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

The other secondary objectives of the study are as follows:

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

case report form (eCRF)	
CD	Crohn's disease
CEC	Clinical Events Committee
cGMP	current Good Manufacturing Practices
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
clinical research physician (CRP)	Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CLRM	Clinical Laboratory Results Modernization
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
consent	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
CRS	clinical research scientist
C-CASA	Columbia Classification Algorithm of Suicide Assessment
C-SSRS	Columbia-Suicide Severity Rating Scale
CVA	cerebrovascular accident
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram

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

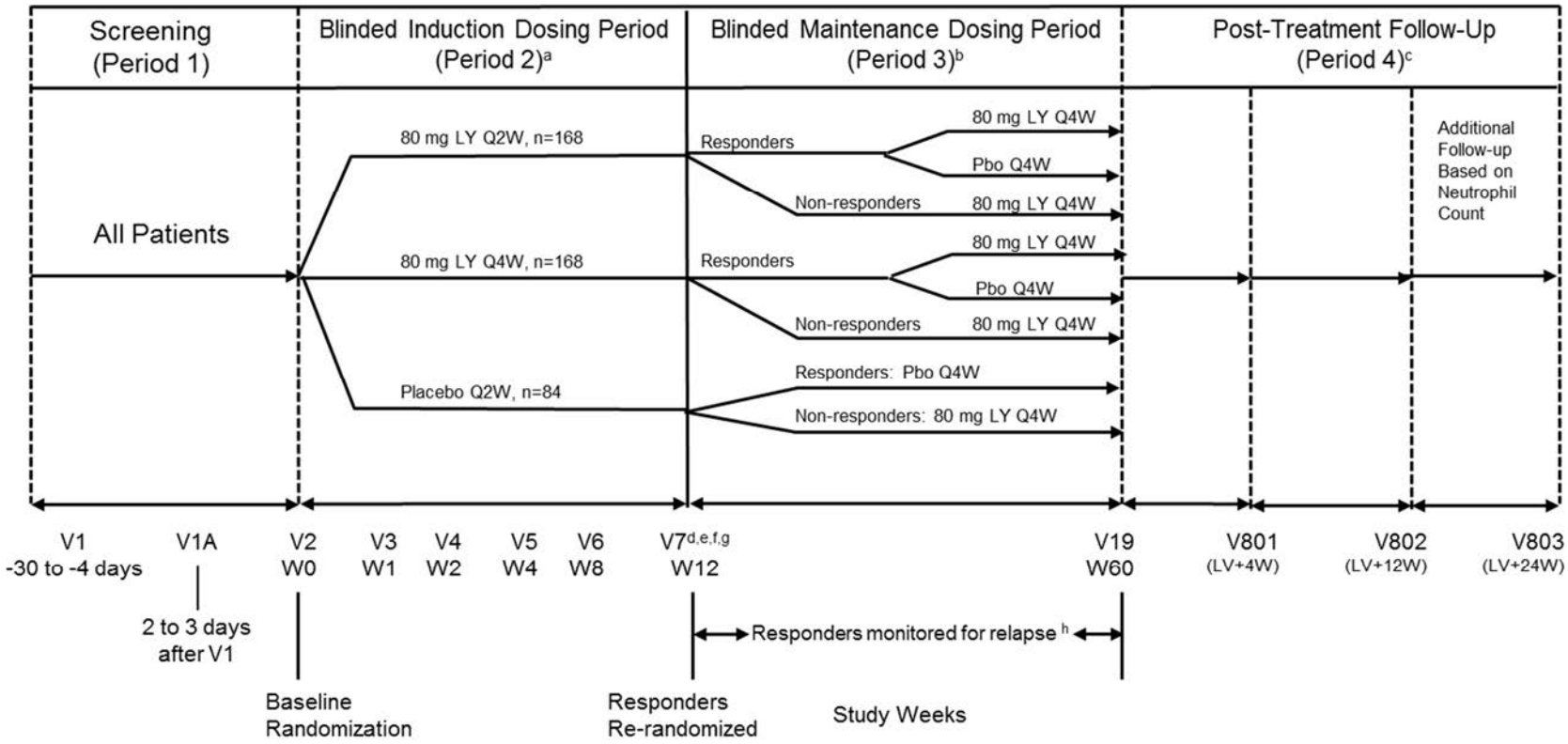

Figure 7.1. Illustration of study design for Clinical Protocol I1F-MC-RHBH (not to scale).

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

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

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

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

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

10.1.2.2. Psoriasis Scalp Severity Index (PSSI)

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

10.1.2.3. Palmoplantar Psoriasis Area and Severity Index (PPASI)

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

10.1.2.4. Percentage of Body Surface Area (BSA)

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

10.2. Health Outcome/Quality of Life Measures

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

10.2.1. Itch Numeric Rating Scale (NRS)

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

10.2.2. Dermatology Life Quality Index (DLQI)

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

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

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

10.2.4. Patient's Global Assessment of Disease Severity

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

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

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

10.3. Safety Evaluations

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

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

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

10.3.1. Adverse Events

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

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

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

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

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or designee.

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

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, investigational product, concomitant therapy, and other medical condition via eCRF.

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

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

10.3.1.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

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

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

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

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

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

10.3.1.1.1. Adverse Events of Special Interest

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

Adverse events of special interest for ixekizumab are:

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

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

available at the site and in the judgment of the investigator preferred as an alternative to the PPD skin test for the evaluation of TB infection, it may be used instead of the PPD test (positive test excluded) and would be sent to central lab for testing. If the QuantiFERON®-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, the patient will be excluded from the study. If the retest is positive but without clinical evidence of TB, the patients will be considered as latent TB for study purpose.

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

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

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

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

10.3.2.3. Vital Signs

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

10.3.2.4. Electrocardiograms

For each patient, 12-lead digital ECGs will be obtained locally as single ECGs according to the Study Schedule (Attachment 1). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high quality records.

11. Data Quality Assurance

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

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

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

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

11.1. Data Capture System

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

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

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

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

Proportion of Patients with PASI 100 at Week 12

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

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

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

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

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

Change from Baseline in DLQI at Week 12

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

Change from Baseline in NAPSI at Week 12

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

12.2.6.3. Other Secondary Analyses

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

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

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

12.2.8. Safety Analyses

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

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

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

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

12.2.8.1. Adverse Events

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

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

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

12.2.8.2. Clinical Laboratory Tests

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

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

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

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

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

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

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

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

12.2.9. Subgroup Analyses

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

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

12.2.10. Planned Analyses

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

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

12.2.10.1. Data Monitoring Committee

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

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

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

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

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

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

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

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

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

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

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

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

Study Schedule, Protocol I1F-MC-RHBH

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

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

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

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

The study consists of 4 periods:

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

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

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

8. Study Population

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

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

Individuals who do not meet the criteria for participation in this study (not qualify at screening under exclusion criteria [28] or [29] and latent TB patients after receiving at least 4 weeks of appropriate treatment [see section for 10.3.2.2 for additional requirements]) may be rescreened (1 time) at least 4 weeks after documented resolution of symptoms or appropriate treatment of latent TB. Each time re-screening is performed, the individual must sign a new ICF and will be assigned a new identification number. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

8.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

[1] Are male or female patients 18 years or older

[1a] Male patients agree to use a reliable method of birth control during the study and for at least 12 weeks following the last dose of investigational product. Examples of reliable methods include abstinence, vasectomy, and male condom with spermicide.

[1b] Female patients:

Are women of childbearing potential who test negative for pregnancy and agree to use a reliable method of birth control or remain abstinent during the study and for at least 12 weeks following the last dose of investigational product, whichever is longer. Methods of contraception considered acceptable include oral contraceptives, contraceptive patch, intrauterine device, vaginal ring, diaphragm with contraceptive gel, or condom with contraceptive gel.

-or-

Are women of non-childbearing potential, defined as:

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

-or-

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

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

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

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

10.3.1.1.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

10.3.2. Other Safety Measures

10.3.2.1. Physical Examination

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

10.3.2.2. Chest X-Ray and Tuberculosis Testing

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

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

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, and for immediate patient management, should any clinically relevant findings be identified. The qualified physician must document his/her review of the ECG at the time of evaluation. Any clinically significant findings that result in a diagnosis should be captured on the eCRF.

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

10.3.2.5. Immunogenicity

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

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

10.3.2.6. Safety-Related Immune Markers

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

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

10.3.2.7. Quick Inventory of Depressive Symptomatology-Self Report

QIDS-SR16 is a self-administered, 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (APA 1994). The QIDS-SR16 scale is used to assess the potential impact of treatment on new onset or changes in depression, thoughts of death, and/or suicidal ideation severity. A patient is asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are

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

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

12.2.6.3.1. Period 2 (Induction Dosing Period)

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

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

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

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

12.2.6.3.2. Period 3 (Maintenance Dosing Period)

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

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

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

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

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

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

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

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

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

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are submitted to the ERB and are used at clinical sites(s). All ICFs must be compliant with the ICH guideline on GCP.

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

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

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

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

13.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

2) the ICH GCP Guideline [E6]

3) applicable laws and regulations

7.1.1. Screening Period (Period 1)

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

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

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

7.1.2. Induction Dosing Period (Period 2)

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

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

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

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

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

7.1.3. Maintenance Dosing Period (Period 3)

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

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