclusion/exclusion criteria (Sections 8.1 and 8.2).
- Live vaccines.
- Phototherapy.

The following medications will be permitted during the course of the study:

Topical Steroids: mild and least potent topical steroids used for psoriasis [such as desonide, fluocinolone acetonide, hydrocortisone] will be permitted for use limited to 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.

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

Other Concomitant Therapies: Prior to Week 60, the following will be allowed as needed: shampoos that do not contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues; and topical moisturizers/emollients and other non-prescription topical products that

do not contain urea, >3% salicylic acid, alpha- or beta-hydroxyl acids, corticosteroids, or vitamin D3 analogues; bath oils and oatmeal bath preparations. After the Week 60 (Visit 19) assessments, shampoos that contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues; topical moisturizers/emollients and other non-prescription topical products that contain urea, >3% salicylic acid, alpha- or beta-hydroxyl acids, corticosteroids, or vitamin D3 analogues; and bath oils and oatmeal bath preparations may be used. These topical therapies are not to be used within 12 hours prior to a study visit. Acetaminophen or aspirin will also be allowed as needed.

For patients who discontinued study treatment and have entered the Post-Treatment Follow-Up Period (Period 4), Ps therapy is allowed, as determined appropriate by the investigator. These allowed Ps therapies include the treatment patients received during the double-blind trial when approved.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. If the need for concomitant medication arises for an AE or for appropriate medical management (including the limited use of therapeutic agents which, if used under treatment regimens other than for treating an AE or for appropriate medical management, might be considered Ps therapies), the investigator should base decisions on the patient and clinical factors. Any additional medication, whether prescription or over-the-counter, used at baseline (Week 0; Visit 2) and/or during the course of the study must be documented with the start and stop dates on the Concomitant Medications CRF.

Patients will maintain their usual medication regimen for other concomitant diseases throughout the study unless specifically excluded in the protocol. Patients taking concomitant medications should be on stable doses at the time of baseline (Week 0; Visit 2) and should remain at a stable dose throughout the study, unless changes need to be made for an AE or for appropriate medical management. Additional systemic drugs are to be avoided during the study, unless required to treat an AE. Other medications may be allowed, if approved by the sponsor or its designee.

Any changes in medications not addressed above should be discussed with the investigator. Patients should be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements.

9.9. Treatment Compliance

Every attempt will be made to select patients who have the ability to understand and comply with instructions. The investigator is responsible for discussing methods to ensure high treatment compliance with the patient before randomization.

The time and day of each investigational product administration must be transcribed into the eCRF by site personnel. Patient compliance with the investigational product will be assessed at each study visit by review of the Study Drug Administration Log, return of empty investigational product packaging, and/or direct questioning (except Week 1 [Visit 3]). Deviation(s) from the prescribed dosage regimen should be documented.

Noncompliant patients may be discontinued from the study (see Section 12.2.5).

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule (Attachment 1). Additionally, Attachment 2 provides a list of the specific laboratory tests to be performed for this study.

10.1. Efficacy Measures

10.1.1. Primary Efficacy Measures

The primary efficacy endpoints are sPGA (0, 1) and PASI 75 response at Week 12 (Visit 7).

10.1.1.1. Static Physician Global Assessment (sPGA)

The sPGA is the physician's determination of the patient's Ps lesions overall at a given time point. The sPGA is recommended as an endpoint to use to assess efficacy in the treatment of Ps (EMEA 2004 [WWW]). Overall lesions are categorized by descriptions for induration, erythema, and scaling. For the analysis of responses, the patient's Ps is assessed as clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).

10.1.1.2. Psoriasis Area and Severity Index (PASI)

The PASI is another accepted primary efficacy measurement for this phase of development of Ps treatments (EMEA 2004 [WWW]). The PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head and neck, 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 Ps to 72 for the most severe disease (Fredriksson and Pettersson 1978). The PASI has been the most frequently used endpoint and measure of Ps severity in clinical trials (EMEA 2004 [WWW]; Menter et al. 2008). A clinically meaningful response is a PASI 75, which represents at least a 75% decrease (improvement) from the baseline PASI score. Higher levels of clearance (PASI 90) as well as complete resolution of plaque Ps (PASI 100) were additional endpoints due to the increasing recognition of the association of higher clearance with greater health-related quality of life (HRQoL) (Puig 2015).

10.1.2. Secondary Efficacy Measures

The following secondary efficacy endpoints will be assessed in this study: PASI 50, PASI 90, PASI 100, NAPSI, PSSI, PPASI 50, PPASI 75, PPASI 100, and BSA.

10.1.2.1. Nail Psoriasis Severity Index (NAPSI)

If the patient has fingernail Ps at baseline, the NAPSI will be used. The NAPSI is a numeric, reproducible, objective tool for evaluation of fingernail Ps. This scale is used to evaluate the severity of fingernail bed Ps and fingernail matrix Ps by area of involvement in the fingernail unit. In this study, only fingernail involvement will be assessed. The fingernail is divided with imaginary horizontal and longitudinal lines into quadrants. Each fingernail is given a score for fingernail bed Ps (0 to 4) and fingernail matrix Ps (0 to 4) depending on the presence (score of 1)

or absence (score of 0) of any of the features of fingernail bed and fingernail matrix Ps in each quadrant. The NAPSI score of a fingernail is the sum of scores in fingernail bed and fingernail matrix from each quadrant (maximum of 8). Each fingernail is evaluated, and the sum of all the fingernails is the total NAPSI score (range 0 to 80).

10.1.2.2. Psoriasis Scalp Severity Index (PSSI)

If the patient has scalp Ps at baseline, the PSSI will be used. The PSSI is a composite score derived from the sum scores for erythema, induration, and desquamation multiplied by a score for the extent of scalp area involved (range 0 to 72).

10.1.2.3. Palmoplantar Psoriasis Area and Severity Index (PPASI)

If the patient has palmoplantar Ps at baseline, the PPASI will be used. The PPASI is a composite score derived from the sum scores for erythema, induration, and desquamation multiplied by a score for the extent of palm and sole area involvement (range 0 to 72).

10.1.2.4. Percentage of Body Surface Area (BSA)

The investigator will evaluate the percentage involvement of Ps on each patient's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), in which 1% corresponds to the size of the patient's palm of the hand (including the palm, fingers, and thumb) (NPF 2009 [WWW]).

10.2. Health Outcome/Quality of Life Measures

The following health outcome measures will be assessed in this study: Itch NRS, DLQI, SF-36, patient's global assessment of disease severity, and joint pain VAS.

10.2.1. Itch Numeric Rating Scale (NRS)

The Itch NRS is a single-item, patient-reported outcome (PRO) measure designed to capture information on the overall severity of a patient's itching due to their psoriatic skin condition by having the patient circle the integer that best describes the worst level of itching in the past 24 hours on a 11-point NRS anchored at 0 representing "no itch" and 10 representing "worst itch imaginable."

10.2.2. Dermatology Life Quality Index (DLQI)

The DLQI is a validated, dermatology-specific, patient-reported measure that evaluates patient's HRQoL. This questionnaire has 10 items that are grouped in 6 domains, namely symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the "last week". Response categories include "not at all," "a little," "a lot," and "very much," with corresponding scores of 0, 1, 2, and 3, respectively, and unanswered ("not relevant") responses denoted as "9". Totals range from 0 to 30 (less to more impairment) (Finlay and Khan 1994; Basra et al. 2008). A DLQI total score of 0 to 1 is considered as having no effect on a patient's HRQoL, and a 5-point change from baseline is considered as the minimal clinically important difference threshold (Khilji et al. 2002; Hongbo et al. 2005).

10.2.3. Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)

The SF-36 is a 36-item, patient-completed measure designed to be a short, multi-purpose assessment of health in the areas of physical functioning, role-physical, role-emotional, bodily pain, vitality, social functioning, mental health, and general health. The 2 overarching domains of mental well-being and physical well-being are captured by the MCS and PCS scores, respectively. The summary scores range from 0 to 100, with higher scores indicating better levels of function and/or better health. Items are answered on Likert scales of varying lengths. The SF-36 acute version will be used, which has a 1-week recall period (The SF Community – SF-36 Health Survey Update [WWW]).

10.2.4. Patient's Global Assessment of Disease Severity

In the Patient's Global Assessment of Disease Severity, patients are asked to rank on a 0 to 5 NRS the severity of their Ps "today" from 0 (Clear) = no Ps to 5 (Severe) = the worst their Ps has ever been.

10.2.5. Joint Pain Visual Analog Scale (VAS) Psoriatic Arthritis

Patients diagnosed with psoriatic arthritis at baseline will complete the Joint Pain VAS. The Joint Pain VAS is a patient-administered scale designed to measure current joint pain from PsA using a 100-mm horizontal VAS. Overall severity of a patient's joint pain from PsA is indicated by placing a single mark on the horizontal scale (0 = none; 100 = as severe as you can imagine).

10.3. 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.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study that caused the patient to discontinue the investigational product 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.

10.3.1. Adverse Events

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

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

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

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, 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.

All AEs occurring after the patient receives the first dose of investigational product must be reported to Lilly or its designee via eCRF.

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, investigational product, concomitant therapy, and other medical condition via eCRF.

Study site personnel must alert Lilly or its designee within 24 hours of the investigator **unblinding** a patient's treatment group assignment for any reason.

If a patient's treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to discontinuation of treatment.

10.3.1.1. Serious Adverse Events

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 be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE

reporting requirements and timelines (see Section 10.3.1) if it is considered reasonably possibly related to study procedure.

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. Patients with a serious hepatic adverse event should have additional data collected using the eCRF.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Serious adverse events occurring after a patient has taken the last dose of investigational product will be collected throughout the patient's participation in the study (through Period 4), regardless of the investigator's opinion of causation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

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.

10.3.1.1.1. Adverse Events of Special Interest

The following adverse events of special interest (AESIs) will be used to determine the safety and tolerability of ixekizumab over the range of doses selected for this clinical study.

Adverse events of special interest for ixekizumab are:

- cytopenias (leukopenia, neutropenia, and thrombocytopenia)
- liver function test changes/enzyme elevations (ALT, AST, bilirubin, and ALP)
- infection
- injection-site reactions
- allergic reactions/hypersensitivities
- cerebro-cardiovascular events (potential and adjudicated endpoints)
- malignancies
- IBD (CD and UC)
- depression
- pneumocystis pneumonia (PCP) and interstitial lung disease (ILD).

If infections, injection-site reactions, allergic reactions/hypersensitivities or inflammatory bowel disease are reported, sites will provide details on these events as instructed on the CRF. Investigators will also educate patients and/or authorized adults who have been trained about the symptoms of allergic reactions/hypersensitivities and will provide instructions on dealing with

these reactions. A blood sample will be collected when possible for any patient who experiences an AE of potential systemic allergic reactions/hypersensitivities during the study.

Data on preferred terms (PTs) that could potentially result in cerebro-cardiovascular events (defined as death, MI, stroke, hospitalization for unstable angina, hospitalization for heart failure, coronary revascularization procedure, peripheral revascularization procedure, cardiogenic shock due to MI, resuscitated sudden death, serious arrhythmia, hospitalization for hypertension, and peripheral arterial event) and associated events based on Medical Dictionary for Regulatory Activities (MedDRA). PT codes will be collected and the events will be adjudicated by an external Clinical Events Committee (CEC) made up of a chairman, 2 cardiologists, and a neurologist.

Data on suspected IBD, as identified by events possibly indicative of ulcerative colitis and CD, will be collected and the events will be adjudicated by an external CEC made up of gastroenterologists with expertise in IBD.

The role of the CECs is to adjudicate defined clinical events, in a blinded, consistent, and unbiased manner throughout the course of a study. The importance of the CECs is to ensure that a single group evaluates all events that have been reported uniformly.

10.3.1.1.2. 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. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

10.3.2. Other Safety Measures

10.3.2.1. Physical Examination

One complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at screening. This examination will determine whether the patient meets the criteria required to participate in the study and will also serve as a monitor for preexisting conditions and as a baseline for TEAE assessment. All physical examinations throughout the study should include a symptom-directed physical evaluation as well as an examination of the heart, lungs, abdomen, and a visual examination of the skin.

10.3.2.2. 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 on the Study Schedule (Attachment 1) for evidence of active or latent TB (positive PPD [≥5-mm induration] or positive QuantiFERON®-TB Gold test/T-SPOT®.TB at screening but no other evidence of active TB). In sites where sample collection and proper incubation for the QuantiFERON®-TB Gold test are

available at the site 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 would be sent to central lab for testing. If the QuantiFERON®-TB Gold 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 patients will be considered as latent TB for study purpose.

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 PPD skin test ≥5 mm induration or a positive QuantiFERON®-TB Gold or positive T-SPOT®.TB test at screening, but no other evidence of active TB may be rescreened 1 time and may be enrolled without repeating a PPD or QuantiFERON®-TB Gold or T-SPOT®.TB test if the following conditions are met:

- after receiving at least 4 weeks of appropriate latent TB infection (LTBI) therapy,
- with no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) 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/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.

10.3.2.3. Vital Signs

Vital signs (BP and pulse) and body temperature will be measured (sitting) after resting for a minimum of 10 minutes at times indicated in the Study Schedule (Attachment 1). At baseline (Week 0; Visit 2) and Week 12 (Visit 7), BP and pulse should be measured prior to administration of the investigational product and again approximately 1 hour post administration. Any clinically significant findings that result in a diagnosis should be captured on the eCRF. Additional measurements of vital signs may be performed at the discretion of the investigator.

10.3.2.4. Electrocardiograms

For each patient, 12-lead digital ECGs will be obtained locally as single ECGs according to the Study Schedule (Attachment 1). 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 more ECGs than expected at a particular time point is allowed when needed to ensure high quality records.

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, and ideally while the patient is still present, and for immediate patient management, should any clinically relevant findings be identified. The qualified physician must document his/her review of the ECG at the time of evaluation. Any clinically significant findings that result in a diagnosis should be captured on the eCRF.

The ECGs will be maintained at the site and made available to the sponsor as requested.

10.3.2.5. Immunogenicity

Samples for immunogenicity testing will be collected at time points indicated in the Study Schedule (Attachment 1) and for any event judged by the investigator to be a potential systemic allergic reaction/hypersensitivity, when possible. Venous blood samples will be collected into tubes and used to determine antibody production against ixekizumab. The actual date of each sampling will be recorded on the laboratory requisition.

Immunogenicity will be assessed by a validated assay designed to perform in the presence of ixekizumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of ixekizumab. Treatment-emergent immunogenicity is defined as any occurrence of a 4-fold or 2 dilution increase in titer over the pre-treatment baseline titer. In the case of a negative result at baseline, treatment-emergent immunogenicity is defined as an increase in titer to ≥1:10. Blood samples are also being collected to determine serum ixekizumab concentration at same time as immunogenicity samples to facilitate interpretation of immunogenicity data (Section 10.4.2). Samples may be stored for a maximum of 15 years following last patient visit to enable further analysis of immune responses to ixekizumab. The duration allows the sponsor to respond to regulatory requests related to the investigational product.

10.3.2.6. Safety-Related Immune Markers

IL-17 is believed to play a role in neutrophil homeostasis and in neutrophil-dependent host defense against extracellular infections (Happel et al. 2003; Huang et al. 2004; Milner et al. 2008). Neutrophil counts will therefore serve as a safety marker in the current investigation.

Ixekizumab is not expected to affect the numbers of B, T, and natural killer (NK) lymphocytes or serum immunoglobulin subclasses A, G, and M (IgA, IgG, and immunoglobulin M [IgM], respectively) in peripheral blood. However, since this is a novel immunomodulatory drug, these parameters will be measured in patients.

10.3.2.7. Quick Inventory of Depressive Symptomatology-Self Report

QIDS-SR16 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). The QIDS-SR16 scale is used to assess the potential impact of treatment on new onset or changes in depression, thoughts of death, and/or suicidal ideation severity. 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-SR16 questions may be found at the University of Pittsburgh IDS/QIDS internet page [WWW]. A QIDS-SR16 assessment will be taken at times indicated in the Study Schedule (Attachment 1).

10.3.2.8. Columbia-Suicide Severity Rating Scale

The C-SSRS (Posner et al. 2007a, 2007b; Columbia University Medical Center [WWW]) is a scale that captures the occurrence, severity, and frequency of suicide-related ideations and behaviors during the assessment period. The C-SSRS must be administered by appropriately trained site personnel. The tool was developed by the National Institute of Mental Health Treatment of Adolescent Suicide Attempters trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events. Patients will be assessed according to the Study Schedule (Attachment 1).

The Self-Harm Supplement Form is a one-question form that asks for the number of suicidal or nonsuicidal self-injurious behaviors the patient has experienced since the last assessment. For each unique event identified, a questionnaire (Self-Harm Follow-Up Form) which collects supplemental information on the self-injurious behavior is to be completed. This information is then documented in the eCRF. The Self-Harm Supplement Form will be completed according to the Study Schedule (Attachment 1).

10.3.3. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the DMC (an advisory group for this study formed to protect the integrity of data [refer to Section 12.2.10.1]) can conduct additional analyses of the safety data.

The Lilly CRP/CRS will monitor safety data throughout the course of the study and will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist.

The sponsor will review SAEs within time frames mandated by company procedures and will review trends, laboratory analytes, and AEs at periodic intervals.

See Section 8.3 for discontinuation criteria related to specific AEs and Sections 10.3.3.1, 10.3.3.2, 10.3.3.3, and 10.3.3.4 for the monitoring of neutropenia, hepatic injury, hepatitis B, and hypertension, respectively.

Vital signs will be monitored pre- and post-dose as indicated in the Study Schedule (Attachment 1).

10.3.3.1. Neutropenia

Patients with neutrophil counts <1500 cells/μL should be managed for neutropenia as follows:

- <500 cells/μL (<0.50×10^3/μL or <0.50 GI/L), see Discontinuation Criteria (Section 8.3.1.1)
- ≥500 cells/μL and <1000 cells/μL (≥ 0.50 × 10^3/μL and <1.00×10^3/μL or ≥0.50 GI/L and <1.00 GI/L), see Discontinuation Criteria (Section 8.3.1.1)
- ≥1000 cells/μL and <1500 cells/μL (≥1.00 × 10^3/μL and <1.50 × 10^3/μL or ≥1.00 GI/L and <1.50 GI/L), and the patient has a concurrent infection that requires systemic anti-infective therapy (for example, antibiotic, antifungal agent, antiviral agent):
    - The dose of investigational product should be withheld, the patient should receive appropriate medical care, and a repeat test for neutrophil count should be performed within 4 weeks from knowledge of the initial report. If the repeat neutrophil count has returned to ≥1500 cells/μL (≥1.50 × 10^3/μL or ≥1.50 GI/L) and the infection has resolved or is resolving, the patient may resume dosing of investigational product and evaluation at scheduled visits. If the neutrophil count remains ≥1000 cells/μL and <1500 cells/μL (≥1.00 × 10^3/μL and <1.50×10^3/μL or ≥1.00 GI/L and <1.50 GI/L), investigational product should continue to be withheld and a repeat neutrophil count should again be performed within another 4 weeks. If, after 2 repeat tests, the neutrophil count still remains ≥1000 cells/μL and <1500 cells/μL (≥1.00 × 10^3/μL and <1.50 × 10^3/μL or ≥1.00 GI/L and <1.50 GI/L), and:
        a. the infection has not fully resolved, the patient will be discontinued from the study.
        b. the infection has resolved, the patient may resume dosing and evaluation at scheduled visits. However, if resumption of dosing is not deemed appropriate by the investigator, the patient will be discontinued from the study.
- ≥1000 cells/μL and <1500 cells/μL (≥1.00 × 10^3/μL and <1.50 × 10^3/μL or ≥1.00 GI/L and <1.50 GI/L), and the patient has no concurrent infection that requires systemic anti-infective therapy (for example, antibiotic, antifungal agent, antiviral agent):
    - Dosing may continue, and a repeat neutrophil count should be performed 4 to 8 weeks from knowledge of the initial report. Testing may be at a regularly scheduled visit or at an unscheduled visit, as necessary.

      Repeat testing should be performed at 4- to 8-week intervals until the neutrophil count has returned to ≥1500 cells/μL (≥1.50 × 10^3/μL or 1.50 GI/L). If the patient has 3 or more postbaseline neutrophil counts of ≥1000 cells/μL and <1500 cells/μL (≥1.00 × 10^3/μL and <1.50 × 10^3/μL or ≥1.00 GI/L and <1.50 GI/L), no value of <1000 cells/μL (<1.00 × 10^3/μL or <1.00 GI/L), and no

post-baseline infection requiring systemic anti-infective therapy, the patient may continue or resume further evaluation at scheduled visits, as deemed appropriate by the investigator.

If a patient without initial concurrent infection develops an infection that requires systemic anti-infective therapy, then the patient should be managed as indicated above for patients with concurrent infection. Management of neutropenia during Period 4 is described in Section 7.1.4.1.

10.3.3.2. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver testing (Attachment 3) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

Additional safety data should be collected via the eCRF if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE

10.3.3.3. Hepatitis B Monitoring

Patients that are HBcAb+ at screening, regardless of hepatitis B surface antibody (HBsAB) status, will have a serum HBV DNA obtained by the central laboratory. Patients that are found to be HBV DNA positive (detectable) at screening will be excluded from the trial. Patients that are HBV DNA negative (undetectable) may be enrolled into the study with required HBV DNA monitoring every 3 months during treatment and 12 weeks after the last dose of ixekizumab. Patients who are HBcAb negative and HBsAb positive will not require screening for HBV DNA as they are likely to have been vaccinated for HBV and have a very low risk of reactivation. These patients will be followed-up by liver tests as part of the study routine.

If the result of the HBV DNA testing is positive, the patient must be discontinued from the study treatment and should receive appropriate follow-up medical care, including consideration for antiviral therapy. A specialist physician in the care of patients with hepatitis (for example, infectious disease or hepatologist subspecialists) should be consulted and potentially start antiviral therapy prior to discontinuation of any immunosuppressant therapy (including

investigational drug). Timing of discontinuation from the study and of any immunosuppressant therapy (including investigational product) needs to be based on the recommendations of the consulting specialist physician in conjunction with the investigator and medical guidelines/standard of care.

10.3.3.4. Hypertension

Patients who experience changes in BP (systolic BP at ≥160 mmHg plus ≥20 mmHg increase from baseline [Week 0; Visit 2]; and/or diastolic BP at ≥100 mm Hg plus ≥10 mm Hg increase from baseline) on 2 consecutive visits should receive intervention for the management of hypertension. Intervention could include the maximal intervention of withholding the dose of investigational product and/or the introduction of an anti-hypertensive agent. See Section 8.3.1 for the discontinuation criterion related to hypertension.

10.3.4. Complaint Handling

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

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.

Complaints related to unblinded concomitant drugs/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or delegate will be reported.

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.

10.4. Sample Collection and Testing

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific tests that will be performed for this study.

10.4.1. Samples for Standard Laboratory Testing

As applicable, blood and urine samples will be collected at the time points specified in the Study Schedule (Attachment 1) and after ECG, vital signs, and clinical efficacy measurements.

Clinical laboratory tests will be analyzed by a central laboratory unless otherwise specified. Attachment 2 lists the specific tests that will be performed for this study.

Female patients of childbearing potential will undergo a urine pregnancy test at the site on a monthly basis during periods between scheduled visits until Week 60.

Blood will be drawn at the visits specified in the Study Schedule (Attachment 1) for routine safety laboratories including clinical chemistry, hematology, thyroid function test, coagulation panel, and lipid panel. Additional blood samples may be drawn if needed for safety purposes and/or if warranted and agreed upon between the investigator and Lilly or its designee. An additional blood sample may be drawn at screening for viral serologies.

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.

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

10.4.2. Samples for Pharmacokinetics

At the visits and times specified in the Study Schedule (Attachment 1), blood samples will be collected to determine the serum concentrations of ixekizumab.

These blood samples for PK analysis are matched to the timing of samples for the assessment of immunogenicity (Section 10.3.2.5). It is expected that these PK samples will allow sufficient description of ixekizumab PK profiles at steady state throughout the study and may facilitate in the interpretation of the immunogenicity data. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Samples collected for PK analysis will be tested at a laboratory approved by Lilly or its designee. Concentrations of immunoreactive ixekizumab in human serum will be determined by a validated method.

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

10.5. Appropriateness of Measurements

All of the clinical and safety assessments in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant. Blood inflammatory/immunologic molecules will provide information on safety and PD. Immunogenicity monitoring will provide information for future development of ixekizumab.

11. 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 a start-up training session to instruct the investigators and study coordinators. This session 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 use standard computer edits to detect errors in data collection.

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

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

All data entry and data management processes and procedures for this study will be documented within a Data Management Plan.

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site personnel into the sponsor or designee-provided electronic data capture system.

Any data for which paper documentation provided by the patient will serve as the source document and will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper Study Drug Administration Log to collect the date, time, and location of administration of investigational product (for treatment compliance), syringe number, who administered the investigational product, and the reason if investigational product was not fully administered or not administered at all.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Clinical Laboratory Results Modernization (CLRM).

Case report form data collected by the TPO will be encoded by the TPO and stored electronically in the TPO's database system. Validated data will subsequently be transferred to Lilly's data warehouse, using standard Lilly file transfer processes.

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

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

The total sample size for the study is 420 patients randomized at a 2:2:1 ratio in the blinded Induction Dosing Period to 80 mg Q2W, 80 mg Q4W, and placebo, respectively. In order to account for multiple testing for the 2 ixekizumab groups, a 2-sided Fisher's exact test at the 0.025 level is assumed. Assuming the response rates for both sPGA (0,1) and PASI 75 at Week 12 (Visit 7) are 75% for each ixekizumab treatment group and 5% for the placebo group, 168 patients in 80 mg Q2W or 80 mg Q4W versus 84 patients in placebo group will provide >99% power to test the superiority of each ixekizumab dose regimen to placebo for sPGA (0,1) and for PASI 75. These assumptions are based on the integrated results from the pivotal Phase 3 Studies RHAZ, RHBA, and RHBC.

Assuming 70% of the ixekizumab patients are re-randomized in the Maintenance Dosing Period at Week 12 (Visit 7) at a 2:1 ratio to 80 mg Q4W or placebo, approximately 78 patients will be included in 80 mg Q4W group and 39 patients in placebo group. This sample size will:

- provide >99% power to test the difference in the proportion of patients maintaining sPGA (0, 1) from Week 12 (Visit 7) after re-randomization at start of Maintenance Dosing Period to Week 60 (Visit 19) in the Maintenance Dosing Period Primary population between the ixekizumab dosing interval and placebo within the original treatment group, assuming the proportions of patients maintaining sPGA (0, 1) are 70% for 80 mg Q4W and 10% for placebo within each original treatment group (Visit 19). A 2-sided Fisher's exact test at the 0.025 significance level is assumed.
- provide >99% power to test the difference in the proportion of patients maintaining a PASI 75 from Week 12 (Visit 7) after re-randomization at start of Maintenance Dosing Period to Week 60 (Visit 19) in the Maintenance Dosing Period Primary population between the ixekizumab dosing interval and placebo within each original treatment group, assuming the proportions of patients maintaining a PASI 75 are 70% for 80 mg Q4W and 10% for placebo within each original treatment group. A 2-sided Fisher's exact test at the 0.025 significance level is assumed.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

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

In general, continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, median, and number of observations. Categorical data will be summarized as frequency counts and percentages.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described

in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Complete details of the planned analyses will be documented in the statistical analysis plan (SAP).

12.2.1.1. General Considerations for Analyses during Period 2 (Induction Dosing Period)

Comparisons between each ixekizumab dose regimen (80 mg Q2W or 80 mg Q4W) and placebo will be performed for all analyses in Period 2. Baseline will be defined as the last available value before the first injection for both efficacy and safety analyses. For efficacy measures, if the patient does not take any injection, the last available value on or prior to randomization date will be used. In most cases, this will be the measure recorded at Week 0 (Visit 2). Change from baseline will be calculated as the visit value of interest minus the baseline value. For safety analyses using a baseline period, the baseline period is defined as the time from Visit 1 to the date/time of the first injection.

Treatment comparisons of categorical efficacy variables will be conducted using a logistic regression analysis with treatment in the model. The proportions and 95% confidence intervals (CIs), the difference in proportions, and the 95% CI of the difference will be reported. Secondary analysis on the categorical efficacy variables will be conducted using a Fisher's exact test.

The primary analysis for all continuous efficacy and health outcome variables will be made using mixed effects for repeated measures (MMRM) analysis. In addition, treatment comparisons for continuous efficacy and health outcomes variables may also be made using analysis of covariance (ANCOVA).

When MMRM is used, the model will include treatment, baseline value, visit, treatment-by-visit, and baseline-by-visit interactions as fixed factors. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by compound symmetry will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least-squares (LS) means will be used for the statistical comparison; the 95% CI will be reported. Treatment group comparisons with placebo at Week 12 (Visit 7) and all other visits will be tested.

When the ANCOVA model is used, the model includes treatment and baseline value. Type III sums of squares for the LS means will be used for the statistical comparison; the 95% CI will also be reported.

For variables that are not collected at each postbaseline visit, data may exist at visits where the variable was not scheduled to be collected, due to early discontinuation visits. In these situations, data from the early discontinuation visit that does not correspond to the planned collection schedule will be excluded from the MMRM analyses. However, the data will still be

used in other analyses, including shift analyses, change from baseline to last-observation carried forward (LOCF) endpoint analyses, and other categorical analyses.

The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to-event variables, such as time-to-first response (e.g. sPGA [0, 1], PASI 75), time to relapse, time to discontinuation. Treatment comparisons will be performed using the log-rank test.

Fisher's exact test may be used for all AE, baseline, discontinuation, and other categorical safety data. The continuous baseline characteristics will be analyzed using an analysis of variance (ANOVA) model with dosing regimen as a factor. Continuous vital sign and laboratory values will be analyzed by an ANCOVA with treatment and baseline value in the model where appropriate.

12.2.1.2. General Considerations for Analyses during Period 3 (Maintenance Dosing Period)

Unless otherwise specified, the following treatment comparisons during the Maintenance Dosing Period will be performed for the Maintenance Dosing Period Primary Population (defined in Section 12.2.1.3) as shown in Table RHBH.12.1.

Table RHBH.12.1. Treatment Comparisons during the Maintenance Dosing Period

Induction Dosing	Maintenance Dosing	Treatment Group Comparisons during the Maintenance Dosing Period
80 mg Q2W = Dose 1	80 mg Q4W = Dose 1A Placebo = Dose 1B	Dose 1A versus Dose 1B
80 mg Q4W = Dose 2	80 mg Q4W = Dose 2A Placebo = Dose 2B	Dose 2A versus Dose 2B

Abbreviations: Q2W = once every 2 weeks; Q4W = once every 4 weeks.

For the efficacy and health outcomes analyses, baseline is defined as the last available value before the first injection in Period 2; in most cases it will be the value recorded at Week 0 (Visit 2).

Unless otherwise specified, for the Period 3 safety analyses, baseline and baseline period are defined as the last non-missing assessment prior to the first injection of study treatment at Week 12 (Visit 7). In most cases, this will be the measure recorded at Week 12 (Visit 7). For treatment-emergent adverse events, baseline value is the measure recorded at the last visit prior to the study drug injection at Week 12 (Visit 7).

Change from baseline will be calculated as the visit value of interest minus the baseline value.

For patients who met relapse criteria and were retreated with ixekizumab, only data up to the time of relapse will be included in the maintenance of effect analyses. These patients will be

considered non-responders to categorical assessments per the NRI imputation method (see Section 12.2.1.4.1).

Treatment comparisons of categorical efficacy variables will be made using a logistic regression analysis with treatment in the model. The proportions and 95% CI, the difference in proportions, and the 95% CI of the difference will be reported. Secondary analysis on the categorical efficacy variables may be conducted using a Fisher's exact test.

Treatment comparisons for continuous efficacy variables will be made using MMRM model. An ANCOVA model may also be used.

When MMRM is used, the model will include treatment, baseline value, visit, treatment-by-visit, and baseline-by-visit interactions as fixed factors. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by compound symmetry will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least-squares (LS) means will be used for the statistical comparison; the 95% CI will be reported. Treatment arm comparisons with placebo at Week 60 (Visit 19) and all other visits will be tested.

When the ANCOVA model is used, the model includes treatment and baseline value in the model. Type III sums of squares for the LS means will be used for the statistical comparison; the 95% CI will also be reported.

The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to relapse (loss of response). Treatment comparisons will be performed using the log-rank test.

Fisher's exact test will be used for all AE, baseline, discontinuation, and other categorical data. Continuous vital sign and laboratory values will be analyzed by an ANCOVA model with treatment and baseline value as independent variables.

Efficacy, health outcomes, and safety analysis will also be conducted on a Maintenance Dosing Period Secondary Population as defined in Section 12.2.1.3. Further details will be specified in the SAP.

12.2.1.3. Analysis Populations

Unless otherwise specified, efficacy and health outcomes analyses for Period 2 (Induction Dosing Period) will be conducted on the intent-to-treat population (ITT), defined as all randomized patients, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment to which they were assigned.

In addition, the primary analyses will be repeated using the per protocol set (PPS), which is defined as all randomized patients who are compliant with therapy, who do not have a subset of important protocol deviations that impact the primary efficacy endpoints, and whose investigator site does not have significant GCP issues that require a report to the regulatory agencies prior to

Week 12 (Visit 7). Compliance with therapy is defined to be missing no more than 20% of expected doses, not missing 2 consecutive doses, and no double dosing (that is, taking more injections at the same time point than specified in the protocol) during the period that patients participated in the study and prior to Week 12 (Visit 7) (see Section 12.2.5). Important protocol deviation will be described in the SAP. Patients will be analyzed according to the treatment to which they were assigned.

Safety analyses for Period 2 will be conducted on the safety population, defined as all randomized patients who received at least 1 dose of study treatment. Patients will be analyzed according to the treatment to which they were assigned.

Efficacy, health outcomes, and safety analyses for Period 3 (Maintenance Dosing Period) will be conducted on the Maintenance Dosing Period Primary population, defined as all re-randomized patients (that is, patients randomized to ixekizumab in Period 2 who achieved a sPGA [0, 1] and were re-randomized at Week 12) who received at least 1 dose of study treatment during Period 3 (Maintenance Dosing Period). Patients will be analyzed according to the treatment to which they were re-randomized.

Efficacy, health outcomes, and safety analyses for Period 3 will also be conducted on the Maintenance Dosing Period Secondary population, defined as the ixekizumab patients who were not re-randomized at Week 12 or patients who were randomized to placebo at Week 0, who received at least 1 dose of study treatment during the maintenance dosing period. Patients will be analyzed according to the treatment to which they were assigned upon entry into Period 3.

Safety analyses for Period 4 (Post-Treatment Follow-up Period) will be conducted on the follow-up population, defined as all randomized patients who received at least 1 dose of study treatment and have entered the post-treatment follow-up period. Patients will be analyzed according to the treatment they actually received prior to entering Period 4.

Additional analysis populations will be described in the SAP.

12.2.1.4. Missing Data Imputation

The methods for imputation of missing data to be used in this study are in accordance with precedent set with other Phase 3 Ps trials (Leonardi et al. 2008; Papp et al. 2008).

12.2.1.4.1. Non-Responder Imputation for Clinical Response (PASI 50/75/90/100, sPGA [0 or 1]/[0])

Analysis of categorical efficacy and health outcome variables will be assessed using a NRI method. In both Periods 2 (Induction Dosing Period) and 3 (Maintenance Dosing Period), patients will be considered a non-responder for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data at the analysis time point. Randomized patients without at least 1 post-baseline observation will also be defined as non-responders for the NRI analysis.

12.2.1.4.2. Last Observation Carried Forward

A last observation carried forward (LOCF) analysis may be performed on all continuous efficacy and health outcome variables. For patients discontinuing investigational product for any reason,

the last non-missing postbaseline observation before discontinuation will be carried forward to the corresponding endpoint for evaluation. Randomized patients without at least 1 postbaseline observation will not be included for evaluation.

12.2.1.5. Adjustment for Multiple Comparisons

A gatekeeping testing strategy for the primary and major secondary analyses will be implemented to control the overall type I error rate at a 2-sided alpha level of 0.05. This will allow simultaneous inference of all of the primary and major secondary endpoints. The underlying procedure is derived using the methodology developed in Dmitrienko and Tamhane 2011. The gatekeeping procedure is based on the Bonferroni test and utilizes an intuitive, stepwise testing algorithm. The alpha levels for the p-values associated with the primary and secondary analyses are computed at each step depending on the outcomes of the preceding significance tests.

In order to reflect the test order and how the multiple doses will be analyzed, the doses have been renamed and the treatment comparisons to be performed in each dosing period are shown in Table RHBH.12.2.

Table RHBH.12.2. Treatment Comparisons during the Induction Dosing Period and Maintenance Dosing Period

Induction Dosing	Treatment Group Comparisons during the Induction Dosing Period (Week 12)	Maintenance Dosing	Treatment Group Comparisons during the Maintenance Dosing Period (Week 60)
80 mg Q2W = Dose 1	Dose 1 versus Placebo	80 mg Q4W = Dose 1A Placebo = Dose 1B	Dose 1A versus Dose 1B
80 mg Q4W = Dose 2	Dose 2 versus Placebo	80 mg Q4W = Dose 2A Placebo = Dose 2B	Dose 2A versus Dose 2B

Abbreviations: Q2W = once every 2 weeks; Q4W = once every 4 weeks.

Primary 1 (Test 1) – Proportion of patients with an sPGA (0, 1) at Week 12 (Visit 7) compared to placebo

Primary 2 (Test 2) – Proportion of patients with PASI 75 at Week 12 (Visit 7) compared to placebo

Secondary 1 (Test 3) – Proportion of patients achieving an sPGA (0) at Week 12 (Visit 7) compared to placebo.

Secondary 2 (Test 4) – Proportion of patients with PASI 90 at Week 12 (Visit 7) compared to placebo

Secondary 3 (Test 5) – Proportion of patients with PASI 100 at Week 12 (Visit 7) compared to placebo

Secondary 4 (Test 6) – Proportion of patients maintaining an sPGA (0,1) from Week 12 (Visit 7) after re-randomization at start of Maintenance Dosing Period to Week 60 (Visit 19) compared to placebo for ixekizumab-treated patients who had an sPGA (0,1) at Week 12 and were re-randomized

Secondary 5 (Test 7) – Proportion of patients maintaining or achieving an sPGA (0) from Week 12 (Visit 7) after re-randomization at start of Maintenance Dosing Period to Week 60 (Visit 19) compared to placebo for ixekizumab-treated patients who had an sPGA (0,1) at Week 12 and were re-randomized

Secondary 6 (Test 8) – Proportion of patients achieving an Itch NRS ≥4 point reduction from baseline at Week 12 (Visit 7) compared to placebo for patients who had baseline Itch NRS ≥4

Secondary 7 (Test 9) – Change from baseline in DLQI at Week 12 (Visit 7) compared to placebo

Secondary 8 (Test 10) – Change from baseline in NAPSI (for fingernails) at Week 12 (Visit 7) compared to placebo.

The 10 statistical tests will be grouped into 2 parallel branches. The first branch includes tests of Dose 1 versus placebo in Period 2 (Induction Dosing Period) as well as Dose 1A versus Dose 1B in Period 3 (Maintenance Dosing Period). The second branch includes tests of Dose 2 versus placebo in Period 2 (Induction Dosing Period) as well as Dose 2A versus Dose 2B in Period 3 (Maintenance Dosing Period). Test 2 will be performed at a dose only if Test 1 of that dose is significant. Similarly, each test for a particular dose will be performed only if all prior tests of that dose are significant. For each dose, if a test is not significant, all subsequent tests are not significant.

Step 1: Test 1 for Doses 1 and 2 compared to placebo will be carried out using the Bonferroni procedure, that is, each test will be carried out at a 2-sided $\alpha = 0.025$.

Step 2: Test 2 for Doses 1 and 2 compared to placebo will be carried out using the Bonferroni procedure. If Test 1 for Dose 1 is significant, Test 2 for Dose 1 will be carried out at a 2-sided $\alpha = 0.025$ and, if Test 1 for Dose 2 is significant, Test 2 for Dose 2 will be carried out at a 2-sided $\alpha = 0.025$.

Steps 3 through 10 will be carried out similar to Step 2 with the current step depending on the result of the previous step.

There will be no adjustment for multiple comparisons for any other analyses.

12.2.2. Patient Disposition

Patient disposition will be summarized for each treatment period. Reasons for discontinuation from the study will be summarized. The reasons for discontinuation during Period 2 (Induction Dosing Period) will be tested between treatment groups using Fisher's exact test.

12.2.3. Patient Characteristics

Patient characteristics and baseline clinical measures will be summarized for each treatment period. Baseline characteristics will include gender, age, age category, weight, race, baseline disease severity, duration of disease, previous systemic therapy, and previous biologic therapy. Baseline clinical measurements will include sPGA score, PASI total score, BSA, Itch NRS score, DLQI total score, and NAPSI score.

Treatment group comparisons among the ixekizumab dose regimens and placebo in Period 2 (Induction Dosing Period) will be conducted using Fisher's exact test for categorical data and a one-way ANOVA for continuous data.

12.2.4. Concomitant Therapy

Previous and concomitant medications (including concomitant topical products such as emollients and other non-prescription topical products) will be summarized for patients who enter each treatment period and presented by World Health Organization Anatomic Therapeutic Class (WHOATC) Level 4 and WHO preferred name. Treatment group comparisons between each ixekizumab dose regimen and placebo in Period 2 (Induction Dosing Period) through Week 12 (Visit 7) will be conducted using Fisher's exact test.

12.2.5. Treatment Compliance

Treatment compliance with investigational product will be summarized for patients who enter Periods 2 and 3 (Induction Dosing Period and Maintenance Dosing Period, respectively). A patient will be considered overall compliant for each study period if he/she is missing no more than 20% of the expected doses and does not miss 2 consecutive doses, and does not double-dose (that is, takes more injections at the same time point than specified in the protocol). Proportions of patients compliant by visit and overall will be compared between treatment groups during Period 2 (Induction Dosing Period) using Fisher's exact test.

12.2.6. Efficacy and Health Outcome Analyses

12.2.6.1. Primary Analyses

The primary analysis will be based on the ITT population. In addition, an analysis of the PPS population will be used to support the primary efficacy analysis.

Proportion of Patients with sPGA (0 or 1) at Week 12

Treatment comparisons between each ixekizumab dose regimen and placebo in the proportion of patients achieving a sPGA (0, 1) response at Week 12 (Visit 7) will be analyzed using the logistic regression model defined in Section 12.2.1.1. Missing data will be imputed using the NRI method described in Section 12.2.1.4.1.

Proportion of Patients with PASI 75 at Week 12

Treatment comparisons between each ixekizumab dose regimen and placebo in the proportion of patients achieving PASI 75 at Week 12 (Visit 7) will be analyzed using the logistic regression model defined in Section 12.2.1.1. Missing data will be imputed using the NRI method described in Section 12.2.1.4.1.

12.2.6.2. Major Secondary Analyses

Unless otherwise specified, the major secondary analysis at Week 12 will be based on the ITT population. The major secondary analysis for maintenance (Week 60) is based on the Maintenance Dosing Period Primary Population.

Proportion of Patients with sPGA of 0 at Week 12

Treatment comparisons between each ixekizumab dose regimen and placebo in the proportion of patients achieving sPGA (0) at Week 12 (Visit 7) will be analyzed using the logistic regression model defined in Section 12.2.1.1. Missing data will be imputed using the NRI method described in Section 12.2.1.4.1.

Proportion of Patients with PASI 90 at Week 12

Treatment comparisons between each ixekizumab dose regimen and placebo in the proportion of patients achieving PASI 90 at Week 12 (Visit 7) will be analyzed using the logistic regression model defined in Section 12.2.1.1. Missing data will be imputed using the NRI method described in Section 12.2.1.4.1.

Proportion of Patients with PASI 100 at Week 12

Treatment comparisons between each ixekizumab dose regimen and placebo in the proportion of patients achieving PASI 100 at Week 12 (Visit 7) will be analyzed using the logistic regression model defined in Section 12.2.1.1. Missing data will be imputed using the NRI method described in Section 12.2.1.4.1.

Proportion of Patients with sPGA (0, 1) at Week 60

Treatment comparisons during maintenance dosing as described in Section 12.2.1.2 in the proportion of patients maintaining an sPGA (0, 1) from Week 12 (Visit 7) after re-randomization at start of Maintenance Dosing Period to Week 60 (Visit 19) will be analyzed using a logistic regression model defined in Section 12.2.1.2. Missing data will be imputed using the NRI method described in Section 12.2.1.4.1.

Proportion of Patients with an Itch NRS ≥4 point reduction from baseline at Week 12 for patients who had a baseline Itch NRS ≥4

For patients who had a baseline Itch NRS ≥4, the number and percentage of patients achieving an Itch NRS ≥4 point reduction from baseline at Week 12 (Visit 7) will be presented by treatment group. Treatment comparisons between each ixekizumab dose regimen and placebo in the proportion of patients achieving an Itch NRS ≥4 point reduction from baseline at Week 12 (Visit 7) will be analyzed using the logistic regression model defined in Section 12.2.1.1. Missing data will be imputed using the NRI method described in Section 12.2.1.4.1.

Change from Baseline in DLQI at Week 12

Treatment comparisons between each ixekizumab dose regimen and placebo in the change from baseline in DLQI score at Week 12 (Visit 7) will be analyzed using MMRM as defined in Section 12.2.1.1. Treatment comparisons between each ixekizumab dose regimen and placebo will also be analyzed using the ANCOVA model defined in Section 12.2.1.1. For the ANCOVA analysis, missing data will be imputed by the LOCF method as described in Section 12.2.1.4.2.

Change from Baseline in NAPSI at Week 12

The analysis of NAPSI score will be conducted in patients who have baseline fingernail involvement. Treatment comparisons between each ixekizumab dose regimen and placebo in the change from baseline in NAPSI score at Week 12 (Visit 7) will be analyzed using MMRM as defined in Section 12.2.1.1. Treatment comparisons between each ixekizumab dose regimen and placebo will also be analyzed using the ANCOVA model defined in Section 12.2.1.1. For the ANCOVA analysis, missing data will be imputed by the LOCF method as described in Section 12.2.1.4.2.

12.2.6.3. Other Secondary Analyses

There will be no adjustment for multiple comparisons in analyses of these secondary objectives. Analyses will be conducted for the other secondary objectives defined in Section 6.2.2.

12.2.6.3.1. Period 2 (Induction Dosing Period)

Unless otherwise specified, the other secondary analyses during Period 2 will be based on the ITT population.

For all categorical efficacy variables that are collected at repeated visits, treatment group comparisons will be analyzed at each visit using the logistic regression model and Fisher's exact test described in Section 12.2.1.1 where appropriate. Missing data will be imputed using the NRI method described in Section 12.2.1.4.1.

For all continuous efficacy variables that are collected at repeated visits, treatment group comparisons will be analyzed at each visit using the MMRM model as described in Section 12.2.1.1 when appropriate. No imputation methods are applied to MMRM analysis.

Time to sPGA response (sPGA [0,1]) is defined as the number of days from initial randomization to the first visit at which the patient has an sPGA [0,1] during Period 2 (Induction Dosing Period). Time to PASI 75 response is defined as the number of days from initial randomization to the first visit at which the patient has met the PASI 75 criterion during Period 2 (Induction Dosing Period). For patients who discontinue early in Period 2 or who complete Period 2 without meeting criteria for response, the time-to-first response will be censored and defined as the number of days from initial randomization to the patient's last visit during Period 2. Time to first response for each treatment group in Period 2 will be estimated using the Kaplan-Meier product limit method. Treatment group comparisons will be performed using the log-rank test.

12.2.6.3.2. Period 3 (Maintenance Dosing Period)

Unless otherwise specified, the other secondary analyses during Period 3 will be based on the Maintenance Dosing Period Primary Population.

Time to loss of response (that is, relapse defined as an sPGA score of ≥3) is defined as the number of days from the Week 12 re-randomization to the first visit at which the patient has an sPGA score of ≥3 during Period 3. For patients who discontinue early in Period 3 or who complete Period 3 without meeting the criteria, the time to loss of response will be censored and defined as the number of days from Week 12 re-randomization to the patient's last visit during Period 3. Time to loss of response for each treatment group in Period 3 will be estimated using the Kaplan-Meier product limit method. Treatment group comparisons will be performed using the log-rank test.

The proportion of patients who meet sPGA (0), PASI 75, PASI 90, PASI 100 criteria, and any other categorical efficacy endpoint will be summarized at each visit. Treatment group comparisons will be performed using the logistic regression model described in Section 12.2.1.2 and a Fisher's exact test when appropriate. Missing data will be imputed using the NRI method described in Section 12.2.1.4.1.

For all continuous efficacy variables that are collected at repeated visits, treatment group comparisons will be analyzed at each visit using the MMRM model described in Section 12.2.1.2 when appropriate. The Week 60 (Visit 19) comparison will be the main interest, and those at earlier time points will be considered secondary.

For patients who were retreated with ixekizumab following loss of response (relapse), the following analyses will be performed:

- The proportion of patients who regain an sPGA (0, 1) and an sPGA (0) within 12 weeks after ixekizumab retreatment will be summarized by the original re-randomization treatment group.
- The proportion of patients who achieve a PASI 75, PASI 90, and PASI 100 within 12 weeks after ixekizumab retreatment will be summarized by the original re-randomization treatment group.

12.2.6.4. Health Outcome Analyses

There will be no adjustment for multiple comparisons for the health outcome analyses. Analyses will be conducted for the other secondary health outcome objectives as defined in Section 6.2.2.

Period 2 (Induction Dosing Period):

Unless otherwise specified, health outcomes analyses in Period 2 will use the ITT population. For all continuous secondary health outcomes measures (Itch NRS, DLQI, SF-36 PCS and MCS scores, patient's global assessment of disease severity and joint pain VAS), the treatment group comparisons will be analyzed using the MMRM model described in Section 12.2.1.1 when appropriate. The Week 12 (Visit 7) comparison will be the main interest, and those at earlier time points will be considered secondary.

Period 3 (Maintenance Dosing Period):

Unless otherwise specified, all health outcomes analyses in Period 3 will use the Maintenance Dosing Period Primary Population. For all continuous secondary health outcomes measures (Itch NRS, DLQI, SF-36 PCS and MCS scores, patient's global assessment of disease severity, and joint pain VAS), treatment group comparisons will be analyzed using the MMRM model described in Section 12.2.1.2 when appropriate. The Week 60 (Visit 19) comparison will be the main interest, and those at earlier time points will be considered secondary.

Additional analyses of health outcome measures will be specified in the SAP.

12.2.7. Pharmacokinetic/Pharmacodynamic/Immunogenicity Analyses

Observed ixekizumab serum concentrations will be summarized by treatment regimen, visit and corresponding time when sampling occurred.

Pharmacokinetic data may also be analyzed using a population approach with a nonlinear mixed-effects modeling program (NONMEM) on a computer that meets or exceeds the minimum system requirements. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation.

As appropriate, the exposure-response relationship between ixekizumab trough concentrations and clinically important efficacy measures (for example, sPGA and PASI endpoints) may be explored using graphical methods and/or a modeling approach. The potential impact of immunogenicity on ixekizumab exposure may be evaluated by graphical assessments, as

appropriate, to compare drug levels between ADA negative and ADA positive patients at corresponding visits, or before and after ADA development for patients who develop ADA. Both treatment-emergent only and all ADA positive/negative patients may be explored. Neutralizing anti-drug antibody positive samples may be identified.

Additional analyses may be performed upon receipt of the data. Data from this study may be combined with data from previous efficacy studies for additional population PK and/or exposure -efficacy modelling if deemed appropriate.

12.2.8. Safety Analyses

Safety will be assessed by summarizing and analyzing AEs, QIDS-SR16, C-SSRS, laboratory analytes including neutrophil counts and immunogenicity, vital signs, and concomitant medications.

The primary safety analyses will focus on comparison of the ixekizumab dosing regimens to placebo for Period 2 (Induction Dosing Period). Treatment group comparisons will be analyzed using the methods described in Section 12.2.1.1.

For Period 3 (Maintenance Dosing Period), the same safety measures as in Period 2 will be summarized. Treatment group comparisons will be analyzed using the methods described in Section 12.2.1.2.

Summaries of safety data collected during the Post-Treatment Follow-up Period will be presented separately. The categorical safety measures will be summarized with incidence rates. The mean change of the continuous safety measures will be summarized by visits. Unless otherwise specified, the follow-up baseline is defined as the last non-missing assessment on or prior to the Week 60 (Visit 19) or early discontinuation visit. Further details will be described in the SAP.

12.2.8.1. Adverse Events

A TEAE is defined as an event that first occurred or worsened in severity after baseline and on or prior to the date of the last visit within the treatment period.

Treatment-emergent adverse events (TEAEs), SAEs including deaths, AEs that led to investigational product discontinuation, and AEs by maximum severity and relationship to investigational product will be summarized by the MedDRA system organ class (SOC) and PT. For events that are gender specific, the denominator and computation of the percentage will include only patients from the given gender.

MedDRA groupings of PTs will be used to investigate AESIs. Adverse events of special interest (AESIs) may also be presented by severity.

12.2.8.2. Clinical Laboratory Tests

Laboratory assessments will be presented as mean changes from baseline to last observation, change from baseline to minimum postbaseline value, change from baseline to maximum postbaseline value and as incidence of treatment-emergent abnormal, high, or low laboratory values. Shift tables will be presented for selected parameters.

- Treatment-emergent **abnormal** value = a change from normal at all baseline visits to abnormal at any time postbaseline.
- Treatment-emergent **high** value = a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time postbaseline.
- Treatment-emergent **low** value = a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time postbaseline.

12.2.8.3. Vital Signs, Physical Findings, and Other Safety Evaluations

Vital signs will be presented as mean changes from baseline and as incidence of abnormal values (as defined in the SAP) and will be summarized both pre- and post-dose, as applicable.

The maximum postbaseline QIDS-SR16 total score will be summarized by treatment, and shift table will be produced for the change from baseline in QIDS-SR16 total score category.

Suicide-related thoughts and behaviors and self-injurious behavior with no suicidal intent, based on the C-SSRS, will be listed by patient.

Assessment of immunogenicity with respect to safety will include comparison of patients who experience TEAEs of systemic allergy/hypersensitivity and of injection-site reactions and who also develop treatment-emergent anti-ixekizumab antibody positivity with patients who experience the same types of TEAEs but who remain treatment-emergent anti-ixekizumab antibody negative. Anti-ixekizumab antibody titers will also be evaluated in anti-ixekizumab antibody positive patients who experience these events.

Other covariate data, including body weight, will be descriptively summarized by treatment groups. Further analyses may be performed comparing the treatment groups.

12.2.9. Subgroup Analyses

Subgroup analyses will be conducted for sPGA (0, 1) and PASI 75 at Week 12 (NRI) using the ITT population and Week 60 (NRI) using the Maintenance Dosing Period Primary Population.

Subgroups to be evaluated may include gender, age, body weight, baseline disease severity, duration of disease. Detailed description of the subgroup variables and method of analysis will be provided in the SAP.

12.2.10. Planned Analyses

The final database lock will occur after study completion, when all patients have completed or discontinued study treatment and have completed all required follow up visits.

Details of the analysis plan will be described in the statistical analysis plan.

12.2.10.1. Data Monitoring Committee

An independent data monitoring committee (DMC) will review unblinded safety data during this trial. The DMC will consist of suitably qualified people who are external to Lilly. This DMC will follow the rules defined in the DMC charter, focusing on the safety results for this antibody.

The DMC will be authorized to review unblinded results of analyses by treatment group prior to Week 60, including study discontinuation data, SAEs, clinical laboratory data, etc. The DMC may recommend continuation of the study, as designed; temporary suspension of enrollment; or the discontinuation of a particular dose regimen or the entire study. While the DMC may request to review efficacy data to investigate the benefit/risk relationship in the context of safety observations for ongoing patients in the study, no information regarding efficacy will be communicated. The study will not be stopped for positive efficacy results nor will it be stopped for futility; hence, no alpha is spent. Details of the DMC, including its operating characteristics, will be documented in a DMC charter.

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 risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. 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 investigational product.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are submitted to the ERB and are used at clinical sites(s). 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 clinical site(s). The ERB(s) will review the protocol as required.

Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol.

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

- the current IB or package labeling 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).

All investigators are expected to comply with GCP and all applicable local clinical trial regulations.

All or some of the obligations of the sponsor will be assigned to a TPO.

An identification code assigned by the investigator 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. 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.

13.3.2. Final Report Signature

The clinical study report coordinating investigator will sign the final 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 clinical study report coordinating investigator will be selected by the sponsor. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

The sponsor's responsible medical officer will 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.

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Attachment 1. Protocol RHBH Study Schedule

Study Schedule, Protocol I1F-MC-RHBH

	Screening		Baseline	Induction Dosing Period (Period 2)					Maintenance Dosing Period (Period 3)		
Visit No (V)	V1	V1A	V2	V3	V4	V5	V6	V7	V8	V9	V10
Study Week			W0	W1	W2	W4	W8	W12	W16	W20	W24
Study Days	-30 to -4d	2-3d post V1	0	7±2d	14±2d	28±2d	56±4d	84±4d	112±7d	140±7d	168±7d
Informed consent	×										
Complete medical history	×										
Demographics [a]	×										
Physical exam [b]	×							×			×
Weight [c]			×					×			×
Waist circumference			×					×			×
Height			×								
Habits [d]			×								×
Chest X-ray	×[e]										
Body temperature			×								
Inclusion/Exclusion criteria [f]	×		×								
Randomization			×					×			
Concomitant medications	×		×	×	×	×	×	×	×	×	×
Vital signs (BP and pulse)	×		×[g]	×	×	×	×	×[g]	×	×	×
Review preexisting conditions	×										
AE			×	×	×	×	×	×	×	×	×
Administer IP			Blinded 160mg LY (2 injections 80mg each) or LY placebo (2 injections) [g,h]		Blinded 80mg LY Q2W*, 80mg LY Q4W*, or LY placebo Q2W* [h] (1 injection given Q2W)			Blinded 80mg LY Q4W**, or LY placebo Q4W** [i,j] (2 injections)	Blinded 80mg LY Q4W** or LY placebo Q4W** [i,j] (1 injection Q4W)		
Dispense IP			×		×	×	×	×	×	×	×

	Screening		Baseline	Induction Dosing Period (Period 2)					Maintenance Dosing Period (Period 3)		
Visit No (V)	V1	V1A	V2	V3	V4	V5	V6	V7	V8	V9	V10
Study Week			W0	W1	W2	W4	W8	W12	W16	W20	W24
Study Days	-30 to -4d	2-3d post V1	0	7±2d	14±2d	28±2d	56±4d	84±4d	112±7d	140±7d	168±7d
IP compliance			×		×	×	×	×	×	×	×
Dispense Study Drug Administration Log [k]			×		×	×	×	×	×	×	×
Collect, review, and enter data from Study Drug Administration Log			×		×	×	×	×	×	×	×
Clinical Efficacy/ Health Outcomes											
sPGA	×		×	×	×	×	×	×	×	×	×
PASI	×		×	×	×	×	×	×	×	×	×
BSA	×		×	×	×	×	×	×	×	×	×
NAPSI[z]			×	×	×	×	×	×	×	×	×
PSSI[z]			×	×	×	×	×	×	×	×	×
PPASI[z]			×	×	×	×	×	×	×	×	×
Itch NRS			×	×	×	×	×	×	×	×	×
DLQI [l]			×		×	×		×			×
QIDS-SR16	×		×					×			×
C-SSRS[x]			×	×	×	×	×	×	×	×	×
Self-Harm Supplement Form			×	×	×	×	×	×	×	×	×
Joint Pain VAS[z]			×	×	×	×	×	×	×	×	×
SF-36			×					×			×
Patient's Global Assessment of Disease severity			×	×	×	×	×	×	×	×	×
Laboratory Tests											
Administer PPD/QuantiFERON®-TB Gold/ T-SPOT®.TB [m]	×										

	Screening		Baseline	Induction Dosing Period (Period 2)					Maintenance Dosing Period (Period 3)		
Visit No (V)	V1	V1A	V2	V3	V4	V5	V6	V7	V8	V9	V10
Study Week			W0	W1	W2	W4	W8	W12	W16	W20	W24
Study Days	-30 to -4d	2-3d post V1	0	7±2d	14±2d	28±2d	56±4d	84±4d	112±7d	140±7d	168±7d
Read PPD		×									
ECGs [n]	×										
FSH [o]	×										
HIV/HCV	×										
HBV [p,q]	×		×					×			×
Serum pregnancy test [r]	×										
Urine pregnancy test [r]			×			×	×	×	×	×	×
Serum chemistry	×		×	×	×	×	×	×	×	×	×
Lipase/Amylase	×		×					×			
Lipid panel [s]	×		×			×		×			×
Advanced lipid profile			×					×			
Hematology	×		×	×	×	×	×	×	×	×	×
PTT and INR	×		×					×			
Urinalysis	×		×			×		×			×
TSH and Free T4	×										
IgA, IgG, IgM	×		×			×		×			×
CRP			×	×	×	×	×	×			×
Cell flow cytometry panel (B, T, CD4+T, CD8+T, and NK Cells)			×			×		×			×
Immunogenicity testing [t]			×		×	×		×			×
PK sampling [y]			×		×	×		×			×

	Maintenance Dosing Period (Period 3)									Post Treatment Follow up [u] (Period 4)			
Visit No (V)	V11	V12	V13	V14	V15	V16	V17	V18	V19	V801	V802	V803 [v]	ETV [w]
Study Week	W28	W32	W36	W40	W44	W48	W52	W56	W60	LV+4 W	LV+12W	LV+24W	
Study Days	196± 7d	224± 7d	252± 7d	280± 7d	308± 7d	336± 7d	364± 7d	392± 7d	420±7 d	±4d	±4d	±4d	
Physical exam [b]									×				×
Weight [c]									×				×
Waist circumference									×				×
Habits [d]									×				×
Concomitant medications	×	×	×	×	×	×	×	×	×	×	×	×	×
Vital signs (BP and pulse)	×	×	×	×	×	×	×	×	×	×	×	×	×
AE	×	×	×	×	×	×	×	×	×	×	×	×	×
Administer IP	Blinded 80mg LY Q4W** or LY placebo Q4W** [i,j] (1 injection)												
Dispense IP	×	×	×	×	×	×	×	×					
IP compliance	×	×	×	×	×	×	×	×	×	×			×
Dispense Study Drug Administration Log [k]	×	×	×	×	×	×	×	×					
Collect, review, and enter data from Study Drug Administration Log	×	×	×	×	×	×	×	×	×	×			×
sPGA	×	×	×	×	×	×	×	×	×				×
PASI	×	×	×	×	×	×	×	×	×				×
BSA	×	×	×	×	×	×	×	×	×				×
NAPSI [z]	×	×	×	×	×	×	×	×	×				×
PSSI [z]	×	×	×	×	×	×	×	×	×				×
PPASI [z]	×	×	×	×	×	×	×	×	×				×
Itch NRS	×	×	×	×	×	×	×	×	×				×

	Maintenance Dosing Period (Period 3)									Post Treatment Follow up [u] (Period 4)			
Visit No (V)	V11	V12	V13	V14	V15	V16	V17	V18	V19	V801	V802	V803 [v]	ETV [w]
Study Week	W28	W32	W36	W40	W44	W48	W52	W56	W60	LV+4 W	LV+12W	LV+24W	
Study Days	196± 7d	224± 7d	252± 7d	280± 7d	308± 7d	336± 7d	364± 7d	392± 7d	420±7 d	±4d	±4d	±4d	
DLQI [l]			×				×		×				×
QIDS-SR16			×				×		×				×
C-SSRS[x]	×	×	×	×	×	×	×	×	×	×	×	×	×
Self-Harm Supplement Form	×	×	×	×	×	×	×	×	×	×	×	×	×
Joint pain VAS [z]	×	×	×				×		×				×
SF-36			×				×		×				×
Patient's Global Assessment of Disease severity	×	×	×				×		×				×
ECGs [n]									×				×
HBV [p,q]			×			×			×		×		×
Urine pregnancy test [r]	×	×	×	×	×	×	×	×	×				×
Serum chemistry		×		×		×			×	×	×	×	×
Lipase/Amylase									×				×
Lipid panel [s]									×				×
Advanced lipid profile		×		×		×			×				×
Hematology		×		×		×			×	×	×	×	×
PTT and INR													
Urinalysis		×		×		×			×				×
TSH and Free T4													
IgA, IgG, IgM			×			×			×				×
CRP			×			×			×				×
Cell flow cytometry panel (B, T, CD4+T, CD8+T,			×						×		×		×

	Maintenance Dosing Period (Period 3)									Post Treatment Follow up [u] (Period 4)			
Visit No (V)	V11	V12	V13	V14	V15	V16	V17	V18	V19	V801	V802	V803 [v]	ETV [w]
Study Week	W28	W32	W36	W40	W44	W48	W52	W56	W60	LV+4 W	LV+12W	LV+24W	
Study Days	196± 7d	224± 7d	252± 7d	280± 7d	308± 7d	336± 7d	364± 7d	392± 7d	420±7 d	±4d	±4d	±4d	
and NK Cells)													
Immunogenicity testing [t]			×						×		×		×
PK sampling [y]			×						×		×		×

Abbreviations: AE = adverse event; BP = blood pressure; BSA = body surface area; CRP = C-reactive protein; C-SSRS = Columbia-Suicide Severity Rating Scale; d = days; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ETV or Early Term Visit = early termination visit; FSH = follicle stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; IP = investigational product; LV= last visit; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PPASI = palmoplantar Psoriasis Area and Severity Index; PPD = purified protein derivative; Ps = psoriasis; PSSI = Psoriasis Scalp Severity Index; PTT = partial thromboplastin time; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; sPGA = static Physician's Global Assessment; T4 = thyroxine; TB = tuberculosis; TSH = thyroid stimulating hormone; V = study visit; W = study week.

* **Period 2:** 80 mg Q2W = A starting dose of 160 mg (Week 0) given as 2 SC injections followed by 80 mg given as 1 SC injection Q2W (Weeks 2, 4, 6, 8, and 10); 80 mg Q4W = A starting dose of 160 mg (Week 0) given as 2 SC injections followed by 80 mg given as 1 SC injection Q4W (Weeks 4 and 8). To maintain blinding, placebo is given as 1 SC injection at Weeks 2, 6, and 10; Placebo = Placebo (Week 0) given as 2 SC injections followed by placebo Q2W (Weeks 2, 4, 6, 8, and 10). To maintain the study blind, all patients will receive 2 SC doses of investigational product at Week 0 (Visit 2) and 1 SC dose Q2W from Week 2 (Visit 4) through Week 10.

** **Period 3:** 80 mg Q4W = A dose of 80 mg given as 1 SC injection + a placebo injection at (Week 12); 80 mg given as 1 SC injection Q4W thereafter.; Placebo = Placebo given as 2 SC injections at Week 12 followed by placebo given as 1 SC injection Q4W thereafter. To maintain the study blind, all patients will receive 2 SC doses of investigational product at Week 12 (Visit 7) and 1 SC dose Q4W from Week 16 (Visit 8) through Week 56 (Week 60, no IP administration). Study visits will occur at least Q4W during Period 3; Refer to Section 7.1.3 for the treatment assignments for Responders, Non-Responders, and patients who relapse in Period 3.

[a] Demographics includes recording of year of birth, gender, and ethnicity.

[b] One complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at screening. All physical examinations throughout the study should include a symptom directed physical as well as examination of heart, lungs, abdomen, and visual examination of the skin.

[c] Weight collection is also used for calculating creatinine clearance.

[d] Habits include recording of caffeine, alcohol and tobacco consumption.

[e] A chest x-ray will be taken at screening unless one has been obtained within the past 6 months (provided the x-ray and/or report are available for review).

[f] Patients who test positive for latent TB at screening may be rescreened following appropriate treatment as described in Section 10.3.2.2. Additionally, patients who do not qualify at screening under Exclusion Criteria [28] (active or recent infection) or Exclusion Criteria [29] (body temperature ≥38°C [100.5°F]) may be rescreened (1 time) as described in Section 8.2.

[g] At baseline (Week 0) and Week 12, BP and pulse should be measured prior to administration of the investigational product and again approximately 1 hour post administration. At Week 12, the injection of the investigational product will be administered by the patient or an authorized adult who has been trained at the clinical site.

[h] In Period 2, dose regimens, training, and subsequent dosing will be performed as described in Section 9.1.

[i] All patients will receive 2 SC doses of investigational product at Weeks 0 and 12 to maintain the double blind (Sections 7.1.2 and 7.1.3).

[j] In Periods 3, dosing will be assigned as described in Section 7.1.3, with applicable procedures as described in Section 9.1.

[k] Patients will record information in the Study Drug Administration Log, including the date, time, and location of administration of investigational product (for treatment compliance), syringe number, who administered the investigational product, and the reason if investigational product was not fully administered or not administered at all.

[l] See Section 10.2.2 for detailed description of DLQI
[m] See Section 10.3.2.2 for detailed description of QuantiFERON Gold TB / T-SPOT®.TB and PPD testing.
[n] ECGs should be performed prior to injection of investigational product, as applicable.
[o] FSH test performed for women ≥40 and <60 years of age who have had a cessation of menses for at least 12 months to confirm non-childbearing potential (≥40 mIU/mL).
[p] All patients will be tested for HBV panel at screening.
[q] Patients that are HBcAb+ at screening, regardless of hepatitis B surface antibody (HBsAb) status, will have a serum HBV DNA tested by the central laboratory. Patients that are HBV DNA negative (undetectable) may be enrolled into the study with required HBV DNA monitoring every 3 months during treatment and 12 weeks after the last dose of ixekizumab.
[r] To be performed for females of childbearing potential only. Predose urine pregnancy testing will be performed at scheduled visits from Week 4 (Visit 5) through Week 60 (Visit 19). Patients will undergo urine pregnancy test at the site on a monthly basis during periods between scheduled visits until Week 60. Patients with a positive pregnancy test will be discontinued from treatment and will no longer be administered investigational product (See Section 8.3.1.1).
[s] Fasting lipid profile: patients should not eat or drink anything except water for 12 hours prior to test.
[t] Immunogenicity samples may also be analyzed for ixekizumab serum concentration to facilitate in the interpretation of the immunogenicity data. In addition, a blood sample will be collected prior to administration of investigational product, when possible, for any patient who experiences a potential systemic allergic reaction /hypersensitivity during the study as judged by the investigator.
[u] All patients receiving investigational product must enter into Period 4 and complete through Visit 802. Patients may be followed beyond Visit 802 for continued monitoring of their neutrophil counts.
[v] This visit will only occur if a patient's neutrophil counts have not returned to the criteria defined in Section 7.1.4.1.
[w] If a patient discontinues investigational product early, the patient will complete the ETV and then enter the Post-Treatment Follow-Up Period (Period 4).
[x] A Self-Harm Follow-Up Form is to be completed for each discrete self-harm event identified on the C-SSRS and the Self-harm Supplement Form.
[y] PK samples will be collected after ECG are performed, and prior to administration of investigational product, as applicable.
[z] If the subject has nail psoriasis, scalp psoriasis, palmoplantar psoriasis, joint pain at baseline, then the NAPSI, PSSI, PPASI, joint pain VAS, respectively, will be administered at subsequent visits, as indicated in the Study Schedule.

Attachment 2. Protocol RHBH Clinical Laboratory Tests

Clinical Safety Laboratory Tests

Hematology[a,b]
Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Mean cell volume (MCV)
Mean cell hemoglobin concentration (MCHC)
Leukocytes (WBC)
Cell Morphology
Platelets

Absolute counts of:
Neutrophils
Neutrophils, juvenile (bands)
Lymphocytes
Monocytes
Eosinophils
Basophils
Lymphocyte subset (B cells, T cells, CD4+ T cells, CD8+ T cells, NK cells)

Urinalysis (dipstick) [a,b]
Color
Specific gravity
pH
Protein
Glucose
Ketones
Bilirubin
Urobilinogen
Blood
Nitrite
Urine creatinine
Leukocyte esterase
Urinalysis (Microscopic):
Sediment, Cells, Casts

Other Tests[a]
Serum immunoglobulins (IgA, IgG, and IgM)
Human immunodeficiency virus antibody (HIV)[g]
Hepatitis B Surface antigen (HBsAg)[g]
Anti-Hepatitis B Surface antibody (HBsAb)[g]
Anti-Hepatitis B Core antibody (HBcAb)[g]
Anti-Hepatitis C antibody[g,h]
HBV DNA[k]
Double-stranded DNA antibody[i]
High Sensitivity C-reactive protein (CRP)
QuantiFERON®-TB Gold/ T-SPOT®.TB test[j]

Serum Chemistry[a,b]
Sodium
Potassium
Bicarbonate
Chloride
Phosphorus
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Alanine aminotransferase (ALT/SGPT)
Aspartate aminotransferase (AST/SGOT)
Blood urea nitrogen (BUN)
Uric acid
Creatinine
Calcium
Glucose
Albumin

Cholesterol (total)
Total protein
Calculated creatinine clearance[c]
Creatine phosphokinase (CPK)
Triglycerides
Gamma-Glutamyl Transferase (GGT)

Lipase[a]
Total Amylase[a]
Lipid Panel[a,d]
Low Density Lipoprotein (LDL)
High Density Lipoprotein (HDL)
Very Low Density Lipoprotein (VLDL)
Advanced lipid profile
Oxidized LDL
Apolipoprotein A1
Apolipoprotein B

Pregnancy Test (serum and urine)[e]
Follicle-stimulating hormone (FSH)[f]

Thyroid-stimulating hormone (TSH) and Free T4
Ixekizumab serum concentration
Partial Thromboplastin Time (PTT)
Prothrombin Time/International Normalized Ratio (PT/INR)

Immunogenicity testing (anti-ixekizumab Ab)

Clinical Safety Laboratory Tests (abbreviations and footnotes)

Abbreviations: Ab = antibody; DNA = deoxyribonucleic acid; HBcAb+ = positive for anti-hepatitis B core antibody; HBsAb = anti-hepatitis B surface antibody; HBsAb+ = positive for anti-hepatitis B surface antibody; HBsAg- = negative for hepatitis B surface antigen; HBV = hepatitis B virus; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; NK = natural killer; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T4 = thyroxine; TB = tuberculosis; WBC = white blood cells.

[a] Assayed by sponsor-designated laboratory.

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

[c] Cockcroft-Gault calculation is used for the calculated creatinine clearance. Creatinine clearance calculation will be performed at W0, W12, W24, W60 and ETV.

[d] For the fasting lipid profile patients should not eat or drink anything except water for 12 hours prior to test.

[e] Serum pregnancy test (women <60 years of age who are still of childbearing potential) and urine pregnancy test (women of childbearing potential).

[f] Women ≥40 and <60 years of age who have had a cessation of menses for ≥12 months will have an FSH test confirming non-childbearing potential (≥40 mIU/mL).

[g] Test required at Visit 1 only to determine eligibility of patient for the study.

[h] See exclusion criteria (Section 8.2) specific to Hepatitis C antibody.

[i] Double-stranded DNA antibody is not a part of routine screening for this study; however, it may be required during the study for follow-up.

[j] See Section 10.3.2.2: In countries where the QuantiFERON®-TB Gold/ T-SPOT®.TB test is available, it may be used instead of the PPD TB test.

[k] HBV DNA testing will be done in patients who are HBcAb+.

Attachment 3. Protocol RHBH Hepatic Monitoring Tests for Treatment Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with patients in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated or local laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability

Attachment 4. Protocol Amendment I1F-MC-RHBH(b) Summary (A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Maintenance Dosing Period to Evaluate the Efficacy and Safety of LY2439821 in Chinese Patients with Moderate-to-Severe Plaque Psoriasis)

Overview

Protocol I1F-MC-RHBH(a) (A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Maintenance Dosing Period to Evaluate the Efficacy and Safety of LY2439821 in Chinese Patients with Moderate-to-Severe Plaque Psoriasis) has been amended. The new protocol is indicated by amendment (b) 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:

- Updated relevant statements regarding administration of IP to reduce repetition and to allow administration performed at trial site and by clinical site staff for safety concerns of the local patients (Section 7.1.2 and Section 9.1.1).
- Updated the statement of treatment assignment for non-responders to address ethical concern (Section 7.1.3).
- Revised language describing other concomitant therapy for patients who discontinue treatment and enter the Period 4 to address ethical concerns (Section 9.8).
- Revised analysis population description of primary analyses as well as the safety analyses for Period 2 and Period 4 to address statistical concern (Section 2 and Section 12.2.1.3).
- Revised analysis population description of efficacy, health outcomes, and safety analyses for Period 3 to reduce reiteration (Section 2 and Section 12.2.1.3).
- Revised the statement on statistical test of secondary analysis regarding Itch NRS to be consistent with corresponding description of major secondary objectives (Section 12.2.1.5).
- Removed the interim analysis and the corresponding descriptions to accommodate with requirements of local registered trials (Section 4 and Section 12.2.10).
- Removed the collection of habits on V7 from the Study Schedule table, as deemed unnecessary by the study team (Attachment 1).
- Updated the Clinical Laboratory Tests by adding footnote “a” to Urinalysis (dipstick) to be consistent with current practice (Attachment 2).

Other minor typographical corrections and clarifications not affecting content have been made in the document.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

Section 2. Synopsis

In addition, the primary analyses will be repeated using the per protocol set (PPS), which is defined as all randomized patients who are compliant with therapy, who do not have a subset of important protocol deviations that impact the primary efficacy endpoint, and whose investigator site does not have significant Good Clinical Practice (GCP) issues that require a report to the regulatory agencies prior to Week 12 (Visit 7). Safety analyses for Period 2 will be conducted on the safety population, defined as all randomized patients who received at least 1 dose of study treatment. Patients will be analyzed according to the treatment to which ~~they actually received~~they were assigned.

Section 4. Abbreviations and Definitions

~~**interim analysis**~~	~~An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.~~

Section 7.1.2 Induction Dosing Period (Period 2)

~~For training purposes, the first injection of investigational product will be administered by clinical site staff at Week 0 (Visit 2). The second injection at Week 0 (Visit 2) of investigational product will be administered by the patient or an authorized adult who has been trained while under supervision of clinical site staff. If additional training is necessary, an injection of investigational product will be administered by the patient or an authorized adult who has been trained while under supervision of clinical site staff at Week 2 (Visit 4) (Section 9.1.1). Subsequent injections of investigational product will be administered by the patient or an authorized adult who has been trained under supervision by the clinical site staff, regardless of whether there is a study visit scheduled. All subsequent injections may be administered either outside the trial site, preferably at the patient's home, or at the trial site for safety concerns of the patient.~~

Section 7.1.3 Maintenance Dosing Period (Period 3)

A discontinuation criterion for patients who remain at or above their baseline sPGA score at both Week 12 and Week 24 is included (see Section 8.3.1) to ensure that patients who have not shown any benefit from treatment with ixekizumab can be treated with any other psoriasis therapy as determined appropriate by the investigator~~are offered alternative therapies~~.

Section 9.1.1 Administration of Investigational Product

Injections will be administered by the patient or clinical site staff or an authorized adult who has been trained by the clinical site staff.

Administration: If the patient is unable to perform the injection, clinical site staff or an authorized adult who has been trained may inject the investigational product. ~~It is recommended that f~~For these subsequent injections, the investigational product may be administered either at the trial site for safety concerns of the patient or ~~the patient/an authorized adult who has been trained administer the investigational product~~ outside the trial site, preferably at the patient's home, except for the Week 12 visit when the injections are to be given at the trial site for post-dose monitoring.

Observation: Patients should remain under observation for at least 1 hour after dosing at Week 0 (Visit 2) and Week 12 (Visit 7) to monitor for safety. At Week 12 (Visit 7), injections of the investigational product will be administered at the clinical site by the patient or a clinical site staff or an authorized adult who has been trained at the clinical site to allow for observation for any AEs and collection of post-injection BP and pulse measurements ~~at the clinical site~~ (Section 10.3.2.3 and Attachment 1).

Section 9.8 Concomitant Therapy

For patients who discontinued study treatment and have entered the Post-Treatment Follow-Up Period (Period 4), Ps therapy ~~with another agent,~~ is allowed, as determined appropriate by the investigator~~, is allowed~~. These allowed Ps therapies include the treatment patients received during the double-blind trial when approved.

Section 12.2.1.3 Analysis Populations

In addition, the primary analyses will be repeated using the per protocol set (PPS), which is defined as all randomized patients who are compliant with therapy, who do not have a subset of important protocol deviations that impact the primary efficacy endpoints, and whose investigator site does not have significant GCP issues that require a report to the regulatory agencies prior to Week 12 (Visit 7). Compliance with therapy is defined to be missing no more than 20% of expected doses, not missing 2 consecutive doses, and no double dosing (that is, taking more injections at the same time point than specified in the protocol) during the period that patients participated in the study and prior to Week 12 (Visit 7) (see Section 12.2.5). Important protocol deviation will be described in the SAP. Patients will be analyzed according to the treatment to which they were assigned.

Safety analyses for Period 2 will be conducted on the safety population, defined as all randomized patients who received at least 1 dose of study treatment. Patients will be analyzed according to the treatment to which ~~they actually received~~they were assigned.

Efficacy, health outcomes, and safety analyses for Period 3 (Maintenance Dosing Period) will be conducted on the Maintenance Dosing Period Primary population, defined as all re-randomized patients (that is, patients randomized to ixekizumab in Period 2 who achieved a sPGA [0, 1] and

were re-randomized at Week 12) who received at least 1 dose of study treatment during Period 3 (Maintenance Dosing Period). Patients will be analyzed according to the treatment to which they were re-randomized ~~for efficacy and health outcome analyses. For safety analyses patients will be analyzed according to the treatment which they actually received~~.

Efficacy, health outcomes, and safety analyses for Period 3 will also be conducted on the Maintenance Dosing Period Secondary population, defined as the ixekizumab patients who were not re-randomized at Week 12 or patients who were randomized to placebo at Week 0, who received at least 1 dose of study treatment during the maintenance dosing period. ~~For efficacy and health outcome analyses, p~~Patients will be analyzed according to the treatment to which they were assigned upon entry into Period 3. ~~For safety analyses, patients will be analyzed according to the treatment they actually received.~~

Safety analyses for Period 4 (Post-Treatment Follow-up Period) will be conducted on the follow-up population, defined as all randomized patients who received at least 1 dose of study treatment and have entered the post-treatment follow-up period. Patients will be analyzed according to the treatment they actually received prior to entering Period 4.

Section 12.2.1.5 Adjustment for Multiple Comparisons

Secondary 6 (Test 8) – Proportion of patients achieving an ~~Change from baseline in~~ Itch NRS ≥4 point reduction from baseline at Week 12 (Visit 7) compared with~~to~~ placebo (for patients who had baseline Itch NRS ≥4)

Section 12.2.10 Planned Analysis

~~There will be one final database lock after all patients complete the study and one interim database lock when all patients complete the maintenance dosing period (Visit 19; Week 60).~~

~~The interim database lock after the completion of the maintenance period will occur after all patients complete or discontinue Week 60 (Visit 19). Study team members will become unblinded to the induction and maintenance dosing treatment allocations following this interim database lock.~~

Attachment 1. Protocol RHBH Study Schedule

Habits [d]			×					~~×~~			×

Attachment 2. Protocol RHBH Clinical Laboratory Tests

Urinalysis (dipstick) [a,b]~~:~~

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