Protocol I1F-MC-RHBF(b)

A Phase 3, Multicenter Study with a 36-Week Open-Label Period Followed by a Randomized Double-Blind Withdrawal Period from Week 36 to Week 104 to Evaluate the Long-Term Efficacy and Safety of Ixekizumab (LY2439821) 80 mg Every 2 Weeks in Biologic Disease-Modifying Antirheumatic Drug–Naive Patients with Active Psoriatic Arthritis

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1. Protocol I1F-MC-RHBF(b)
A Phase 3, Multicenter Study with a 36-Week Open-Label Period Followed by a Randomized Double-Blind Withdrawal Period from Week 36 to Week 104 to Evaluate the Long-Term Efficacy and Safety of Ixekizumab (LY2439821) 80 mg Every 2 Weeks in Biologic Disease-Modifying Antirheumatic Drug–Naive Patients with Active Psoriatic Arthritis

Ixekizumab (LY2439821)

Study I1F-MC-RHBF is a Phase 3, multicenter study with a 36-week initial open-label treatment period examining the effect of ixekizumab 80 mg every 2 weeks (Q2W) in patients with active psoriatic arthritis (PsA) who are conventional disease-modifying antirheumatic drug (cDMARD) inadequate responders (IRs) and biological disease-modifying antirheumatic drug (bDMARD) naive followed by a randomized, double-blind withdrawal period from Week 36 to Week 104 examining the effect of ixekizumab 80 mg Q2W compared to that of placebo.

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2. Synopsis

Study Rationale

Ixekizumab (LY2439821) is an immunoglobulin G subclass 4 monoclonal antibody that binds with high affinity (<3 pM) and specificity to interleukin17A (IL-17A), a proinflammatory cytokine. Ixekizumab does not bind to ligands IL-17B, IL-17C, IL-17D, IL-17E, or IL-17F. IL-17 has been shown to be elevated in peripheral blood, synovial fluid, and tissue of patients with psoriatic arthritis (PsA). Specific inhibition of IL-17A represents a targeted approach to the management of PsA and a novel mechanism of action compared to other PsA therapies. Specifically targeting IL-17A with ixekizumab is hypothesized to provide meaningful therapeutic benefit while reducing the risk of impacting host defenses, which may be inherent with some other biologic-based immunomodulatory treatments that target multiple immune components. As such, it 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; and may potentially offer a more favorable safety profile compared to currently marketed therapies. Because PsA is a chronic relapsing and remitting condition, it is important to understand the long-term effects of biologic treatment, including whether it is necessary to continue treatment for maintenance of effect. This study fulfills global regulatory advice from the European Medicines Agency for establishing maintenance of treatment effect and assessing reintroduction of treatment upon relapse.

Clinical Protocol Synopsis: Study I1F-MC-RHBF

Name of Investigational Product:
ixekizumab (LY2439821)

Title of Study: A Phase 3, Multicenter Study with a 36-Week Open-Label Period Followed by a Randomized Double-Blind Withdrawal Period from Week 36 to Week 104 to Evaluate the Long-Term Efficacy and Safety of Ixekizumab (LY2439821) 80 mg Every 2 Weeks in Biologic Disease-Modifying Antirheumatic Drug–Naive Patients with Active Psoriatic Arthritis

Number of Planned Patients/Subjects:	**Phase of Development:** 3
Entered: 560 Enrolled/Randomized: 400 Completed: 360	

Length of Study: 3 years
Estimated first patient visit: Nov 2015 Estimated last patient visit: Dec 2018

Objectives: The primary objective of the study is to compare ixekizumab 80 mg every 2 weeks (Q2W) with placebo in maintenance of treatment response, as measured by the time to relapse during the randomized double-blind withdrawal period in conventional disease-modifying antirheumatic drug (cDMARD)–inadequate responder (IR) and biological disease-modifying antirheumatic drug (bDMARD)–naive patients with active PsA who meet randomization criteria (Coates criteria for minimal disease activity [MDA] for 3 consecutive months over 4 consecutive visits).

The secondary objectives of the study are:

- to compare ixekizumab 80 mg Q2W with placebo in maintenance of treatment response, as measured by the proportion of patients who meet relapse criteria during the randomized double-blind withdrawal period in cDMARD-IR and bDMARD-naive patients with active PsA who meet randomization criteria (Coates criteria for MDA for 3 consecutive months over 4 consecutive visits)
- to evaluate the time to loss of response for each individual component of MDA in the randomized double-blind withdrawal period
- to evaluate time to first meet Coates criteria for MDA during the initial open-label treatment period (Period 2)
- to evaluate time to achieve Coates criteria for MDA during the initial open-label treatment period (Period 2) (Coates criteria for MDA for 3 consecutive months over 4 consecutive visits)
- to assess the efficacy of ixekizumab 80 mg Q2W following disease relapse after randomization in the randomized double-blind treatment period
- to assess the effect of treatment response as measured by the Health Assessment Questionnaire–Disability Index of ixekizumab 80 mg Q2W throughout the study

Study Design: Study I1F-MC-RHBF is a Phase 3, multicenter study with a 36-week initial open-label treatment period examining the effect of ixekizumab 80 mg Q2W in patients with active PsA who are cDMARD-IRs and are bDMARD naive followed by a randomized double-blind withdrawal period from Week 36 to Week 104 examining the effect of ixekizumab 80 mg Q2W compared with that of placebo. Patients who do not meet the randomized withdrawal criteria will continue on ixekizumab 80 mg Q2W uninterrupted during the randomized double-blind withdrawal period. All randomized patients who no longer meet Coates criteria for MDA at any visit after entering the randomized double-blind withdrawal period will receive ixekizumab 80 mg Q2W for the remainder of the study period. In addition, efficacy and safety will be assessed for up to a total of 2 years for patients who participate throughout the entire 2-year study.

The study consists of 4 periods:

- Period 1: screening period (Visits 1 and 1A) lasting from 4 to 30 days before Week 0 (Visit 2)
- Period 2: initial open-label treatment period from Week 0 (baseline, Visit 2) up to Week 36 (Visit 12)
- Period 3: randomized double-blind withdrawal period from Week 36 to Week 104 (Visit 29). Patients who have been treated with ixekizumab 80 mg Q2W for at least 36 weeks and have achieved 4 consecutive visits of meeting Coates criteria for MDA from Week 36 up to Week 64 will be eligible for randomization at the visit at which these criteria are met.

- Patients who meet the eligibility criteria for randomization any time from Week 36 through Week 64 will be randomized in a 1:1 ratio to 1 of 2 treatment arms: ixekizumab 80 mg Q2W or placebo. Patients will be assessed for the Coates criteria for MDA at each visit during this study period and will remain on their assigned treatments until they relapse (no longer meet the Coates criteria for MDA), at which time they will be treated with ixekizumab 80 mg Q2W until Week 104.
- Patients who are participating in the randomized double-blind withdrawal period who do not meet randomization criteria will continue on ixekizumab 80 mg Q2W until Week 104 and then move into the posttreatment follow-up period.

- Period 4, the posttreatment follow-up period occurring from the early termination visit or the last scheduled visit for a minimum of 12 weeks after that visit, up to 24 weeks if the patient's neutrophil count is low. All patients withdrawing from the study after receiving even 1 dose of study treatment will proceed directly to Period 4.

Diagnosis and Main Criteria for Inclusion and Exclusions: The planned study population will include patients aged 18 years or older who have had a diagnosis of PsA for ≥6 months and currently meet Classification for Psoriatic Arthritis criteria, have at least 3 of 68 tender and 3 of 66 swollen joints, have had inadequate response or intolerance to treatment with 1 or more conventional DMARDs, have active psoriatic skin lesions (plaques) or a documented history of plaque psoriasis, and who are bDMARD naive.

Investigational Product, Dosage, and Mode of Administration or Intervention:
Ixekizumab 80 mg Q2W = At Week 0, receive a starting dose of 160 mg (given as 2 subcutaneous injections of 80 mg) and at Week 2 begin a dosage of 80 mg Q2W.

Reference Therapy, Dose, and Mode of Administration or Comparative Intervention: Placebo may be given during the randomized double-blind withdrawal period.

Planned Duration of Treatment: Up to 2 years for investigational drug administration and up to 2 years 24 weeks for participation over all 4 study periods:
Screening period: 4-30 days
Initial open-label treatment period: Week 0 to Week 36
Randomized double-blind withdrawal period: Week 36 to Week 104
Posttreatment follow-up period: Week 104 to Week 128.

Criteria for Evaluation:
Efficacy: The following efficacy measures will be assessed in this study: American College of Rheumatology Responder Index, Coates criteria for MDA, Composite Psoriatic Disease Activity Index, Disease Activity Score (28 diarthrodial joint count) based on C-reactive protein, Physician's Global Assessment of Disease Activity Visual Analog Scale (VAS), Patient's Global Assessment of Disease Activity VAS, Patient's Assessment of Pain VAS, Patient's Assessment of Physical Function Health Assessment Questionnaire–Disability Index, Tender Joint Count (68 joints), Swollen Joint Count (66 joints), Leeds Enthesitis Index, Spondyloarthritis Research Consortium of Canada enthesitis index, Leeds Dactylitis Index–Basic, Psoriasis Area and Severity Index, percentage of body surface area affected by psoriasis, static Physician's Global Assessment of psoriasis, and Psoriatic Arthritis Disease Activity Score.
Safety: The following safety measures will be assessed in this study: adverse events (AEs), serious adverse events, suspected unexpected serious adverse reactions, AEs of special interest, sitting blood pressure and pulse rate, electrocardiograms, physical examinations, chest radiography and tuberculosis testing, urine pregnancy tests, and laboratory evaluations including, but not limited to, chemistry, hematology, and immunogenicity testing (anti-drug antibodies).
Health Outcomes: The following health outcome measures will be assessed in this study: itch Numeric Rating Scale (NRS), fatigue severity NRS, Medical Outcomes Study 36-Item Short-Form Health Survey, Dermatology Life Quality Index, European Quality of Life–5 Dimensions 5 Level, Work Productivity and Activity Impairment–Specific Health Problem, and Quick Inventory of Depressive Symptomatology–Self Report, (16 items).
Bioanalytical: Concentrations of immunoreactive ixekizumab in human serum as determined by a validated method.

Pharmacokinetics: For each immunogenicity sample, an aliquot of blood will be used to determine the serum concentration of ixekizumab.
Pharmacodynamics: Efficacy endpoints such as American College of Rheumatology 20% response rate (ACR20) response rate and Psoriasis Area and Severity Index and safety endpoints such as neutrophil counts.
Translational Medicine: A multifaceted approach will be employed to explore potential biomarkers in serum, plasma, and whole blood RNA and DNA.

Statistical Methods:

Statistical: Approximately 400 patients will enter the initial open-label treatment period. It is expected that approximately 34% of the patients will meet the randomization criteria for the randomized double-blind withdrawal period. Approximately 136 patients will be randomized in a 1:1 ratio into ixekizumab 80 mg Q2W and placebo treatment groups (68 patients per treatment group). This assumption is based on the Study I1F-MC-RHAP Week 24 results and estimating the number of patients achieving Coates criteria for MDA for 3 consecutive months over 4 consecutive visits of meeting MDA.

It is assumed that approximately 60% and 20% of patients in the placebo and ixekizumab groups, respectively, who enter the randomized double-blind withdrawal period will relapse (no longer meet Coates criteria for MDA). According to these assumptions, a total of 39 patients must meet relapse criteria in the combined treatment groups to achieve 95% power to test the superiority of ixekizumab 80 mg Q2W to placebo for time to relapse at a 2-sided 0.05 α significance level. The dropout rate before relapse for patients randomized in the randomized double-blind withdrawal period is assumed to be 10%. Sample size and power calculations were calculated using nQuery+nTerim 3.0. Randomization and relapse rates will be monitored to assess whether the number of patients who enter the initial open-label treatment period should be increased in order to ensure sufficient sample size and power for the randomized withdrawal period.

Continuous data will be summarized in terms of the number of observations (n); mean; standard deviation and/or standard error of the mean, if applicable; median; minimum; and maximum.

Categorical data will be summarized in terms of the number of observations (n), frequency count, and percentages.

Investigator centers will be pooled by geographical region for statistical analysis purposes.

All tests of treatment effects will be conducted at a 2-sided α level of 0.05 unless otherwise stated.

Efficacy, health outcomes, and safety data collected in Period 2 will be summarized for ixekizumab 80 mg Q2W without inferential statistics. For efficacy, health outcomes, and safety analyses, baseline is defined as the last available value before the first dose of study medication in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2).

For analysis purposes, the endpoint for Period 2 will be defined as the visit of randomization or Week 64 for patients who do not meet the randomization criteria.

Kaplan-Meir estimates will be used to estimate the survival curve for time-to variables.

For patients who are randomized in Period 3, all efficacy, health outcomes, and safety data collected between randomization and either through relapse (no longer meeting Coates criteria for MDA) or through the end of Period 3 will be compared between the ixekizumab 80 mg Q2W and placebo treatment groups. For the efficacy analysis, baseline is defined as the last available value before the first dose of study medication in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2). For the safety analysis, baseline is defined as the last available value before the first dose study treatment in Period 3.

The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to variables for the patients who are randomized to the randomized double-blind withdrawal period. Treatment comparisons will be performed using a log-rank test with treatment, geographic region, and cDMARD use (past use, current use), at the time of randomization in Period 3, in the model.

The primary analysis of the categorical efficacy and health outcome variables will use a logistic regression with treatment, geographic region, and cDMARD use (past use, current use), at the time of randomization in Period 3, in the model. Secondary analysis of the categorical efficacy and health outcome variables will be conducted using the Fisher's exact test.

The analysis for all continuous efficacy and health outcome variables, change from baseline to endpoint analysis, will be made using analysis of covariance with treatment, baseline value, geographic region, and cDMARD use

(past use, current use), at the time of randomization in Period 3, in the model. Missing data will be imputed using last observation carried forward. Type III sums of squares for the least-squares means will be used for the statistical comparison; the 95% CI will also be reported.

The Fisher's exact test will be used for all AE, baseline, discontinuation, and other categorical data. AE data will be analyzed using exposure-adjusted incidence rates. Continuous vital-sign and laboratory values will be analyzed by an analysis of covariance model with treatment and baseline value as independent variables. Other continuous variables will be analyzed by *t*-tests unless otherwise stated.

For patients who are randomized and subsequently relapse in Period 3, efficacy, health outcomes, and safety data collected between relapse and the end of Period 3 will be summarized for ixekizumab 80 mg Q2W without inferential statistics. For the efficacy and health outcomes analyses, baseline is defined as the last available value before the first dose of study medication in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2). For the safety analysis, baseline is defined as the last available value before relapse in Period 3.

For patients who are randomized in Period 3, efficacy, health outcomes, and safety data collected in Periods 2 and 3 combined will be summarized for ixekizumab 80 mg Q2W without inferential statistics. For efficacy, health outcomes, and safety analyses, baseline is defined as the last available value before the first dose of study medication in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2).

For patients who are not randomized in Period 3, efficacy, health outcomes, and safety data collected in Periods 2 and 3 combined will be summarized for ixekizumab 80 mg Q2W without inferential statistics. For efficacy, health outcomes, and safety analyses, baseline is defined as the last available value before the first dose of study medication in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2).

Safety: Safety will be assessed by summarizing and analyzing serious adverse events, AEs, AEs of special interest, vital signs, other measures of cardiovascular function, Columbia–Suicide Severity Rating Scale (C-SSRS), and laboratory evaluations (including chemistry, calculated creatinine clearance, hematology [including white blood cell count and differential], urinalysis [dipstick and microscopic], thyroid-stimulating hormone and free T4, and immunogenicity testing [treatment-emergent anti-drug antibodies]).

Pharmacokinetics/Pharmacodynamics: Observed ixekizumab serum concentrations will be summarized by visits and corresponding time when sampling occurred.

As appropriate, exposure-response relationship will be investigated between ixekizumab exposure and clinically important efficacy and pharmacodynamic (PD) measures (for example, proportion of patients achieving Coates criteria for MDA for 3 consecutive months over 4 consecutive visits and the maintenance of treatment effects) specified in study objectives. In addition, the relationship between the time course of ixekizumab exposure and the time course of the efficacy and PD measures may be explored using graphical methods and a modeling approach. Covariates such as body weight, disease duration, baseline value, and so on, will be investigated to assess their impact on the PD parameters. Model evaluation will include using sensitivity analysis and visual predictive check. If a trend or statistically significant difference between the ixekizumab cohort and the placebo cohort is noted in any safety endpoint, these endpoints will also be explored to investigate exposure-response relationships.

The potential impact of immunogenicity on ixekizumab exposure and/or PD responses will be evaluated, as appropriate, by graphical assessments to compare drug exposure or PD responses between immunogenicity-negative and immunogenicity-positive patients at correspondent visits or before and after immunogenicity development for patients whose immunogenicity was detected. In addition, the effect of immunogenicity may be evaluated in the population pharmacokinetic/PD modeling analyses where immunogenicity will be evaluated as a covariate.

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
ACR	American College of Rheumatology
ACR Responder	**ACR20 Responder** A patient who has at least 20% improvement in both tender and swollen joint counts and at least 20% improvement in a minimum of 3 of the following 5 criteria: patient's assessment of arthritis pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function (Health Assessment Questionnaire-Disability Index), and an acute-phase reactant value (C-reactive protein or ESR). **ACR50 Responder** A patient who has at least 50% improvement in both tender and swollen joint counts and at least 50% improvement in a minimum of 3 of the following 5 criteria: patient's assessment of arthritis pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function (Health Assessment Questionnaire-Disability Index), and an acute-phase reactant value (C-reactive protein or ESR). **ACR70 Responder** A patient who has at least 70% improvement in both tender and swollen joint counts and at least 70% improvement in a minimum of 3 of the following 5 criteria: patient's assessment of arthritis pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function (Health Assessment Questionnaire-Disability Index), and an acute-phase reactant value (C-reactive protein or ESR).
ACR-N Responder Index	A continuous measure of clinical, laboratory, and functional measure that characterizes the percentage of improvement from baseline in rheumatologic disease activity. This index is defined operationally as the lowest of either a) the percentage change in tender joint count, b) the percentage change in swollen joint count, or c) the median percentage change of the remaining 5 ACR core criteria. A patient with an ACR-N of X is a patient who has improvement of at least X% in both tender and swollen joint counts and a median improvement of at least X% in the following 5 criteria: patient's assessment of arthritis pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function (Health Assessment Questionnaire-Disability Index), and an acute-phase reactant value (C-reactive protein or ESR).
AE	adverse event: any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An 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 event of special interest
ALP	alkaline phosphatase

ALT	alanine aminotransferase
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
bDMARD	biological disease-modifying antirheumatic drug
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/her 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/or his/her 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
CASPAR	Classification for Psoriatic Arthritis
C-CASA	Columbia Classification Algorithm of Suicide Assessment
cDMARD	conventional disease-modifying antirheumatic drug
CEC	Clinical Events Committee
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.

CPDAI	Composite Psoriatic Disease Activity Index
CRF/eCRF	case report form/electronic case report form: Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
C-SSRS	Columbia–Suicide Severity Rating Scale
DAS28	Disease Activity Score modified to include the 28 diarthrodial joint count
DAS28-CRP	Disease Activity Score (28 diarthrodial joint count) based on C-reactive protein
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result under controlled conditions.
end of trial (study)	End of trial is the date of the last visit or last scheduled procedure shown in the study schedule for the last patient.
enroll	the act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
enthesitis	inflammation of tendons and ligaments that can manifest as localized pain and tenderness
EQ-5D 5L	European Quality of Life–5 Dimensions 5 Level
ERB/IRB	ethical review board/institutional review board: 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
ETV	early termination visit
GCP	good clinical practice
HAQ-DI	Health Assessment Questionnaire–Disability Index
HBcAb+	positive for hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IBD	Inflammatory bowel disease (e.g. Crohn's disease and ulcerative colitis)
IL	Interleukin
informed consent	a process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
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.
investigational product	a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
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.
IR	inadequate responder
ITT	intent-to-treat: 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 regimen) 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(ly)
IWRS	interactive web-response system
LDI-B	Leeds Dactylitis Index–Basic
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
LEI	Leeds Enthesitis Index
LTBI	latent tuberculosis infection
LY2439821	ixekizumab
mBOCF	modified baseline observation carried forward

MDA	minimal disease activity
MedDRA	*Medical Dictionary for Regulatory Activities*
MTX	methotrexate
NRI	nonresponder imputation
NRS	Numeric Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
OMERACT	Outcome Measures in Rheumatology
open-label	a study in which there are no restrictions on knowledge of treatment allocation; therefore, the investigator and the study participant are aware of the drug therapy received during the study
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area and Severity Index
PASI 75	at least a 75% improvement from baseline in PASI score
PASI 90	at least a 90% improvement from baseline in PASI score
PASI 100	at least a 100% improvement from baseline in PASI score
patient	a study participant who has the disease or condition for which the investigational product is targeted
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPD	purified protein derivative
PsA	psoriatic arthritis
Q2W	every 2 weeks
Q4W	every 4 weeks
QIDS-SR16	Quick Inventory of Depressive Symptomatology-self report 16 items
RA	rheumatoid arthritis
randomize	the process of assigning patients to an experimental group on a random basis
rescreen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
SAP	statistical analysis plan

SC	subcutaneous(ly)
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 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	36-Item Short Form Health Survey
SJC	swollen joint count
SPARCC	Spondyloarthritis Research Consortium of Canada
sPGA	static Physician's Global Assessment of psoriasis
SSZ	sulfasalazine
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
TE-ADA	treatment-emergent anti-drug antibody
TEAE	treatment-emergent adverse event: 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
TJC	tender joint count
TNF	tumor necrosis factor
TPO	third-party organization
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cell
WHO	World Health Organization

A Phase 3, Multicenter Study with a 36-Week Open-Label Period Followed by a Randomized Double-Blind Withdrawal Period from Week 36 to Week 104 to Evaluate the Long-Term Efficacy and Safety of Ixekizumab (LY2439821) 80 mg Every 2 Weeks in Biologic Disease-Modifying Antirheumatic Drug–Naive Patients with Active Psoriatic Arthritis

5. Introduction

Psoriatic arthritis (PsA), an immune-mediated chronic inflammatory disorder commonly associated with psoriasis, is one of the most common rheumatic arthritides, occurring in 0.04% to 0.1% of the general population but in 6% to 42% of patients with psoriasis. It is a progressive, destructive disease that results in deformities, impaired physical function, loss of quality of life, and increased mortality (Gladman et al. 1998; Leung et al. 2008). PsA also has a considerable negative impact on multiple physical and emotional aspects of patients' lives (Gladman et al. 2005; Rosen et al. 2012). Patients with PsA have reported poorer health-related quality of life than the general population and patients with psoriasis (Husted et al. 1997; Rosen et al. 2012) and suffer from a level of functional impairment similar to that of patients with rheumatoid arthritis (RA) (Husted et al. 2001).

The current standard of care for PsA includes nonsteroidal anti-inflammatory drugs (NSAIDs); intra-articular and/or systemic glucocorticoids; conventional disease-modifying antirheumatic drugs (cDMARDs) such as methotrexate (MTX), sulfasalazine (SSZ), leflunomide, and cyclosporine A; and biologic agents such as tumor necrosis factor (TNF) α inhibitors (Gossec et al. 2012; Smolen et al. 2014). Although leflunomide has been shown to be effective in improving signs and symptoms of PsA as assessed by the Psoriatic Arthritis Response Criteria and the American College of Rheumatology 20% response rate (ACR20), there is only weak evidence that other cDMARDs are effective, though limited controlled clinical trial data are available (Gossec et al. 2012; Mease and Armstrong 2014). In a recent randomized controlled trial of patients with PsA treated with MTX, no significant improvement was demonstrated in peripheral arthritis (Kaltwasser et al. 2004; Kingsley et al. 2012). Additionally, cDMARDs have not demonstrated efficacy in treating axial involvement, enthesitis, or dactylitis, though limited data are available (Gossec et al. 2012; Mease and Armstrong 2014). SSZ has been shown to be effective for axial manifestations in only 1 open-label trial but not effective for enthesitis or dactylitis (Dougados et al. 1995). Data on the effects of MTX on radiographic progression (joint damage) have not been conclusive and have been analyzed in only a small case-controlled study. Additionally, radiographic progression (joint damage) was not inhibited in a small case-controlled study of 20 SSZ-treated patients and 20 matched controls (Ash et al. 2012).

In patients with PsA, TNF inhibitors are effective in treating signs and symptoms, inhibiting or slowing structural joint progression (mainly bone degradation), and improving skin lesions (Mease et al. 2000, 2004, 2005; Antoni et al. 2005a, 2005b; Kavanaugh et al. 2006, 2009). However, only between 30% and 40% of patients with PsA have a partial response, and others

become resistant or intolerant to treatment with TNF inhibitors and continue to accrue disability (Nash and Clegg 2005; Rudwaleit et al. 2010). In addition, infections, malignancies, blood dyscrasias, peripheral neuropathy, and central nervous system and spinal cord demyelination can occur in some patients treated with these agents (Singh et al. 2011; Ruderman 2012; Deepak et al. 2013). Therefore, there is an unmet need for alternative effective medications with a different mechanism of action and an improved safety profile for patients with PsA.

Higher numbers of circulating Th17 cells have been found in the peripheral blood of patients with PsA (Jandus et al. 2008). These cells secrete substantially more interleukin (IL)-17, have shown advanced differentiation, and are polyfunctional in T-cell receptor–driven cytokine production (Jandus et al. 2008). Higher numbers of Th17 cells, evidenced by a higher Th17:Th1 ratio, are observed in the PsA synovial fluid than in peripheral blood. The higher numbers of Th17 cells are seen early in the disease course, suggesting a role of Th17 in induction of clinical disease activity in PsA (Leipe et al. 2010). In addition, studies in the peripheral blood and synovial tissue and fluid in PsA have shown evidence of higher levels of IL-17 and other proinflammatory cytokines. Furthermore, higher levels of IL-17 correlated with higher frequencies of Th17 cells, indicating that Th17 cells are a major source of IL-17 in the production of local inflammation at the onset of disease (Fitzgerald and Winchester 2009; Leipe et al. 2010).

Ixekizumab (LY2439821) is an immunoglobulin G subclass 4 monoclonal antibody that binds with high affinity (<3 pM) and specificity to IL-17A, a proinflammatory cytokine. Ixekizumab does not bind to ligands IL-17B, IL-17C, IL-17D, IL-17E, or IL-17F. IL-17 has been shown to be elevated in peripheral blood, synovial fluid, and tissue of patients with PsA. Specific inhibition of IL-17A represents a targeted approach to the management of PsA and a novel mechanism of action compared to other PsA therapies. Specifically targeting IL-17A with ixekizumab is hypothesized to provide meaningful therapeutic benefit while reducing the risk of impacting host defenses, which may be inherent with some other biologic-based immunomodulatory treatments that target multiple immune components.

To date, ixekizumab has been evaluated in the completed primary treatment periods of one Phase 2 and five Phase 3 clinical psoriasis studies; these studies are ongoing to collect longer-term data. In addition, Eli Lilly and Company (Lilly) has completed four Phase 1 studies (3 in patients with RA, 1 in patients with psoriasis) and has completed one Phase 2 study (patients with RA).

To evaluate ixekizumab's efficacy and safety in PsA, Lilly has 2 Phase 3 studies that are ongoing (Studies I1F-MC-RHAP [RHAP] and I1F-MC-RHBE [RHBE]). Both Studies RHAP and RHBE are randomized, double-blind, placebo-controlled, 24-week studies with long-term open-label extensions. These studies are designed to establish the efficacy and safety profiles of ixekizumab 80 mg every 2 weeks (Q2W) and 80 mg every 4 weeks (Q4W) compared with those of placebo.

Because PsA is a chronic relapsing and remitting condition, it is also important to understand the long-term effects of biologic treatment, including whether it is necessary to continue treatment for maintenance of effect. Once a treatment target is achieved and sustained on therapy, a

relevant question is whether treatment can be discontinued to avoid unnecessary exposure. There is a lack of large controlled trials with the current standard of care to assess withdrawal of treatment in PsA, although several small studies suggest that many patients experience relapse upon standard of care (primarily TNF inhibitor) treatment withdrawal (Araujo et al. 2015; Moverly et al. 2015). The maintenance of effect for biologics that target the IL-23/IL-17 pathway has not been previously reported.

A further complication in the assessment of long-term outcomes in PsA is the lack of established definitions of remission, flare, and relapse. Remission criteria and activity indices used in RA have sometimes been applied in PsA (Gladman et al. 2004; Kavanaugh and Cassell 2005). The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis has recognized several domains in the treatment of PsA, including peripheral arthritis, skin and nail disease, axial disease, dactylitis, and enthesitis. The American College of Rheumatology (ACR) Index and the Disease Activity Score modified to include the 28 diarthrodial joint count (DAS28) have historically been used for measuring disease activity in PsA clinical trials (van der Heijde et al. 1990; Felson et al. 1995). However, these outcomes do not capture all of the domains of PsA disease activity and may lead to the misclassification of patient's overall disease response or severity. The overall state of disease activity is a useful target of treatment by both the patient and the physician, given current treatment possibilities and limitations. Some newer indices have been specifically developed for PsA to measure disease activity: Composite Psoriatic Disease Activity Index (CPDAI), Disease Activity Index for Psoriatic Arthritis, Psoriatic Arthritis Disease Activity Score (PASDAS), Arithmetic Mean of Desirability Function, and minimal disease activity (MDA) criteria in PsA (Coates et al. 2010; Schoels et al. 2010; Mumtaz et al. 2011; Helliwell et al. 2013).

While no remission criteria have been standardized for PsA, data from several clinical series and from the Swedish Early Psoriatic Arthritis Register reported a frequency of clinical remission (using different remission criteria) ranging from 17.6% to 68%; the highest rate was observed in patients treated with anti-TNFα agents (Cantini et al. 2008; Haddad et al. 2015). Recent studies have suggested that stringent response/remission targets such as MDA may be appropriate treatment goals in PsA (Coates et al. 2010).

The Coates criteria for MDA (described below) has been developed on the basis of current expert opinion and uses a composite of 7 key outcome measures used in PsA to encompass the disease domains to measure the overall state of a patient's disease (Coates et al. 2010; Coates and Helliwell 2010). The criteria were developed specifically for PsA and have been validated in observational and interventional cohorts. The specific MDA criteria are described below and include assessment of joints; enthesis; skin; and patient assessment of pain, overall disease, and functioning. The Coates criteria for MDA have evidence supporting their use within the Outcome Measures in Rheumatology (OMERACT) filter of truth, discrimination, and feasibility. In a retrospective analysis of infliximab treatment in patients with PsA, the Coates criteria for MDA were shown to be discriminative between drug and placebo, and there was a strong association between achieving MDA and achievement of the ACR outcomes, reductions in inflammatory markers and physician opinion of disease activity (Coates and Helliwell 2010).

Patients who maintained the Coates criteria for MDA for 38 Weeks or more have better long-term functional improvement, patient global assessment, and radiography outcomes after 5 years (Kavanaugh et al. 2015). In addition, the Coates criteria for MDA has been recently advocated as a feasible and clinically relevant treatment target in clinical practice (Coates and Helliwell 2015) that is acceptable for patients and physicians (Coates et al. 2012). The duration of treatment needed to achieve MDA is variable; as many as 52% patients meet the Coates criteria for MDA within 6 months of starting a TNF inhibitor, but even higher percentages meet the criteria at 1 year or more (Coates and Helliwell 2010; Haddad et al. 2015).

The Coates criteria for MDA are:

- MDA-Psoriasis Area and Severity Index (PASI): Patients are classified as achieving MDA if they fulfill 5 of 7 outcome measures:
  - tender joint count (TJC) ≤1
  - swollen joint count (SJC) ≤1,
  - PASI total score ≤1 or body surface area (BSA) ≤3
  - patient pain visual analog scale (VAS) score of ≤15
  - patient global disease activity VAS score of ≤20
  - Health Assessment Questionnaire–Disability Index (HAQ-DI) score ≤0.5
  - tender entheseal points ≤1

On the basis of these previous data, MDA is considered a valid, clinically relevant, and implementable target for assessing long-term efficacy and maintenance of effect of an investigational compound. Study I1F-MC-RHBF (RHBF) is a Phase 3, multicenter study with a 36-week initial open-label treatment period examining the effect of ixekizumab 80 mg Q2W in patients with active PsA who are cDMARD–inadequate responders (IRs) and are biological disease-modifying antirheumatic drug (bDMARD) naive followed by a randomized double-blind withdrawal period from Week 36 to Week 104. The primary objective of the study is to compare ixekizumab 80 mg Q2W and placebo in maintenance of treatment response, as measured by the time to relapse during the randomized double-blind withdrawal period in cDMARD-IR and bDMARD-naive patients with active PsA who meet Coates criteria for MDA for 3 consecutive months over 4 consecutive visits. This study fulfills global regulatory advice for establishing maintenance of treatment effect and assessing reintroduction of treatment upon relapse.

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

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

6. Objectives

6.1. Primary Objective

The primary objective of the study is to compare ixekizumab 80 mg Q2W with placebo in maintenance of treatment response, as measured by the time to relapse during the randomized double-blind withdrawal period in cDMARD-IR and bDMARD-naive patients with active PsA who meet randomization criteria (Coates criteria for MDA for 3 consecutive months over 4 consecutive visits).

6.2. Secondary Objectives

The secondary objectives of the study are:

- to compare ixekizumab 80 mg Q2W with placebo in maintenance of treatment response, as measured by the proportion of patients who meet relapse criteria during the randomized double-blind withdrawal period in cDMARD-IR and bDMARD-naive patients with active PsA who meet randomization criteria (Coates criteria for MDA for 3 consecutive months over 4 consecutive visits)
- to evaluate the time to loss of response for each individual component of MDA in the randomized double-blind withdrawal period
- to evaluate time to first meeting Coates criteria for MDA during the initial open-label treatment period (Period 2)
- to evaluate time to achieving Coates criteria for MDA during the initial open-label treatment period (Period 2) (Coates criteria for MDA for 3 consecutive months over 4 consecutive visits)
- to assess the efficacy of ixekizumab 80 mg Q2W after disease relapse after randomization in the randomized double-blind treatment period
- to assess the effect of treatment response as measured by the HAQ-DI of ixekizumab 80 mg Q2W throughout the study

6.3. Exploratory Objectives

The exploratory objectives of the study are:

- to assess the clinical factors that predict Coates criteria for MDA
- to assess the time to achieve other composite measurements of low disease activity, such as DAS28 based on C-reactive protein (DAS28-CRP), PASDAS, CPDAI, and others during the initial open-label treatment period (Period 2)
- to assess the changes in health utility (European Quality of Life–5 Dimensions 5 Level [EQ-5D 5L]), Work Productivity and Activity Impairment–Specific Health Problem, and Dermatology Life Quality Index (DLQI) throughout the study
- to assess the changes in the health outcome endpoints fatigue severity Numeric Rating Scale (NRS) score, itch NRS score (in the subgroup of patients with psoriatic skin lesions involving ≥3% BSA at baseline), Quick Inventory of Depressive Symptomatology-self report 16 items (QIDS-SR16) score, and Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) Physical Component Summary and Mental Component Summary

scores and the 8 associated domains of SF-36 (Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health) throughout the study

- to explore biomarkers of disease or drug activity that may be contained in serum, plasma, whole-blood messenger RNA and DNA samples
- to assess the pharmacokinetic (PK)/pharmacodynamic (PD) relationship and immunogenicity of ixekizumab throughout the study by:
    - characterizing the PK of ixekizumab, determining the magnitude of within- and between-patient variability, and identifying the potential intrinsic and extrinsic factors that may have an effect on the PK of ixekizumab
    - characterizing the exposure-response relationships for efficacy endpoints (for example, proportion of patients achieving Coates criteria for MDA from Week 36 through Week 64 and the maintenance of treatment effects), and identifying potential factors that may impact the efficacy endpoints
    - evaluating the potential development of anti-ixekizumab antibodies and its impact on patient safety, efficacy, and PK of ixekizumab

7. Investigational Plan

7.1. Summary of Study Design

Study I1F-MC-RHBF is a Phase 3, multicenter study with a 36-week initial open-label treatment period examining the effect of ixekizumab 80 mg Q2W in patients with active PsA who are cDMARD-IRs and are bDMARD naive followed by a randomized double-blind withdrawal period from Week 36 to Week 104 examining the effect of ixekizumab 80 mg Q2W compared with that of placebo. Patients who do not meet the randomized withdrawal criteria will continue on ixekizumab 80 mg Q2W uninterrupted during the randomized double-blind withdrawal period. All randomized patients who no longer meet Coates criteria for MDA at any visit after entering the randomized double-blind withdrawal period will receive ixekizumab 80 mg Q2W for the remainder of the study period. In addition, efficacy and safety will be assessed for up to a total of 2 years for patients who participate throughout the entire 2-year study.

The study consists of 4 periods:

- **Period 1 (Section 7.1.1):** screening period (Visits 1 and 1A) lasting from 4 to 30 days before Week 0 (Visit 2)
- **Period 2 (Section 7.1.2):** initial open-label treatment period from Week 0 (baseline, Visit 2) up to Week 36 (Visit 12)
- **Period 3 (Section 7.1.3):** randomized double-blind withdrawal period from Week 36 to Week 104 (Visit 29). Patients who have been treated with ixekizumab 80 mg Q2W for at least 36 weeks and have achieved 4 consecutive visits of meeting Coates criteria for MDA from Week 36 up to Week 64 will be eligible for randomization at the visit at which these criteria are met.
- **Period 4 (Section 7.1.4):** posttreatment follow-up period occurring from the early termination visit (ETV) or the last scheduled visit for a minimum of 12 weeks after that visit, up to 24 weeks if the patient's neutrophil count is low. All patients withdrawing from the study after receiving even 1 dose of study treatment will proceed directly to Period 4.

Figure RHBF.1 illustrates the study design.

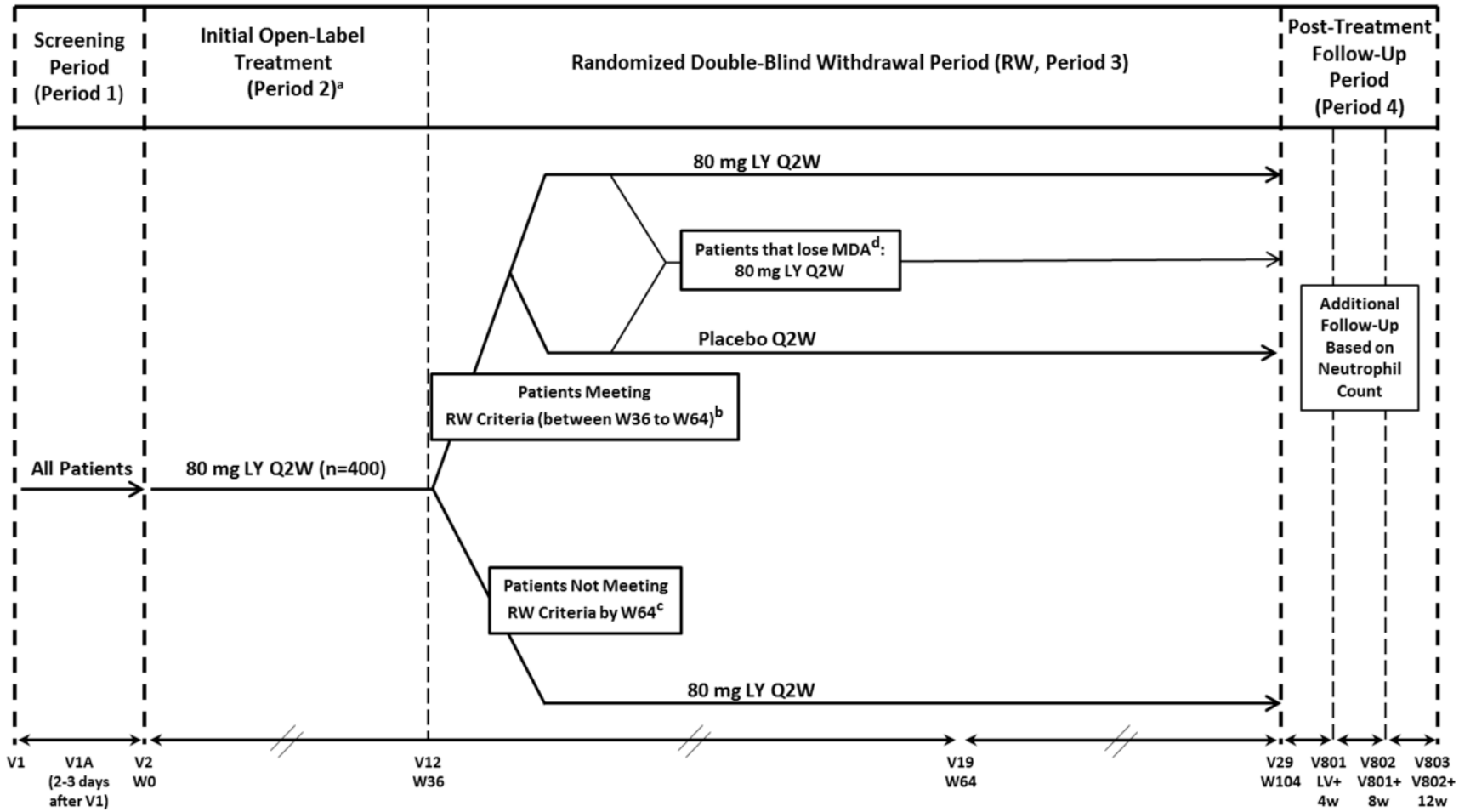
All procedures to be conducted during the study, including timing of all procedures, are indicated in the study schedule (Attachment 1). Selected study procedures should be performed before administration of the investigational product, as applicable, according to the study schedule. Section 10.4 describes collection of laboratory samples; Attachment 2 lists the specific laboratory tests that will be performed for this study.

Patients discontinuing from the study who have received at least 1 dose of investigational product should complete the ETV before proceeding to the posttreatment follow-up period (Period 4). For the management of patient safety, all patients should be monitored through the posttreatment follow-up period at least as frequently as indicated on the study schedule (Attachment 1).

All treatment groups are described in Section 9.1. Details of the administration of the investigational product are described in Section 9.1.1, special treatment considerations are outlined in Section 9.5.1, and the use of the study drug administration log is detailed in Section 9.5.2.

Excluded and restricted therapies are detailed in Section 9.8.

PK sampling is detailed in Section 10.4.4.



See footnotes on the following page.

Figure RHBF.1. Illustration of study design for Clinical Protocol I1F-MC-RHBF.

Abbreviations: LV = date of last visit; LY = LY2439821 (ixekizumab); MDA = minimal disease activity; n = number of patients; Q2W = every 2 weeks; RW = randomized withdrawal; V = study visit; W = study week.

[a] The initial open-label treatment period (Period 2) encompasses Week 0 up to Week 36. During Period 2, all patients will receive open-label ixekizumab 80 mg Q2W.

[b] Between Weeks 36 and 64 (inclusive), patients who have been treated with ixekizumab 80 mg Q2W for at least 36 weeks and have achieved 4 consecutive visits of meeting Coates criteria for MDA will be eligible for randomization at the visit at which these criteria are met. Eligible patients will be randomized in a 1:1 ratio to 1 of 2 treatment arms: ixekizumab 80 mg Q2W or placebo Q2W. Patients will remain in their RW treatment arms until they no longer meet Coates criteria for MDA, at which point they will receive ixekizumab 80 mg Q2W. Patients who do not meet Coates criteria for MDA at Week 52 are not eligible for randomization.

[c] Patients who do not meet the RW eligibility criteria by Week 64 will remain on ixekizumab 80 mg Q2W uninterrupted for the duration of Period 3.

[d] Patients who no longer meet Coates criteria for MDA during Period 3 (the RW period) will be switched to ixekizumab 80 mg Q2W. Patients who continue to meet Coates criteria for MDA during Period 3 (the RW period) will continue treatment until Week 104 and move to Period 4 (the posttreatment follow-up period).

Figure RHBF.1. Illustration of study design for Clinical Protocol I1F-MC-RHBF (concluded).

7.1.1. Screening Period (Period 1)

The duration of the screening period is between 4 and 30 days, and the period 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) before any study assessments, examinations, or procedures are 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 or a T-SPOT®.TB assay for tuberculosis (TB) will be performed or patients will be administered a purified protein derivative (PPD) test for TB (Section 10.3.2.3). For those patients administered a PPD test at Visit 1, the test results will be read approximately 2 to 3 days after test application, at Visit 1A. Subsequent visits denoted with the letter "A" (see study schedule, Attachment 1) are for PPD reads, where applicable.

Patients who test positive for latent TB at screening may be rescreened after appropriate treatment as described in Section 10.3.2.3. Additionally, patients who do not qualify at screening under exclusion criterion [40] or [41] may be rescreened once, ≥4 weeks after documented resolution of symptoms.

7.1.2. Initial Open-Label Treatment Period (Period 2)

The initial open-label treatment period (Period 2) will occur from Week 0 (baseline, Visit 2) through Week 36 (Visit 12).

At Week 0 (baseline, Visit 2), routine safety assessments, blood draws for laboratory tests, and clinical efficacy assessments will be performed on eligible patients according to the study schedule (Attachment 1).

All patients will receive a starting dose of open-label ixekizumab 160 mg followed by open-label ixekizumab 80 mg Q2W during the initial open-label treatment period.

7.1.3. Randomized Double-Blind Withdrawal Period (Period 3)

The randomized double-blind withdrawal period (Period 3) will be a double-blind treatment period with ixekizumab 80 mg Q2W and placebo and will occur from Week 36 (Visit 12) to Week 104 (Visit 29).

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

Not all patients will be randomized in Period 3 and the timing of randomization will be flexible for those patients who meet criteria for randomization. The criteria for randomization in Period 3 are having received ixekizumab 80 mg Q2W for at least 6 months and meeting Coates criteria for MDA for 3 consecutive months over 4 consecutive visits.

Patients who meet the randomization criteria at any time from Week 36 through Week 64 will be randomized in a 1:1 ratio to 1 of 2 treatment arms: ixekizumab 80 mg Q2W or placebo. Patients will be assessed for the Coates criteria for MDA at each visit during this study period. Patients

who continue to meet Coates criteria for MDA will continue in their assigned treatment arms until Week 104. Patients who no longer meet the Coates criteria for MDA at any visit will be treated with ixekizumab 80 mg Q2W until Week 104. Patients receiving 80 mg ixekizumab Q2W who relapse will continue on 80 mg ixekizumab Q2W to maintain the study blind and to see if response can be regained with continued treatment. Patients who fail to demonstrate a 20% improvement from baseline in both TJC and SJC at Week 24 or at any subsequent visit will be discontinued (see Section 8.3.1).

Patients who do not meet the randomization criteria before or at Week 64 will continue ixekizumab 80 mg Q2W throughout Period 3.

Patients who complete Period 3 will enter the posttreatment follow-up period. Patients who discontinue the study treatment early during Period 3 will proceed to the ETV before entering the posttreatment follow-up period (Period 4, Section 7.1.4).

7.1.4. Posttreatment Follow-Up Period (Period 4)

All patients receiving at least 1 dose of investigational product will enter the posttreatment follow-up period (Period 4) for a minimum of 12 weeks after their last regularly scheduled visits (or the date of their ETVs). Required study visits should occur at 4 weeks after and at 12 weeks after the last regularly scheduled visit (or the date of the patient's ETV) (Visits 801 and 802, respectively), except for patients with concurrent infections that require systemic anti-infective therapy (described below).

If, at the last scheduled visit or ETV, a patient's neutrophil count is <1500 cells/μL (<1.50 × 10^3/μL or <1.50 GI/L) and less than the patient's baseline neutrophil count, the following measures should be taken:

- Patients <u>with concurrent infection:</u> 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 posttreatment follow-up period (Period 4) design at Visits 801 (4 weeks after 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 <u>without concurrent infection:</u> 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 posttreatment 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 (<1.00 × 10^3/μL or <1.00 GI/L) at any follow-up visit, the patient should return for additional visits at least Q4W (unscheduled visits may be required).

- As long as a patient's neutrophil count is ≥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) at any follow-up visit, the patient should return for additional visit(s) at least every 4 to 8 weeks (unscheduled visits may be required).
- If at Visit 803 the patient's neutrophil count remains <1500 cells/μL (<1.50 × 10^3/μL or <1.50 GI/L) 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).
- If at Visit 802 or Visit 803 the patient's neutrophil count is ≥1500 cells/μL (≥1.50 × 10^3/μL or ≥1.50 × 10^3/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 necessary.

For patients who completed or discontinued study treatment and have entered the posttreatment follow-up period (Period 4), PsA therapy with another agent is allowed, as determined appropriate by the investigator.

7.2. Discussion of Design and Control

A dosage regimen of ixekizumab 80 mg Q2W will be studied as detailed in Section 9.1, with the dose justification as outlined in Section 9.4.

The Week 36 to Week 64 randomization window will allow sufficient time for responding patients to reach randomization criteria.

The overall level of disease activity is a useful target of treatment for both the patient and the physician, given current available treatment options. Recent studies have suggested that stringent response/remission targets such as MDA may be appropriate treatment goals in PsA (Coates et al. 2010). The Coates criteria for MDA has been developed on the basis of current expert opinion and uses a composite of 7 key outcome measures (see Section 10.1.1.1) used in PsA to encompass domains of the disease to measure the overall state of a patient's disease (Coates et al. 2010; Coates and Helliwell 2010). The criteria were developed specifically for PsA and have been validated in observational and interventional cohorts. The PsA Coates criteria for MDA have evidence supporting their use within the OMERACT filter of truth, discrimination, and feasibility. In a retrospective analysis of infliximab in PsA, the criteria were shown to be discriminative between drug and placebo, and there was a strong association between achieving MDA and achievement of the ACR outcomes, reductions in inflammatory markers, and physician opinion of disease activity (Coates and Helliwell 2010). Patients who maintained the Coates Criteria for MDA for 38 Weeks or more have better long-term functional improvement, patient global assessment, and radiography outcomes after 5 years (Kavanaugh et al. 2015). In addition, MDA has been recently advocated as a feasible and clinically relevant treatment target in clinical practice (Coates and Helliwell 2015) that is acceptable for patients

and physicians (Coates et al. 2012). Loss of MDA has also been used to define relapse upon withdrawal of treatment (Araujo et al. 2015; Haddad et al. 2015; Moverly et al. 2015).

On the basis of these previous data, MDA is a valid, clinically relevant, and implementable target for assessing long-term efficacy and maintenance of effect of an investigational compound. The duration of treatment needed to achieve MDA is variable; as many as 52% of patients meet the Coates criteria for MDA within 6 months of starting a TNF inhibitor, but even higher percentages meet the criteria at 1 year or more (Coates and Helliwell 2010; Haddad et al. 2015). The flexible timing of randomization up to Week 64 will allow sufficient time for patients to meet Coates criteria for MDA and ensure that patients' response to treatment is stable by requiring 4 consecutive visits of MDA before potential treatment withdrawal.

The study blind is maintained as described in Section 9.7. The placebo-controlled randomized double-blind withdrawal period is blinded to minimize bias in the evaluation of ixekizumab treatment in patients with PsA. Patients receiving placebo may still receive treatment in the form of the allowed concomitant therapies as described in the study exclusion criteria (Section 8.2) and concomitant therapy (Section 9.8). Patients receiving placebo who relapse will be re-treated with ixekizumab 80 mg Q2W at the first visit at which relapse (loss of MDA) occurs to minimize the time patients may be off previously effective treatment and to be able to assess whether response upon retreatment is attained. Patients receiving 80 mg ixekizumab Q2W who relapse will continue on 80 mg ixekizumab Q2W to maintain the study blind and to see if response can be regained with continued treatment.

Both the time to relapse (loss of MDA) and the number of patients who relapse in the ixekizumab and placebo groups after randomization will be compared. The time to relapse was chosen as the primary objective because it is a clinically relevant outcome and is not restricted to a single time point and thus incorporates the time course of response and relapse by individual patients.

The posttreatment follow-up period (Period 4) is for safety monitoring after the last treatment period and study visit.

8. Study Population

This study will enroll patients aged 18 years or older who are cDMARD-IRs and are bDMARD naive, have a diagnosis of PsA as defined by the Classification for Psoriatic Arthritis (CASPAR) criteria, have active psoriatic skin lesions or a documented history of psoriasis, and have at least 3 tender and 3 swollen joints.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only in the following circumstances: Patients who test positive for latent TB at screening may be rescreened after appropriate treatment as described in Section 10.3.2.3. Additionally, patients who do not qualify at screening under exclusion criterion [40] or [41] may be rescreened once, 4 or more weeks after documented resolution of symptoms. When rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number.

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 (criteria [3], [35], [41], and [42]) to determine if the patient meets all inclusion and exclusion criteria to qualify for participation in the study.

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.

[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 after the last dose of investigational product, whichever is longer. Methods of contraception considered acceptable when used properly include oral contraceptives, contraceptive patch, injectable or implantable contraceptives, intrauterine device, vaginal ring, diaphragm with contraceptive gel, or condom with contraceptive foam.

-or-

are women of nonchildbearing potential, defined as:

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

-or-

women who are ≥60 years of age;

-or-

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

[2] have had diagnosis of active PsA for at least 6 months (according to a detailed medical history provided by the patient, a physical examination by the study investigator, and/or other evidence such as that provided by hand [wrist] and foot radiographs that establishes a history consistent with a diagnosis of active PsA of at least 6 months duration) and currently meet the CASPAR criteria (Attachment 4)

[3] have active PsA defined as the presence of at least 3 of 68 tender and at least 3 of 66 swollen joints as determined by the Tender and Swollen Joint Count Assessment Form at Visit 1 (screening) and Visit 2 (Week 0, baseline)

[4] have been treated with 1 or more cDMARDs (MTX, SSZ, leflunomide, hydroxychloroquine, or cyclosporine) and had a documented inadequate response (in a minimum of 12 weeks of therapy) or intolerance

[5] have active psoriatic skin lesions (plaque) or a documented history of plaque psoriasis

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

8.2. Exclusion Criteria

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

[7] have received any previous treatment or are currently receiving treatment with any biologic or small-molecule therapy for PsA or psoriasis, including investigational therapies (such as but not limited to TNF inhibitors, IL-1 receptor antagonists, IL-6 inhibitor, anti–IL-12/23p40, T-cell or B-cell targeted therapies, or Janus kinase inhibitors). Exception: previous treatment of phosphodiesterase type 4 inhibitors will be permitted. Treatment with phosphodiesterase type 4 inhibitors must be discontinued at least 8 weeks before baseline (Week 0, Visit 2).

[8] have previously completed or withdrawn from this study or any other study investigating ixekizumab or other IL-17 inhibitors, for example, anti–IL-17 or anti–IL-17 receptor monoclonal antibodies

[9] have history of drug-induced psoriasis

[10] have had, in the opinion of the investigator, inadequate response to treatment with ≥4 cDMARDs or immune modifiers (such as MTX, leflunomide, azathioprine, cyclosporine, hydroxychloroquine, gold salts, or SSZ) prescribed alone or in combination for a minimum of 3 months

[11] have used DMARDs other than MTX, leflunomide, SSZ, or hydroxychloroquine (for example, gold salts, cyclosporine, azathioprine, dapsone, 6 mercaptopurine, mycophenolate mofetil, or any other immunosuppressive agents) in the 8 weeks before baseline (Week 0, Visit 2)

Have discontinued MTX or SSZ within the 8 weeks before baseline or hydroxychloroquine within 12 weeks before baseline

If taking MTX, leflunomide, SSZ, or hydroxychloroquine, must have been treated for at least 12 weeks before baseline and on stable dosages for at least 8 weeks before baseline as follows: oral or parenteral MTX = up to 25 mg/wk, leflunomide = up to 20 mg/d, SSZ = up to 3 g/d, or hydroxychloroquine = up to 400 mg/d. Local standard of care should be followed for concomitant administration of folic acid with MTX.

[12] are receiving treatment with more than 1 cDMARD (MTX, leflunomide, SSZ, hydroxychloroquine, or cyclosporine) at study entry. Note: Under no circumstances will simultaneous use of MTX and leflunomide be allowed at any time during the study for safety reasons.

[13] have discontinued leflunomide within 4 weeks before baseline or have received leflunomide from 4 to 12 weeks before baseline (Week 0, Visit 2) and have not undergone a drug elimination procedure

[14] use of oral corticosteroids at average daily doses of >10 mg of prednisone or its equivalent or use of variable dosages of any oral corticosteroids within 4 weeks before baseline (Week 0, Visit 2)

[15] have received any parenteral glucocorticoid administered by intraarticular, intramuscular, or intravenous (IV) injection within 6 weeks before baseline (Week 0, Visit 2) or anticipate a parenteral injection of glucocorticosteroids during the initial open-label treatment period (Period 2) of the study

[16] are using concomitant NSAIDs, including cyclooxygenase-2 inhibitors, unless the patient is on a stable dosage for at least 2 weeks before baseline (Week 0, Visit 2)

[17] within 6 weeks before baseline (Week 0, Visit 2) have used any opiate analgesic at average daily doses of >30 mg of morphine or its equivalent or have used variable dosages of any opiate analgesic

[18] have received systemic nonbiologic psoriasis therapy other than DMARDs or corticosteroids as indicated above (including but not limited to oral psoralens and ultraviolet A light therapy, oral retinoids, thioguanine, hydroxyurea, fumaric acid derivatives, or topical 1,25 dihydroxy vitamin D3 and analogues) or phototherapy (including either oral and topical psoralens and ultraviolet A, ultraviolet B, or self-treatment with tanning beds/booths or therapeutic sunbathing) within 4 weeks before baseline (Week 0, Visit 2)

OR had topical psoriasis treatment within 2 weeks before baseline (Week 0, Visit 2). Exceptions: weak potency (World Health Organization [WHO] Group 1 classification) topical steroids will be permitted.

[19] for those patients with plaque psoriasis, cannot avoid use of tanning beds/booths for at least 4 weeks before baseline (Week 0, Visit 2) and during the study

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

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

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

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

[23] had a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months before 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

[24] have a diagnosis of other inflammatory arthritic syndromes such as RA, ankylosing spondylitis, reactive arthritis, or enteropathic arthritis

[25] have active Crohn's disease or active ulcerative colitis

[26] have a current diagnosis of fibromyalgia

[27] have a chronic pain condition that would confound evaluation of the patient

[28] have evidence of active vasculitis or uveitis

[29] have had surgical treatment of a joint within 8 weeks before baseline or will require such up to Week 24

[30] have had any major surgery that in the opinion of the investigator and in consultation with Lilly or its designee would pose an unacceptable risk to the patient within 8 weeks before baseline or will require such during the study

[31] have current lymphoproliferative disease or a history of it

[32] have diagnosis or history of malignant disease within 5 years before baseline (Week 0, Visit 2). Note: Patients with successfully treated basal-cell carcinoma (no more than 3) or squamous-cell carcinoma of the skin (no more than 2) within the 5 years before baseline may participate in the study

[33] have significant uncontrolled cerebrocardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic, or neuropsychiatric disorders (for example, myocardial infarction, unstable angina, unstable arterial hypertension, moderate to severe [New York Heart Association class III/IV] heart failure, or cerebrovascular accident); abnormal laboratory values; or use of illicit drugs (including cannabinoids, whether legalized or not) 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

[34] have a history of uncompensated heart failure, fluid overload, or myocardial infarction or have evidence of new-onset ischemic heart disease or other serious cardiac disease within 12 weeks before baseline (Week 0, Visit 2)

[35] have history of suicide attempt, have a score of 3 on Item 12 (Thoughts of Death or Suicide) on the QIDS-SR16 at screening (Visit 1) or at baseline (Week 0, Visit 2), or are clinically judged by the investigator to be at risk for suicide

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

[37] have or had an opportunistic infection characteristic of an immunocompromised host and/or that occurs with increased incidence in an immunocompromised host (including but not limited to *Pneumocystis jiroveci* pneumonia, histoplasmosis, coccidioidomycosis, or cryptococcosis) or have a known immunodeficiency

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

[39] have evidence of or suspicion of active or latent TB (refer to Section 10.3.2.3 for details on determining full TB exclusion criteria)

[40] within 4 weeks of baseline (Week 0, Visit 2), have any active or recent infection other than those mentioned above 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 once ≥4 weeks after documented resolution of symptoms

[41] have body temperature ≥38°C (100.5°F) at baseline (Week 0, Visit 2); these patients may be rescreened once ≥4 weeks after documented resolution of temperature ≥38°C (100.5°F)

[42] have uncontrolled arterial hypertension characterized by a sitting systolic blood pressure (BP) >160 mm Hg or diastolic BP >100 mm Hg at baseline (Week 0, Visit 2)

Note: Determined by 2 consecutive readings. If an initial sitting 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.

[43] are positive for human immunodeficiency virus serology, that is, positive for human immunodeficiency virus antibody

[44] have evidence of or test positive for hepatitis B by any of the following criteria: (1) positive for hepatitis B surface antigen (HBsAg+); (2) positive for anti–hepatitis B core antibody (HBcAb+) and negative for anti–hepatitis B surface antibody (HBsAb–); (3) positive for HBcAb+ and positive for anti–hepatitis B surface antibody (HBsAb+) with concentration of HBsAb <200 mIU/mL; or (4) HBcAb+, HBsAb+ (regardless of HBsAb level), and positive for serum hepatitis B virus (HBV) DNA

(Note: Patients who are negative for hepatitis B surface antigen (HBsAg–), HBcAb+, HBsAb+ with a concentration of HBsAb ≥200 mIU/mL, and negative for serum HBV DNA may participate in the study. Patients who meet these criteria at screening must be monitored during the study as detailed in Section 10.3.3.4.

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

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

[46a] neutrophil count <1500 cells/μL (<1.50 × 10^3/μL or <1.50 GI/L)

[46b] lymphocyte count <800 cells/μL (<0.80 × 10^3/μL or <0.80 GI/L)

[46c] platelet count <100,000 cells/μL (<100 × 10^3/μL or <100 GI/L)

[46d] aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level >2.5 times (x) the upper limit of normal (ULN).

(Note: The AST and ALT tests may be repeated once within a week if the initial response exceeds this limit, and the repeat value may be accepted if it is within the limit).

[46e] total white blood cell (WBC) count <3000 cells/μL (<3.00 × 10^3/μL or <3.00 GI/L)

[46f] hemoglobin level <8.5 g/dL (85.0 g/L) for male patients and <8.0 g/dL (80 g/L) for female patients

[46g] serum creatinine level >2.0 mg/dL (177µmol/L).

Note: Laboratory tests should not be repeated unless there is a technical error or clinical reason to believe a result may be erroneous.

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

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

[49] have donated blood of more than 1 unit (approximately 500 mL) within the last 4 weeks or intend to donate blood during the course of the study

[50] are women who are lactating or breastfeeding

[51] 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.

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

[53] are currently enrolled in a clinical trial involving an investigational product or nonapproved use of a drug or device (other than the investigational product used in this study) or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

[54] have been 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 at least 5 half-lives of the last administration of the drug, whichever is longer

8.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion criteria [7] through [49], [53], and [54] 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 [50] provides protection to offspring. Exclusion criteria [51] and [52] 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. Discontinuations

8.3.1. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor clinical research physician and the investigator to determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the Lilly clinical research physician agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without investigational product if the Lilly clinical research physician does not agree with the investigator's determination that it is medically appropriate for the subject to continue. The investigator must obtain documented approval from the Lilly clinical research physician to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

For any patient discontinued from the study and who has received at least 1 dose of investigational product, the investigational product will be withheld, and the patient will complete the ETV and the posttreatment follow-up period (Period 4) as shown in the study schedule (Attachment 1).

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

8.3.1.1. Discontinuation Criteria

- Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a patient meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:
  - ALT or AST level >8× ULN
  - ALT or AST level >5× ULN for more than 2 weeks
  - ALT or AST level >3× ULN and total bilirubin level >2× ULN or prothrombin time >1.5 × ULN
  - ALT or AST level >3× ULN with fatigue, nausea, vomiting, abdominal right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - alkaline phosphatase (ALP) level >3× ULN
  - ALP level >2.5× ULN and total bilirubin >2× ULN
    - ALP level >2.5× ULN with fatigue, nausea, vomiting, abdominal right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- neutrophil (segmented) counts (see safety monitoring for neutropenia in 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) (from 2 test results; the second test must be 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) (from 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 × 103/μL or <2.00 GI/L)
- lymphocyte count <500 cells/μL (<0.50 × 10^3/μL or <0.50 GI/L)
- platelet count <50,000 cells/μL (<50 × 10^3/μL or <50 GI/L)
- changes in BP defined as sitting systolic BP at ≥160 mm Hg plus ≥20 mm Hg increase from baseline (Week 0, Visit 2) and/or diastolic BP at ≥100 mm Hg plus ≥10 mm Hg increase from baseline that do not respond after maximal allowed intervention (Section 10.3.3.2)
- If the investigator decides that the patient should be withdrawn because of an SAE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately. Refer to Safety Evaluations, Section 10.2.7).
- clinically significant systemic hypersensitivity reaction after subcutaneous (SC) administration of investigational product
- the patient becomes pregnant
- The patient develops a malignancy. Note: Patients may be allowed to continue if they develop no more than 2 nonmelanoma skin cancers over any 12-month period during the study.
- Any positive TB test that indicates TB test conversion since prior testing (based on patient medical history or Visit 1 screening test), AND the patient does not receive appropriate treatment for latent TB; or there is evidence of active TB infection at any time (see Section 10.3.2.3)
- the patient develops symptoms suggestive of a lupus-like syndrome or is positive for antibodies against double-stranded DNA
- If the patient for any reason requires treatment with another therapeutic agent that has been demonstrated to be effective for the treatment of PsA or psoriasis before the posttreatment follow-up period, discontinuation from the study must occur before introduction of the new agent. For patients who completed or discontinued study treatment and have entered the posttreatment follow-up period (Period 4), PsA therapy with another agent is allowed, as determined appropriate by the investigator.
- enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- 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 subject is to be discontinued from the study.

- failure to demonstrate at least a 20% improvement from baseline in both TJC and SJC at Week 24 or at any subsequent visit through Week 104 except from the point of randomization until the visit after relapse for those patients who are randomized in Period 3
- the investigator decides that the patient should be withdrawn from the study
- the patient requests to be withdrawn from the study
- Lilly or its designee stops the patient's participation in the study or Lilly stops the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- 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 10.3.3.4.

If a patient is noncompliant with study procedures and/or study drug administration (see Section 12.2.5), the investigator should assess the patient to determine the reason for noncompliance and educate and/or manage the patient as appropriate to improve compliance. If in consultation with Lilly or its designee the noncompliance is deemed to be significant or if further noncompliance occurs, the patient should be discontinued from the study.

Any patient who discontinues the study for any reason will stop treatment and continue to the ETV before entering the posttreatment follow-up period (Period 4).

8.3.2. Patients 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.

8.3.3. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the IRB/ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

8.3.4. Discontinuation of the Study

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

9. Treatment

9.1. Treatments Administered

During the initial open-label treatment period (Period 2), all patients will receive ixekizumab 80 mg Q2W (Table RHBF.1). The randomized double-blind withdrawal period (Period 3) involves a comparison of ixekizumab 80 mg Q2W with placebo for those patients who meet randomization criteria based on Coates Criteria for MDA. Patients who do not meet randomization criteria will receive ixekizumab 80 mg Q2W for the duration of Period 3 (Table RHBF.1). All doses are administered as SC injections.

Table RHBF.1. Treatment Regimens

Treatment Group	Description
Initial Open-Label Treatment Period (Period 2)	
80 mg ixekizumab Q2W	Starting dose of 160 mg of ixekizumab will be given as 2 SC injections at Week 0 followed by 80 mg given as 1 SC injection Q2W from Week 2 to Week 36
Randomized Double-Blind Withdrawal Period (Period 3)	
80 mg ixekizumab Q2W	80 mg given as 1 SC injection Q2W any time from Week 36 to Week 104
Placebo	Placebo given as 1 SC injection Q2W any time from Week 36 to Week 104

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

The investigator or his/her designee is responsible for

- explaining the correct use of the investigational agent(s) to the patient and/or patient's caregiver,
- 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.

Patients will be instructed to contact the investigator as soon as possible if they have complaints or problems with the investigational product so that the situation can be assessed.

Further instructions regarding administration of the investigational products are provided in Section 9.5.1 and 9.5.2.

9.1.1. Administration of Investigational Product

Injections will be administered SC by the patient or caregiver after training by the clinical staff.

Training: At Week 0 (baseline, Visit 2) each patient is scheduled to receive 2 injections of ixekizumab 80 mg. For training purposes, the proper procedures for administration of the initial injection will be performed by clinical staff and the second injection of investigational product at that visit will be administered by the patient or caregiver under the supervision of clinical staff.

If additional training is necessary, an injection may be administered by the patient or caregiver under the supervision of clinical staff at Week 2 (Visit 3).

Administration: If the patient is unable to perform the injection, a caregiver, who will also be trained under supervision of site staff, may administer the investigational product. All subsequent injections will be administered by the patient or caregiver and should be administered unsupervised by the clinical staff. It is recommended that for these subsequent injections, the patient or caregiver administer the investigational product outside the trial site, preferably at the patient's home. If the patient or caregiver is not able to administer the second injection of the starting dose, or any dose through the study, study site personnel may administer that injection.

Refer to the appropriate *Manual Syringe Directions for Use* provided by the sponsor for the investigational product. Note that injections should not be given in the same arm from which immunogenicity samples are being drawn at relevant visits.

Study drug administration logs will be dispensed to each patient as needed for recording pertinent data about each injection; details of the use of these logs is provided in Section 9.5.2.

Observation: Patients should remain under observation for at least 1 hour after dosing at Week 0 (baseline, Visit 2) for safety monitoring because patients will be receiving ixekizumab for the first time at this visit. This allows for observation for any AEs and collection of postinjection sitting BP and pulse measurements approximately 1 hour after administration of the investigational product (Section 10.3.2.4 and Attachment 1).

9.2. Materials and Supplies

The investigational products will be supplied by the sponsor or its designee in accordance with current good manufacturing practices and will be supplied with lot numbers, expiry dates, and certificates of analysis, as applicable.

Ixekizumab and Placebo to Match (excipients only) will be supplied as injectable solutions in 1-mL, single-dose, disposable manual, prefilled syringes with study-specific labels. Each syringe of ixekizumab is designed to deliver ixekizumab 80 mg. The syringes (and contents) containing either ixekizumab or matching 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.

The investigational product should be stored at 2°C to 8°C (36°F to 46°F) and in its original carton to protect it from light. Sites will be required to monitor temperature of the on-site storage conditions of the syringes.

Study drug administration logs will be dispensed to each patient as needed for recording pertinent data about each injection; details of the use of these logs are provided in Section 9.5.2.

9.3. Method of Assignment to Treatment

Patients who meet the eligibility criteria for randomization any time from Week 36 through Week 64 will be randomized to double-blind treatment groups as 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. Patients will be stratified by geographic region and cDMARD use at the time of randomization in Period 3.

9.4. Rationale for Selection of Doses in the Study

Rationale for the 80-mg Q2W Dose Regimen: The 80-mg Q2W dose regimen has been selected for evaluation in Study RHBF. In Study RHAK, the Phase 2 dose-ranging study in patients with RA, a dose-response relationship was detected for ACR20 at the Week 12 primary endpoint across the dose range tested (3-, 10-, 30-, 80-, and 180-mg ixekizumab Q2W) in the bDMARD-naive population. In that study, 80- and 180-mg ixekizumab Q2W doses demonstrated significantly better ACR20 responses compared to placebo in the TNF-IR population. Similar to ACR20 responses, a dose-related reduction in the mean change from baseline in DAS28-CRP was observed with increasing doses of ixekizumab at Week 12 in both patient populations. Numerically higher ACR20 and DAS28-CRP responses were observed at the 180-mg Q2W dose level compared to all other doses across most time points in the 12-week time course in both patient populations. This was evident from the ACR20 and DAS28-CRP responses observed within the first week of the study as well as the consistency in clinical efficacy compared to other doses, which was maintained up to the Week 12 time point. The ACR20 and DAS28-CRP response rates for the 80-mg Q2W dose begin to approximate the responses for the 180-mg Q2W dose around Week 12. Results for the mean ACR-N responses in both populations were consistent with those observed for the ACR20 and DAS28-CRP responses. Given that the 80-mg Q2W and 180-mg Q2W dose regimens appear to demonstrate similar ACR20 and DAS28-CRP response rates around Week 12 in both bDMARD-naive and TNF-IR patient populations, Lilly believes that evaluating an 80-mg Q2W dose in Phase 3 studies in patients with PsA may provide close to maximal efficacious response while reducing the overall exposure to ixekizumab.

Rationale for the 160-mg Starting Dose: A starting dose of 160 mg ixekizumab will be used to achieve steady state concentrations earlier and allow a rapid onset of responses.

According to PK analyses conducted with pooled data from clinical trials in psoriasis patients, over 80% of the steady state drug exposure of 80 mg Q2W regimen was achieved after the 160-mg starting dose.

In Study RHAK, the 180-mg dose demonstrated the greatest magnitude of ACR20 and DAS28-CRP responses at Week 1 in both the bDMARD-naive and TNF-IR populations. Similarly, in Study I1F-MC-RHAJ (RHAJ), the 150-mg dose demonstrated the greatest magnitude of PASI responses at Week 2 in patients with psoriasis. This early onset of efficacy is hypothesized to be related to the increased IL-17 neutralization at higher doses of ixekizumab.

Therefore, 160-mg ixekizumab used as a starting dose at Week 0 should provide an early onset of clinical responses in PsA similar to the ACR20 and DAS28-CRP responses observed with the first dose of 180-mg ixekizumab in Study RHAK and of PASI response similar to that observed with the first 150-mg dose in Study RHAJ.

9.5. Selection and Timing of Doses

Patients are assigned to treatment (Section 9.3) and will receive their assigned treatments as outlined in Sections 9.1 and 9.1.1.

Investigational product should be administered at approximately the same time each day as much as possible. For injections not administered on the scheduled day of the week, the missed dose should be administered within 4 days of the scheduled day or as close as possible to the scheduled day and within the visit window as allowed according to the study schedule (Attachment 1). Dates of subsequent study visits should not be modified because of this delay.

Study drug administration logs will be dispensed to each patient as needed for recording pertinent data about each injection; details of the use of these logs are provided in Section 9.5.2.

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 requirements and restrictions 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/hypersensitivity reactions**. Clinical manifestations of these reactions may include, but are not limited to:

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

Proteins may also cause redness, itching, swelling, or pain locally at the injection site.

Sometimes these reactions can be life-threatening. 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 after an injection. If a patient experiences an acute allergic or hypersensitivity reaction after an injection of investigational product, he or she should be managed appropriately and given instruction to receive relevant supportive care. Additionally, for an event judged by the investigator to be a potential systemic allergic or hypersensitivity reaction, a blood sample should be drawn to test for anti-drug antibodies as soon as feasible.

For patients who experience a potential allergic or hypersensitivity reaction, consideration for any premedication for future injections will be agreed upon between the investigator and sponsor. Examples of potential allergic or hypersensitivity reactions that might merit premedication include mild to moderate skin rashes, mild to moderate generalized pruritus and/or urticaria, and mild to moderate injection-site reactions (for example, injection-site erythema, injection-site pruritus). Patients who develop clinically significant systemic allergic or hypersensitivity reactions after administration of investigational product (for example, a reaction that causes 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 or paracetamol up to 1000 mg and antihistamines (for example, oral diphenhydramine 50 mg); premedications should be given after all efficacy assessments have been completed for a given visit and 30 to 60 minutes before investigational product SC injection for visits where injections are administered at the clinic. For all other injections, patients may self-premedicate at home before administration of investigational product as directed by the investigator. All such premedications will be recorded as concomitant therapy. Corticosteroids are not permitted as agents for premedication.

9.5.2. Use of Study Drug Administration Log

A study drug administration log will be completed for each injection throughout all patients' participation in the study per the study schedule (Attachment 1).

The study drug administration log collects information on the date, time, and anatomical location of administration (for treatment compliance); syringe number; the person who administered the investigational product (patient, study staff, or caregiver); and whether the investigational product was fully administered and, if not, the appropriate reason(s) from the list provided:

1) study drug leaked from syringe/device
2) study drug leaked from injection site
3) hard to hold
4) syringe/device jammed during injection
5) study drug administration instructions difficult to understand
6) other

Patients will be instructed to contact their study sites in the event of an injection problem. In addition, site personnel will review all study drug administration logs at each visit to identify any product complaints, and they will complete a product complaint form for each operation failure reported on a study drug administration log (see Section 10.3.4 for additional instructions regarding complaint handling).

9.6. Continued Access to Investigational Product

Investigational product will not be made available after conclusion of the study to patients.

9.7. Blinding

In the randomized double-blind withdrawal period (Period 3), patients and study site personnel will be blinded to study treatment assignment (ixekizumab 80 mg Q2W or placebo). 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.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly clinical research physician before unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

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 posttreatment 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 clinical research physician or representative for the patient to continue in the study.

Unblinding will be performed through the IWRS. All transactions resulting in an unblinding event are recorded and reported by the IWRS.

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 PsA and coexisting psoriasis therapies during the study is permitted only as outlined in the exclusion criteria (Section 8.2) and as described in the paragraphs below. Patients taking permitted medications should be on chronic stable dosages at baseline (Week 0, Visit 2) as specified in Section 8.2.

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

- PsA and coexisting psoriasis therapies that are excluded as described in the exclusion criteria (Section 8.2)
- any therapy within the washout periods specified in exclusion criteria (Section 8.2)
- live vaccines (including BCG)
- phototherapy

The following medications *will* be permitted during the course of the study (but note restrictions):

NSAIDs and analgesics: NSAIDs, including cyclooxygenase-2 inhibitors, will be allowed up to the maximum recommended dosages for pain. Nonopioid analgesics (for example, acetaminophen or paracetamol) up to the maximum recommended dosages for pain may be administered on an as-needed basis during the study but should be withheld within 24 hours of a visit. Aspirin (dosage not exceeding 350 mg/d) may be taken to manage cardiovascular risk.

During the initial open-label treatment period (Period 2), any dosage adjustment, change of NSAIDs, and/or introduction of a new NSAID may be made. For patients who are not randomized during the randomized double-blind withdrawal period (Period 3), any dosage adjustment, change of NSAIDs, and/or introduction of a new NSAID may continue to be made throughout Period 3. For patients who are randomized during Period 3, dosage adjustment, change of NSAIDs, and/or introduction of a new NSAID may *not* be made until the point of relapse (if relapse occurs). Any changes must be recorded on the concomitant medication CRF.

During study Periods 2 and 3, the use of variable doses of opiate analgesics is allowed but may not exceed an average daily dose of 30 mg morphine or its equivalent. Any changes must be recorded on the concomitant medication CRF.

Conventional DMARDs: During the initial open-label treatment period (Period 2), alteration of cDMARD dosage and/or introduction of a new cDMARD are permitted. For patients who are not randomized during the randomized double-blind withdrawal period (Period 3), alteration of cDMARD dosage and/or introduction of a new cDMARD may continue to be made throughout Period 3. For patients who are randomized during Period 3, alteration of cDMARD dosage and/or introduction of a new cDMARD may *not* be made until the point of relapse (if relapse occurs). If, at any time, the investigator believes that side effects or laboratory abnormalities may be attributable to the cDMARD, the cDMARD dosage should be lowered or the medication should be stopped. In this case, reintroduction of the cDMARD may occur when the investigator deems clinically appropriate. Not more than 1 adjustment of cDMARDs within 12 weeks is recommended. Any changes must be recorded on the concomitant medication CRF.

The maximum allowed dosage during the study is 25 mg/wk for MTX, 400 mg/d for hydroxychloroquine, 20 mg/d for leflunomide, and 3 g/d for SSZ. The local standard of care should be followed for concomitant administration of folic acid if MTX is taken and for administration of other cDMARDs. Under no circumstances will simultaneous use of MTX and leflunomide be allowed at any time during the study for safety reasons.

Topical steroids: Topical steroids of weak potency (WHO Group 1 classification) will be permitted for use as needed during the study. More-potent topical steroids may be used, as needed, for an individual patient except from the point of randomization to the point of relapse (if relapse occurs). These topical medications should not be used within approximately 24 hours before study visits requiring static Physician's Global Assessment of psoriasis (sPGA) and PASI measures.

Other topical therapies: The following will be allowed as needed: shampoos that do not contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues; topical moisturizers or emollients and other nonprescription topical products that do not contain urea, >3% salicylic acid, α- or β-hydroxyl acids, corticosteroids, or vitamin D3 analogues; bath oils and oatmeal bath preparations. These topical therapies are not to be used within 12 hours before a study visit. Shampoos that contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues may be used, as needed, for an individual patient except from the point of randomization to the point of relapse (if relapse occurs).

Oral corticosteroids: During the initial open-label treatment period (Period 2), adjustments of oral corticosteroids (for example, dose change, introduction) are allowed. The maximum dosage is not to exceed 10 mg/d of prednisone or its equivalent at any time during this period.

During the randomized double-blind withdrawal period (Period 3), adjustments of oral corticosteroids are allowed for an individual patient but are strongly discouraged from the point of randomization to the point of relapse (if relapse occurs). The maximum dosage is not to exceed 10 mg/d of prednisone or its equivalent at any time during these periods.

IV, intramuscular, soft tissue (bursa, tendons, and ligaments) and intra-articular corticosteroids: Treatment with any parenteral corticosteroids is not permitted within 6 weeks before baseline or during the study.

However, except from the point of randomization to the point of relapse (if relapse occurs), intra-articular injection of a corticosteroid may be allowed on a limited basis: it is recommended that there be no more than 1 injection within any 1-year period (1 injection = 1 large joint or up to 5 small joints or 1 soft tissue). The joint(s) injected must be designated along with the medication taken on the concomitant medications CRF and must be recorded as unevaluable on the TJC/SJC assessment CRF.

Inhaled steroids: Regular use of inhaled steroids for asthma or nasal corticosteroids for allergies will be permitted during the study.

Additional guidance: Patients requiring surgery at any time during the study should interrupt administration of the investigational product beginning 8 weeks prior to the surgery, or as early as possible within 8 weeks of surgery, and resume administration of the Investigational product only after complete wound healing.

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, 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 allowed 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. Unless urgent medication is indicated by the patient's medical condition, 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 study instructions. The investigator is responsible for discussing methods to ensure high treatment compliance with the patient before randomization.

Patients will record the date and time of administration of investigational product in a study drug administration log throughout their participation in the study (see also Section 9.5.2). The data from the study drug administration log must be transcribed into the electronic case report form (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. Deviation(s) from the prescribed dosage regimen should be documented in the CRF.

If a patient is noncompliant with study procedures and/or study drug administration (see Section 12.2.5), the investigator should assess the patient to determine the reason for noncompliance and educate and/or manage the patient as appropriate to improve compliance. If, in consultation with Lilly or its designee, the noncompliance is deemed to be significant or if further noncompliance occurs, the patient should be discontinued from the study.

10. Efficacy, Health Outcome 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, a list of the specific planned laboratory tests to be performed for this study is provided in Attachment 2.

10.1. Efficacy Measures

10.1.1. Primary Efficacy Measures

The primary objective is to compare ixekizumab 80 mg Q2W with placebo in maintenance of treatment outcome, as measured by the time to relapse during the randomized double-blind withdrawal period in cDMARD-IR and bDMARD-naive patients with active PsA who met Coates criteria for MDA.

10.1.1.1. Coates Criteria for Minimal Disease Activity

The Coates criteria for MDA (described below) has been developed on the basis of current expert opinion and uses a composite of 7 key outcome measures used in PsA to encompass all of the domains of the disease to measure the overall state of a patient's disease (Coates et al. 2010; Coates and Helliwell 2010). The criteria were developed specifically for PsA and have been validated in observational and interventional cohorts. The Coates criteria for MDA have evidence supporting their use within the OMERACT filter of truth, discrimination, and feasibility. In a retrospective analysis of infliximab in PsA, the criteria were shown to be discriminative between drug and placebo and there was a strong association between achieving MDA and achievement of the ACR outcomes, reductions in inflammatory markers, and physician opinion of disease activity (Coates and Helliwell 2010). Patients who maintain Coates Criteria for MDA for 38 Weeks or more have better long-term functional improvement, patient global assessment, and radiography outcomes after 5 years (Kavanaugh et al. 2015). In addition, MDA has been recently advocated as a feasible and clinically relevant treatment target in clinical practice (Coates and Helliwell 2015) that is acceptable for patients and physicians (Coates et al. 2012). The duration of treatment needed to achieve MDA is variable; as many as 52% of patients meet the Coates criteria for MDA within 6 months of starting a TNF inhibitor, but even higher percentages meet the criteria at 1 year or more (Coates and Helliwell 2010; Haddad et al. 2015).

Two version of the MDA have been defined. The Coates criteria for MDA will be used to determine randomization eligibly and for the primary analysis. Modified Coates criteria for MDA that use the sPGA in place of the PASI will be used as a secondary analysis. The criteria are:

- Coates criteria for MDA: Patients are classified as achieving MDA if they fulfill 5 of 7 outcome measures:
  - TJC ≤1
  - SJC ≤1
  - PASI total score ≤1 or BSA ≤3
  - patient pain VAS score of ≤15
  - patient global disease activity VAS score of ≤20
  - HAQ-DI score ≤0.5
  - tender entheseal points ≤1
- modified Coates criteria for MDA: For the modified criteria for MDA, sPGA "skin clear" or "skin almost clear" (as MDA-sPGA [0,1]) is substituted for PASI ≤1 (Mease et al. 2013).

10.1.2. Secondary Efficacy Measures

10.1.2.1. Tender and Swollen Joint Counts (68 and 66 Joints)

10.1.2.1.1. Tender Joint Count

For ACR measures, the number of tender and painful joints will be determined by examination of 68 joints (34 joints on each side of the patient's body). The 68 joints to be assessed and classified as tender or not tender are detailed in Attachment 5. Any joints that require intra-articular injections during the study (according to Section 9.8) should be excluded from evaluation from the time of the injection to the conclusion of the study.

Joints will be assessed for tenderness by pressure and joint manipulation on physical examination. The patient will be asked for pain sensations on these manipulations and watched for spontaneous pain reactions. Any positive response on pressure, movement, or both will then be translated into a single tender-versus–not tender dichotomy.

Joint assessments will be performed by an independent, blinded assessor to minimize bias. The same assessor should perform the TJC and SJC for a given patient if possible, particularly during the initial open-label treatment period (Period 2) to minimize interobserver variation. The blinded joint assessor will not be involved in patient care and is asked not to discuss disease activity or treatment with patients or principal investigator.

Missing, replaced, ankylosed, or arthrodesed joints will be identified by the investigator at the screening visit and will be excluded from evaluation during the trial.

10.1.2.1.2. Swollen Joint Count

For ACR measures, the number of swollen joints will be determined by examination of 66 joints (33 joints on each side of the patient's body). The 66 joints to be assessed and classified as swollen or not swollen are detailed in Attachment 5. Any joints that require intra-articular injections during the study (according to Section 9.8) should be excluded from evaluation from the time of the injection to the conclusion of the study.

Joints will be classified as either swollen or not swollen. Swelling is defined as palpable fluctuating synovitis of the joint. Swelling secondary to osteoarthritis will be assessed as not swollen unless there is unmistakable fluctuation. Dactylitis should be counted as 1 joint.

Missing, replaced, ankylosed, or arthrodesed joints will be identified by the investigator at the screening visit and will be excluded from evaluation during the trial.

Joint assessments will be performed by an independent, blinded assessor to minimize bias. The same assessor should perform the TJC and SJC for a given patient if possible, particularly during the initial open-label treatment period (Period 2) to minimize interobserver variation. The blinded joint assessor will not be involved in patient care and is asked not to discuss disease activity or treatment with patients or principal investigator.

10.1.2.2. Patient's Assessment of Pain Visual Analog Scale

The patient will be asked to assess his or her current level of joint pain by marking a vertical tick on a 100-mm horizontal VAS where the left end represents no joint pain and the right end represents worst possible joint pain. The Patient's Assessment of Pain VAS should be administered *before* the TJC and SJC examinations.

Results will be expressed in millimeters measured between the left end of the scale and the crossing point of the vertical line of the tick; *this procedure is applicable for all VAS used in the trial.*

10.1.2.3. Patient's Global Assessment of Disease Activity Visual Analog Scale

The patient's overall assessment of his or her PsA activity will be recorded using the 100-mm horizontal VAS where the left end represents no disease activity and the right end represents extremely active disease activity.

10.1.2.4. Patient's Assessment of Physical Function Health Assessment Questionnaire–Disability Index

The HAQ-DI is a patient-reported standardized questionnaire that is commonly used in PsA to measure disease-associated disability (assessment of physical function). It consists of 24 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other daily activities (Fries et al. 1980; Fries et al. 1982).

The disability section of the questionnaire scores the patient's self-perception on the degree of difficulty (0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do), covering the 8 domains. The reported use of special aids or devices and/or the need for assistance of another person to perform these activities is also assessed. The scores for each of the functional domains will be averaged to calculate the functional disability index.

A minimally clinical important difference minimally clinical important difference is a clinically relevant change in a patient's status. The HAQ-DI minimally clinical important difference has been estimated to be about 0.35 for patients with PsA (Mease et al. 2011). Details of scoring and calculations are presented in the statistical analysis plan (SAP).

10.1.2.5. Psoriasis Area and Severity Index

If the patient has plaque psoriasis, the PASI will be administered by site personnel. The PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque induration/infiltration (thickness) in each region, yielding an overall score of 0 for no psoriasis to 72 for the most severe disease (Fredriksson and Pettersson 1978). Patients achieving PASI 75, PASI 90, or PASI 100 are defined as having an improvement of at least 75%, 90%, or 100%, respectively, in PASI score from baseline.

10.1.2.6. Percentage of Body Surface Area

The investigator will evaluate the percentage of involvement of psoriasis on each patient's BSA on a continuous scale from 0% = no involvement to 100% = full involvement, where 1% corresponds to the size of the patient's handprint including the palm, fingers, and thumb (National Psoriasis Foundation 2009).

10.1.2.7. Static Physician's Global Assessment

If the patient has plaque psoriasis, the sPGA will be administered by site personnel. The sPGA is the physician's determination of the patient's psoriasis lesions overall at a given time point. The sPGA is recommended as an endpoint to use to assess efficacy in the treatment of psoriasis (EMEA 2004). Overall lesions are categorized by descriptions for induration, erythema, and scaling. For the analysis of responses, the patient's psoriasis is assessed at a given time point on a 6-point scale in which 0 = cleared, 1 = minimal, 2 = mild, 3 = moderate; 4 = severe, and 5 = very severe.

10.1.3. Exploratory Efficacy Measures

10.1.3.1. American College of Rheumatology Responder Index

Relief of signs and symptoms will be assessed using the ACR Responder Index, a composite of clinical, laboratory, and functional measures in PsA. ACR responses are presented as the minimal numeric percentage improvement from baseline in multiple disease assessment criteria.

ACR20 and American College of Rheumatology 50% (ACR50) and 70% (ACR70) response rates are exploratory efficacy measures for which a patient must have:

- ≥20%, ≥50%, and ≥70% improvements, respectively, in both TJC and SJC
- ≥20%, ≥50%, and ≥70% improvements, respectively, in at least 3 of the following 5 ACR Core Set criteria:
  1. Patient's Assessment of Pain VAS
  2. Patient's Global Assessment of Disease Activity VAS
  3. Physician's Global Assessment of Disease Activity VAS

4. patient's assessment of physical function as measured by the HAQ-DI
5. acute phase reactant as measured by C-reactive protein

10.1.3.2. Physician's Global Assessment of Disease Activity Visual Analog Scale

The investigator will be asked to give an overall assessment of the severity of the patient's current PsA activity using a 100-mm horizontal VAS, where 0 represents no disease activity and 100 represents extremely active disease. The investigator making the assessment must be a rheumatologist or medically qualified physician. The same assessor should perform the Physician's Global Assessment of Disease Activity VAS for a given patient if possible, to minimize interobserver variation.

10.1.3.3. Leeds Enthesitis Index

If the patient has enthesitis, an assessment of 18 entheseal points will be performed by site personnel, and from this assessment the Leeds Enthesitis Index (LEI) will be evaluated. The LEI has been developed specifically for use in PsA. The LEI measures enthesitis at 6 sites (lateral epicondyle [left and right], medial femoral condyle [left and right], and Achilles tendon insertion [left and right]) (Healy and Helliwell 2008). Each site is assigned a score of 0 (absent) or 1 (present); the results from each site are then added to produce a total score (range: 0 to 6).

The LEI will be administered by an independent assessor to minimize bias. The assessor will not be involved in patient care and is asked not to discuss disease activity or treatment with patients or principal investigator.

10.1.3.4. Spondyloarthritis Research Consortium of Canada Enthesitis Index

If the patient has enthesitis, an assessment of 18 entheseal points will be performed by site personnel, and from this assessment the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index will be evaluated. The SPARCC enthesitis index evaluates tenderness in a total of 16 enthesitis sites: the greater trochanter (right and left), quadriceps tendon insertion into the patella (right and left), patellar ligament insertion into the patella and tibial tuberosity (right and left), Achilles tendon insertion (right and left), plantar fascia insertion (right and left), medial and lateral epicondyles (right and left), and the supraspinatus insertion (right and left) (Mease 2011). Tenderness at each site is quantified on a dichotomous basis: 0 = nontender and 1 = tender. The results from each site are then added to produce a total score (range, 0 to 16).

The SPARCC enthesitis index will be administered by an independent assessor to minimize bias. The assessor will not be involved in patient care and is asked not to discuss disease activity or treatment with patients or principal investigator.

10.1.3.5. Leeds Dactylitis Index–Basic

If the patient has dactylitis, the Leeds Dactylitis Index–Basic (LDI-B) will be administered by site personnel. The LDI-B has been developed to measure the severity of dactylitis. Once the presence of dactylitis is established in each digit, the ratio of the circumference of the affected digit to the circumference of the same digit on the patient's other hand or foot is measured (Helliwell et al. 2005). Each dactylitic digit is defined by a minimum increase of 10% in circumference over the contralateral digit. If the same digits on both hands or feet are thought to

be involved, the clinician will refer to a table of normative values (provided to investigative sites) for a value that will be used to provide the comparison. The calculated ratio is then multiplied by a tenderness score of 0 (not tender) or 1 (tender). Tenderness is assessed in the area between the joints. The results of each digit are then added to produce a total score (range: 0 to 20) (Healy and Helliwell 2007).

The LDI-B will be administered by an independent assessor to minimize bias. The assessor will not be involved in patient care and is asked not to discuss disease activity or treatment with patients or principal investigator.

10.1.3.6. Disease Activity Score Based on C-Reactive Protein

The DAS28-CRP is a measure of disease activity in 28 joints that consists of a composite numerical score using the following variables: TJC, SJC, C-reactive protein (measured in mg/L), and Patient's Global Assessment of Disease Activity recorded by patients on a 100-mm VAS.

For DAS28-CRP, the 28 joints to be examined and assessed as tender or not tender for TJC and as swollen or not swollen for SJC are a subset of those assessed for the TJC and SJC and include 14 joints on each side of the patient's body: the 2 shoulders, the 2 elbows, the 2 wrists, the 10 metacarpophalangeal joints, the 2 interphalangeal joints of the thumb, the 8 proximal interphalangeal joints, and the 2 knees (Smolen et al. 1995). The following equation will be used to calculate the DAS28 (Vander Cruyssen et al. 2005):

$$DAS\ 28 - CRP = 0.56\left(\sqrt{TJC\ 28}\right) + 0.28\left(\sqrt{SJC\ 28}\right) + 0.36\left(\ln\left(CRP + 1\right)\right) + 0.014\left(VAS\right) + 0.96$$

10.1.3.7. Composite Psoriatic Disease Activity Index

The CPDAI is a validated instrument intended to assess composite psoriatic disease activity and response to therapy (Mumtaz et al. 2011). This instrument assesses individual domains involved as well as the global effect of disease in all dimensions by which each patient may be affected. Domains include peripheral arthritis as assessed by the number of tender and swollen joints and the HAQ-DI, skin as assessed by the PASI and the DLQI, enthesitis as assessed by the number of sites with enthesitis and the HAQ-DI, and dactylitis as assessed by the number of digits affected and the HAQ-DI. A modified version that does not include the axial domain is being used in this study. Scores range from 0 to 12; a higher score indicates higher disease activity.

10.1.3.8. Psoriatic Arthritis Disease Activity Score

The PASDAS is a weighted index comprising assessments of joints, function, acute-phase response, quality of life, and patient and physician global assessment of disease by VAS. All VAS scores are 0 mm to 100 mm. The TJC is 68 joints, and the SJC is 66. The score range of the PASDAS is 0 to 10; worse disease activity is represented by higher scores (Helliwell et al. 2013).

10.2. Health Outcome Measures

10.2.1. Itch Numeric Rating Scale

The itch NRS is a patient-administered, 11-point horizontal scale anchored at 0 and 10, on which 0 represents "no itch" and 10 represents "worst itch imaginable." Overall severity of a patient's itching from psoriasis is indicated by circling the number that best describes the worst level of itching in the past 24 hours.

10.2.2. Fatigue Severity Numeric Rating Scale

The fatigue severity NRS is a patient-administered single-item 11-point horizontal scale anchored at 0 and 10, on which 0 represents "no fatigue" and 10 represents "as bad as you can imagine." Patients rate their fatigue (feeling tired or worn out) by circling the single number that describes their worst level of fatigue during the past 24 hours.

10.2.3. Dermatology Life Quality Index

The DLQI is a simple, patient-administered, 10-question, validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Response categories include "not at all," "a lot," and "very much," with corresponding scores of 1, 2, and 3, respectively, and unanswered ("not relevant") responses are scored as 0. The recall period is "over the last week," and totals range from 0 to 30 (less to more impairment); a 5-point change from baseline is considered clinically relevant (Basra et al. 2008).

10.2.4. Medical Outcomes Study 36-Item Short-Form Health Survey

The SF-36 is a 36-item patient-administered measure designed to be a short, multipurpose 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 Mental Component Summary and Physical Component Summary scores. The summary scores range from 0 to 100; higher scores indicate better levels of function and/or better health. Items are answered on Likert scales of varying lengths. The SF-36 version 2 (acute version) will be used, which has a 1-week recall period (Brazier et al. 1992; Ware and Sherbourne 1992).

10.2.5. European Quality of Life–5 Dimensions 5 Level

The EQ-5D 5L is a standardized measure of health status that provides a simple, generic measure of health for clinical and economic appraisal. The EQ-5D 5L consists of 2 components: a descriptive system of the respondent's health and a rating of his/her current health state using a 100-mm VAS. The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box associated with the most appropriate statement in each of the 5 dimensions. It should be noted

that the numerals 1 to 5 have no arithmetic properties and should not be used as an ordinal score. The VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labeled "best imaginable health state" and "worst imaginable health state." This information can be used as a quantitative measure of health outcome. The EQ-5D 5L health states, defined by the EQ-5D 5L descriptive system, may be converted into a single summary index by applying a formula that essentially attaches values (also called weights) to each of the levels in each dimension (Brooks 1996; Herdman et al. 2011; EuroQol Group [WWW] 2013).

10.2.6. Work Productivity and Activity Impairment Questionnaire–Specific Health Problem

The Work Productivity and Activity Impairment–Specific Health Problem consists of 6 questions to determine employment status, hours missed from work because of PsA, hours missed from work for other reasons, hours actually worked, the degree to which PsA affected work productivity while at work, and the degree to which PsA affected activities outside of work. Four scores are derived: percentage of absenteeism, percentage of presenteeism (reduced productivity while at work), an overall work impairment score that combines absenteeism and presenteeism, and percentage of impairment in activities performed outside of work. Greater scores indicate greater impairment (Reilly et al. 1993; Reilly Associates Health Outcomes Research [WWW]).

10.2.7. Quick Inventory of Depressive Symptomatology–Self Report (16 Items)

The 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 (APA 1994). A patient is asked to consider each statement as it relates to the way he/she has 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; higher scores denote greater symptom severity. The domains assessed by the instrument are (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 can be found at the University of Pittsburgh IDS/QIDS internet page (Rush et al. 2003; Trivedi et al. 2004; University of Pittsburgh Epidemiology Data Center [WWW]).

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.

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

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 drug effect.

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.

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

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

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

Any clinically significant findings from ECGs, laboratory tests, vital sign measurements, or other procedures that result in a diagnosis should be reported to Lilly or its designee.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, investigational product, and/or drug delivery system via eCRF.

The investigator will decide whether he or she interprets the observed AEs as reasonably possibly related to disease, the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AEs, the following is defined:

> **Reasonably Possibly Related:** Reasonable possibility that there is a cause and effect relationship between the investigational product, study device, and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

If a patient's dosage is reduced or 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 any such dosage reduction or discontinuation of treatment.

10.3.1.1. Serious Adverse Events

SAE collection begins after the patient has signed informed consent and has received investigational product. If a patient has an SAE after signing informed consent but before receiving investigational product, the event will NOT be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

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

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

An SAE is any AE from this study that results in 1 of the following outcomes:

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

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

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

The investigator does not need to actively monitor patients for AEs once the trial has ended unless provided otherwise in the protocol. However, if an investigator becomes aware of SAEs occurring to a patient after the patient's participation in the trial has ended, the investigator should report the SAEs to the sponsor, regardless of the investigator's opinion of causation, and the SAEs will be entered in the pharmacovigilance system at the sponsor.

Information on SAEs that are 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. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries

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

10.3.1.1.2. Adverse Events of Special Interest

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

AESIs for ixekizumab are:

- cytopenias (leukopenia, neutropenia, and thrombocytopenia)
- liver function test result changes/high enzyme levels (ALT, AST, bilirubin, and ALP)
- infection
- injection-site reactions
- allergic reactions or hypersensitivities
- cerebrocardiovascular events
- malignancies
- depression
- Crohn's disease and ulcerative colitis (inflammatory bowel disease [IBD])
- *Pneumocystis* pneumonia and interstitial lung disease

If infections, injection-site reactions, allergic or hypersensitivity reactions, or IBD are reported, sites will provide details on these events as instructed on the eCRF. Investigators will also educate patients and/or caregivers about the symptoms of allergic or hypersensitivity reactions and will provide instructions on dealing with these reactions (see also Section 9.5.1). A blood sample will be collected when possible for any patient who experiences an AE of allergic or hypersensitivity reaction during the study.

Data on cerebrocardiovascular events (defined as death, cardiac ischemic event including myocardial infarction and hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, coronary revascularization procedure, stroke/transient ischemic attack, peripheral revascularization procedure, peripheral arterial event, and hospitalization for hypertension) will be collected, and the events will be adjudicated by an external Clinical Events Committee (CEC) made up of a chairperson, 2 cardiologists, and a neurologist. The role of the CEC is to adjudicate these defined clinical events in a blinded, consistent, and unbiased manner throughout the course of a study. The purpose of the CEC is to ensure that all events that have been reported are evaluated uniformly by a single group (the CEC).

Data on suspected IBD, as identified by events possibly indicative of ulcerative colitis and/or Crohn's disease, 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 CEC will be to adjudicate defined clinical events, in a blinded, consistent, and unbiased manner throughout the course of a study. The importance of the CEC is to ensure that all events that have been reported are evaluated uniformly by a single group.

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 (Visit 1). 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 treatment-emergent adverse event (TEAE) assessment. All remaining physical examinations throughout the study should include a symptom-directed physical evaluation as well as an examination of the heart, lungs, and abdomen and a visual examination of the skin.

10.3.2.2. Electrocardiograms

For each patient, a single 12-lead ECG will be obtained according to the study schedule (Attachment 1). The patient must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs must be recorded before collecting any blood for safety or PK tests. ECGs may be obtained at additional times when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

ECGs will be locally (machine) read and 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 to determine whether the patient meets entry criteria and for immediate patient management should any clinically relevant findings be identified.

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

10.3.2.3. Chest Radiography and Tuberculosis Testing

Eligibility Assessments and Testing for TB

Radiography: At Visit 1, posterior-anterior view chest radiography will be obtained locally unless the radiographs or results from chest radiography obtained within 6 months before the study are available. Chest radiographs or results will be reviewed by the investigator or designee to exclude patients with active TB infection.

TB testing: Patient history of TB test results should be assessed before screening (Visit 1).

> **Patients with no TB test results on file:** These patients will be tested at screening (Visit 1). A PPD skin test response of ≥5-mm induration, between approximately 2 and 3 days after test application, regardless of BCG vaccination history, will be considered a positive result. In countries where the QuantiFERON-TB Gold test or T-SPOT.TB test is available and in the judgment of the investigator preferred as an alternative to the PPD skin test for the evaluation of TB infection, those tests may be used instead of the PPD

test. If the QuantiFERON-TB Gold test or the T-SPOT.TB test is indeterminate, 1 retest is allowed. If the retest is indeterminate, the patient is excluded from the study.

Patients with positive results from a TB test performed at screening (Visit 1) but no other evidence of active TB may be rescreened once and enrolled on the basis of the following requirements:

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

Patients with negative TB test results on file: Patients with documentation of a negative TB test result within 3 months before baseline (Week 0, Visit 2) should not be administered a TB test at Visit 1. Documentation of PPD test results must include a record of the size of the induration response; if it does not, a retest at screening (Visit 1) will be required to determine patient eligibility.

Patients with positive TB test results on file: Patients with history of a positive TB test should not be administered a TB test at Visit 1. Documentation of this history and of at least 4 weeks of appropriate LTBI treatment before baseline (Week 0, Visit 2) is required for study eligibility. Patients who have a documented history of completing an appropriate TB treatment regimen with no history of re-exposure since their treatment was completed and no evidence of active TB are eligible to participate in the study.

TB Testing and Assessment for Patients during the Study:

Tuberculosis testing during the study will be conducted based on clinical assessment of TB risk (symptoms/signs/known or suspected TB exposure), and as required by local regulations and/or local standard of care.

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Patients testing positive for TB at any time during the study must immediately discontinue administration of investigational product. The patient must be evaluated for latent or active infection. Patients with active infection must be discontinued from the study and should receive appropriate follow-up medical care and TB treatment according to local guidelines; patients with latent infection must receive a full course of LTBI treatment but may resume administration of investigational product after receiving 4 weeks of LTBI treatment with no evidence of hepatotoxicity (ALT and AST levels must remain ≤2× ULN) upon retesting of serum ALT and AST before resumption of investigational product. Such patients must complete appropriate LTBI therapy during the course of the study to remain eligible to continue the study treatment.

10.3.2.4. Vital Signs

Vital signs (sitting BP and pulse rate) and body temperature will be measured after the patient has been resting for a minimum of 10 minutes at times indicated in the study schedule (Attachment 1). At baseline (Week 0, Visit 2), sitting BP and pulse rate should be measured before administration of the investigational product and again approximately 1 hour after 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.

10.3.2.5. Immunogenicity

Samples for immunogenicity testing will be collected at time points indicated in the study schedule (Attachment 1) and for each event judged by the investigator to be a potential systemic allergic/hypersensitivity reaction, when possible (Section 9.5.1). Venous blood samples (approximately 10 mL each) 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 pretreatment baseline titer. In the case of a negative result at baseline, treatment-emergent immunogenicity is defined as an increase in titer to ≥1:10. Immunogenicity samples may also be analyzed for ixekizumab serum concentration to facilitate in the interpretation of the immunogenicity data. Samples may be stored for a maximum of 15 years after last patient visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to ixekizumab. The duration allows the sponsor to respond to regulatory requests related to 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 classes A, G, and M (IgA, IgG, and IgM, respectively) in peripheral blood. However, since this is a novel immunomodulatory drug, these parameters will be measured in patients.

10.3.2.7. Columbia–Suicide Severity Rating Scale

The C-SSRS (Posner et al. 2007; 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. The Self-Harm Supplement Form will be completed according to the Study Schedule (Attachment 1).

10.3.3. Safety Monitoring

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

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical research physician/scientist will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist and periodically review trends in safety data, laboratory analytes, and AEs.

See Section 8.3.1.1 for discontinuation criteria and Sections 10.3.3.1, 10.3.3.2, 10.3.3.3, and 10.3.3.4 for the monitoring of neutropenia, hypertension, hepatic monitoring, and hepatitis B monitoring, respectively.

Vitals signs will be monitored before and after dosing 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 × 10^3/µL) 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 × 103/μL or ≥1.50 GI/L). If the patient has 3 or more postbaseline neutrophil counts of ≥1000 cells/μL(≥1.00 × 10^3/μL or ≥1.00 GI/L) and <1500 cells/μL (<1.50 × 10^3/μL or <1.50 GI/L), no value of <1000 cells/μL (<1.00 × 10^3/μL or <1.00 GI/L), and no postbaseline 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.

10.3.3.2. Hypertension

Patients who have changes in sitting BP—defined as systolic BP at ≥160 mm Hg plus ≥20 mm Hg increase from baseline (Week 0, Visit 2) and/or diastolic BP at ≥100 mm Hg plus ≥10 mm Hg increase from baseline (Week 0, Visit 2)—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 8.3.1.1 for criteria for patient discontinuation related to hypertension.

10.3.3.3. Hepatic Monitoring

If a study patient/subject experiences elevated ALT ≥3× ULN, ALP ≥2× ULN, or elevated total bilirubin >2× ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient/subject safety and comply with regulatory guidance, the investigator is to consult with the Lilly designated medical monitor regarding collection of specific recommended clinical information and follow-up laboratory tests. See Attachment 3.

10.3.3.4. Hepatitis B Monitoring

For any patient who is HBsAg–, HBcAb+, and HBsAb+ at screening, a quantitative HBsAb level and an HBV DNA test will be performed by the central laboratory. A patient with an HBsAb level ≥200 mIU/mL and a negative serum HBV DNA test result may be enrolled in the study. However periodic monitoring of the patient's HBsAb level must be performed as indicated in the study schedule (Attachment 1). If the patient's HBsAb level decreases to <200 mIU/mL, then a HBV DNA test will also be performed by the central laboratory. If the HBV DNA test is negative, then the patient may remain in the study. However, repeat testing of the patient's HBsAb level and HBV DNA must be performed at 4- to 8-week intervals, as long as the HBsAb level is <200 mIU/mL. If the HBsAb level increases to ≥200 mIU/mL, the site may resume periodic monitoring of the patient's HBsAb as indicated in the study schedule (Attachment 1).

For any enrolled patient who is HBcAb+, regardless of HBsAb status or level, and who has ALT or AST levels >3 × ULN, an HBV DNA test will be performed by the central laboratory. The investigator should consult with the Lilly medical monitor regarding further management of the patient.

Any enrolled patient with a positive HBV DNA test result at any time must be discontinued from the study and should receive appropriate follow-up medical care, including consideration for antiviral therapy.

Study investigators should consult with a specialist physician in the care of patients with hepatitis (for example, infectious disease or hepatologist subspecialists) on whether to continue any immunosuppressant therapy including investigational product for a period of time while antiviral therapy is being initiated. Timing of withdrawal from investigational product should be based on recommendation of the consulting specialist physician in conjunction with the investigator and local or regional medical guidelines or standards of care.

Upon discontinuation from investigational product, the patient should be discontinued from the study. Any patient who discontinued the study for any reason will complete the ETV before entering the posttreatment follow-up period (Period 4).

10.3.4. Complaint Handling

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

Complaints related to unblinded concomitant drugs are reported directly to the manufacturers of those drugs or 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:

- reviewing all study drug administration logs to identify any product complaints

- 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

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

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

10.4.1. Samples for Study Qualification and Health Monitoring

As applicable, blood and urine samples will be collected at the time points specified in the study schedule (Attachment 1) and after ECG, vital-sign, and clinical efficacy measurements.

Clinical laboratory tests will be analyzed by a central laboratory unless otherwise specified. Protocol RHBF Clinical Laboratory Tests (Attachment 2) lists the specific tests that will be performed for this study.

Blood will be drawn at the visits specified in the study schedule (Attachment 1) for routine safety laboratories including clinical chemistry, hematology, TSH, T4, coagulation panel, and lipid panel in amounts ranging from 5 mL to 50 mL, depending on the visit. 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 10 mL (approximate) of blood 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.

10.4.2. Samples for Biomarker Research

Pharmacogenetic Evaluations:

There is growing evidence that genetic variation may affect a patient's response to therapy. Variable response to therapy may be caused by genetic determinants that affect drug absorption, distribution, metabolism, and excretion; the mechanism of action of the drug; the disease etiology; and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, blood samples (approximately 10 mL) will be collected for pharmacogenetic and epigenetic analyses, as noted in the study schedule (Attachment 1).

Samples will be stored, and DNA and RNA analyses may be performed on genetic variants thought to play a role in PsA including but not limited to HLA-C, IL-2, IL-21, IL-12B, IL-13, TNFAIP3, TNIP1, TRAF3IP2, NFKB1A, LCE3 locus, NOS2, and FBXL19; the IL-17 and IL-23 family, receptors, and signaling pathways; MTX metabolizing genes such as methylene tetrahydrofolate reductase; and other folate reductases to evaluate their association with observed response to ixekizumab.

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic samples may be genotyped and analyses may be performed to evaluate a genetic association with response to ixekizumab. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic samples will be used for only investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analyses.

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the investigational product.

Samples will be destroyed according to a process consistent with local regulation.

Nonpharmacogenetic/Biomarker Evaluation:

Samples will be collected for potential nonpharmacogenetic biomarker research where local regulations allow. Serum, plasma, and whole blood RNA samples will be collected at the times specified in the study schedule (Attachment 1).

It is increasingly recognized that in addition to the ability of germline DNA sequence to influence disease susceptibility, so called epigenetic modification of DNA may also have influence on disease susceptibility and disease phenotype. These modifications include DNA methylation, histone modification, and other modifications of less defined significance. To be able to investigate the potential of epigenetic changes on drug response, we plan to collect 1 DNA sample at baseline and 1 additional DNA sample after treatment with ixekizumab.

Therefore, to be able to test for epigenetic changes, 2 DNA samples will be collected during this study.

Samples may be used for research on the drug target, disease process, pathways associated with PsA, mechanism of action of ixekizumab, and/or research method or in validating diagnostic tools or assay(s) related to PsA.

Samples will be identified by the patient number (coded) and stored for up to a maximum of 15 years after the last patient visit for the study at a facility selected by the sponsor.

Samples will be destroyed according to a process consistent with local regulations.

10.4.3. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against the investigational product. See Section 10.3.2.5 for further details.

10.4.4. Samples for Drug Concentration Measurements

As described in Section 10.3.2.5, an aliquot for every immunogenicity sample will be used to determine ixekizumab serum concentration by a validated enzyme-linked immunosorbent assay. It is expected that the obtained PK samples will allow sufficient description of ixekizumab PK profiles at steady state through the study. The actual date and exact timing (24-hour clock time) of each sample collected will be recorded on the laboratory requisition.

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

10.5. Appropriateness of Measurements

In general, 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.

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

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly 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-provided or designee-provided electronic data capture system.

Any data for which paper documentation provided by the patient will serve as the source document 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 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. These data will also be entered electronically by study site personnel.

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 Lilly generic labs system.

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. Electronic patient-reported outcome measures (for example, a rating scale) or other data reported directly by the subject (for example, VAS, health outcome questionnaires) are entered into an ePRO instrument (a hand-held tablet) at the time that the information is obtained. In these instances for which there is no prior written or electronic source data at the site, the ePRO instrument record will serve as the source.

If ePRO records are stored at a third-party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the ePRO instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

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

Approximately 400 patients will enter the initial open-label treatment period. It is expected that approximately 34% of the patients will meet the randomization criteria for the randomized double-blind withdrawal period. Approximately 136 patients will be randomized in a 1:1 ratio into ixekizumab 80 mg Q2W and placebo treatment groups (68 patients per treatment group). This assumption is based on the Study RHAP Week 24 results and estimating the number of patients achieving Coates criteria for MDA for 3 consecutive months over 4 consecutive visits of meeting MDA.

It is assumed that approximately 60% and 20% of patients in the placebo and ixekizumab groups, respectively, who enter the randomized double-blind withdrawal period will relapse (no longer meet Coates criteria for MDA). According to these assumptions, a total of 39 patients must meet relapse criteria in the combined treatment groups to achieve 95% power to test the superiority of ixekizumab 80 mg Q2W to placebo for time to relapse at a 2-sided 0.05 α significance level. The dropout rate before relapse for patients randomized in the randomized double-blind withdrawal period is assumed to be 10%. Sample size and power calculations were calculated using nQuery+nTerim 3.0.

Randomization and relapse rates will be monitored to assess whether the number of patients who enter the initial open-label treatment period should be increased to ensure sufficient sample size and power for the randomized withdrawal period.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

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

Continuous data will be summarized in terms of the number of observations (n); mean; standard deviation and/or standard error of the mean, if applicable; median; minimum; and maximum.

Categorical data will be summarized in terms of the number of observations (n), frequency count, and percentages.

Investigator centers will be pooled by geographical region for statistical analysis purposes.

All tests of treatment effects will be conducted at a 2-sided α level of 0.05 unless otherwise stated.

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 SAP.

12.2.1.1. General Considerations for Analyses during Period 2 (Initial Open-Label Treatment Period)

Efficacy, health outcomes, and safety data collected in Period 2 will be summarized for ixekizumab 80 mg Q2W without inferential statistics. For efficacy, health outcomes, and safety analyses, baseline is defined as the last available value before the first dose of study medication in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2). For analysis purposes, the endpoint for Period 2 will be defined as the visit of randomization or Week 64 for patients who do not meet the randomization criteria.

Kaplan-Meir estimates will be used to estimate the survival curve for time-to variables.

12.2.1.2. General Considerations for Analyses during Period 3 (Randomized Double-Blind Withdrawal Period)

For patients who are randomized in Period 3, all efficacy, health outcomes, and safety data collected between randomization and either through relapse (no longer meeting Coates criteria for MDA) or through the end of Period 3 will be compared between the ixekizumab 80 mg Q2W and placebo treatment groups. For the efficacy analysis, baseline is defined as the last available value before the first dose of study medication in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2). For the safety analysis, baseline is defined as the last available value before the first dose of study treatment in Period 3.

The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to variables for the patients who are randomized to the randomized double-blind withdrawal period. Treatment comparisons will be performed using a log-rank test with treatment, geographic region, and cDMARD use (past use, current use), at the time of randomization in Period 3, in the model.

The primary analysis of the categorical efficacy and health outcome variables will use a logistic regression with treatment, geographic region, and cDMARD use (past use, current use), at the time of randomization in Period 3, in the model. Secondary analysis of the categorical efficacy and health outcome variables will be conducted using the Fisher's exact test.

The analysis for all continuous efficacy and health outcome variables, change from baseline to endpoint analysis, will be made using analysis of covariance with treatment, baseline value, geographic region, and cDMARD use (past use, current use), at the time of randomization in Period 3, in the model. Missing data will be imputed using modified baseline observation carried forward (mBOCF). Type III sums of squares for the least-squares means will be used for the statistical comparison; the 95% CI will also be reported.

The Fisher's exact test will be used for all AE, baseline, discontinuation, and other categorical data. AE data will be analyzed using exposure-adjusted incidence rates. Continuous vital sign and laboratory values will be analyzed by an analysis of covariance model with treatment and baseline value as independent variables. Other continuous variables will be analyzed by t-tests unless otherwise stated.

For patients who randomize and subsequently relapse in Period 3, efficacy, health outcomes, and safety data collected between relapse and the end of Period 3 will be summarized for ixekizumab

80 mg Q2W without inferential statistics. For the efficacy and health outcomes analyses, baseline is defined as the last available value before the first dose of study medication in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2). For the safety analysis, baseline is defined as the last available value before relapse in Period 3.

12.2.1.3. General Considerations for Analyses during Periods 2 and 3 Combined (Initial Open-Label Treatment and Randomized Double-Blind Withdrawal Periods)

For patients who are randomized in Period 3, efficacy, health outcomes, and safety data collected in Periods 2 and 3 combined will be summarized for ixekizumab 80 mg Q2W without inferential statistics. For efficacy, health outcomes, and safety analyses, baseline is defined as the last available value before the first dose of study medication in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2).

For patients who are not randomized in Period 3, efficacy, health outcomes, and safety data collected in Periods 2 and 3 combined will be summarized for ixekizumab 80 mg Q2W without inferential statistics. For efficacy, health outcomes, and safety analyses, baseline is defined as the last available value before the first dose of study medication in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2).

12.2.1.4. Analysis Populations

Unless otherwise specified, efficacy, health outcomes, and safety summaries for Period 2 (initial open-label treatment period) will be conducted on the **initial open-label treatment period population**, defined as all patients who receive at least 1 dose of ixekizumab 80 mg Q2W in Period 2.

Efficacy and health outcomes analyses for Period 3 (randomized double-blind withdrawal period) will be conducted on the **randomized withdrawal intent-to-treat (ITT) population**, defined as all randomized patients, even if the patient 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.

Safety analyses for Period 3 will be conducted on the **randomized withdrawal safety population**, defined as all randomized patients who received at least 1 dose of study treatment after randomization. Patients will be analyzed according to the treatment to which they were assigned.

Efficacy, health outcomes, and safety summaries for combined Periods 2 and 3 will be conducted on the **nonrandomized population**, defined as all patients who were not randomized and who received at least 1 dose of ixekizumab 80 mg Q2W.

Efficacy, health outcomes, and safety summaries will be conducted on the **relapse population**, defined as all randomized patients who relapsed (no longer met Coates criteria for MDA) after randomization and who received at least 1 dose of ixekizumab 80 mg Q2W after relapse.

Safety analyses for Period 4 (posttreatment follow-up period) will be conducted on the **follow-up period population**, defined as all patients who receive at least 1 dose of study treatment at any

time during Periods 2 and 3 and have entered the posttreatment follow-up period. Patients will be analyzed according to the treatment they were taking before entering Period 4.

12.2.1.5. Missing Data Imputation

12.2.1.5.1. Nonresponder Imputation for Clinical Response

Patients will be considered a nonresponder for the nonresponder imputation (NRI) analysis if they do not meet the clinical response criteria at any specified analysis time point. All nonresponders at any specified time point as well as all patients who discontinue study treatment before the specified analysis time point, for any reason, will be defined as a nonresponder for the NRI analysis. Patients without at least 1 observation on study treatment will also be defined as a nonresponder for the NRI analysis.

12.2.1.5.2. Modified Baseline Observation Carried Forward

An mBOCF analysis will be performed on all continuous efficacy and health outcome variables. In this approach, the baseline observation will be carried forward to the corresponding endpoint for evaluation for patients who discontinue study treatment due to an AE. The last nonmissing observation before discontinuation of study treatment will be carried forward to the corresponding primary endpoint for evaluation for patients who discontinue study treatment for any reason other than due to an AE. Patients without at least 1 postbaseline observation will not be included for evaluation, with the exception of patients who discontinue study treatment due to an AE.

12.2.1.6. Adjustment for Multiple Comparisons

There will be no adjustment for multiple comparisons in this study.

12.2.2. Patient Disposition

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

Patient disposition will be summarized for each treatment period. Reasons for discontinuation from the study will be summarized. The reasons for discontinuation during Period 3 will be tested between treatment groups using Fisher's exact test for the randomized withdrawal ITT population.

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, geographic region, baseline disease severity, duration of disease, disease diagnosis, previous cDMARDs, and subtypes of PsA. Baseline clinical measurements may include Coates criteria for MDA components, ACR components, sPGA score, PASI total score, BSA, Psoriatic Arthritis Response Criteria, DAS28-CRP, Joint Pain VAS, Physician's or Patient's Global Assessment of Disease Activity VAS, HAQ-DI, SPARCC, CPDAI, Itch NRS score, DLQI total score, LDI-B, SF-36, Fatigue Severity NRS.

Treatment group comparisons between ixekizumab 80 mg Q2W and placebo in Period 3 will be conducted using Fisher's exact test for categorical data and a 1-way analysis of variance for continuous data for the randomized withdrawal ITT population.

12.2.4. Concomitant Therapy

Previous and concomitant medications will be summarized for patients who enter each treatment period and presented by WHO Anatomic Therapeutic Class Level 1 and generic name. Treatment group comparisons between ixekizumab 80 mg Q2W and placebo in Period 3 will be conducted using Fisher's exact test for the randomized withdrawal ITT population.

12.2.5. Treatment Compliance

Treatment compliance with investigational product will be summarized for each treatment period. Patient compliance with investigational product will be assessed at each visit. 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 not missing 2 consecutive doses. Proportions of patients compliant by visit and overall compliance will be compared between treatment groups for Period 3 using Fisher's exact test for the randomized withdrawal ITT population.

12.2.6. Efficacy and Health Outcome Analyses

12.2.6.1. Primary Analyses

The primary analysis is the time-to relapse (no longer meeting Coates criteria for MDA) for the randomized withdrawal ITT population. Time-to relapse will be calculated in weeks as follows:

$$\frac{(Date\ of\ Relapse - Date\ of\ First\ Injection\ of\ Randomized\ Study\ Treatment\ in\ Period\ 3) + 1}{7}$$

If the date of first dose is missing, the date of randomization will be used. Patients completing Period 3 will be censored at the date of completion (that is, the date of the last scheduled visit in the period). Patients without a date of completion or discontinuation for Period 3 will be censored at the latest nonmissing date out of the following dates: date of last dose and date of last attended visit in Period 3 (scheduled or unscheduled).

Treatment comparison between ixekizumab 80 mg Q2W and placebo in time-to relapse for the randomized withdrawal ITT population will be analyzed using a log-rank test with treatment, geographic region, and cDMARD use (past use, current use), at the time of randomization in Period 3, in the model. The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to relapse. Time-to relapse will also be summarized graphically by treatment group using Kaplan-Meier techniques.

12.2.6.2. Secondary Analyses

The secondary efficacy and health outcomes analyses for Period 2 will be based on the initial open-label treatment period population. The secondary efficacy and health outcomes analyses for Period 3 will be based on either the randomized withdrawal ITT population or the relapse population, as specified below. Additional efficacy and health outcome analyses for combined

Periods 2 and 3 analyses will be based on both the randomized withdrawal ITT population and the nonrandomized population.

12.2.6.2.1. Initial Open-Label Treatment Period (Period 2)

Time to achieve Coates criteria for MDA and time to achieve Coates criteria for MDA for 3 consecutive months over 4 consecutive visits during the initial open-label treatment period (Period 2) will be summarized. The summarizations will include Kaplan-Meier estimates for the probability of achieving Coates criteria for MDA and achieving Coates criteria for MDA for 3 consecutive months over 4 consecutive visits. The Kaplan-Meier product limit method will be used to estimate the survival curve for time-to to achieve Coates criteria for MDA for 3 consecutive months over 4 consecutive visits.

12.2.6.2.2. Randomized Double-Blind Withdrawal Period (Period 3)

Treatment comparisons between ixekizumab 80 mg Q2W and placebo in proportion of patients who relapse will be analyzed using a logistic regression with treatment, geographic region, and cDMARD use in the model and a Fisher's exact test for the randomized withdrawal ITT population. Missing data will be imputed using the NRI method.

Time to loss of response for each of the below individual components (in weeks) of the Coates criteria for MDA will be calculated and treatment comparisons will be conducted using the same methods as described for the primary analysis (see Section 12.2.6.1) for randomized withdrawal ITT population patients who meet the individual component criteria at the time of randomization:

- TJC ≤1
- SJC ≤1
- PASI total score ≤1 or BSA ≤3
- sPGA (0,1) or BSA ≤3
- pain VAS score of ≤15
- global disease activity scale VAS score ≤20
- HAQ-DI score ≤0.5
- tender entheseal points ≤1

12.2.6.2.3. Combined Initial Treatment and Randomized Double-Blind Withdrawal Periods (Periods 2 and 3)

The HAQ-DI score will be summarized for the ixekizumab 80 mg Q2W treatment group at each visit and endpoint (mBOCF) during the combined Periods 2 and 3 for the randomized withdrawal ITT and the nonrandomized withdrawal populations. Summarizations will include observed scores, change from baseline, percentage improvement, and response rates ≥0.35.

12.2.6.3. Exploratory Efficacy Analyses

Analyses will be conducted for the exploratory efficacy objectives as defined in Section 6.3. Complete details will be described in the SAP.

12.2.7. Pharmacokinetic/Pharmacodynamic Analyses

Observed ixekizumab serum concentrations will be summarized by visits and corresponding time when sampling occurred.

As appropriate, exposure-response relationship will be investigated between ixekizumab exposure and clinically important efficacy and PD measures (for example, proportion of patients achieving Coates criteria for MDA for 4 consecutive visits and the maintenance of treatment effects) specified in study objectives. In addition, the relationship between the time course of ixekizumab exposure and the time course of the efficacy and PD measures may be explored using graphical methods and a modeling approach. Covariates such as body weight, disease duration, baseline value, and so on, will be investigated to assess their impact on the PD parameters. Model evaluation will include using sensitivity analysis and visual predictive check.

If a trend or statistically significant difference between the ixekizumab cohort and the placebo cohort is noted in any safety endpoint, this endpoint will also be explored to investigate exposure-response relationships.

The potential impact of immunogenicity on ixekizumab exposure and/or PD responses will be evaluated, as appropriate, by graphical assessments to compare drug exposure or PD responses between immunogenicity-negative and immunogenicity-positive patients at correspondent visits or before and after immunogenicity development for patients whose immunogenicity was detected. In addition, the effect of immunogenicity may be evaluated in the population PK/PD modeling analyses where immunogenicity will be evaluated as a covariate.

12.2.8. Safety Analyses

Safety will be assessed by summarizing and analyzing SAEs, AEs, AESIs, vital signs, other measures of cardiovascular function, C-SSRS, laboratory evaluations (including chemistry, calculated creatinine clearance, hematology [including WBC count and differential], urinalysis [dipstick and microscopic], thyroid-stimulating hormone and free T4, and immunogenicity testing [treatment-emergent antidrug antibodies (TE-ADAs)]). Primary safety analyses will focus on comparison of ixekizumab 80 mg Q2W to placebo for the randomized withdrawal safety population in Period 3. Treatment group comparisons will be analyzed using the methods described in Section 12.2.1.2.

For the Period 2 and the combined Periods 2 and 3, the same safety variables as in Period 3 will be summarized as described in Sections 12.2.1.1 and 12.2.1.3, respectively.

Summaries of safety data collected during the Period 4 (posttreatment follow-up period) will be presented separately.

12.2.8.1. Adverse Events

AEs are considered TEAEs if they first occur or worsen after the start of treatment during a study period. In the case of a missing onset date for an AE, an AE with a start date equal to or greater than the dosing date will be considered a TEAE. For each TEAE, the severity is recorded

according to the patient's or physician's perceived severity of the event (mild, moderate, or severe).

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 *Medical Dictionary for Regulatory Activities* (MedDRA) system organ class and preferred term. TEAEs will also be summarized by preferred term sorted by decreasing frequency within system organ class for all TEAEs, TEAEs by maximum severity, and TEAEs considered possibly related to study drug. For events that are gender specific, the denominator and computation of the percentage will include only patients from the given gender. MedDRA groupings of preferred terms will be used to investigate AESIs.

AESIs will also be presented by severity. AESIs will include cytopenias, liver function test changes/enzyme elevations, infections, injection-site reactions, allergic/hypersensitivity reactions, cerebrocardiovascular events, malignancies, depression, Crohn's disease and ulcerative colitis, and Pneumocystis pneumonia and interstitial lung disease.

12.2.8.2. Clinical Laboratory Tests

Laboratory assessments will be presented as mean changes from baseline, 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 before and after dosing, as applicable.

The analyses of TE-ADA effects will be conducted on all evaluable patients within the defined safety population. Evaluable patients will be identified as positive, negative, or inconclusive for TE-ADA (as defined in the SAP). The frequency and percentage (incidence) of patients with positive, negative, or inconclusive TE-ADA and neutralizing anti-drug antibody at baseline and postbaseline will be summarized by treatment group. Patients who are TE-ADA positive (persistent positive or transient positive), TE-ADA persistent positive, and TE-ADA transient positive will also be summarized.

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

Other 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 time to relapse and the proportion of patients who relapse for the randomized withdrawal ITT population.

Subgroups to be evaluated may include variables such as gender, age category, race, geographic region, and cDMARDs therapy at the time of randomization in Period 3. Additional subgroups may be described in the SAP.

The Kaplan-Meier product limit method will be used to estimate the survival curves for time to relapse. Analyses will be performed using a log-rank test with treatment, subgroup, and the interaction of treatment-by-subgroup included as factors in the model.

For the proportion of patients who relapse, a logistic regression model with treatment, subgroup, and the interaction of treatment-by-subgroup included as factors will be used. Missing data will be imputed using NRI as described in Section 12.2.1.5.1.

The subgroup-by-treatment interactions will be tested at the significance level of 0.10. Treatment group differences will be evaluated within each category of the subgroup, regardless of whether the interaction is statistically significant.

Detailed description of the subgroup variables and detailed analysis methodology will be defined in the SAP. Additional subgroup analyses may be performed as deemed necessary.

12.2.10. Interim Analyses

The study will have approximately 2 interim and 1 final database locks. The first interim database lock may occur once all patients complete or discontinue in the initial open-label treatment period; only data from the initial open-label treatment period will be summarized. For analysis purposes, the end of the initial open-label treatment period will be defined as the visit of randomization or Week 64 for patients who do not meet the randomization criteria. The second interim database lock may occur when all patients complete Week 104 or discontinue study treatment prior to the end of the randomized double-blind withdrawal period. The final database lock will occur when all patients complete or discontinue the study. However, the second interim may not be performed depending upon the timing of the final database lock once all patients complete the post-treatment follow up period. Analyses for these interim analyses will be specified in the SAP along with the unblinding plan. Additional analyses and snapshots of study data may be performed to fulfill the need for regulatory interaction or publication purposes.

Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded. All investigators and patients will remain blinded to treatment assignments until the last patient completes the randomized double-blind withdrawal period and the final database lock occurs.

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 before the performance of any protocol procedures and before 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 investigative sites. All ICFs must be compliant with the ICH guideline on GCP.

The investigator must give assurance that the ERB was properly constituted and convened as required by ICH guidelines and other applicable laws and regulations.

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

The study site's ERBs should be provided with the following:

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

13.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences 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 ERBs.

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

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 and statistician 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.

14. References

Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, Zhou B, Dooley LT, Kavanaugh A. IMPACT 2 Investigators. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis.* 2005a;64(8):1150–1157.

Antoni CE, Kavanaugh A, Kirkham B Tutuncu Z, Burmester GR, Schneider U, Furst DE, Molitor J, Keystone E, Gladman D, Manger B, Wassenberg S, Weier R, Wallace DJ, Weisman MH, Kalden JR, Smolen J. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). *Arthritis Rheum*. 2005b;52(4):1227-1236.

[APA] American Psychiatry Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington DC:APA;1994.

Araujo EG, Finzel S, Englbrecht M, Schreiber DA, Faustini F, Hueber A, Nas K, Rech J, Schett G. High incidence of disease recurrence after discontinuation of disease-modifying antirheumatic drug treatment in patients with psoriatic arthritis in remission. *Ann Rheum Dis.* 2015;74(4):655-660.

Ash Z, Gaujoux-Viala C, Gossec L, Hensor EM, FitzGerald O, Winthrop K, van der Heijde D, Emery P, Smolen JS, Marzo-Ortega H. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis*. 2012;71(3):319-326.

Basra MKA, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol*. 2008;159(5):997-1035.

Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, Westlake L. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ*. 1992;305(6846):160-164.

Brooks R. EuroQol: the current state of play. *Health Policy.* 1996;37(1):53–72.

Cantini F, Niccoli L, Nannini C, Cassarà E, Pasquetti P, Olivieri I, Salvarani C. Frequency and duration of clinical remission in patients with peripheral psoriatic arthritis requiring second-line drugs. *Rheumatology.* 2008;47(6):872–876.

Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis*. 2010;69(1):48–53.

Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. *Arthritis Care Res*. 2010;62(7):965–969.

Coates LC, FitzGerald O, Gladman DD, McHugh NJ, Mease P, Strand V, Helliwell PS. MDA criteria for PsA show good correlation with physician and patient opinion and proposed composite measures. *Ann Rheum Dis*. 2012;71(3):575.

Coates LC, Helliwell PS. Treat to target in psoriatic arthritis-evidence, target, research agenda. *Curr Rheumatol Rep*. 2015;17(6):517.

Columbia University Medical Center. Columbia–Suicide Severity Rating Scale (C-SSRS) web site. Available at: http://www.cssrs.columbia.edu. Accessed April 21, 2011.

Deepak P, Stobaugh DJ, Ehrenpreis ED. Infectious complications of TNF-α inhibitor monotherapy versus combination therapy with immunomodulators in inflammatory bowel disease: analysis of the Food and Drug Administration Adverse Event Reporting System. *J Gastrointestin Liver Dis.* 2013;22(3):269-276.

Dougados M, vam der Linden S, Leirisalo-Repo M, Huitfeldt B, Juhlin R, Veys E, Zeidler H, Kvien TK, Olivieri I, Dijkmans B, Bertouch J, Brooks P, Edmonds J, Major G, Amor B, Calin A. Sulfasalazine in the treatment of spondylarthropathy. a randomized, multicenter, double-blind, placebo-controlled study. *Arthritis Rheum*. 1995;38(5):618-627.

[EMEA] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. 2004;CHMP/EWP/2454/02 corr. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003329.pdf. Accessed July 8, 2014.

The EuroQol Group. EQ-5D-5L User Guide. Version 2.0. October 2013. Available at: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/UserGuide_EQ-5D-5L_v2.0_October_2013.pdf. Accessed July 08, 2014.

Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, Katz LM, Lightfoot R Jr, Paulus H, Strand V, Tugwell P, Weinblatt M, Williams HJ, Wolfe F, Kieszak S. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum*. 1995;38(6):727-735.

Fitzgerald O, Winchester R. Psoriatic arthritis: from pathogenesis to therapy. *Arthritis Res Ther*. 2009;11(1):214.

Fredriksson T, Pettersson U. Severe psoriasis—oral therapy with a new retinoid. *Dermatologica*. 1978;157(4):238-244.

Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum*. 1980;23(2):137-145.

Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol*. 1982;9(5):789-793.

Gladman DD, Farewell VT, Wong K, Husted J. Mortality studies in psoriatic arthritis: results from a single outpatient center. II. Prognostic indicators for death. *Arthritis Rheum*. 1998;41(6):1103-1110.

Gladman DD, Helliwell P, Mease PJ, Nash P, Ritchlin C, Taylor W. Assessment of patients with psoriatic arthritis: a review of currently available measures. *Arthritis Rheum*. 2004;50(1):24-35.

Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis*. 2005;64(suppl 2):ii14-ii17.

Gossec L, Smolen JS, Gaujoux-Viala C, Ash Z, Marzo-Ortega H, van der Heijde D, FitzGerald O, Aletaha D, Balint P, Boumpas D, Braun J, Breedveld FC, Burmester G, Cañete JD, de Wit M, Dagfinrud H, de Vlam K, Dougados M, Helliwell P, Kavanaugh A, Kvien TK, Landewé R, Luger T, Maccarone M, McGonagle D, McHugh N, McInnes IB, Ritchlin C, Sieper J, Tak PP, Valesini G, Vencovsky J, Winthrop KL, Zink A, Emery P; European League Against Rheumatism. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis*. 2012;71(1):4–12.

Haddad A, Thavaneswaran A, Arruza IR, Pellet F, Chandran V, Cook RJ, Gladman DD. Minimal disease activity and anti-tumor necrosis factor therapy in psoriatic arthritis. *Arthritis Care Res (Hoboken)*. 2015;67(6):842-847.

Happel KI, Zheng M, Young E, Quinton LJ, Lockhart E, Ramsay AJ, Shellito JE, Schurr JR, Bagby GJ, Nelson S, Kolls JK. Cutting edge: roles of Toll-like receptor 4 and IL-23 in IL-17 expression in response to Klebsiella pneumoniae infection. *J Immunol*. 2003;170(9):4432-4436.

Healy PJ, Helliwell PS. Measuring dactylitis in clinical trials: which is the best instrument to use? *J Rheumatol*. 2007;34:1302-1306.

Healy PJ, Helliwell PS. Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. *Arthritis Rheum*. 2008;59(5):686-691.

Helliwell PS, Firth J, Ibrahim GH, Melsom RD, Shah I, Turner DE. Development of an assessment tool for dactylitis in patients with psoriatic arthritis. *J Rheumatol*. 2005;32:1745-1750.

Helliwell PS, FitzGerald O, Fransen J, Gladman DD, Kreuger GG, Callis-Duffin K, McHugh N, Mease PJ, Strand V, Waxman R, Azevedo VF, Beltran Ostos A, Carneiro S, Cauli A, Espinoza LR, Flynn JA, Hassan N, Healy P, Kerzberg EM, Lee YJ, Lubrano E, Marchesoni A, Marzo-Ortega H, Porru G, Moreta EG, Nash P, Raffayova H, Ranza R, Raychaudhuri SP, Roussou E, Scarpa R, Song YW, Soriano ER, Tak PP, Ujfalussy I, de Vlam K, Walsh JA. The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). *Ann Rheum Dis*. 2013;72(6):986-991.

Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727-1736.

Huang W, Na L, Fidel PL, Schwarzenberger P. Requirement of interleukin-17A for systemic anti- Candida albicans host defense in mice. *J Infect Dis*. 2004;190(3):624-631.

Husted JA, Gladman DD, Farewell VT, Long JA, Cook RJ. Validating the SF-36 health survey questionnaire in patients with psoriatic arthritis. *J Rheumatol*. 1997;24(3):511-517.

Husted JA, Gladman DD, Farewell VT, Cook RJ. Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. *Arthritis Rheum*. 2001;45(2):151-158.

Jandus C, Bioley G, Rivals JP, Dudler J, Speiser D, Romero P. Increased numbers of circulating polyfunctional Th17 memory cells in patients with seronegative spondylarthritides. *Arthritis Rheum*. 2008;58(8):2307-2317.

Kaltwasser JP, Nash P, Gladman D, Rosen CF, Behrens F, Jones P, Wollenhaupt J, Falk FG, Mease P; Treatment of Psoriatic Arthritis Study Group. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum*. 2004;50(6):1939–1950.

Kavanaugh A, Cassell S. The assessment of disease activity and outcomes in psoriatic arthritis. *Clin Exp Rheumatol*. 2005;23(5 suppl 39):S142-S147.

Kavanaugh A, Antoni CE, Gladman D, Wassenberg S, Zhou B, Beutler A, Keenan G, Burmester G, Furst DE, Weisman MH, Kalden JR, Smolen J, van der Heijde D. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year. *Ann Rheum Dis*. 2006;65(8):1038-1043.

Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, Papp K, Zrubek J, Mudivarthy S, Mack M, Visvanathan S, Beutler A. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four–week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum*. 2009;60(4):976–986.

Kavanaugh A, van der Heijde D, Beutler A, Gladman D, Mease P, Krueger GG, McInnes IB, Helliwell P, Coates LC, Xu S. Patients with psoriatic arthritis who achieve minimal disease activity in response to golimumab therapy demonstrate less radiographic progression: Results through 5 years of the randomized, placebo-controlled, GO-REVEAL study. *Arthritis Care Res (Hoboken)*. 2015 Mar 16. doi: 10.1002/acr.22576. [Epub ahead of print].

Kingsley GH, Kowalczyk A, Taylor H, Ibrahim F, Packham JC, McHugh NJ, Mulherin DM, Kitas GD, Chakravarty K, Tom BD, O'Keeffe AG, Maddison PJ, Scott DL. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology*. 2012;51(8):1368-1377.

Leipe J, Grunke M, Dechant C, Reindl C, Kerzendorf U, Schulze-Koops H, Skapenko A. Role of Th17 cells in human autoimmune arthritis. *Arthritis Rheum*. 2010;62(10):2876-2885.

Leung Y-Y, Tam L-S, Kun E, Li E. Psoriatic Arthritis: an update on classification, clinical features and therapies. *Hong Kong Bull Rheum Dis*. 2008;8:1-11.

Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Enteracept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. *Lancet*. 2000;356(9227):385-390.

Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, Salonen D, Rubenstein J, Sharp JT, Tsuji W. Etanercept treatment of psoriatic arthritis safety, efficacy, and effect on disease progression. *Arthritis Rheum*. 2004;50(7):2264–2272.

Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, Sharp JT, Ory PA, Perdok RJ, Weinberg MA; Adalimumab Effectiveness in Psoriatic Arthritis Trial Study

Group. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum*. 2005;52(10):3279–3289.

Mease PJ. Measures of psoriatic arthritis: Tender and Swollen Joint Assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). *Arthritis Care Res*. 2011;63(S11):S64–S85.

Mease PJ, Woolley JM, Bitman B, Wang BC, Globe DR, Singh A. Minimally important difference of Health Assessment Questionnaire in psoriatic arthritis: relating thresholds of improvement in functional ability to patient-rated importance and satisfaction. *J Rheumatol*. 2011;38(11):2461-2465.

Mease PJ, Heckaman M, Kary S, Kupper H. Application and modifications of minimal disease activity measures for patients with psoriatic arthritis treated with adalimumab: subanalyses of ADEPT. *J Rheumatol.* 2013 May;40(5):647-52. doi: 10.3899/jrheum.120970. Epub 2013 Mar 15.

Mease PJ, Armstrong AW. Managing patients with psoriatic disease: the diagnosis and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. *Drugs*. 2014;74(4);423-441.

Milner JD, Brenchly JM, Laurence A, Freeman AF, Hill BJ, Elias KM, Kanno Y, Spalding C, Elloumi HZ, Paulson ML, Davis J, Hsu A, Asher AI, O'Shea J, Holland SM, Paul WE, Douek DC. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. *Nature*. 2008;452(7188):773-776.

Moverley A, Coates L, Marzo-Ortega H, Waxman R, Torgerson D, Cocks K, Watson J, Helliwell PS. A feasibility study for a randomised controlled trial of treatment withdrawal in psoriatic arthritis (REmoval of treatment for patients in REmission in psoriatic ArThritis (RETREAT (F)). *Clin Rheumatol*. 2015 Feb 3. [Epub ahead of print]

Mumtaz A, Gallagher P, Kirby B, Waxman R, Coates LC, Veale JD, Helliwell P, FitzGerald O. Development of a preliminary composite disease activity index in psoriatic arthritis. *Ann Rheum Dis.* 2011;70(2):272-277.

Nash P, Clegg DO. Psoriatic arthritis therapy: NSAIDs and traditional DMARDs. *Ann Rheum Dis.* 2005;64(suppl 2):ii74-ii77.

National Psoriasis Foundation. The Psoriasis and Psoriatic Arthritis Pocket Guide. Portland, OR. 2009.

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Pyschiatry.* 2007;164(7):1035-1043.

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics.* 1993;4(5):353-365.

Reilly Associates - Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP). Available at: http://www.reillyassociates.net/WPAI_SHP.html. Accessed July 8, 2014.

Rosen CF, Mussani F, Chandran V, Eder L, Thavaneswaran A, Gladman DD. Patients with psoriatic arthritis have worse quality of life than those with psoriasis alone. *Rheumatology*. 2012;51(3):571-576.

Ruderman EM. Overview of safety of non-biologic and biologic DMARDs. *Rheumatology*. 2012;51(suppl 6):vi37-43.

Rudwaleit M, Van den Bosch F, Kron M, Kary S, Kupper H. Effectiveness and safety of adalimumab in patients with ankylosing spondylitis or psoriatic arthritis and history of anti-tumor necrosis factor therapy. *Arthritis Res Ther*. 2010;12(3):R117.

Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB. The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biological Psychiatry*. 2003;54(50):573-583. Erratum in Biol Psychiatry. 2003;54(5);585.

Schoels M, Aletaha D, Funovits J, Kavanaugh A, Baker D, Smolen JS. Application of the DAREA/DAPSA score for assessment of disease activity in psoriatic arthritis. *Ann Rheum Dis*. 2010;69(8):1441-1447.

Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, Filippini G, Skoetz N, Francis D, Lopes LC, Guyatt GH, Schmitt J, La Mantia L, Weberschock T, Roos JF, Siebert H, Hershan S, Lunn MP, Tugwell P, Buchbinder R. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev*. 2011 16;(2):CD008794.

Smolen JS, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, Kirkpatrick J. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. *Arthritis Rheum.* 1995;38(1):38-43.

Smolen JS, Braun J, Dougados M, Emery P, Fitzgerald O, Helliwell P, Kavanaugh A, Kvien TK, Landewé R, Luger T, Mease P, Olivieri I, Reveille J, Ritchlin C, Rudwaleit M, Schoels M, Sieper J, Wit Md, Baraliakos X, Betteridge N, Burgos-Vargas R, Collantes-Estevez E, Deodhar A, Elewaut D, Gossec L, Jongkees M, Maccarone M, Redlich K, van den Bosch F, Wei JC, Winthrop K, van der Heijde D. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. *Ann Rheum Dis*. 2014;73(1):6-16.

Trivedi MH, Rush AJ, Ibrahim HM, Carmody TJ, Biggs MM, Suppes T, Crismon ML, Shores-Wilson K, Toprac MG, Dennehy EB, Witte B, Kashner TM. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. *Psychol Med.* 2004;34(1):73-82.

University of Pittsburgh Epidemiology Data Center. Inventory of Depressive Symptomatology (IDS) and Quick Inventory of Depressive Symptomatology (QIDS). Available at: http://www.ids-qids.org. Accessed July 08, 2014.

Vander Cruyssen B, Van Looy S, Wyns B, Westhovens R, Durez P, Van den Bosch F, Veys EM, Mielants H, De Clerck L, Peretz A, Malaise M, Verbruggen L, Vastesaeger N, Geldhof A, Boullart L, De Keyser F. DAS28 best reflects the physician's clinical judgment of response to infliximab therapy in rheumatoid arthritis patients: validation of the DAS28 score in patients under infliximab treatment. *Arthritis Res Ther.* 2005;7(5):R1063-R1071.

van der Heijde DM, van't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, van Rijswijk MH, van de Putte LB. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis*. 1990;49(11):916-920.

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36), I: Conceptual framework and item selection. *Med Care.* 1992;30(6):473-483.

Attachment 1. Protocol RHBF Study Schedule

Study Schedule, Protocol I1F-MC-RHBF

	Screening (Period 1)		Baseline	Initial Open-Label Treatment Period[a]								
Visit No. (V)	V1	V1A	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Study Week (W)			W0	W2	W4	W8	W12	W16	W20	W24	W28	W32
Study Days	-30 to -4	2-3d post V1	0	14 ± 2d	28 ± 2d	56 ± 4d	84 ± 4d	112 ± 4d	140 ± 4d	168 ± 4d	196 ± 4d	224 ± 4d
Informed consent	X											
Complete medical history	X											
Review preexisting conditions	X											
Age, gender, ethnicity	X											
Physical examination[b]	X						X			X		
PsA diagnosis (CASPAR criteria)	X											
Inclusion/exclusion criteria	X		X									
Body temperature			X									
Height			X									
Weight	X		X		X		X			X		
Sitting blood pressure and pulse	X		X[c]	X	X	X	X	X	X	X	X	X
Habits (tobacco, alcohol, caffeine use)			X							X		
TB risk factors			X									
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X
Review adverse events			X	X	X	X	X	X	X	X	X	X
Administer IP[d]			X[d]	Open-label IP Q2W								
Dispense IP			X	X	X	X	X	X	X	X	X	X
Dispense study drug administration log				Complete study drug administration log immediately after each IP administration.								
IP compliance[e]			X	X	X	X	X	X	X	X	X	X
TJC/SJC entry to IWRS[f]			X							X	X	X
MDA entry to IWRS										X	X	X
Patient Global Assmt Disease Activity VAS			X	X	X	X	X	X	X	X	X	X
Physician Global Assmt Disease Activity VAS			X	X	X	X	X	X	X	X	X	X
Patient's Assessment of Pain VAS			X	X	X	X	X	X	X	X	X	X

	Screening (Period 1)		Baseline	Initial Open-Label Treatment Period[a]								
Visit No. (V)	V1	V1A	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Study Week (W)			W0	W2	W4	W8	W12	W16	W20	W24	W28	W32
Study Days	-30 to -4	2-3d post V1	0	14 ± 2d	28 ± 2d	56 ± 4d	84 ± 4d	112 ± 4d	140 ± 4d	168 ± 4d	196 ± 4d	224 ± 4d
TJC/SJC (68/66 joints)	X		X	X	X	X	X	X	X	X	X	X
HAQ-DI			X	X	X	X	X	X	X	X	X	X
Enthesitis assessment (SPARCC and LEI)			X	X	X	X	X	X	X	X	X	X
LDI-B			X				X	X		X	X	X
PASI			X	X	X	X	X	X	X	X	X	X
% BSA			X	X	X	X	X	X	X	X	X	X
sPGA			X	X	X	X	X	X	X	X	X	X
Itch NRS	X		X	X	X	X	X	X	X	X	X	
Fatigue Severity NRS			X	X	X	X	X	X	X	X	X	
SF-36 v2 acute			X		X		X	X		X	X	
QIDS-SR16	X		X		X		X			X		
EQ-5D 5L			X		X	X	X	X		X	X	
WPAI-SHP			X		X		X	X		X	X	
DLQI			X	X	X		X	X		X		
C-SSRS[r]			X	X	X	X	X	X	X	X	X	X
Self-Harm Supplement Form[r]			X	X	X	X	X	X	X	X	X	X
Administer TB test	X											
Read PPD (if applicable)[g]		X										
Chest radiography	X[h]											
ECG[i]	X											
FSH	X[j]											
HIV/HCV	X											
HBV[k,l]	X		X									
Serum pregnancy test[m]	X											
Urine pregnancy test[m]			X		X	X	X	X	X	X	X	X
Serum chemistry	X		X		X		X			X		
Lipase/total amylase	X											

	Screening (Period 1)		Baseline	Initial Open-Label Treatment Period[a]								
Visit No. (V)	V1	V1A	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Study Week (W)			W0	W2	W4	W8	W12	W16	W20	W24	W28	W32
Study Days	-30 to -4	2-3d post V1	0	14 ± 2d	28 ± 2d	56 ± 4d	84 ± 4d	112 ± 4d	140 ± 4d	168 ± 4d	196 ± 4d	224 ± 4d
Lipid panel (fasting)			X		X		X			X		X
Advanced lipid profile			X				X					
Hematology	X		X		X		X			X		
PTT and PT	X											
TSH and free T4	X											
Urinalysis	X		X							X		X
IgA, IgG, IgM	X		X				X			X		
RF	X											
anti-CCP Ab (ACPA)			X									
hs-CRP			X	X	X	X	X	X	X	X	X	X
Lymphocyte subset (B, T, CD4+ T, CD8+ T, and NK)	X		X				X			X		X
Exploratory storage samples (serum, plasma and RNA)			X				X			X		X
Exploratory storage samples (DNA for pharmacogenetics)			X									
Exploratory storage samples (DNA for epigenetics)			X							X		
Immunogenicity testing[n]			X		X		X			X		
PK[o]			X		X		X			X		

	Randomized Double-Blind Withdrawal Period[a]										
Visit No. (V)	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22
Study Week (W)	W36	W40	W44	W48	W52	W56	W60	W64	W68	W72	W76
Study Days	252 ± 4d	280 ± 4d	308 ± 4d	336 ± 4d	364 ± 4d	392 ± 4d	420 ± 4d	448 ± 4d	476 ± 4d	504 ± 4d	532 ± 4d
Physical examination[b]					X						X
Weight	X	X	X	X	X	X	X	X	X	X	X
Sitting blood pressure and pulse	X	X	X	X	X	X	X	X	X	X	X
Habits (tobacco, alcohol, caffeine use)					X						
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Review adverse events	X	X	X	X	X	X	X	X	X	X	X
Administer IP[d]	Blinded IP Q2W per randomization schedule										
Dispense IP	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug administration log	Complete study drug administration log immediately after each IP administration.										
IP compliance[e]	X	X	X	X	X	X	X	X	X	X	X
TJC/SJC entry to IWRS[f]	X	X	X	X	X	X	X	X	X	X	X
MDA entry to IWRS	X	X	X	X	X	X	X	X	X	X	X
Patient Global Assmt Disease Activity VAS	X	X	X	X	X	X	X	X	X	X	X
Physician Global Assmt Disease Activity VAS	X	X	X	X	X	X	X	X	X	X	X
Patient's Assessment of Pain VAS	X	X	X	X	X	X	X	X	X	X	X
TJC/SJC (68/66 joints)	X	X	X	X	X	X	X	X	X	X	X
HAQ-DI	X	X	X	X	X	X	X	X	X	X	X
Enthesitis assessment (SPARCC and LEI)	X	X	X	X	X	X	X	X	X	X	X
LDI-B	X	X	X	X	X	X	X	X	X	X	X
PASI	X	X	X	X	X	X	X	X	X	X	X
%BSA	X	X	X	X	X	X	X	X	X	X	X

	Randomized Double-Blind Withdrawal Period[a]										
Visit No. (V)	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22
Study Week (W)	W36	W40	W44	W48	W52	W56	W60	W64	W68	W72	W76
Study Days	252 ± 4d	280 ± 4d	308 ± 4d	336 ± 4d	364 ± 4d	392 ± 4d	420 ± 4d	448 ± 4d	476 ± 4d	504 ± 4d	532 ± 4d
sPGA	X	X	X	X	X	X	X	X	X	X	X
Itch NRS	X	X	X	X	X	X	X	X	X	X	X
Fatigue Severity NRS	X		X		X		X		X		X
SF-36 v2 acute	X		X		X		X		X		X
QIDS-SR16	X		X			X			X		
EQ-5D 5L	X	X	X	X	X	X	X	X	X	X	X
WPAI-SHP	X		X		X		X		X		X
DLQI	X	X	X	X	X	X	X	X	X	X	X
C-SSRS[p]	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Supplement Form[p]	X	X	X	X	X	X	X	X	X	X	X
HBV[k,l]					X						
Urine pregnancy test[m]	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X
Lipid panel (fasting)					X						X
Advanced lipid profile					X						X
Hematology	X	X	X	X	X	X	X	X	X	X	X
Urinalysis					X						X
IgA, IgG, IgM					X						X
hs-CRP	X	X	X	X	X	X	X	X	X	X	X
Lymphocyte subset (B, T, CD4+ T, CD8+ T, and NK)					X						X
Exploratory storage samples (serum, plasma, RNA)					X						X
Immunogenicity testing[n]	X				X				X		
PK[o]	X				X				X		

	Randomized Double-Blind Withdrawal Period[a]							Early Termination	Posttreatment Follow-Up Period (Period 4)[q]		
Visit No. (V)	V23	V24	V25	V26	V27	V28	V29	ET	V801	V802	V803
Study Week (W)	W80	W84	W88	W92	W96	W100	W104		LV + 4W	V801 + 8W	V802 + 12W
Study Days	560 ± 4d	588 ± 4d	616 ± 4d	644 ± 4d	672 ± 4d	700 ± 4d	728 ± 4d		± 4d	± 4d	± 4d
Physical examination[b]							X	X			
Weight	X	X	X	X	X	X	X	X	X	X	X
Sitting blood pressure and pulse	X	X	X	X	X	X	X	X	X	X	X
Habits (tobacco, alcohol, caffeine use)							X	X			
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Review adverse events	X	X	X	X	X	X	X	X	X	X	X
Administer IP[d]	Blinded IP Q2W per randomization schedule										
Dispense IP	X	X	X	X	X	X					
Dispense study drug administration log	Complete study drug administration log immediately after each IP administration.										
IP compliance[e]	X	X	X	X	X	X	X	X			
TJC/SJC entry to IWRS[f]	X	X	X	X	X	X	X				
MDA entry to IWRS	X	X	X	X	X	X					
Patient Global Assmt Disease Activity VAS	X	X	X	X	X	X	X	X			
Physician Global Assmt Disease Activity VAS	X	x	X	X	X	X	X	X			
Patient's Assessment of Pain VAS	X	X	X	X	X	X	X	X			
TJC/SJC (68/66 joints)	X	X	X	X	X	X	X	X			
HAQ-DI	X	X	X	X	X	X	X	X			
Enthesitis assessment (SPARCC and LEI)	X	X	X	X	X	X	X	X			

	Randomized Double-Blind Withdrawal Period[a]							Early Termination	Posttreatment Follow-Up Period (Period 4)[q]		
Visit No. (V)	V23	V24	V25	V26	V27	V28	V29	ET	V801	V802	V803
Study Week (W)	W80	W84	W88	W92	W96	W100	W104		LV + 4W	V801 + 8W	V802 + 12W
Study Days	560 ± 4d	588 ± 4d	616 ± 4d	644 ± 4d	672 ± 4d	700 ± 4d	728 ± 4d		± 4d	± 4d	± 4d
LDI-B	X	X	X	X	X	X	X	X			
PASI	X	X	X	X	X	X	X	X			
%BSA	X	X	X	X	X	X	X	X			
sPGA	X	X	X	X	X	X	X	X			
Itch NRS	X	X	X	X	X	X	X	X			
Fatigue Severity NRS	X	X	X	X	X	X	X	X			
SF-36 v2 acute		X		X			X	X			
QIDS-SR16					X			X			
EQ-5D 5L	X	X	X	X	X	X	X	X			
WPAI-SHP		X		X			X	X			
DLQI	X	X	X	X	X	X	X	X			
C-SSRS[p]	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Supplement Form[p]	X	X	X	X	X	X	X	X	X	X	X
ECG							X				
HBV[k,l]							X	X		X	
Urine pregnancy test[m]	X	X	X	X	X	X	X	X			
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X
Lipid panel (fasting)							X	X			
Advanced lipid profile							X	X			
Hematology	X	X	X	X	X	X	X	X	X	X	X
Urinalysis							X	X			
IgA, IgG, IgM							X			X	
hs-CRP	X	X	X	X	X	X	X	X			

	Randomized Double-Blind Withdrawal Period[a]							Early Termination	Posttreatment Follow-Up Period (Period 4)[q]		
Visit No. (V)	V23	V24	V25	V26	V27	V28	V29	ET	V801	V802	V803
Study Week (W)	W80	W84	W88	W92	W96	W100	W104		LV + 4W	V801 + 8W	V802 + 12W
Study Days	560 ± 4d	588 ± 4d	616 ± 4d	644 ± 4d	672 ± 4d	700 ± 4d	728 ± 4d		± 4d	± 4d	± 4d
Lymphocyte subset (B, T, CD4+ T, CD8+ T, and NK)							X	X		X	
Exploratory storage samples (serum, plasma, RNA)							X	X		X	
Immunogenicity testing[on]				X				X	X	X	
PK[po]				X				X			

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Abbreviations: anti-CCP Ab = anti-cyclic citrullinated peptide antibodies, also known as ACPA (anti-citrullinated protein antibodies); ALT = alanine aminotransferase; Assmt = assessment; AST = aspartate aminotransferase; BSA = body surface area; CASPAR = Classification of Psoriatic Arthritis; C-SSRS = Columbia–Suicide Severity Rating Scale; d = days; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; EQ-5D 5L = European Quality of Life–5 Dimensions 5 Level; ET = Early Termination; ETV = early termination visit; FSH = follicle-stimulating hormone; HAQ-DI = Health Assessment Questionnaire–Disability Index; HBcAb+ = positive for anti-hepatitis B core antibody; HBsAb = anti-hepatitis B surface antibody; HBsAg– = negative for hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity (assay) C-reactive protein; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; IP = investigational product; IWRS = interactive web-response system; LDI-B = Leeds Dactylitis Index–Basic; LEI = Leeds Enthesitis Index; LV = date of last visit; MDA = minimal disease activity; NK = natural killer; No. = number; NRS = Numeric Rating Scale; PASI = Psoriasis Area and Severity Index; PK = pharmacokinetic; PPD = purified protein derivative; PsA = psoriatic arthritis; PT = prothrombin time; PTT = partial thromboplastin time; Q2W = every 2 weeks; QIDS-SR16 = Quick Inventory of Depressive Symptomatology-self report (16 items); RF = rheumatoid factor; RNA = ribonucleic acid; SF-36 V2 = Medical Outcomes Study 36-Item Short Form Health Survey, Version 2; SJC = swollen joint count; SPARCC = Spondyloarthritis Research Consortium of Canada; sPGA = Static Physician Global Assessment of Psoriasis; T4 = thyroxine; TB = tuberculosis; TJC = tender joint count; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; V = study visit; VAS = visual analog scale; W = study week; WPAI-SHP = Work Productivity and Activity Impairment–Specific Health Problem.

[a] If a patient discontinues the IP early, the patient will complete the ETV and then enter the posttreatment follow-up period of the protocol.

[b] One complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at Visit 1 (Screening). All remaining physical examinations throughout the study should include a symptom-directed physical evaluation as well as an examination of the heart, lungs, and abdomen and a visual examination of the skin.

[c] Sitting blood pressure and pulse will be recorded before IP dosing and 1 hour postdosing at baseline (Week 0, Visit 2) (Section 10.3.2.4).

[d] At Week 0 (baseline, Visit 2), initial injection will be performed by clinical staff and the second injection of IP at that visit will be administered by the patient or caregiver under the supervision of clinical staff (as described in Section 9.1.1). If additional training is necessary, an injection may be administered by the patient or caregiver under the supervision of clinical staff at Week 2 (Visit 3). Thereafter, IP will be administered by the patient or caregiver and should be administered unsupervised by the clinical staff. It is recommended that for these subsequent injections, the patient/caregiver administer the IP outside the trial site, preferably at the patient's home.

[e] IP compliance assessment begins with site personnel collecting, reviewing, and entering data from the patient's study drug administration log(s).

[f] Failure to demonstrate at least a 20% improvement from baseline in both TJC and SJC at Week 24 and at any subsequent visit through Week 104 will require treatment discontinuation except from the point of randomization until the visit after relapse for those patients who are randomized in Period 3.

[g] PPD results will be read approximately 2 to 3 days after test application.

[h] Chest radiography will be performed at screening (Visit 1) and assessed at site unless chest radiography has been obtained within past 6 months and the radiographs and/or report are available for review.

[i] ECGs may be obtained at additional times when deemed clinically necessary.

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[j] For female patients ≥40 and <60 years of age who have had a cessation of menses for at least 12 months, an FSH test will be performed to confirm nonchildbearing potential (FSH ≥40 mIU/mL).

[k] For any patient who is HBsAg–, HBcAb+, and HBsAb+ at screening, a quantitative HBsAb level, and a HBV DNA test will be performed by the central laboratory. A patient with an HBsAb level ≥200 mIU/mL and a negative serum HBV DNA test result may be enrolled in the study. However periodic monitoring of the patient's HBsAb level must be performed, as indicated in the study schedule. If the patient's HBsAb level decreases to <200 mIU/mL, then a HBV DNA test will also be performed by the central laboratory. If the HBV DNA test is negative, then the patient may remain in the study. However, repeat testing of the patient's HBsAb level and HBV DNA must be performed, at 4- to 8-week intervals, as long as the HBsAb level is <200 mIU/mL. If the HBsAb level increases to ≥200 mIU/mL, then the site may resume periodic monitoring of the patient's HBsAb, as indicated in the study schedule. See Section 10.3.3.4 for additional details.

[l] Any enrolled patient who is HBcAb+, regardless of HBsAb status or level, and who has an ALT or AST level >3xULN must undergo HBV DNA testing (see Section 10.3.3.4).

[m] Only for females of childbearing potential.

[n] Immunogenicity samples may also be analyzed for ixekizumab serum concentration to facilitate in the interpretation of immunogenicity data. An additional blood sample will be collected, when possible, for any patient who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator.

[o] PK samples will be from an aliquot of the immunogenicity samples.

[p] 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.

[q] Patients receiving investigational product who discontinue at any time prior to the end of the study or who complete the study (Week 104) will have safety Follow-Up Visits 801 and 802 at 4 weeks and 12 weeks, respectively, after the date of their last regularly scheduled visit. Visit 803 will only occur if a patient's neutrophil counts have not returned to the criteria defined in Section 7.1.4.

Attachment 2. Protocol RHBF Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Serum Chemistry[a]**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	Total bilirubin
Platelets	Direct bilirubin
	Alkaline phosphatase
Absolute counts of:	Alanine aminotransferase (ALT/SGPT)
Neutrophils, segmented	Aspartate aminotransferase (AST/SGOT)
Neutrophils, juvenile (bands)	Blood urea nitrogen
Lymphocytes	Uric acid
Monocytes	Creatinine
Eosinophils	Calcium
Basophils	Glucose, random
Lymphocyte subset (B cells, T cells, CD4+ T cells,	Albumin
CD8+ T cells, NK cells) (absolute and percentage)	Cholesterol (total)
	Total protein
Urinalysis (dipstick)[a]:	Calculated creatinine clearance[b]
Color	Creatine phosphokinase
Specific gravity	Triglycerides
pH	Gamma-glutamyl transferase
Protein	Lipase
Glucose	Total amylase
Ketones	Lipid panel (fasting)[c]
Bilirubin	LDL
Urobilinogen	HDL
Blood	Very low density lipoprotein (VLDL)
Nitrite	Advanced lipid profile
Urine creatinine	Oxidized LDL
Leukocyte esterase	Apolipoprotein A1
	Apolipoprotein B
Other Tests	
Serum immunoglobulins (IgA, IgG, and IgM)	
HIV antibody[d]	Pregnancy test (serum)[e]
Hepatitis B surface antigen (HBsAg)[d]	Urine pregnancy test (assayed by clinical study site)
Hepatitis B surface antibody (HBsAb)[d]	Follicle-stimulating hormone (FSH)[f]
Hepatitis B core antibody (HBcAb)[d]	Thyroid-stimulating hormone (TSH) and free T4
HBV DNA[d]	Ixekizumab serum concentration
Double-stranded DNA antibody[g]	Partial thromboplastin time
Hepatitis C antibody[h]	Prothrombin time
HCV RNA PCR[i]	Rheumatoid factor
PPD, QuantiFERON-TB Gold, T-SPOT.TB[j]	High-sensitivity C-reactive protein
anti-cyclic citrullinated peptide antibodies (also known as	Immunogenicity testing (anti-ixekizumab Ab)
ACPA, anti-citrullinated protein antibodies)	Exploratory storage samples (serum, plasma, urine,
	DNA, and RNA)

Clinical Laboratory Tests

Abbreviations: Ab = antibody; FSH = follicle-stimulating hormone; HBcAb+ = positive for anti-hepatitis B core antibody; HBsAb+ = positive for anti-hepatitis B surface antibody; HBsAg- = negative for hepatitis B surface antigen; HBV = hepatitis B virus; HDL = high low-density lipoprotein; HIV = human immunodeficiency virus; HCV = hepatitis C virus; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; LDL = low-density lipoprotein; NK = natural killer; PCR = polymerase chain reaction; PPD = purified protein derivative; RBC = red blood cell; RNA = ribonucleic acid; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T4 = thyroxine; TB = tuberculosis; WBC = white blood cell.

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

[b] Cockcroft-Gault calculation is used for the calculated creatinine clearance.

[c] For the fasting lipid profile, patients should not eat or drink anything except water for 12 hours before test.

[d] Test required at Visit 1 only to determine eligibility of patient for the study. Quantitative HBsAb and HBV DNA testing will be done in those patients who are HBsAg–, HBcAb+, and HBsAb+ at screening.

[e] Serum pregnancy test for all women <60 years of age who are still of childbearing potential; urine pregnancy test (performed locally) for all 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 nonchildbearing potential (≥40 mIU/mL).

[g] 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.

[h] See exclusion criterion [45] (Section 8.2) specific to hepatitis C antibody.

[i] Confirmatory test for anti–hepatitis C antibody.

[j] See Section 10.3.2.3: In countries where the QuantiFERON-TB Gold test or T-SPOT.TB test is available, it may be used instead of the PPD TB test.

Attachment 3. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils, segmented	
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; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

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

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

Attachment 4. Protocol RHBF CASPAR Criteria

The CASPAR criteria for psoriatic arthritis (PsA) consist of inflammatory articular disease (joint, spine, or entheseal) with ≥**3 points** from the following 5 categories.

- Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis **(2 points)**
  - Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.†
  - A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.
  - A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.
- Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination **(1 point)**
- A negative test result for the presence of rheumatoid factor by any method except latex **(1 point)**
- Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist **(1 point)**
- Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot **(1 point)**

† Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

Taylor, W, Gladman, D, Helliwell, P, Marchesoni, A, Mease, P, Mielants, H, CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum.* 2006;54(8):2665–2673.

Attachment 5. Protocol RHBF Tender and Swollen Joint Count Assessment Form

68/66 JOINT EVALUATION												
	Patient Right						Patient Left					
	Pain/ Tenderness			Swelling			Pain/Tenderness			Swelling		
JOINT* (Circle Correct Answer)	0 = Absent 1 = Present 9 = N/A*			0 = Absent 1 = Present 9 = N/A*			0 = Absent 1 = Present 9 = N/A*			0 = Absent 1 = Present 9 = N/A*		
1. Temporomandibular	0	1	9	0	1	9	0	1	9	0	1	9
2. Sternoclavicular	0	1	9	0	1	9	0	1	9	0	1	9
3. Acromioclavicular	0	1	9	0	1	9	0	1	9	0	1	9
4. Shoulder	0	1	9	0	1	9	0	1	9	0	1	9
5. Elbow	0	1	9	0	1	9	0	1	9	0	1	9
6. Wrist	0	1	9	0	1	9	0	1	9	0	1	9
7. Metacarpophalangeal I	0	1	9	0	1	9	0	1	9	0	1	9
8. Metacarpophalangeal II	0	1	9	0	1	9	0	1	9	0	1	9
9. Metacarpophalangeal III	0	1	9	0	1	9	0	1	9	0	1	9
10. Metacarpophalangeal IV	0	1	9	0	1	9	0	1	9	0	1	9
11. Metacarpophalangeal V	0	1	9	0	1	9	0	1	9	0	1	9
12. Thumb interphalangeal	0	1	9	0	1	9	0	1	9	0	1	9
13. Proximal interphalangeal II	0	1	9	0	1	9	0	1	9	0	1	9
14. Proximal interphalangeal III	0	1	9	0	1	9	0	1	9	0	1	9
15. Proximal interphalangeal IV	0	1	9	0	1	9	0	1	9	0	1	9
16. Proximal interphalangeal V	0	1	9	0	1	9	0	1	9	0	1	9
17. Distal interphalangeal II	0	1	9	0	1	9	0	1	9	0	1	9
18. Distal interphalangeal III	0	1	9	0	1	9	0	1	9	0	1	9
19. Distal interphalangeal IV	0	1	9	0	1	9	0	1	9	0	1	9
20. Distal interphalangeal V	0	1	9	0	1	9	0	1	9	0	1	9
21. Hip	0	1	9	N/A			0	1	9	N/A		
22. Knee	0	1	9	0	1	9	0	1	9	0	1	9
23. Ankle	0	1	9	0	1	9	0	1	9	0	1	9
24. Tarsus	0	1	9	0	1	9	0	1	9	0	1	9
25. Metatarsophalangeal I	0	1	9	0	1	9	0	1	9	0	1	9
26. Metatarsophalangeal II	0	1	9	0	1	9	0	1	9	0	1	9
27. Metatarsophalangeal III	0	1	9	0	1	9	0	1	9	0	1	9
28. Metatarsophalangeal IV	0	1	9	0	1	9	0	1	9	0	1	9
29. Metatarsophalangeal V	0	1	9	0	1	9	0	1	9	0	1	9
30. Great toe	0	1	9	0	1	9	0	1	9	0	1	9
31. Interphalangeal II	0	1	9	0	1	9	0	1	9	0	1	9

68/66 JOINT EVALUATION												
	Patient Right						Patient Left					
	Pain/ Tenderness			Swelling			Pain/Tenderness			Swelling		
JOINT* (Circle Correct Answer)	0 = Absent 1 = Present 9 = N/A*			0 = Absent 1 = Present 9 = N/A*			0 = Absent 1 = Present 9 = N/A*			0 = Absent 1 = Present 9 = N/A*		
32. Interphalangeal III	0	1	9	0	1	9	0	1	9	0	1	9
33. Interphalangeal IV	0	1	9	0	1	9	0	1	9	0	1	9
34. Interphalangeal V	0	1	9	0	1	9	0	1	9	0	1	9

*For replaced, ankylosed, or arthrodesed joints, please record as 9 (not applicable) and record details of replaced, ankylosed, or arthrodesed joints.

Abbreviation: N/A = not applicable.

Attachment 6. Protocol Amendment I1F-MC-RHBF(b) Summary

Overview

Protocol I1F-MC-RHBF, A Phase 3, Multicenter Study with a 36-Week Open-Label Period Followed by a Randomized Double-Blind Withdrawal Period from Week 36 to Week 104 to Evaluate the Long-Term Efficacy and Safety of Ixekizumab (LY2439821) 80 mg Every 2 Weeks in Biologic Disease-Modifying Antirheumatic Drug–Naive Patients with Active Psoriatic Arthritis, 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:

- Change the 2nd interim analysis (which includes the primary outcome) from when 39 patients relapse or when all patients complete Week 104, whichever comes first to when all patients complete Week 104.
- Remove annual TB testing consistent with compound level decision.
- Add IBD adjudication consistent with compound level decision.
- Adjust the language for the first Interim DBL for more clarity.
- Add in language clarifying withholding study treatment for surgery and the use of concomitant medication for AEs.

Revised Protocol Sections

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

4. Abbreviations and Definitions

Term	Definition
IBD	Inflammatory bowel disease (e.g. Crohn's disease and ulcerative colitis)
~~**LOCF**~~	~~last observation carried forward~~
mBOCF	modified baseline observation carried forward

8.3.1.1 Discontinuation Criteria

- Any positive TB test that indicates TB test conversion since prior testing (based on patient medical history or Visit 1 screening test), AND the patient does not receive appropriate treatment for latent TB; or there is evidence of active TB infection at any time ~~the result of the TB test is positive at Week 52 (Visit 16) or later AND the patient is diagnosed with active infection~~ (see Section 10.3.2.3).

9.8. Concomitant Therapy

Additional guidance: Patients requiring surgery at any time during the study should interrupt administration of the investigational product beginning 8 weeks prior to the surgery, or as early as possible within 8 weeks of surgery, and resume administration of the Investigational product only after complete wound healing.

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, 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 allowed 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. Unless urgent medication is indicated by the patient's medical condition, patients should be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements.

10.3.1.1.2. Adverse Events of Special Interest

Data on suspected IBD, as identified by events possibly indicative of ulcerative colitis and/or Crohn's disease, 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 CEC will be to adjudicate defined clinical events, in a blinded, consistent, and unbiased manner throughout the course of a study. The importance of the CEC is to ensure that all events that have been reported are evaluated uniformly by a single group.

10.3.2.3. Chest Radiography and Tuberculosis Testing

TB testing: Patient history of TB test results should be assessed before screening (Visit 1).

Patients with no TB test results on file: These patients will be tested at screening (Visit 1). A PPD skin test response of ≥5-mm induration, between approximately 2 and 3 days after test application, regardless of BCG vaccination history, will be considered a positive result. In countries where the QuantiFERON-TB Gold test or T-SPOT.TB test is available and in the judgment of the investigator preferred as an alternative to the PPD skin test for the evaluation of TB infection, those tests may be used instead of the PPD test. If the QuantiFERON-TB Gold test or the T-SPOT.TB test is indeterminate, 1 retest is allowed. If the retest is indeterminate, the patient is excluded from the study.

Patients with positive results from a TB test performed at screening (Visit 1) but no other evidence of active TB may be rescreened once and enrolled on the basis of the following requirements:

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

~~The same TB test method used for determining eligibility should be used for all TB testing throughout the study for a given patient.~~

TB Testing and Assessment for Patients during the Study:

~~Eligible patients with negative TB test results at screening (Visit 1) or on file are required to have annual TB tests as per the study schedule (Attachment 1).~~

~~Eligible patients with positive TB test results at screening (Visit 1) or on file are not required to have annual TB tests.~~

~~Patients who develop positive TB test results during the study and are eligible to continue the study are not required to have subsequent annual TB tests.~~

Tuberculosis testing during the study will be conducted based on clinical assessment of TB risk (symptoms/signs/known or suspected TB exposure), and as required by local regulations and/or local standard of care.

Patients testing positive for TB at any time during the study must immediately discontinue administration of investigational product. The patient must be evaluated for latent or active infection. Patients with active infection must be discontinued from the study and should receive appropriate follow-up medical care and TB treatment according to local guidelines; patients with latent infection must receive a full course of LTBI treatment but may resume administration of investigational product after receiving 4 weeks of LTBI treatment with no evidence of hepatotoxicity (ALT and AST levels must remain ≤2× ULN) upon retesting of serum ALT and AST before resumption of investigational product. Such patients must complete appropriate LTBI therapy during the course of the study to remain eligible to continue the study treatment.

12.2.1.2. General Considerations for Analyses during Period 3 (Randomized Double-Blind Withdrawal Period)

For patients who are randomized in Period 3, all efficacy, health outcomes, and safety data collected between randomization and either through relapse (no longer meeting Coates criteria for MDA) or through the end of Period 3 will be compared between the ixekizumab 80 mg Q2W and placebo treatment groups. For the efficacy analysis, baseline is defined as the last available value before the first dose of study medication in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2). For the safety analysis, baseline is defined as the last available value before the first dose of study treatment in Period 3.

The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to variables for the patients who are randomized to the randomized double-blind withdrawal period. Treatment comparisons will be performed using a log-rank test with treatment, geographic region, and cDMARD use (past use, current use), at the time of randomization in Period 3, in the model.

The primary analysis of the categorical efficacy and health outcome variables will use a logistic regression with treatment, geographic region, and cDMARD use (past use, current use), at the time of randomization in Period 3, in the model. Secondary analysis of the categorical efficacy and health outcome variables will be conducted using the Fisher's exact test.

The analysis for all continuous efficacy and health outcome variables, change from baseline to endpoint analysis, will be made using analysis of covariance with treatment, baseline value, geographic region, and cDMARD use (past use, current use), at the time of randomization in Period 3, in the model. Missing data will be imputed using modified baseline ~~last~~ observation

carried forward (mB~~L~~OCF). Type III sums of squares for the least-squares means will be used for the statistical comparison; the 95% CI will also be reported.

The Fisher's exact test will be used for all AE, baseline, discontinuation, and other categorical data. AE data will be analyzed using exposure-adjusted incidence rates. Continuous vital sign and laboratory values will be analyzed by an analysis of covariance model with treatment and baseline value as independent variables. Other continuous variables will be analyzed by t-tests unless otherwise stated.

For patients who randomize and subsequently relapse in Period 3, efficacy, health outcomes, and safety data collected between relapse and the end of Period 3 will be summarized for ixekizumab 80 mg Q2W without inferential statistics. For the efficacy and health outcomes analyses, baseline is defined as the last available value before the first dose of study medication in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2). For the safety analysis, baseline is defined as the last available value before relapse in Period 3.

12.2.1.5.2. Modified Baseline ~~Last~~ Observation Carried Forward

An mBOCF analysis will be performed on all continuous efficacy and health outcome variables. In this approach, the baseline observation will be carried forward to the corresponding endpoint for evaluation for patients who discontinue study treatment due to an AE. The last nonmissing observation before discontinuation of study treatment will be carried forward to the corresponding primary endpoint for evaluation for patients who discontinue study treatment for any reason other than due to an AE. Patients without at least 1 postbaseline observation will not be included for evaluation, with the exception of patients who discontinue study treatment due to an AE.

~~A LOCF analysis will be performed on all continuous efficacy and health outcome variables. In this approach the last nonmissing postbaseline observation before study treatment discontinuation will be carried forward to the corresponding endpoint for evaluation. Patients without at least 1 postbaseline observation will not be included for evaluation.~~

12.2.6.2.3. Combined Initial Treatment and Randomized Double-Blind Withdrawal Periods (Periods 2 and 3)

The HAQ-DI score will be summarized for the ixekizumab 80 mg Q2W treatment group at each visit and endpoint (mB~~L~~OCF) during the combined Periods 2 and 3 for the randomized withdrawal ITT and the nonrandomized withdrawal populations. Summarizations will include observed scores, change from baseline, percentage improvement, and response rates $\geq$0.35.

12.2.10. Interim Analysis

The study will have approximately 2 interim and 1 final database locks. The first interim database lock may ~~will~~ occur once all patients complete or discontinue in the ~~initial~~ open-label treatment period; only data from the ~~initial~~ open-label treatment period will be summarized. For analysis purposes, the end of the ~~initial~~ open-label treatment period will be defined as the visit of randomization or Week 64 for patients who do not meet the randomization criteria. The second

interim database lock may ~~will~~ occur ~~when 39 patients meet relapse criteria or~~ when all patients complete Week 104 or discontinue study treatment prior to the end of the randomized double-blind withdrawal period~~, whichever comes first~~. The final database lock will occur when all patients complete or discontinue the study. ~~The study will not be terminated early on the basis of efficacy after the second interim database lock.~~ However, the second interim may not be performed depending upon the timing of the final database lock once all patients complete the post-treatment follow up period. Analyses for these interim analyses will be specified in the SAP along with the unblinding plan. Additional analyses and snapshots of study data may be performed to fulfill the need for regulatory interaction or publication purposes. ~~Analyses for these interim analyses will be specified in the SAP along with the unblinding plan.~~

Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded. All investigators and patients will remain blinded to treatment assignments until the last patient completes the randomized double-blind withdrawal period and the final database lock occurs.

Attachment 1. Protocol RHBF Study Schedule

Study Schedule, Protocol I1F-MC-RHBF (changes/additions)

	Screening (Period 1)		Baseline	Initial Open-Label Treatment Period[a]								
Visit No. (V)	V1	V1A	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Study Week (W)			W0	W2	W4	W8	W12	W16	W20	W24	W28	W32
Study Days	-30 to -4	2-3d post V1	0	14 ± 2d	28 ± 2d	56 ± 4d	84 ± 4d	112 ± 4d	140 ± 4d	168 ± 4d	196 ± 4d	224 ± 4d
Read PPD (if applicable)[g]		X[hi]										
Chest radiography	X[hi]											
ECG[hi]	X											
FSH	X[hj]											
HBV[hk,ml]	X		X									
Serum pregnancy test[enm]	X											
Urine pregnancy test[enm]			X		X	X	X	X	X	X	X	X
Immunogenicity testing[epq]			X		X		X			X		
PK[epo]			X		X		X			X		

	Randomized Double-Blind Withdrawal Period[a]										
Visit No. (V)	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22
Study Week (W)	W36	W40	W44	W48	W52	W56	W60	W64	W68	W72	W76
Study Days	252 ± 4d	280 ± 4d	308 ± 4d	336 ± 4d	364 ± 4d	392 ± 4d	420 ± 4d	448 ± 4d	476 ± 4d	504 ± 4d	532 ± 4d
~~TB risk factors~~					~~X~~						
C-SSRS[ep]	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Supplement Form[fq]	X	X	X	X	X	X	X	X	X	X	X
~~Administer TB test~~					~~X~~						
~~Read PPD (if applicable)[g]~~					~~X~~						
HBV[ik,mj]					X						
Urine pregnancy test[qm]	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity testing[on]	X				X				X		
PK[po]	X				X				X		

Study Schedule, Protocol I1F-MC-RHBF (changes/additions - concluded)

	Randomized Double-Blind Withdrawal Period[a]							Early Termination	Posttreatment Follow-Up Period (Period 4)[q]		
Visit No. (V)	V23	V24	V25	V26	V27	V28	V29	ET	V801	V802	V803
Study Week (W)	W80	W84	W88	W92	W96	W100	W104		LV + 4W	V801 + 8W	V802 + 12W
Study Days	560 ± 4d	588 ± 4d	616 ± 4d	644 ± 4d	672 ± 4d	700 ± 4d	728 ± 4d		± 4d	± 4d	± 4d
~~TB risk factors~~							~~X~~				
C-SSRS[ql]	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Supplement Form[ql]	X	X	X	X	X	X	X	X	X	X	X
~~Administer TB test~~							~~X~~				
~~Read PPD (if applicable)[c]~~							~~X~~				
HBV[jk,ql]							X	X		X	
Urine pregnancy test[qm]	X	X	X	X	X	X	X	X			
Immunogenicity testing[on]				X				X	X	X	
PK[po]				X				X			

Study Schedule, Protocol I1F-MC-RHBF

~~h. Patients with a PPD TB skin test ≥5 mm induration or a positive QuantiFERON-TB Gold test at Screening (Period 1), or who have a documented treatment history as defined in Section 10.3.2.3, should not undergo the TB test at Week 52 (Visit 16) or the yearly testing.~~

ih Chest radiography will be performed at screening (Visit 1) and assessed at site unless chest radiography has been obtained within past 6 months and the radiographs and/or report are available for review.

ii ECGs may be obtained at additional times when deemed clinically necessary.

~~ij~~ For female patients ≥40 and <60 years of age who have had a cessation of menses for at least 12 months, an FSH test will be performed to confirm nonchildbearing potential (FSH ≥40 mIU/mL).

~~jk~~ For any patient who is HBsAg–, HBcAb+, and HBsAb+ at screening, a quantitative HBsAb level, and a HBV DNA test will be performed by the central laboratory. A patient with an HBsAb level ≥200 mIU/mL and a negative serum HBV DNA test result may be enrolled in the study. However periodic monitoring of the patient's HBsAb level must be performed, as indicated in the study schedule. If the patient's HBsAb level decreases to <200 mIU/mL, then a HBV DNA test will also be performed by the central laboratory. If the HBV DNA test is negative, then the patient may remain in the study. However, repeat testing of the patient's HBsAb level and HBV DNA must be performed, at 4- to 8-week intervals, as long as the HBsAb level is <200 mIU/mL. If the HBsAb level increases to ≥200 mIU/mL, then the site may resume periodic monitoring of the patient's HBsAb, as indicated in the study schedule. See Section 10.3.3.4 for additional details.

~~kl~~ Any enrolled patient who is HBcAb+, regardless of HBsAb status or level, and who has an ALT or AST level >3xULN must undergo HBV DNA testing (see Section 10.3.3.4).

~~lm~~ Only for females of childbearing potential.

~~mn~~ Immunogenicity samples may also be analyzed for ixekizumab serum concentration to facilitate in the interpretation of immunogenicity data. An additional blood sample will be collected, when possible, for any patient who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator.

~~no~~ PK samples will be from an aliquot of the immunogenicity samples.

~~op~~ 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.

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