Stat Analysis Plan V3

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

NCT02584855

Approval Date: 25-Oct-2018

1. Statistical Analysis Plan: I1F-MC-RHBF: 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) Psoriatic Arthritis

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 biologic 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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Protocol I1F-MC-RHBF
Phase 3

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 30 October 2015
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly: 20 April 2017
Statistical Analysis Plan Version 3 electronically signed and approved by Lilly on date provided below

Approval Date: 25-Oct-2018 GMT

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved on 30 October 2015 prior to first patient visit.

Two protocol amendments were completed after the SAP Version 1 was approved. Protocol amendment (a) was approved on 10 February 10 2016 and protocol amendment (b) was approved on 21 March 2017.

Statistical Analysis Plan (SAP) Version 2 was approved on 20 April 2017 prior to unblinding of patients randomized in the double-blind randomized withdrawal period. The changes incorporated in SAP Version 2 are as follows:

- Conventional disease-modifying antirheumatic drug (cDMARD) use was added as a stratification parameter to the primary analysis log-rank model. Protocol I1F-MC-RHBF (RHBF) Section 12.2.6.1 indicates that only geographic region is used as a stratification parameter in the model. However, cDMARD use (past, current) is also a stratification parameter in the randomization scheme and should be added to the primary analysis model.
- Similarly, cDMARD use will be added as stratification parameter to the logistic regression model for the categorical efficacy and health outcomes analyses (see Protocol Section 12.2.1.2).
- Psoriatic arthritis (PsA) subtypes will not be included in the baseline patient characteristic analysis. Although this was stated in the protocol, the information is not collected.
- The missing data imputation method, modified baseline observation carried forward (mBOCF) was added to the SAP. This method will be used in addition to last observation carried forward (LOCF). If a case arises in which using these 2 methods is not consistent, the mBOCF method will be the primary method.
- Clarified the population for the Health Assessment Questionnaire–Disability Index (HAQ-DI) total score improvement ≥0.35 analysis. Patients need to have baseline HAQ-DI total score ≥0.35 to be considered for improvement.
- Clarified the definition for the analysis on tender entheseal points will be based on the assessment of the 18 entheseal points.
- Corrected the derivation for duration of exposure for Period 2 and Period 3 combined.
- Updates to the safety analysis per program safety analysis plan (PSAP) Version 7.
- Updates to the immunogenicity analysis per PSAP Version 7.
- Clarified that the longitudinal analyses will be summarized by treatment week instead of by visit and through 40 weeks of treatment.
- Added secondary analyses for C-reactive protein (CRP).

Statistical Analysis Plan (SAP) Version 3 was approved prior to unblinding of patients randomized in the double-blind randomized withdrawal period. The changes incorporated in SAP Version 3 are as follows:

- Added analyses for disease activity in PsA (DAPSA).
- Removed analyses for DLQI (0).
- Clarified that longitudinal analyses will be done by treatment week through the last observation for the Randomized Double-Blind Withdrawal Period and the Relapse Period.
- Clarified that only analyses within the Randomized Double-Blind Withdrawal Period will include missing data imputations (NRI for categorical endpoints and mBOCF for continuous endpoints).
- Clarified that pre-existing conditions are defined as having a start date prior to the date of informed consent and not prior to the date of first study drug injection.
- Clarified that the treatment compliance calculation for Period 3 does not include the loading dose.
- Removed analyses for treatment compliance and protocol deviation analyses for the relapse period and the combined Periods 2 and 3.
- Clarified that the time-to endpoints in Period 3 are calculated with respect to the start of Period 3 and not Period 2.
- Removed a majority of the safety analyses for the post-treatment follow-up period.
- Clarified that categorical analyses assessed during Period 3 will be assessed through 40 weeks of randomized treatment with the exception of the proportion of patients who relapse. The analyses for the proportion of patients who relapse will be assessed over the entire randomized withdrawal study period with cumulative rate. Additionally, the proportion of patients who relapse will be described by treatment week for the entire randomized withdrawal study period.
- Removed laboratory and vital sign analyses for change from baseline to each scheduled post-baseline visit.
- Removed laboratory and vital sign box plots.
- Added laboratory shift tables for neutrophils, leukocytes, platelets, and lymphocytes.
- Removed common adverse event section and moved the exposure-adjusted analysis details to the general consideration section.
- Removed the region pooling statement.
- For AESIs:
    - removed analyses for elevated hepatic criteria;

  - removed the TEAE table for opportunistic infections by preferred term;
  - removed TEAE table for ISRs by preferred term within high-level terms; and
  - removed analyses for IBD and ILD with the except of TEAE by preferred tem by max severity by preferred term within category.

- Added a protocol deviation for patients who start on IXE in the Randomized Double-Blind Withdrawal Period prior to experiencing a relapse (no longer meeting Coates criteria for MDA in Period 3). These patients will also be removed from the PPS.
- Updated the derivation of the protocol deviations for entry criteria [1] and [4].
- Updated the statistical model for testing efficiacy subgroup interactions to the Cox-proprotional hazards model.
- Added Appendix 2 for calculating Coates criteria for minimal disease activity (MDA).
- Clarified the algorithm for calculating Joint Counts (see Appendix 3).
- AESIs were updated per the updated with changes from the PSAP Verions 7 and 8.
- Made other minor typographical corrections and clarifications not affecting content.

4. Study Objectives

4.1. Primary Objective

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 cDMARD inadequate responders (cDMARD-IR) and biologic DMARD-naive (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).

4.2. 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.

4.3. 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 Disease Activity Score modified to include the 28 diarthrodial joint count, based on C-reactive protein (DAS28-CRP), Psoriatic Arthritis Disease Activity Score (PASDAS), Composite Psoriatic Disease Activity Index (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% body surface area [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 (PCS), and Mental Component Summary (MCS) 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, and whole-blood messenger ribonucleic acid (RNA) and deoxyribonucleic acid (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.

5. Study Design

5.1. Summary of Study Design

Study 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.
- **Period 4:** post-treatment 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.5.1 illustrates the study design.

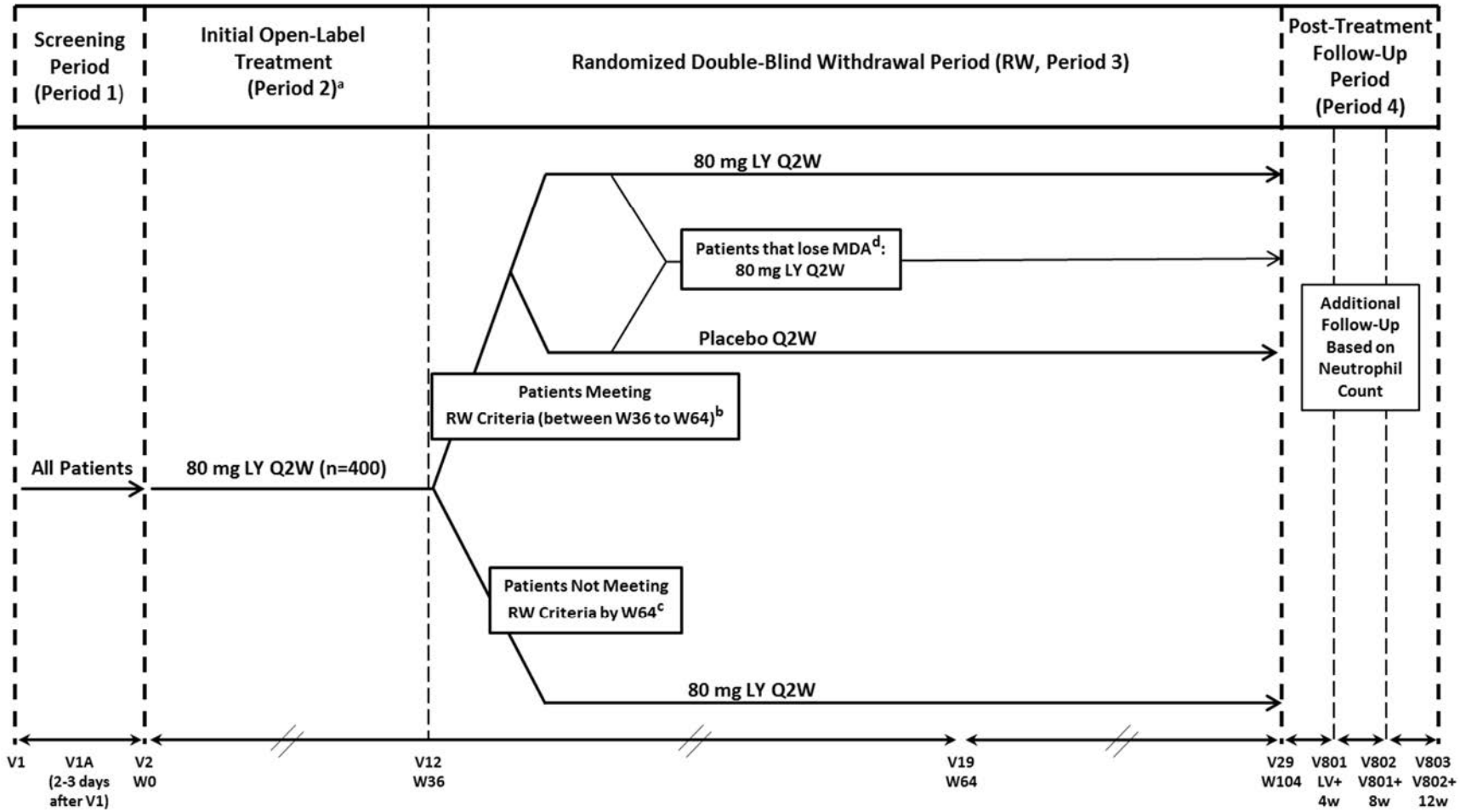
All procedures to be conducted during the study, including timing of all procedures, are indicated in the study schedule (Protocol Attachment 1). Selected study procedures should be performed before administration of the investigational product, as applicable, according to the study schedule. Protocol Section 10.4 describes collection of laboratory samples; Protocol 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 early termination visit (ETV) before proceeding to the post-treatment follow-up period (Period 4). For the management of patient safety, all patients should be monitored through the post-treatment follow-up period at least as frequently as indicated on the study schedule (Protocol Attachment 1).

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

Excluded and restricted therapies are detailed in Protocol Section 9.8.

Pharmacokinetic sampling is detailed in Protocol Section10.4.4.



See footnotes on the following page.

Figure RHBF.5.1. 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 Week 36 and Week 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 post-treatment follow-up period).

5.2. 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 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.

5.3. 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 (past use, current use) at the time of randomization in Period 3.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (hereafter Lilly). The statistical analyses will be performed using SAS® Version 9.2 or higher.

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), minimum, median, and maximum. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to 1 more decimal place than the raw data recorded in the database. The SD will be reported to 2 more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be 4 for any summary statistic.

Categorical data will be summarized in terms of the number of patients in the analysis population, the number of patients providing data at the relevant time point, frequency counts, and the percentages corresponding to the appropriate method. Percentages will be presented to 1 decimal place. Percentages will not be presented for zero counts.

Change from baseline will be calculated as the post-baseline value minus the baseline value. Percent change from baseline is defined as (100 x [post-baseline – baseline] / baseline). Percent improvement from baseline is calculated as the positive percent change from baseline if a higher value at postbaseline means improvement from baseline. Similarly, percent improvement from baseline is calculated as the negative percent change from baseline if a lower value at postbaseline means improvement from baseline.

Data collected at ETVs will be mapped to the next planned visit number for that patient. For by-visit and by-treatment-week summaries, only visits in which a measure was scheduled to be collected will be summarized. Unplanned/unscheduled measurements will be excluded from the mixed-effects model of repeated measures (MMRM) analysis. However, the data will still be used in other analyses as indicated in the SAP. Such analyses will include, but are not limited to, shift analyses and change from baseline to last-observation (e.g., mBOCF) endpoint analyses.

All confidence intervals (CIs) and statistical tests will be 2-sided with an α level of 0.05 unless otherwise specified. P-values that are greater than or equal to 0.001, and less than or equal to 0.999, will be presented to 3 decimal places. All other p-values which are less than 0.001 will be presented as <0.001, while p-values greater than 0.999 will be presented as >0.999. Confidence intervals will be presented to one more decimal place than the raw data.

Age, sex, and race will be reported on all by-patient listings unless otherwise specified. Sex will be abbreviated as follows: female (F) and male (M). Race will be abbreviated as follows: American Indian or Alaska Native (AI), Asian (AS), Black or African American (BL), Native Hawaiian or other Pacific Islander (NH), White (WH), and Multiple (MU).

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

6.1.1.1. Initial Open-Label Treatment Period Population

Efficacy, health outcomes, and safety data collected in Period 2 will be summarized for ixekizumab 80 mg Q2W without inferential statistics.

Baseline for Period 2 is defined as the last available value on or before the first injection of ixekizumab 80 mg Q2W in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2). For patients who do not take any injections of ixekizumab 80 mg Q2W in Period 2, the last available value prior to Week 0 (Visit 2) will be their baseline. The baseline period is defined as the start of screening and ends prior to the first injection of ixekizumab 80 mg Q2W at Week 0 (Visit 2). If the date of first injection is missing, the date of Visit 2 will be used.

Period 2 starts at the time of first injection of ixekizumab 80 mg Q2W (or after the date of Visit 2, if the date of first injection is missing) and ends for the following study events:

- Prior to the first injection of study treatment in the randomized double-blind withdrawal period (Period 3) for patients who meet the randomization criteria,
- Week 64 (Visit 19) for patients who do not meet the randomization criteria, or
- Visit of early discontinuation of study treatment in the initial open-label treatment.

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

For longitudinal continuous and categorical efficacy and health outcome variables, summaries will be performed by treatment week through the last observation during the study period. The last observation is defined as the value reported for the last visit prior to the first injection of randomized study treatment for patients who randomize or the value reported for Week 64 (Visit 19) for patients who do not meet randomization criteria or the last observation prior to discontinuation for patients who discontinue early.

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

6.1.2.1. Randomized Withdrawal ITT and Randomized Withdrawal Safety Populations

Efficacy, health outcomes, and safety data collected in Period 3 will be summarized and treatment group comparisons (ixekizumab 80 mg Q2W versus placebo) will be performed for randomized patients.

Period 3 starts at the first injection of study treatment after randomization (or at randomization if missing the first injection of study treatment) and ends at the following study events:

- Relapse (no longer meeting Coates criteria for MDA),
- Week 104 (Visit 29) for patients who do not relapse, or

- Visit of early discontinuation of study treatment in the randomized double-blind withdrawal period.

For the efficacy and health outcome analyses, baseline is defined as the last available value on or before the first injection of study treatment in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2). If the date of first injection is missing, the date of Week 0 (Visit 2) will be used. For the safety analysis, baseline is defined as the last available value on or before the first injection of randomized study treatment in Period 3. If the date of first injection is missing, the date of randomization will be used.

The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to variables. 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. Time-to analyses will be calculated in weeks from the date of first injection on the randomized study treatment in Period 3 (see Section 6.11.1).

For longitudinal continuous and categorical efficacy and health outcome variables, the analysis will be summarized by randomized treatment week through 40 weeks of randomized treatment. For the proportion of patients who relapse, additional descriptive summaries will be provided by randomized treatment week beyond 40-week without inferential statistics.

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. In general, missing data will be imputed using the nonresponder imputation (NRI) method. For relapse analysis, the cumulative relapse will be provided at each randomized treatment week and is defined as a relapse on or before the randomized treatment week or a study treatment discontinuation. If a patient has missing components for Coates criteria for MDA that results in missing MDA at a particular visit, the patient will not be considered as relapse.

The primary analyses for all continuous efficacy and health outcome variables, change from baseline to endpoint, and percent improvement from baseline analyses, will be made using MMRM. Secondary analyses will be performed using an analysis of covariance (ANCOVA) model.

The MMRM includes treatment group, baseline measure, geographic region, cDMARD use (past use, current use), treatment week, baseline measure-by-treatment week interaction term, and treatment week-by-treatment interaction term as fixed factors. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. For each treatment comparison performed, the least squares (LS) mean for each treatment group, an estimate of the difference between treatments, corresponding 95% CI and p-value will be presented. The estimate, 95% CI, and p-value for the overall difference between treatments over Period 3 will also be presented

for each treatment comparison. Type III tests for the LS means will be used for the statistical comparison.

The ANCOVA model includes treatment as a factor and baseline value, geographic region, and cDMARD use (past use, current use) as covariates. Missing data will be imputed using the mBOCF. Type III sums of squares for the LS means will be used for the statistical comparison. For each treatment comparison performed, the LS mean for each treatment group, an estimate of the difference between treatments, corresponding 95% CI and p-value will be presented. Type III sums of squares for the LS means will be used for the statistical comparison.

The Fisher's exact test will be used for all adverse event (AE), baseline, discontinuation, and other categorical data. Adverse event data will be analyzed using exposure-adjusted incidence rates (per 100 patient years). Summary tables comparing exposure-adjusted incidence rate (that is, person-time-adjusted incidence rates) over the entire time period will be generated where total number of patients who experienced the TEAE for each PT will be divided by the sum of all patients' time (in 100 years) of exposure during the treatment period. The entire time on study during the treatment period will be used instead of the time up to the first event (for those patients that have an event) due to implementation and display considerations. These tables will include the total number of patients in each treatment group, the total person years, the incidence rate ([number of patients with the event / total person years]*100), the relative risk (all ixekizumab in numerator), and p-value. Both the relative risk and p-value will be derived from a Poisson regression model with treatment as explanatory variable. The p-value will be based on the likelihood ratio test. Statistical comparisons will be applied at each MedDRA level (that is, SOC, and PT).

Continuous vital sign and laboratory values will be analyzed by an ANCOVA model with treatment and baseline value as independent variables. Other continuous variables will be analyzed by t-tests unless otherwise stated.

6.1.2.2. Relapse Population

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 by the randomized treatment group (ixekizumab 80 mg Q2W or Placebo) without inferential statistics for the relapse period.

For the efficacy and health outcomes analyses, baseline is defined as the last available value on or before the initial first injection of ixekizumab 80 mg Q2W in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2). If the date of first injection is missing, the date of Visit 2 will be used. For the safety analysis, baseline is defined as the last available value on or before relapse in Period 3.

The relapse period, for the relapse population, starts at the time of first injection of ixekizumab 80 mg Q2W following relapse and ends on the date of Week 104 (Visit 29) or the visit of early discontinuation.

A subset of the efficacy and health outcomes (refer to Section 6.11.2) will be summarized after the re-treatment of ixekizumab 80 mg Q2W for:

- the relapse population
- the relapse population who, following relapse, were re-treated with ixekizumab 80 mg Q2W after relapse for at least 16 weeks.

Categorical safety measures will be summarized with incidence rates.

For longitudinal continuous and categorical efficacy and health outcome variables, summaries will be performed by treatment week through the last observation during the study period. The last observation is defined as the value reported for Week 104 (Visit 29) or the last observation prior to discontinuation for patients who discontinue early.

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

6.1.3.1. Ixekizumab 80 mg Q2W-Treated Patients from the Randomized Withdrawal ITT Population

For patients who are randomized in Period 3, efficacy, health outcomes, and safety data collected in Period 2 and Period 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 on or before the first initial injection of ixekizumab in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2). If the date of first injection is missing, the date of Visit 2 will be used.

For patients who are randomized in Period 3, the combined Period 2 and Period 3 will start after the first initial injection of ixekizumab 80 mg Q2W in Period 2 (or after the date of Visit 2, if the date of first injection is missing) and ends at the following study events:

- Relapse (no longer meeting Coates criteria for MDA),
- Week 104 (Visit 29) for patients who do not relapse, or
- Visit of early discontinuation of study treatment in the randomized double-blind withdrawal period.

That is, Period 2 and Period 3 combined will end prior to the first injection of placebo for patients who randomize to placebo in Period 3.

A subset of the efficacy and health outcomes (refer to Section 6.11.2) will be summarized.

Categorical safety measures will be summarized with incidence rates.

For longitudinal continuous and categorical efficacy and health outcome variables, summaries will be performed by treatment week through the last observation during the study period. The last observation is defined as follows:

- the value reported for the last visit prior to the first injection of placebo for patients who randomize to placebo in Period 3,
- the value reported for the relapse visit for patients randomized to ixekizumab 80 mg Q2W and who relapse,
- the value reported at Week 104 (Visit 29) for patients randomized to ixekizumab 80 mg Q2W and who do not relapse, or
- the last observation prior to discontinuation for patients who discontinue early and for patients who do not relapse.

6.1.3.2. Nonrandomized Population

For patients who are not randomized in Period 3, efficacy, health outcomes, and safety data collected in Period 2 and Period 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 on or before the first injection of ixekizumab 80 mg Q2W in Period 2 and in most cases will be the value recorded at Week 0 (Visit 2). If the date of first injection is missing, the date of Visit 2 will be used.

Period 2 and Period 3 combined, for the nonrandomized patients, starts at the first injection of ixekizumab 80 mg Q2W in Period 2 (or after the date of Visit 2, if the date of first injection is missing) and ends at the following study events: Week 104 (Visit 29) or Visit of early discontinuation of study treatment in the Initial Open-Label Treatment period or randomized double-blind withdrawal period.

A subset of the efficacy and health outcomes (refer to Section 6.11.2) will be summarized.

Categorical safety measures will be summarized with incidence rates.

For longitudinal continuous and categorical efficacy and health outcome variables, summaries will be performed by treatment week through the last observation during the study period. The last observation is defined as the value reported for Week 104 (Visit 29) or the last observation prior to discontinuation for patients who discontinue early.

6.1.4. General Considerations for Analyses during Period 4 (Post-Treatment Follow-up Period)

Safety data collected in Period 4 will be summarized by treatment group without inferential statistics. Patients will be analyzed according to the treatment they were taking before entering Period 4.

Baseline is defined as the last available value on or before entering Period 4. Period 4 starts at Visit 801 and ends at the last visit prior to study discontinuation.

Categorical safety measures will be summarized with incidence rates.

6.2. Adjustments for Covariates

The randomization at the beginning of the Period 3 (randomized double-blind withdrawal period) is stratified by geographic region and cDMARD use (past use, current use) at the time of randomization in Period 3. Unless otherwise specified, all categorical efficacy and health outcome analyses during Period 3 on the randomized withdrawal intent-to-treat (ITT) population will include geographic region in the analysis model. Unless otherwise specified, all continuous efficacy and health outcome analyses during Period 3 on the randomized withdrawal ITT population will include geographic region and cDMARD use (past use, current use) at the time of randomization in Period 3, in the analysis model.

In general for Period 3, when an MMRM is to be used for analyses, baseline value, and baseline-by-treatment week interactions will be included as covariates; when an ANCOVA is to be used for analyses, baseline value will be included as a covariate.

6.3. Handling of Dropouts or Missing Data

6.3.1. Nonresponder Imputation (NRI) for Clinical Response

For secondary analyses assessed during Period 3, patients will be considered a nonresponder for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data 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. The NRI analyses will be performed on categorical efficacy and health outcome variables.

6.3.2. Modified Baseline Observation Carried Forward (mBOCF)

A mBOCF analysis for Period 3 through 40 weeks of randomized treatment 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 or death. The last non-missing 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 post-baseline observation will not be included for evaluation with the exception of patients who discontinue study treatment due to an AE.

Period 2, combined periods 2 and 3, and Relapse Period summaries will also include a mBOCF summary. Summaries will be performed on all continuous efficacy and health outcome variables.

6.4. Multicenter Studies

This study will be conducted by multiple investigators at multiple sites internationally. The countries will be categorized into geographic regions, as described in Table RHBF.6.1, for analysis.

Table RHBF.6.1. Geographic Regions

Geographic Region	Country
Africa	South Africa
Central America	Mexico
North America	United States
Eastern Europe	Bulgaria, Czech Republic, Estonia, Poland, Russia, Slovak Republic, and Ukraine
Western Europe	Spain and United Kingdom

Unless otherwise specified, the statistical analysis models will adjust for geographic region at the time of randomization.

For analysis of the primary endpoint, the presence of a treatment-by-region interaction will be tested at 10% significance level for the randomized withdrawal ITT population. Where there is evidence of an interaction ($p<.10$), descriptive statistics will be used to assess whether the interaction is quantitative (that is, the treatment effect is consistent in direction but not the size of effect is not consistent) or qualitative (the treatment is beneficial for some but not other regions).

6.5. Multiple Comparisons/Multiplicity

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

6.6. Use of an "Efficacy Subset" of Patients

The per protocol set (PPS) is defined below in Section 6.6.1 and is an Efficacy Subset of patients. Analysis details for the PPS can be found in Section 6.11.1.

6.6.1. 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 injection of ixekizumab 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.

The primary analyses will be repeated using the **PPS**. The PPS is defined as patients included in the randomized withdrawal ITT population who are compliant with therapy, who do not have significant protocol deviations (refer to Section 6.17), and whose investigator's site did not have significant good clinical practice (GCP) issues that occurred during the randomized, double-blind withdrawal period which would require reporting to regulatory agencies. Compliance with

therapy is defined to be missing no more than 20% of expected doses and not missing 2 consecutive doses (all injections at a visit are counted as 1 dose) during the randomized double-blind treatment period. 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 receive at least 1 injection of study treatment after randomization. Patients will be analyzed according to the treatment to which they were assigned.

Efficacy and health outcomes summaries for Period 2 and Period 3 combined will be conducted on the **Ixekizumab 80 mg Q2W-Treated Patients: Nonrandomized Population and Randomized Withdrawal ITT Population**, defined as all patients who were not randomized and who receive at least 1 injection of ixekizumab and all randomized patients who receive at least 1 injection of study treatment after randomization, respectively.

Safety summaries for Period 2 and Period 3 combined will be conducted on the **Ixekizumab 80 mg Q2W-Treated Patients: Nonrandomized Population and Randomized Withdrawal Safety Population**, defined as all patients who were not randomized and who receive at least 1 injection of ixekizumab and all randomized patients who receive at least 1 injection of study treatment after randomization, respectively. 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 receive at least 1 injection of ixekizumab after relapse.

Safety analyses for Period 4 (post-treatment follow-up period) will be conducted on the **follow-up period population**, defined as all patients who receive at least 1 injection of study treatment at any time during Period 2 and Period 3 and have entered the post-treatment follow-up period. Patients will be analyzed according to the treatment they were taking before entering Period 4.

6.7. Patient Disposition

Patient flow will be summarized from entered to randomized to completion.

Analysis populations will be listed and summarized by treatment group for all entered patients.

Patient disposition from study and study treatment will be listed for all entered patients.

Patient disposition from study treatment will be summarized with reasons for disposition for:

- Period 2 (initial open-label treatment period population),
- Period 3 (randomized withdrawal ITT population),
- Relapse period (relapse population), and
- Combined Period 2 and Period 3 (ixekizumab 80 mg Q2W-treated patients from the randomized withdrawal ITT population, and nonrandomized population).

Patient disposition for Period 3 will be compared between treatment groups using the Fisher's exact test for the randomized withdrawal ITT population.

Patient disposition from study treatment by visit will be summarized with reasons for:

- Combined Period 2 and Period 3 (ixekizumab 80 mg Q2W-treated patients from the randomized withdrawal ITT population, and nonrandomized population).

Patient disposition from study by visit will be summarized with reasons for disposition for:

- Period 4 (post-treatment follow-up period population).

Time-to study treatment discontinuation due to an AE (in weeks) will be summarized by treatment group and graphically presented using Kaplan-Meier technique. The log-rank test will be used to compare time-to study treatment discontinuation between treatment groups for randomized withdrawal ITT population.

Time-to study treatment discontinuation will be calculated as:

$$\frac{Date\ of\ study\ treatment\ discontinuation - Date\ of\ first\ injection + 1}{7}$$

The date of first injection varies across the period and the analysis populations. Table RHBF.6.2 defines the date of first injection for each period and analysis population.

Table RHBF.6.2. Date of First Injection by Period and Analysis Population

Period	Analysis Population	Date of First Injection
Period 2	initial open-label treatment population	date of the first injection of ixekizumab 80 mg Q2W in Period 2
Period 3	randomized withdrawal ITT population	date of the first injection of study treatment after randomization in Period 3
Relapse Period	relapse population	date of the first injection of ixekizumab 80 mg Q2W after relapse
Combined Periods 2 and 3	ixekizumab 80 mg Q2W-treated patients from the randomized withdrawal IIT population	date of the first injection of ixekizumab 80 mg Q2W in Period 2
Combined Periods 2 and 3	nonrandomized population	date of the first injection of ixekizumab 80 mg Q2W in Period 2

Abbreviations: ITT = intent-to-treat; Q2W = every 2 weeks.

Patient allocation by region, country, and center/site will be summarized with number of patients who entered the study, number of patients who entered the initial open-label treatment period, number of patients discontinued from study treatment, and number of patients discontinued from study.

6.8. Patient Characteristics

Patient characteristics will be listed for all entered patients and summarized for the following populations:

- initial open-label treatment period population
- randomized withdrawal ITT population
- relapse population
- nonrandomized population

The continuous variables will be summarized using descriptive statistics and the categorical variables will be summarized using frequency counts and percentages.

For the randomized withdrawal ITT population, comparisons between treatment groups will be conducted using an analysis of variance (ANOVA) model with treatment group as a factor for continuous data, and using the Fisher's exact test for categorical data. (For categorical variables that have more than 2 categories, Monte Carlo estimates of exact p-values will be used.)

The following patient characteristics will be summarized:

- Age (in years): calculated using an imputed date of birth of July 1 in the year of birth collected in the electronic case report form (eCRF). Age will be calculated as:

  Age = floor((intck('month', brthdtc, rfstdtc) - (day(rfstdtc) < day(brthdtc)))/12)

  where brthdtc = Imputed date of birth, and rfstdtc = patient reference start date (that is, the date when patient is first exposed to study treatment)
- Age group: <65 years, ≥65 years to <75 years, ≥75 years
- Age group: <40 years, ≥40 years
- Gender
- Age groups within gender
- Race: AI, AS, BL, NH, WH, MU
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Applicable
- Country: South Africa, Mexico, Bulgaria, Czech Republic, Estonia, Poland, Russia, Slovak Republic, Ukraine, United States (US), Spain, and United Kingdom (UK)
- Geographic region: Europe, US, Rest of the World
- Geographic region:
  - Africa (South Africa)
  - Central America (Mexico)
  - North America (US)

  - Eastern Europe (Bulgaria, Czech Republic, Estonia, Poland, Russia, Slovak Republic, and Ukraine)
  - Western Europe (Spain and UK)
- Geographic region at the time of randomization for the randomized withdrawal ITT population:
  - Africa (South Africa)
  - Central America (Mexico)
  - North America (US)
  - Eastern Europe (Bulgaria, Czech Republic, Estonia, Poland, Russia, Slovak Republic, and Ukraine)
  - Western Europe (Spain and UK)
- Height (cm): last non-missing result before first study treatment injection
- Weight (kg): last non-missing result before first study treatment injection
- Weight category: <100 kg, ≥100 kg
- Weight category: <80 kg, ≥80 kg and <100 kg, ≥100 kg
- Body mass index (BMI) (kg/m^2): BMI will be calculated as:

$$BMI\ (kg\ /\ m^2) = \frac{Weight\ (kg)}{(Height\ (m))^2}$$

- BMI category: underweight (<18.5 kg/m^2); normal (≥18.5 and <25 kg/m^2); overweight (≥25 and <30 kg/m^2); obese (≥30 and 40 kg/m^2); extreme obese (≥40 kg/m^2)
- Waist circumference (cm)
- Alcohol use: never, current, former
- Caffeine use: never, current, former
- Tobacco use: never, current, former
- Number of pipefuls, cigarettes, cigars, and smokeless (pinches) tobacco consumed per day
- Time since PsA onset (years) – calculated as

  (date of informed consent – date of PsA onset + 1) / 365.25

  Patients who have a completely missing date of onset will have a missing value for the time since PsA onset, otherwise, "January" and "01" will be imputed for the missing month and day respectively in cases where these 2 date components are missing.
- Time since PsA diagnosis (years) – calculated as

(date of informed consent – date of PsA diagnosis + 1) / 365.25

Patients who have a completely missing date of diagnosis will have a missing value for the time since diagnosis, otherwise "January" and "01" will be imputed for the missing month and day respectively in cases where for these 2 date components are missing.

- Time since plaque psoriasis (Ps) onset (years) – calculated as

  (date of informed consent – date of Ps onset + 1) / 365.25

  Patients who have a completely missing date of onset will have a missing value for the time since Ps onset, otherwise, "January" and "01" will be imputed for the missing month and day respectively in cases where these 2 date components are missing.

- Time since Ps diagnosis (years) – calculated as

  (date of informed consent – date of Ps diagnosis + 1) / 365.25

  Patients who have a completely missing date of diagnosis will have a missing value for the time since diagnosis, otherwise "January" and "01" will be imputed for the missing month and day respectively in cases where for these two date components are missing.

- Previous cDMARD use (none, past use, current use) for:
  - methotrexate (MTX)
  - sulfasalazine (SSZ)
  - leflunomide (LEF)
  - hydroxychloroquine (HCQ)
  - cyclosporine (CSA)
  - apremilast
- Previous cDMARD use (past use, current use)
- Previous cDMARD use at the time of randomization for the randomized withdrawal ITT and safety populations:
  - Previous cDMARD use (yes, no) for:
    - methotrexate
    - sulfasalazine
    - leflunomide
    - hydroxychloroquine
    - cyclosporine
    - apremilast
  - Previous cDMARD use; yes or no

- Methotrexate dose at baseline (weekly)
- Methotrexate dose at the time of randomization for the randomized withdrawal ITT and safety populations
- Tender joint count (TJC) based on 68 joints
- Swollen joint count (SJC) based on 66 joints
- Physician's global assessment of disease activity (mm)
- Patient's global assessment of disease activity (mm)
- Patient's assessment of joint pain (mm)
- Health Assessment Questionnaire–Disability Index total score
- C-reactive protein (mg/L)
- C-reactive protein categories; >6 mg/L or ≤6 mg/L
- classification for psoriatic arthritis (CASPAR) total score (see Appendix 1 for additional details)
- Rheumatoid Factor Positive (RF+); yes or no
- Anti-cyclic citrullinated peptide positive (Anti-CCP +); yes or no
- Disease Activity Score modified to include the 28 diarthrodial joint count, based on C-reactive protein
- Enthesitis (based on 18 point entheseal point assessment); yes or no
- Enthesitis (Spondyloarthritis Research Consortium of Canada [SPARCC] >0); yes or no
- Spondyloarthritis Research Consortium of Canada for patients with baseline Enthesitis (SPARCC>0)
- Enthesitis (Leeds Enthesitis Index [LEI]>0); yes or no
- Leeds Enthesitis Index for patients with baseline enthesitis (LEI >0)
- Dactylitis (as reported on the eCRF); yes or no
- Dactylitis (Leeds Dactylitis Index – Basic [LDI-B] >0); yes or no
- Leeds Dactylitis Index – Basic for patients with baseline dactylitis (LDI-B >0)
- Modified CPDAI without the spinal disease assessment (Ankylosing Spondylitis Quality of Life Questionnaire [AsQoL] and Bath Ankylosing Spondylitis Disease Activity Index [BASDAI])
- Psoriasis Area and Severity Index (PASI) total score for patients who have baseline plaque psoriasis (PASI >0)
- Psoriasis Area and Severity Index total score for patients who have baseline psoriatic lesion(s) involving BSA ≥3%

- Psoriasis Area and Severity Index total score ≥12 for patients who have baseline plaque psoriasis (PASI >0); yes or no
- Psoriasis Area and Severity Index total score ≥12 for patients who have baseline psoriatic lesion(s) involving BSA ≥3%: yes or no
- Static Physician Global Assessment (sPGA) score for patients who have baseline plaque psoriasis (sPGA >0)
- Static Physician Global Assessment ≥3 for patients who have baseline plaque psoriasis (sPGA >0); yes or no
- Moderate to severe psoriasis (defined as PASI ≥12, sPGA ≥3, and BSA ≥10%); yes or no
- Percentage of BSA for patients who have baseline plaque psoriasis (BSA >0)
- Body surface area ≥3%; yes or no for patients with baseline plaque psoriasis (BSA >0)
- Body surface area ≥10%; yes or no for patients with baseline plaque psoriasis (BSA >0)
- Itch NRS score for patients who have baseline psoriatic lesion(s) involving BSA ≥3%
- Fatigue Severity NRS score
- Quick Inventory of Depressive Symptomatology-self report 16 items total score
- Medical Outcomes Study 36-Item Short Form Health Survey PCS score
- Medical Outcomes Study 36-Item Short Form Health Survey MCS score
- Dermatology Life Quality Index total score for patients who have baseline psoriatic lesion(s) involving BSA ≥3%
- Latent tuberculosis (TB); yes or no.

6.8.1. Previous Therapy for Psoriatic Arthritis

The number and percentage of patients who received previous therapy for PsA (as recorded on the *Previous Therapy: Psoriatic Arthritis* eCRF page) will be summarized by treatment group, overall and Preferred Term (PT). The number and percentage of patients with each reason for discontinuing previous therapy for PsA will also be presented by treatment group.

Previous therapy for PsA will be summarized for the following populations:

- initial open-label treatment period population
- randomized withdrawal ITT population
- nonrandomized population

Treatment group comparisons for the randomized withdrawal ITT population will be conducted using the Fisher's exact test.

Listing of previous therapy for PsA will be provided for the initial open-label treatment period population.

6.8.2. Historical Illness and Preexisting Conditions

Historical illnesses and preexisting conditions will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Preexisting conditions for the Open-label Treatment Period (Period 2) are defined as those conditions recorded on the *Pre-existing Conditions and AEs or the Historical Events* eCRF pages with a start date prior to the date of informed consent and no end date (that is, the event is ongoing) or an end date after the date of informed consent. Adverse events occurring prior to the date of first study injection will also be reported as preexisting condition for the open-label treatment period (Period 2). Preexisting conditions for subsequent treatment periods are defined as those preexisting conditions and AEs which are ongoing at the treatment period baseline. If a preexisting condition worsens in severity on or after date of informed consent, it will be considered an AE from the date of worsening onwards. Note that conditions with a partial or missing start date will be assumed to be "not preexisting" unless there is evidence, through comparison of partial dates, to suggest otherwise. Patients will only be counted once, regardless of how many conditions are included under the same System Organ Class (SOC) and PT.

The number and percentage of patients with historical illnesses and preexisting conditions will be provided by treatment group, overall and by SOC and PT for each treatment period.

Preexisting conditions will be summarized for the following periods and populations:

- initial open-label treatment period population;
- randomized withdrawal ITT population

Historical illnesses will be summarized for the following populations:

- initial open-label treatment period population
- randomized withdrawal ITT population
- nonrandomized population

Treatment group comparisons for randomized withdrawal ITT Population will be conducted using Fisher's exact test.

Listing of historical illnesses and preexisting conditions will be provided for initial open-label treatment period population.

6.9. Treatment Compliance

The randomization schedule will be listed by center for the randomized withdrawal ITT population. Study treatment dispensed will be listed (including the clinical trial [CT] Lot

number) for all entered patients. Study treatment administration and compliance will be listed for all entered patients.

Throughout Period 2 and Period 3, patients will record information in a Study Drug Administration Log (captured in the *Exposure* eCRF page), including the date, time, and anatomical location of administration of investigational product, syringe number, who administered the investigational product, and the reason if the investigational product was not fully administered.

Treatment compliance (%) for each patient will be calculated as:

$$100 \times \frac{Total\ number\ of\ injections\ administered}{Total\ number\ of\ injections\ prescribed}$$

- Number of injections prescribed (that is, expected) will be calculated as:
  - For Period 2:

$$2 + \frac{Number\ of\ weeks\ in\ the\ study\ period}{2}$$

  - For Period 3:

$$\frac{Number\ of\ weeks\ in\ the\ study\ period}{2}$$

    Note that the number of injections dispensed will vary across patients for each study period by analysis population, refer to Section 6.1 for the study period duration definitions by analysis populations.

    Note there are 2 ixekizumab 80 mg injections at Week 0 and there is 1 ixekizumab 80 mg or placebo injection every 2 weeks, thereafter, starting at Week 2.

- For patients who discontinue during Period 2 or Period 3, the number of injections prescribed can be derived from the IWRS study drug dispense dataset.
- The total number of injections administered will be derived using the response to the question "Was dose administered?" on the Exposure eCRF page.

A patient will be considered overall compliant for Period 2 or Period 3 if he/she is missing no more than 20% of the expected doses, does not miss 2 consecutive doses, and does not over-dose (that is, take more injections at the same time point than specified in the protocol) within the respective study period.

Treatment compliance with investigational product will be summarized for the following periods:

- Period 2 (initial open-label treatment period population)
- Period 3 (randomized withdrawal safety population)

Treatment group comparisons will be conducted for Period 3 for the randomized withdrawal safety population using the Fisher's exact test.

6.10. Concomitant Therapy

Previous therapy is defined as therapy that starts and ends before the first day of study treatment in Period 2.

Concomitant therapy for each treatment period (Period 2, Period 3, and Period 2 and Period 3 combined) is defined as the therapy that starts before, on, or after the first day of study treatment in the treatment period and before the last visit date in the treatment period, and has either no end date (the therapy is ongoing) or an end date on or after the first day of study treatment in the treatment period. Notice, concomitant therapy will belong to a period if the therapy starts and ends on the exact same day as the first day of study treatment in the study period.

Concomitant therapy for the post-treatment follow-up period (Period 4) is defined as the therapy that starts before, on, or after the last visit date of Period 3 or ETV and continues into Period 4, that is, either no end date (the therapy is ongoing) or an end date after the last visit date of Period 3 or ETV.

The following summaries will be provided:

- Previous therapy by World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) Level 4 and WHO PT
    - Initial Open-Label Treatment Period Population
- Concomitant therapy by WHO ATC Level 4 and WHO PT for:
    - Period 2 (initial open-label treatment period population)
    - Period 3 (randomized withdrawal safety population)
    - Relapse Period (relapse population)
    - Combined Period 2 and Period 3 (ixekizumab 80 mg Q2W-treated patients from the randomized withdrawal safety population, and nonrandomized population).

  Comparisons between treatment groups will be conducted for Period 3 for the randomized withdrawal safety population using the Fisher's exact test.

  A by-patient listing of all prior and concomitant medications will be provided for the initial open-label treatment period population.

If a partial or completely missing medication start date/time or end date/time is present, the following imputation rules will be utilized in the analysis:

- For the start date:
    - If year, month, and day are missing, then use the consent date.
    - If either month or month and day are missing, then use January 1.

  - If only day is missing, impute the first day of the month.
- For the start time:
  - Impute as 23:59.
- For the end date:
  - If year, month, and day are missing, then use the patient's last visit date.
  - If either month or month and day are missing, then use December 31.
  - If only day is missing, then use the last day of the month.
  - The imputed date will not be beyond the patient's last visit date.
- For the end time:
  - Impute as 23:59.
- If there is any doubt, the medication will be flagged as concomitant.

6.11. Efficacy Analyses

Table RHBF.6.3 includes the description and derivation of the primary and secondary efficacy outcomes.

Table RHBF.6.4 provides the detailed analyses including analysis type, method and imputation, population, time point, and comparisons for primary and secondary efficacy analyses.

Table RHBF.6.3. Description and Derivation of Primary and Secondary Efficacy Outcomes

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
Coates Criteria for Minimal Disease Activity (MDA)	Uses a composite of 7 key outcome measures (includes PASI) used in PsA to encompass all of the domains of the disease to measure the overall state of a patients' disease (Coates et al. 2010; Coates and Helliwell 2010).	MDA Flag	Patients are classified as achieving MDA if they fulfill 5 of 7 outcome measures: 1. TJC ≤1 2. SJC ≤1 3. PASI total score ≤1 or BSA ≤3 4. patient pain VAS score of ≤15 5. patient global VAS score of ≤20 6. HAQ-DI score ≤0.5 7. tender entheseal points (of 18 entheseal points) ≤1 See Appendix 2 for complete details.	If the patient achieves MDA with the non-missing measures, then impute as achieving MDA; otherwise, the result is missing.
Modified Coates Criteria for Minimal Disease Activity (MDA)	Uses a composite of 7 key outcome measures (includes sPGA) used in PsA to encompass all of the domains of the disease to measure the overall state of a patients' disease (Mease et al. 2013).	MDA-sPGA Flag	Patients are classified as achieving MDA if they fulfill 5 of 7 outcome measures: 1. TJC ≤1 2. SJC ≤1 3. sPGA (0,1) or BSA ≤3 4. patient pain VAS score of ≤15 5. patient global VAS score of ≤20 6. HAQ-DI score ≤0.5 7. tender entheseal points (of 18 entheseal points) ≤1 See Appendix 2 for complete details.	If the patient achieves MDA with the non-missing measures, then impute as achieving MDA; otherwise, the result is missing.
Tender Joint Count (TJC)	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.	TJC total score	Adjusted sum of the pain/tenderness for all 68 joints: $\left(\frac{sum\ of\ the\ evaluable\ individual\ tender\ joints}{number\ of\ evaluable\ joints}\right) X\ 68$ See Appendix 3 for complete details.	If more than half of the joints are nonevaluable, the total score will be missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
Swollen Joint Count (SJC)	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.	SJC total score	Adjusted sum of the pain/tenderness for all 66 joints. $\left(\frac{sum\ of\ the\ evaluable\ individual\ swollen\ joints}{number\ of\ evaluable\ joints}\right) X\ 66$ See Appendix 3 for complete details.	If more than half of the joint s are nonevaluable, the total score will be missing.
Patient's Assessment of Pain Visual Analog Scale (VAS)	Assesses the patient's current level of joint pain by marking a vertical tick on a 100-mm horizontal VAS.	Patient Pain VAS	Range: 0 to 100 mm	Single item, missing if missing
Patient's Global Assessment of Disease Activity Visual Analog Scale (VAS)	Assesses the patient's overall assessment of his or her PsA activity by marking a 100-mm horizontal VAS.	Patient Global VAS	Range: 0 to 100 mm 0 represents no disease activity 100 represents extremely active disease activity	Single item, missing if missing
Patient's Assessment of Physical Function Health Assessment Questionnaire–Disability Index (HAQ-DI)	Patient-reported standardized questionnaire that is commonly used in PsA total 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	HAQ-DI score	Sum of the highest sub-category scores within 8 categories and adjusted for aids/devices and/or help from another person. See Appendix 4 for complete details.	The patient must have a score for at least 6 of the 8 categories. If there are <6 categories completed, a HAQ-DI will be missing
American College of Rheumatology Responder Index (ACR)	ACR Responder Index: a composite of clinical, laboratory, and functional measures in PsA to assess relief of signs and symptoms; responses are presented as the minimal numeric disease assessment criteria.	ACR20 Flag ACR50 Flag ACR70 Flag	See Appendix 5 for details.	See Appendix 5 for details.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
C-Reactive Protein (CRP)	The ACR Core Set measure of acute phase reactant. It will be measured with a high sensitivity assay at the central laboratory to help assess the effect of ixekizumab on the patient's PsA	▪ CRP (mg/L) ▪ Change from baseline in CRP (mg/L) ▪ % improvement in CRP (mg/L)	Raw laboratory result, no derivation will be applied with the exception of converting the units to mg/L when the results are reported in units other than mg/L	Single lab measure, missing if missing
Static Physician Global Assessment (sPGA)	For patients with plaque psoriasis, the physician's global assessment of the patient's psoriasis (Ps) lesions at a given time point (European Medicines Agency [EMA] 2004 [WWW]). Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given.	sPGA score	Range from 0 to 5: clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).	Single item, missing if missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
Psoriasis Area and Severity Index (PASI)	For patients with plaque psoriasis, combines assessments of the extent of body-surface involvement in 4 anatomical regions (head and neck, trunk, arms, and legs) and the severity of scaling (S), redness (R), and plaque induration/infiltration thickness (T) in each region, yielding an overall score of 0 for no psoriasis to 72 for the most severe disease (Fredriksson and Pettersson 1978). Severity is rated for each index (R, S, T) on a 0-4 scale (0 for no involvement up to 4 for severe involvement): 0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe The body is divided into 4 anatomical regions comprising the head (h), upper limb (u), trunk (t), and lower limb (l). In each of these areas, the fraction of total BSA affected is graded on a 0-6 scale (0 for no involvement; up to 6 for 90% - 100% involvement): 0 = 0% (clear) 1 = >0% to <10% 2 = 10% to <30% 3 = 30% to <50% 4 = 50% to <70% 5 = 70% to <90% 6 = 90% to 100% The various body regions are weighted to reflect their respective proportion of BSA.	PASI total score	The composite PASI score is calculated by multiplying the sum of the individual-severity scores for each area by the weighted area-of-involvement score for that respective area, and then summing the 4 resulting quantities as follows: $PASI = 0.1(R_h + T_h + S_h)A_h + 0.2(R_u + T_u + S_u)A_u + 0.3(R_t + T_t + S_t)A_t + 0.4(R_l + T_l + S_l)A_l$ Where, R_h, R_u, R_t, R_l = redness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively; T_h, T_u, T_t, T_l = thickness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively; S_h, S_u, S_t, S_l = scaliness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively; A_h, A_u, A_t, A_l = numerical value translation of % area of psoriatic involvement score for the head, upper limb, trunk, and lower limb, respectively. PASI scores are treated as a continuous score, with 0.1 increments within these values.	If any individual score is missing, the PASI score will not be calculated, hence missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
Percentage of Body Surface Area (BSA)	The investigator will evaluate the percentage involvement of psoriasis 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 hand (including the palm, fingers, and thumb) (National Psoriasis Foundation [NPF] 2009).	BSA	Collected as a single scale. Range from 0% to 100%.	Single item, missing if missing

Abbreviations: ACR20/50/70 = 20%, 50%, or 70% improvement in American College of Rheumatology criteria; PsA = psoriatic arthritis; PGA = static physician global assessment.

Table RHBF.6.4. Description of Primary and Secondary Efficacy Analyses

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point	Analysis Type
Coates Criteria for Minimal Disease Activity (MDA)	Time-to achieve Coates criteria for MDA	Descriptive Statistics (including Kaplan Meier estimates of the survival curve)	Initial open-label treatment period population	Assessed Period 2	Secondary analysis: 1. Time-to achieve Coates criteria for MDA 2. Time-to achieve Coates criteria for MDA for 3 consecutive months over 4 consecutive visits
			Relapse population	Assessed during Relapse Period	Secondary analysis: Time-to achieve Coates criteria for MDA
			Relapse population who have completed 16 weeks on relapse treatment	Assessed during Relapse Period	Secondary analysis: Time-to achieve Coates criteria for MDA for 3 consecutive months over 4 consecutive visits
	Proportion of patients achieving MDA	Descriptive Statistics	Initial open-label treatment period population	Assessed Period 2	Secondary analysis
			Relapse population	Assessed during Relapse Period	Secondary analysis
			Relapse population who have completed 16 weeks on relapse treatment	Assessed during Relapse Period	Secondary analysis
	Time-to relapse (no longer meeting Coates criteria for MDA)	Log-Rank Test. Kaplan-Meier product limit method	Randomized withdrawal ITT population and PPS	Assessed during Period 3	Primary analysis comparing IXE80Q2W vs. placebo (see Section 6.11.1)

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point	Analysis Type
	Proportion of relapse patients	Logistic regression analysis and Fisher's exact test with cumulative rate Descriptive statistics	Randomized withdrawal ITT population	Assessed during Period 3 (by Treatment Week) through 40 weeks of randomized treatment, then descriptive beyond 40 weeks	Secondary analysis assessed during Period 3
Modified Coates Criteria for Minimal Disease Activity	Time-to achieve modified Coates criteria for MDA	Descriptive statistics for IXE80Q2W	Initial open-label treatment period population	Assessed during Period 2	Sensitivity analysis: 1. Time-to achieve Coates criteria for MDA 2. Time-to achieve Coates criteria for MDA for 3 consecutive months over 4 consecutive visits
	Time-to relapse of modified Coates criteria for MDA	Log-Rank Test. Kaplan-Meier product limit method	Randomized withdrawal ITT population who met modified Coates Criteria for MDA at time of randomization	Assessed during Period 3	Sensitivity analysis
	Proportion of relapse patients of modified Coates criteria for MDA	Logistic regression (primary) and Fisher's exact test (secondary) with cumulative rate Descriptive statistics	Randomized withdrawal ITT population who met modified Coates Criteria for MDA at time of randomization	Assessed during Period 3 (by Treatment Week) through 40 weeks of randomized treatment, then descriptive beyond 40 weeks	Sensitivity analysis
Tender Joint Count (TJC)	Time-to TJC >1 (loss of response)	Log-Rank Test. Kaplan-Meier product limit method	Randomized withdrawal ITT population who had TJC ≤1 at time of randomization	Assessed during Period 3	Secondary analysis
	Time-to Achieve TJC ≤1	Descriptive statistics (including Kaplan Meier estimates of the survival curve)	Relapse population who had TJC >1 at time of relapse	Assessed during Relapse Period	Secondary analysis

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point	Analysis Type
Swollen Joint Count (SJC)	Time-to SJC >1 (loss of response)	Log-Rank Test. Kaplan-Meier product limit method	Randomized withdrawal ITT population who had a SJC ≤1 at time of randomization	Assessed during Period 3	Secondary analysis
	Time-to SJC Achieve ≤1	Descriptive statistics (including Kaplan Meier estimates of the survival curve)	Relapse population who had a SJC >1 at time of relapse	Assessed during Relapse Period	Secondary analysis
Patient's Assessment of Pain Visual Analog Scale (VAS)	Time-to Pain VAS score >15 (loss of response)	Log-Rank Test. Kaplan-Meier product limit method	Randomized withdrawal ITT population who had a Pain VAS score ≤15 at time of randomization	Assessed during Period 3	Secondary analysis
	Time-to Achieve Pain VAS score ≤15	Descriptive statistics (including Kaplan Meier estimates of the survival curve)	Relapse population who had a Pain VAS score >15 at time of relapse	Assessed during Relapse Period	Secondary analysis
Patient's Global Visual Analog Scale (VAS)	Time-to patient global disease activity VAS score >20 (loss of response)	Log-Rank Test. Kaplan-Meier product limit method	Randomized withdrawal ITT population who had a global disease activity VAS score ≤20 at time of randomization	Assessed during Period 3	Secondary analysis
	Time-to Achieve patient global disease activity VAS score ≤20	Descriptive statistics (including Kaplan Meier estimates of the survival curve)	Relapse population who had a global disease activity scale VAS score >20 at time of relapse	Assessed during Relapse Period	Secondary analysis

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point	Analysis Type
Patient's Assessment of Physical Function Health Assessment Questionnaire–Disability Index (HAQ-DI)	Change from baseline in HAQ-DI total score Percent improvement in HAQ-DI total score	Descriptive statistics	Initial open-label treatment period population	Assessed during Period 2	Secondary analysis
			Relapse population	Assessed during Relapse Period	Secondary analysis
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined	Secondary analysis
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assess during Period 3 through 40 Weeks of Randomized Treatment	Secondary analysis
	HAQ-DI total score improvement ≥0.35	Descriptive statistics	Initial open-label treatment period population - Patients with baseline HAQ-DI ≥0.35	Assessed during Period 2	Secondary analysis
			Relapse population- Patients with baseline HAQ-DI ≥0.35	Assessed during Relapse Period	Secondary analysis
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population- Patients with baseline HAQ-DI ≥0.35	Assessed during Period 2 and Period 3 combined	Secondary analysis
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population	Assess during Period 3 through 40 weeks of Randomized Treatment	Secondary analysis
	Time-to HAQ-DI score >0.5 (loss of response)	Log-Rank Test. Kaplan-Meier product limit method	Randomized withdrawal ITT population who had a HAQ-DI score ≤0.5 at time of randomization	Assessed during Period 3	Secondary analysis
	Time-to Achieve HAQ-DI score ≤0.5	Descriptive statistics (including Kaplan Meier estimates of the survival curve)	Relapse population who had a HAQ-DI score >0.5 at time of relapse	Assessed during Relapse Period	Secondary analysis

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point	Analysis Type
American College of Rheumatology Responder Index (ACR)	Time-to achieve ACR20 Time-to achieve ACR50 Time-to achieve ACR70	Descriptive Statistics for ixekizumab 80 mg Q2W (including Kaplan Meier estimates of the survival curve)	Initial open-label treatment period population	Assessed during Period 2	Secondary analysis
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined	Secondary analysis
	Proportion of patients achieving ACR20 Proportion of patients achieving ACR50 Proportion of patients achieving ACR70	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment population	Assessed during Period 2	Secondary analysis
			Ixekizumab-treated patients nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined	Secondary analysis
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population	Assess during Period 3 through 40 weeks of Randomized Treatment	Secondary analysis
C-Reactive Protein (CRP)	CRP (mg/L) Change from baseline in CRP (mg/L) % improvement in CRP (mg/L)	Descriptive statistics	Initial open-label treatment period population	Assessed during Period 2	Secondary analysis
			Relapse population	Assessed during Relapse Period	Secondary analysis
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined	Secondary analysis
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assess during Period 3 through 40 weeks of Randomized Treatment	Secondary analysis
Static Physician's Global Assessment	Time-to sPGA ≥2 (loss of response)	Log-Rank Test. Kaplan-Meier product limit method	Randomized withdrawal ITT population who were sPGA (0,1) at time of randomization	Assessed during Period 3	Secondary analysis

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point	Analysis Type
(sPGA)	Time-to Achieve sPGA (0,1)	Descriptive statistics (including Kaplan Meier estimates of the survival curve)	Relapse population who were sPGA ≥2 at time of relapse	Assessed during Relapse Period	Secondary analysis
Psoriasis Area and Severity Index (PASI)	Time-to PASI total score >1 (loss of response)	Log-Rank Test. Kaplan-Meier product limit method	Randomized withdrawal ITT population who were PASI total score ≤1 at time of randomization	Assessed during Period 3	Secondary analysis
	Time-to Achieve PASI total score ≤1	Descriptive statistics (including Kaplan Meier estimates of the survival curve)	Relapse population who were PASI total score >1 at time of relapse	Assessed during Relapse Period	Secondary analysis
Percentage of Body Surface Area (BSA)	Time-to-BSA >3% (loss of response)	Log-Rank Test. Kaplan-Meier product limit method	Randomized withdrawal ITT population who were BSA ≤3% at time of randomization	Assessed during Period 3	Secondary analysis
	Time-to Achieve BSA ≤3%	Descriptive statistics (including Kaplan Meier estimates of the survival curve)	Relapse population who were BSA >3% at time of relapse	Assessed during Relapse Period	Secondary analysis
Tender Entheseal Points (defined using the 18 entheseal points)	Time-to tender entheseal points >1 (loss of response)	Log-Rank Test. Kaplan-Meier product limit method	Randomized withdrawal ITT population who had a tender entheseal points ≤1 at time of randomization	Assessed during Period 3	Secondary analysis
	Time-to Achieve tender entheseal points ≤1	Descriptive statistics (including Kaplan Meier estimates of the survival curve)	Relapse population who had a tender entheseal points >1 at time of relapse	Assessed during Relapse Period	Secondary analysis

Abbreviations: ACR20/50/70 = 20%, 50%, or 70% improvement in American College of Rheumatology criteria; ANCOVA = analysis of covariance; ITT = intent-to-treat; IXE80Q2W = ixekizumab 80 mg every 2 weeks; mBOCF = modified baseline observation carried forward; MMRM = mixed-effects model of repeated measures; NRI = nonresponder imputation; PPS = per-protocol set; Q2W = every 2 weeks.

6.11.1. Primary Outcome and Methodology

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

Treatment comparison between ixekizumab 80 mg Q2W and placebo in time-to relapse for the randomized withdrawal ITT population and the PPS 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.

6.11.2. Secondary Efficacy Analyses

There will be no adjustment for multiple comparisons for other secondary analyses. The secondary analyses are detailed in Table RHBF.6.3 and Table RHBF.6.4.

6.11.3. Sensitivity Analyses

Sensitivity analyses will be performed for the primary analysis using the 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). The modified Coates criteria for MDA is described in Table RHBF.6.3 and the sensitivity analyses are detailed in Table RHBF.6.4.

6.12. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic, PD, and biomarker analyses to address secondary and exploratory objectives of this study will be described by Lilly in separate PK/PD and biomarker analysis plans.

6.13. Safety Analyses

Safety will be assessed by summarizing and analyzing SAEs, AEs, AESIs, QIDS-SR16, vital signs, other measures of cardiovascular function, 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 [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 6.1.2. the Period 2 (initial open-label treatment population), Period 2 and Period 3 combined (ixekizumab-treated patients within the randomized withdrawal safety population and nonrandomized population), and for Relapse Period (relapse population), the above safety variables will be summarized as described in Sections 6.1.1, 6.1.2, and 6.1.3, respectively.

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

For safety analyses, the following baselines will be used:

- Treatment-emergent adverse events: baseline will be all results recorded during the baseline period (see Section 6.1 for definitions of the baseline period).
- Treatment-emergent abnormal laboratory and vital signs: baseline will be all results recorded during the baseline period (see Section 6.1 for definitions of the baseline period).
- Change from baseline to minimum and maximum: baseline will be all results recorded during the baseline period (see Section 6.1 for definitions of the baseline period).

6.13.1. Extent of Exposure

Duration of exposure to study drug will be summarized by treatment group for Period 2, Period 3, and the Period 2 and Period 3 combined using descriptive statistics.

A by-patient listing of exposure duration with number of active injections and total dose will be provided.

The duration of exposure for Period 2 (initial open-label treatment period population) will be calculated:

For randomized patients:

$$\begin{aligned} &Duration\ of\ exposure\ (days) \\ &\quad = (Date\ of\ randomization \\ &\quad - Date\ of\ first\ injection\ of\ ixekizumab\ 80\ mg\ Q2W\ in\ Period\ 2) + 1 \end{aligned}$$

For nonrandomized patients:

$$\begin{aligned} &Duration\ of\ exposure\ (days) \\ &\quad = (Date\ of\ last\ visit\ (scheduled\ or\ unscheduled) on\ or\ prior\ to\ Visit\ 19) \\ &\quad - Date\ of\ first\ injection\ of\ ixekizumab\ 80\ mg\ Q2W\ in\ Period\ 2) + 1 \end{aligned}$$

The duration of exposure for Period 3 (randomized withdrawal safety population) will be calculated for the randomized patients as:

$$\begin{aligned} &Duration\ of\ exposure\ (days) \\ &\quad = (Date\ of\ last\ visit\ (scheduled\ or\ unscheduled)\ \ or\ relapse\ in\ Period\ 3 \\ &\quad - Date\ of\ first\ injection\ of\ study\ treatment\ after\ randomization\ in\ Period\ 3) + 1 \end{aligned}$$

Note that patients who experience a relapse during Period 3 will only have their Period 3 exposure calculated up until the date of relapse.

The duration of exposure for Relapse Period (relapse population) will be calculated as:

$$\begin{aligned}&Duration\ of\ exposure\ (days)\\&\quad=(Date\ of\ last\ visit\ (scheduled\ or\ unscheduled)\ in\ Period\ 3\\&\quad-Date\ of\ first\ injection\ of\ ixekizumab\ 80\ mg\ Q2W\ in\ Period\ 3\ following\ relapse)+1\end{aligned}$$

The duration of exposure for Period 2 and Period 3 combined (ixekizumab 80 mg Q2W-treated patients from the randomized withdrawal safety population) will be calculated for randomized patients as:

$$\begin{aligned}&Duration\ of\ exposure\ (days)\\&\quad=(Date\ of\ last\ visit\ (scheduled\ or\ unscheduled)\ or\ relapse\ in\ Period\ 3\\&\quad-Date\ of\ first\ injection\ of\ inital\ ixekizumab\ 80\ mg\ Q2W\ treatment\ in\ Period\ 2)+1\end{aligned}$$

The duration of exposure for Period 2 and Period 3 combined (nonrandomized safety population) will be calculated for nonrandomized patients as:

$$\begin{aligned}&Duration\ of\ exposure\ (days)\\&\quad=(Date\ of\ last\ visit\ (scheduled\ or\ unscheduled)\ in\ periods\ 2\ or\ 3\\&\quad-Date\ of\ first\ injection\ of\ inital\ ixekizumab\ 80\ mg\ Q2W\ treatment\ in\ Period\ 2)+1\end{aligned}$$

The number and percentage of patients in each of the following categories will be included in the summaries (as applicable for the treatment period summarized):

- >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥90 days, ≥120 days, ≥183 days, and ≥365 days, ≥548, and ≥730. Note that patients may be included in more than 1 category.
- >0 to <7 days, ≥7 to <14 days, ≥14 to <30 days, ≥30 to <60 days, ≥60 days to <90 days, ≥90 to <120 days, ≥120 to <183 days, ≥183 to <365 days, and ≥365 days.

The summaries will also include the following information:

- Total exposure in patient years, calculated as:

$$=\frac{Sum\ of\ duration\ of\ exposures\ for\ all\ patients\ in\ the\ study\ period\ in\ the\ treatment\ group}{365.25}$$

- Number of active injections taken; derived using the response to the question "Was dose administered?" on the Exposure eCRF page and the actual dose description from IWRS study drug dispense dataset.
- Total dose (in mg); calculated by the number of active injections taken multiplied by a dose of 80 mg.

6.13.2. Adverse Events

Adverse events will be classified based upon the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be recorded at every study visit.

Condition starting on or after the date of informed consent will be considered an AE. A preexisting condition that worsens in severity on or after the date of informed consent will be considered and recorded as an AE on the AE eCRF page from the date of worsening onwards.

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 defined treatment period. Both the date/time of the event and the date/time of the dose (that is, injection) are considered when determining TEAEs. Treatment-emergent adverse events will be assigned to the study period to which it's considered treatment-emergent.

- The MedDRA Lowest Level Term (LLT) will be used when classifying AEs as treatment-emergent.
- The maximum severity recorded for each LLT prior to the first dose date/time in the treatment period will be used as the pretreatment severity for that LLT. If an event during the baseline period has missing severity, and the event persists during the treatment period, then it will be considered as treatment-emergent, regardless of the post-baseline level of severity. Events with a missing severity during the treatment period will be considered treatment-emergent.
- Adverse events with a particular LLT will be classified as treatment-emergent if they first start on or after the first dose date/time in the treatment period (that is, a patient has no preexisting conditions with that LLT), or if the severity is greater than the pretreatment severity for that LLT.

A follow-up emergent adverse event (FEAE) is defined as an event that first occurred or worsened in severity after the date of Visit 29 (that is, Week 104) or the ETV:

- The MedDRA LLT will be used when classifying AEs as follow-up emergent.
- For AEs that are ongoing at the date of Visit 29 (Week 104) or ETV, the maximum severity recorded for each LLT on or prior to the date of Visit 29 (Week 104) or ETV will be used as the follow-up baseline severity for that LLT.

If a partial or completely missing AE start date/time or end date/time is present the following imputation rules will be utilized in the analysis:

- For the start date:
  - If year, month, and day are missing, then use the consent date.
  - If either month or month and day are missing, then use January 1.
  - If only day is missing, impute the first day of the month.
- For the start time:
  - Impute as 23:59
- For the end date:
  - If year, month, and day are missing, then use the patient's last visit date.

  - If either month or month and day are missing, then use December 31.
  - If only day is missing, then use the last day of the month.
  - The imputed date will not be beyond the patient's last visit date in the follow-up period.
- If there is any doubt, the event will be flagged as treatment-emergent or follow-up emergent according the corresponding study period. If a follow-up emergent event was already counted as treatment-emergent during the prior treatment period, it will not be counted as a follow-up emergent event.

Adverse events and TEAEs will be listed for all entered patients and summarized for the following periods:

- Period 2 (initial open-label treatment period population)
- Period 3 (randomized withdrawal safety population)
- Relapse Period (relapse population)
- Combined Period 2 and Period 3 (ixekizumab 80 mg Q2W-treated patients from the randomized withdrawal safety population and nonrandomized population).

Adverse events and TEAEs for Period 3 will be compared between treatment groups using a Fisher's exact test for the randomized withdrawal safety population.

The following summaries/analyses will be performed:

- An overall summary of AEs including the number and percentage of patients who experienced TEAE, TEAE by maximum severity, death, SAE, TEAE related to study drug, discontinuations from the treatment due to an AE, and TEAEs of special interest.
- treatment-emergent adverse event by System Organ Class (SOC) and PT
- treatment-emergent adverse event by maximum severity, SOC, and PT

Follow-up emergent adverse events will be summarized for the follow-up population for the post-treatment follow-up period (Period 4):

- Follow-up emergent adverse event by SOC and PT

In general, for all AE related summaries, the number and percentage of patients experiencing the events will be presented by treatment group. The events will be ordered by decreasing frequency in the ixekizumab treatment group, within SOC and/or PT for sorting. For events that are gender-specific (as defined by MedDRA), the denominator and computation of the percentage will include only patients from the given gender.

6.13.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

6.13.3.1. Deaths

A listing of deaths will be provided for all entered patients. All deaths will be included, regardless of the Investigator's or the Sponsor's judgment about causality, including (1) any deaths occurring during participation in the study, (2) any deaths occurring after a patient leaves (is discontinued from the study or completes the study) any of the studies in the database for which data are being presented if the death is (a) the result of a process initiated during the study, regardless of when it actually occurs, or (b) occurs during the post-treatment follow-up period after discontinuation of study drug. The actual rule used for including deaths will be provided in a footnote to the table. Any discrepancies between what is in the Lilly Safety System (LSS) and what is in the clinical study report (CSR) for individual studies will be explained in the footnote. The information from the LSS listing is used to create a hand-generated listing. Each listing will include study ID, investigator ID, patient ID, treatment group, baseline age, sex, associated AE, whether or not the death and Lilly's assessment of whether the process leading to death (NOT the death itself) began:

- "On study Drug": on study drug or within 14 days after study drug discontinuation
- "During the post-treatment follow-up period": >14 days after study drug discontinuation through the end of the post-treatment follow-up period
- "After the post-treatment follow-up period": any time after the end of the post-treatment follow-up period.

6.13.3.2. Serious Adverse Event Analyses

An SAE is any AE that results in 1 of the following outcomes: death, life-threatening, initial or prolonged hospitalization, disability or permanent damage, congenital anomaly or birth defect, or any other serious/important medical events that may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above.

Exposure-adjusted incidence rates (per 100 patient years) for SAEs will be presented by treatment group using MedDRA PT nested within SOC.

Serious adverse events will be listed for all entered patients and summarized for the following periods:

- Period 2 (initial open-label treatment period population)
- Period 3 (randomized withdrawal safety population)
- Relapse Period (relapse population)
- Combined Period 2 and Period 3 (ixekizumab 80 mg Q2W-treated patients from the randomized withdrawal safety population and nonrandomized population).

Serious adverse events for Period 3 will be compared between treatment groups using the Fisher's exact test for the randomized withdrawal safety population.

A summary table of SAEs by SOC and PT will be provided.

A follow-up emergent serious adverse event (FESAE) is defined as an SAE that first occurred or worsened in severity after the date of Visit 29 (that is, Week 104) or the ETV. The baseline severity for SAEs occurring during the post-treatment follow-up period will be the maximum severity from the preceding visit before entering the post-treatment follow up period. A summary table of FESAEs by SOC and PT will be provided for the follow-up population for Period 4.

The events will be ordered by decreasing frequency in the ixekizumab treatment group, within SOC and/or PT for sorting. For events that are gender-specific, the denominator and computation of the percentage will include only patients from the given gender.

6.13.3.3. Other Significant Adverse Events

Adverse events that lead to treatment discontinuation (including death) will be listed for all entered patients and summarized for the following periods:

- Period 2 (initial open-label treatment period population)
- Period 3 (randomized withdrawal safety population)
- Relapse Period (relapse population)
- Combined Period 2 and Period 3 (ixekizumab 80 mg Q2W-treated patients from the randomized withdrawal safety population and nonrandomized population).

Adverse events that lead to treatment discontinuation (including death) for Period 3 will be compared between treatment groups using the Fisher's exact test for the randomized withdrawal safety population.

A summary table of AEs that lead to treatment discontinuation (including death) by SOC and PT will be provided:

A summary table of FEAEs that lead to study discontinuation (including death) by SOC and PT will be provided for Period 4:

Events will be ordered by decreasing frequency in the combined ixekizumab group within SOC. For events that are gender-specific, the denominator and computation of the percentage will include only patients from the given gender.

6.13.4. Depression and Suicide-Related Patient Reported Outcomes

The QIDS-SR16, the C-SSRS, and the Self-Harm Supplement Form will be administered to patients at baseline and post-baseline to assess depression and the risk of suicide.

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 (APA's)

Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (APA 1994). Refer to Table RHBF.6.11 and Table RHBF.6.12 for further details.

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 was added after study enrollment had been initiated. Given that few or no suicidal ideation or behaviors are anticipated, C-SSRS will be listed by patient and visit. Only patients that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be displayed (that is, if a patient answers are all 'no' for the C-SSRS, then that patient will not be displayed). However, if a patient reported any suicidal ideation/ behavior or self-injurious behavior without suicidal intent at any time point then all their ideation and behavior will be displayed, even if not positive.

The Self-Harm Supplement Form is a 1-question form that is completed, at any visit, including baseline visits, 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. Supplemental information collected will be listed by patient and visit for only the patients that have a number of suicidal or nonsuicidal self-injurious behaviors greater than 0 at any visit.

6.13.5. Clinical Laboratory Evaluation

Clinical laboratory assessments include hematology, serum chemistry, urinalysis, and safety-related immune markers such as neutrophil counts.

By-patient listing of laboratory test values will be provided for all entered patients. Listing of laboratory tests reference ranges (both large clinical trial population based reference limits and Covance reference ranges) will be provided. By-patient listing of abnormal laboratory test results (criteria defined in the shift tables excluding the normal category) for parameters of special interest (hepatic, immunoglobulins, leukocytes and platelets) will be provided.

Laboratory results will be summarized for (unless otherwise noted):

- Period 2 (initial open-label treatment period population);
- Period 3 (randomized withdrawal safety population);
- Combined Period 2 and Period 3 (ixekizumab 80 mg Q2W-treated patients from the randomized withdrawal safety population and nonrandomized population)

Continuous laboratory tests will be summarized as changes from baseline for patients who have both baseline and at least 1 post-baseline result.

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.

- Both international system of unit (SI) and conventional unit will be summarized when different.
- Data will be analyzed based on original scale.

Change from minimum value during the baseline period to the minimum value during the treatment period, as well as change from the maximum value during the baseline period to the maximum value during the treatment period will be summarized for patients who have both a baseline and at least 1 post-baseline result.

For the randomized withdrawal safety population for Period 3, the comparisons between treatment groups will be conducted using an ANCOVA with treatment group and baseline value in the model.

The number and percentage of patients with a treatment-emergent or follow-up emergent abnormal, high, or low for laboratory tests will be summarized by treatment group. These will be displayed for (unless otherwise noted):

- Period 2 (initial open-label treatment period population)
- Period 3 (randomized withdrawal safety population)
- Relapse Period (relapse population)
- Combined Period 2 and Period 3 (ixekizumab 80 mg Q2W-treated patients from the randomized withdrawal safety population and nonrandomized population); and Period 4 (post-treatment follow-up period population)
- Period 4 (post-treatment follow-up period population)

The comparisons between treatment groups will be conducted using the Fisher's exact test for the randomized withdrawal safety population for Period 3.

- All scheduled, unscheduled, and repeated measurements will be included.
- In general, large clinical trial population based reference limits (that is, Lilly reference ranges) will be used to define the low and high limits since it is generally desirable for limits used for analyses to have greater specificity (identify fewer false positive cases) than reference limits used for individual subject management. In the case when the reference limits based on the large clinical trial population is not available for a laboratory measure, Covance reference ranges will be used. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase (ALP) will not be included in the treatment-emergent abnormal, high, or low summary as a separate analysis addressing the risk of liver injury is described in Section 6.13.7 in which Covance Reference Ranges are used.
- Note that the ranges are defined by a lower limit of normal (LLN) and an upper limit of normal (ULN). A result that is greater than or equal to the LLN and less than or equal to the ULN is considered to be within the normal ranges.

- For categorical laboratory tests:
    - Treatment-emergent **abnormal** value is defined as a change from normal at all baseline visits to abnormal at any time post-baseline during the treatment period.
    - Follow-up emergent **abnormal** result is defined as a change from normal at baseline to abnormal at any time during the follow-up period.
- For continuous laboratory tests:
    - Treatment-emergent **high** value is defined as a change from a value less than or equal to the ULN at all baseline visits to a value greater than the ULN at any time post-baseline during the treatment period.
    - Treatment-emergent **low** value is defined as a change from a value greater than or equal to the LLN at all baseline visits to a value less than the LLN at any time post-baseline during the treatment period.
    - Follow-up emergent **high** value is defined as a change from a value less than or equal to the ULN at baseline to a value greater than the ULN at any time post-baseline during the follow-up period.
    - Follow-up emergent **low** value is defined as a change from a value greater than or equal to the LLN at baseline to a value less than the LLN at any time post-baseline during the follow-up period.

Shift tables will be produced using the following categories:

- Neutrophils: ≥1 × LLN (Normal), < LLN to ≥1.5 × 10^9/L (Grade 1), <1.5 × 10^9/L to ≥1.0 × 10^9/L (Grade 2), <1.0 × 10^9/L to ≥0.5 × 10^9/L (Grade 3), and <0.5 × 10^9/L (Grade 4)
- Leukocytes: ≥1 × LLN (Normal), < LLN to ≥3.0 × 10^9/L (Grade 1), <3.0 × 10^9/L to ≥2.0 × 10^9/L (Grade 2), <2.0 × 10^9/L to ≥1.0 × 10^9/L (Grade 3), and <1.0 × 10^9/L (Grade 4)
- Platelets: ≥1 × LLN (Normal), < LLN to ≥75.0 × 10^9/L (Grade 1), <75.0 × 10^9/L to ≥50.0 × 10^9/L (Grade 2), <50.0 × 10^9/L to ≥25.0 × 10^9/L (Grade 3), and <25.0 × 10^9/L (Grade 4)
- Lymphocytes: ≥1 × LLN (Normal), < LLN to ≥0.8 × 10^9/L (Grade 1), <0.8 × 10^9/L to ≥0.5 × 10^9/L (Grade 2), <0.5 × 10^9/L to ≥0.2 × 10^9/L (Grade 3), and <0.2 × 10^9/L (Grade 4)

The following LLN will be defined for analyses:

- Leukocytes: LLN=4.0 ×10^9/L
- Neutrophils: LLN=2.0×10^9/L
- Lymphocytes: LLN=1.1×10^9/L
- Platelets: LLN=150×10^9/L

In addition, for the above parameters (neutrophils, leukocytes, platelets and lymphocytes), the number and percentage of patients with minimum post-baseline results will be presented overall and by treatment group within the following groups using the categories as defined above:

- Decreased; post-baseline category < baseline category
- Increased; post-baseline category > baseline category
- Same; post-baseline category = baseline category

The number and percentages of patients with treatment-emergent low laboratory results at any time will be summarized for these 4 measures by treatment group for each treatment period. Shift tables will be produced showing the number and percentage of patients with a minimum post-baseline result for these 4 measures and will be summarized overall, and by treatment group and baseline result.

6.13.5.1. Leukocytes (WBC) and Platelets

Leukocytes (WBC) and platelets results will be summarized for (unless otherwise noted):

- Period 2 (initial open-label treatment period population)
- Period 3 (randomized withdrawal safety population)
- Relapse period (relapse population)
- Combined Period 2 and Period 3 (ixekizumab 80 mg Q2W-treated patients from the randomized withdrawal safety population and nonrandomized population).

Change from minimum value and maximum value for total leukocytes, neutrophils, platelets, lymphocytes, monocytes, eosinophils, and basophils will be included in summaries described in Section 6.13.5. Unless otherwise specified, neutrophils will be summarized for absolute neutrophils (defined as the sum of segmented neutrophil count and the band neutrophil count). Laboratory values at each visit (starting at baseline) and change from baseline to each scheduled visit for these laboratory tests will be included in box plots (with outliers displayed) described in Section 6.13.5.

6.13.5.2. Neutrophil Follow-Up

Neutrophil counts will be followed throughout the study. Patients will continue in Period 4 until their neutrophil counts have recovered.

The neutrophil follow-up analysis will be conducted on the neutrophil follow-up population defined as patients who have an absolute neutrophil count <1500 cells/µL (SI units: <1.5× 10^9/L) at the last scheduled visit or early termination visit prior to entering the post-treatment follow-up period (Period 4) and less than the patient's baseline absolute neutrophil count (that is, prior to first injection at Week 0). These patients are monitored during the Period 4 until neutrophil recovery.

Neutrophil clinical recovery is defined as an absolute neutrophil count ≥1500 cells/µL (SI units: ≥1.5× 10^9/L) or greater than or equal to a patient's absolute neutrophil count prior to first study drug injection at Week 0.

If a patient's neutrophil count has not recovered, within 12 weeks after entering the follow-up period (Visit 802), the patient will return for Visit 803 (12 weeks after Visit 802). Additional visits may be required for appropriate patient management depending upon the degree of neutropenia. If at Visit 802, a patient has met the criteria for neutrophil recovery, the patient's participation in the study will be considered complete unless the investigator deems additional follow-up may be necessary.

The number and percentage of patients achieving neutrophil clinical recovery will be presented by treatment group and week interval for neutrophil follow-up population for post-treatment follow-up period (Period 4). The number and percentage of patients with an absolute neutrophil cell count that is at least 25%, 50%, 75%, or 100% of the patient's baseline absolute neutrophil count (that is, prior to first injection at Week 0), irrespective of absolute neutrophil minimum, will be included in the summary.

The time to neutrophil recovery will be calculated (for patients entering the Post-Treatment Follow-up Period) as follows:

Time to neutrophil recovery (in weeks) = (Date of neutrophil recovery – Date of last visit prior to entering the follow-up period) / 7.

Kaplan-Meier estimates of the proportion of patients not yet experiencing absolute neutrophil recovery at selected time points will be provided by treatment group. A Kaplan-Meier plot of the time to neutrophil recovery will be presented by treatment group.

If a patient has not experienced neutrophil recovery, he/she will be censored at the date of the last neutrophil count assessment. If they did not have a neutrophil count assessment, they will be censored at the date of last follow-up visit.

6.13.6. Vital Signs and Other Physical Findings

Analyses will be conducted on vital signs and physical characteristics including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse (bpm), weight (kg), and BMI (kg/m^2). By-patient listing of vital signs and physical characteristics will be provided.

Vital signs and other physical finding results will be summarized for (unless otherwise noted):

- Period 2 (initial open-label treatment period population)
- Period 3 (randomized withdrawal safety population)
- Combined Period 2 and Period 3 (ixekizumab 80 mg Q2W-treated patients from the randomized withdrawal safety population and nonrandomized population).

Change from baseline for vital signs and other physical findings will be summarized for patients who have both baseline and at least one post-baseline result.

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.

- For the randomized withdrawal safety population for Period 3, the comparisons between treatment groups will be conducted using an ANCOVA with treatment group and baseline value in the model.
- Data will be analyzed based on original scale.

Change from minimum value during the baseline period to the minimum value during the treatment period, as well as change from the maximum value during the baseline period to the maximum value during the treatment period will be summarized for patients who have both a baseline and at least 1 post-baseline result.

The number and percentage of patients with treatment-emergent or follow-up emergent high or low vital sign and weight at any time will be summarized. These will be displayed for (unless otherwise noted):

- Period 2 (initial open-label treatment period population)
- Period 3 (randomized withdrawal safety population)
- Relapse Period (relapse population)
- Combined Period 2 and Period 3 (ixekizumab 80 mg Q2W-treated patients from the randomized withdrawal safety population and nonrandomized population)
- Period 4 (post-treatment follow-up period population)

The comparisons between treatment groups will be conducted using the Fisher's exact test for the randomized withdrawal safety population for Period 3.

Table RHBF.6.5 defines the high and low baseline values as well as the limits that are specified as treatment-emergent and follow-up emergent. Note that weight does not have an abnormal baseline; therefore, the treatment-emergent and follow-up emergent values are determined by change from baseline.

- All post-baseline scheduled, unscheduled and repeated measurements will be included.
- To assess increases, change from the maximum value during the baseline period or baseline to the maximum value during each study period will be used.
- To assess decreases, change from the minimum value during the baseline period or baseline to the minimum value during each study period will be used.
- For treatment-emergent high and low:
    - A treatment-emergent **high** result is defined as a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at any time that meets the specified change criteria during the treatment period.
    - A treatment-emergent **low** result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any time that meets the specified change criteria during the treatment period.

- For follow-up emergent high and low:
  - A follow-up emergent **high** result is defined as a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at any time that meets the specified change criteria during the follow-up period.
  - A follow-up emergent **low** result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any time that meets the specified change criteria during the follow-up period.

Table RHBF.6.5. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressures and Pulse Measurement, and Categorical Criteria for Weight Changes for Adults

Parameter	Low	High
Systolic BP (mm Hg) [a] (supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) [a] (supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) [a] (supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Weight (kg)	(Loss) decrease from baseline ≥7%	(Gain) increase from baseline ≥7%

Abbreviations: BP = blood pressure; bpm = beats per minute; kg = kilogram; mm Hg = millimeters of mercury.

[a] Baseline abnormal values are defined by the value presented.

To assess the effect of administration of study drug on vital signs (blood pressures and pulse rate) among patients, at Week 0, vital signs will be measured before the first injection and 1 hour after the injection. The box plots will be produced for pre-dose and post-dose vital signs at Week 0 (Visit 2) for the initial open-label treatment period population.

6.13.7. Special Safety Topics including Adverse Events of Special Interest

Safety information on special topics including AESIs will be presented by treatment group and by study period. Table RHBF.6.6 provides the definitions/derivations and analyses methods (including analyses, summaries and by-patient listings) of special safety topics including AESIs.

Potential AESIs will be identified by a standardized MedDRA query (SMQ) or a Lilly-defined MedDRA PT listing. Preferred terms within an SMQ will be classified as broad and narrow. In the Lilly-defined MedDRA PT listings, Lilly has provided the broad and narrow classification. The Lilly-defined broad terms are for a more sensitive search of potential events of interest and the Lilly-defined narrow terms are for a more specific search. Therefore, the summaries will include the classifications of broad term (same as pooling narrow and broad terms together) and narrow term. In the event that the listing of terms or analysis changes for a special safety topic,

it will be documented in the program safety analysis plan (PSAP) which will supersede this document; it will not warrant an amendment to the individual study SAP.

Table RHBF.6.6. Definitions and Analyses of Special Safety Topics Including Adverse Events of Special Interest

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
Hepatic	Hepatic AE analysis will include events that are potentially drug-related hepatic disorders by using the MedDRA PTs contained in any of the following SMQs or sub-SMQs as defined in MedDRA: • Broad and narrow terms in the Liver related investigations, signs and symptoms (20000008) • Broad and narrow terms in the Cholestasis and jaundice of hepatic origin (20000009) • Broad and narrow terms in the Hepatitis, non-infectious (20000010) • Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage (20000013) • Narrow terms in the Liver-related coagulation and bleeding disturbances (20000015)	**Period 2, Period 3, and Combined Periods 2 and 3 (Summary):** **Period 3 randomized withdrawal safety population (Fisher's exact test)**: TEAE by PT within SMQ or sub-SMQ, SAE by PT within SMQ or sub-SMQ, AE leading to treatment discontinuation by PT within SMQ or sub-SMQ **Listing:** TEAE
	Elevations in hepatic laboratory tests (ALT, AST, ALP, total bilirubin) using Performing lab ULN during the treatment period are defined as: • Include scheduled visits, unscheduled visits, and repeat measurements. • ALT or AST: maximum post-baseline measurement ≥3 times (3×), 5×, 10×, and 20× the Covance ULN for all patients with a post-baseline value. o The analysis of 3×ULN will contain 4 subsets: patients whose non-missing maximum baseline value is ≤1×ULN, >1×ULN to <3×ULN, ≥3×ULN, or missing. o The analysis of 5×ULN will contain 5 subsets: patients whose non-missing maximum baseline value is ≤1×ULN, >1×ULN to <3×ULN, ≥3×ULN to <5×ULN, ≥5×ULN, or missing. o The analysis of 10×ULN will contain 6 subsets: patients whose non-missing maximum baseline value is ≤1×ULN, >1×ULN to <3×ULN, ≥3×ULN to <5×ULN, ≥5×ULN to <10×ULN, ≥10×ULN, or missing. o The analysis of 20×ULN will contain 7 subsets: patients whose non-missing maximum baseline value is ≤1×ULN, >1×ULN to <3×ULN, ≥3×ULN to <5×ULN, ≥5×ULN to <10×ULN, ≥10×ULN to <20×ULN, ≥20×ULN, or missing. • Total bilirubin: maximum post-baseline measurement greater ≥2× the Performing lab ULN for all patients with a post-baseline value, and divided into 4 subsets: patients whose non-missing maximum baseline value is ≤1×ULN, >1×ULN to <1.5×ULN, ≥1.5×ULN to <2×ULN, ≥2×ULN, or missing. • ALP: maximum post-baseline measurement >1.5× the Covance ULN for all patients with a	**Period 2, Period 3, and Combined Periods 2 and 3 (Summary)**: Elevations in hepatic laboratory tests: maximum baseline category to abnormal maximum post-baseline category

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	post-baseline value, and divided into 4 subsets: patients whose non-missing maximum baseline value is ≤1×ULN, >1×ULN to ≤1.5×ULN, >1.5×ULN, or missing.	
	Shift for ALT, AST, and total bilirubin from maximum baseline to maximum post-baseline will be produced with the requirements using Performing lab ULN during the treatment period: • Include scheduled visits, unscheduled visits, and repeat measurements. • Use the maximum non-missing value in the baseline period. • Use the maximum non-missing post-baseline value within each study period. • Categories are: o ALT: ≤1×ULN, >1 to <3×ULN, ≥3 to <5×ULN, ≥5 to <10×ULN, ≥10 to <20×ULN, and ≥20×ULN o AST: ≤1×ULN, >1 to <3×ULN, ≥3 to <5×ULN, ≥5 to <10×ULN, ≥10× to <20×ULN and ≥20×ULN o Total bilirubin: ≤1×ULN, >1 to <1.5×ULN, ≥1.5 to <2×ULN, ≥2×ULN o ALP; ≤1× ULN, >1 to ≤1.5× ULN, >1.5× ULN. • With additional categories: o Decreased: post-baseline category < baseline category o Increased: post-baseline category > baseline category o Same: post-baseline category = baseline category	**Period 2, Period 3, and Combined Periods 2 and 3 (Summary)**: Shifts from maximum baseline to maximum post-baseline category
	Elevated hepatic criteria: maximum ALT ≥3×ULN and maximum total bilirubin ≥2×ULN, using Performing lab Reference Ranges. Listing of patients who meet any of the following criteria: • Elevated hepatic criteria: defined as maximum ALT ≥3×ULN and maximum total bilirubin ≥2×ULN • An ALT or AST ≥3×ULN • An alkaline phosphatase (ALP) ≥1.5×ULN • A total bilirubin ≥2×ULN The listing will include: patient demographics, concomitant medications, ALT/AST/ALP/total bilirubin/gamma-glutamyl transferase (GGT) by visit, treatment start and stop dates, and reason for treatment discontinuation.	**Listing**: Elevations in hepatic laboratory tests
	eDISH plot: use maximum ALT measurement and maximum total bilirubin measurement after the first injection of study treatment with patients having at least one post-baseline ALT and total bilirubin, which contributes one point to the plot. The measurements do not need to be taken at the same blood draw.	**Period 2, 3, and 4 combined**: eDISH plot

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
Cytopenias	Cytopenias are defined using the PTs from the following 2 sub-SMQs of the Haematopoietic cytopenias SMQ (20000027) as specified in MedDRA: • Broad and narrow terms in the Haematopoietic leukopenia (20000030) • Broad and narrow terms in the Haematopoietic thrombocytopenia (20000031)	**Period 2, Period 3, and Combined Periods 2 and 3 (Summary)**: **Period 3 randomized withdrawal safety population (Fisher's exact test)**: TEAE by PT within sub-SMQ, SAE by PT within sub-SMQ, AE leading to treatment discontinuation by PT within sub-SMQ **Listing:** TEAE
Infections	Infections are events including all infections (defined using all the MedDRA PTs from the Infections and infestations SOC), serious infections, potential OIs, and infections resulting in anti-infective medication adminstration (i.e., antibacterial, antiviral, antifungal, antiparasitic treatment.) .	**Period 2, Period 3, and Combined Periods 2 and 3 (Summary)**: **Period 3 randomized withdrawal safety population (Fisher's exact test)**: TEAE by PT, TEAE by maximum severity by PT, SAE by PT, AE leading to treatment discontinuation by PT **Listing:** TEAE
	Anti-infective medications are defined in Appendix 7 including antibacterial, antiviral, antifungal, and antiparasitic treatment. Listing of patients experiencing a TEAE of infections will be provided including the following additional information: anti-infective medications use (if treated) with medication start/end dates, indication for use, and route; minimum post-baseline value within treatment Period 2 for leukocytes, platelets, lymphocytes, and absolute neutrophils.	**Listing:** TEAE with anti-infective medications
	• The list of MedDRA terms used to identify infections that are defined as potential OIs are found in Appendix 12. This list contains PTs with Categories (narrow or broad) from the Infections and Infestations SOC and from the Investigations SOC which can assist in indentifying potential OIs. The narrow terms are considered OIs unless medical review	**Period 2, Period 3, and Combined Periods 2 and 3 (Summary)**: **Period 3 randomized withdrawal safety population (Fisher's exact test)**:

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	determines that the reported term is not consistent with the patient's clinical history/presentation/course. Medical review of broad terms is needed for final determination of patients meeting the program definitionof OIs. Listing of patients experiencing a TEAE of potential OIs will be provided including the following additional information: source of identification (CRF or Lilly-defined list), primary/secondary site of infection, primary/secondary infection type, primary/secondary identified by a laboratory diagnostic test (Yes/No), acquired in a health care setting (Yes/No).	TEAE of OIs by maximum severity by PT **Listing:** TEAE of OIs
	The duration of each common (≥1% of total ixekizumab) TEAE PT of Infections is defined as: Duration of treatment-emergent AE Infections (in weeks) = (End date of AE – Start date of AE + 1) / 7. Only TEAEs of infections beginning during treatment Period 3 will be included in the summary. If an AE has not ended by the date of completion of the treatment Period 3, or date of early discontinuation, it will be censored as of that date (last visit within the treatment Period 3, or date of early discontinuation). If a patient has multiple episodes of the same TEAE, the episode with the greatest severity will be used for the duration of event calculation. If a patient has multiple episodes of the same TEAE with the same severity, the episode with the longest duration will be used for the duration of event calculation.	**Period 2, Period 3, and Combined Periods 2 and 3 (Summary)**: **Period 3 randomized withdrawal safety population (Summary)**: Duration of Common TEAE – Infections

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
Allergic Reactions/ Hypersensitiv-ities	Allergic reactions/hypersensitivity events will be categorized as either potential anaphylaxis or non-anaphylaxis events (these will refer to events that are not localized to the site of injection) and summarized separately. Medical reviews are needed for final determination of patients with allergic reactions/hypersensitivities. Allergic Reactions/Hypersensitivity Events, Potential Anaphylaxis: Anaphylaxis has been broadly defined as "a serious allergic reaction that is rapid in onset and may cause death" (Sampson et al. 2006). Identification of cases of potential anaphylaxis from the clinical trial data involves 2 criteria: 1) designed to specifically identify cases (following Criterion 1) based on narrow terms from the MedDRA SMQ for anaphylactic reaction (20000021). Criterion 1 for anaphylaxis is defined by the presence of a TEAE based on the following MedDRA PTs from the anaphylactic reaction SMQ: • Anaphylactic reaction • Anaphylactic shock • Anaphylactoid reaction • Anaphylactoid shock • Anaphylactic treatment • Kounis Syndrome 2) to identify possible cases, following Criterion 2 as defined by Sampson et al. (2006). Criterion 2 for anaphylaxis requires having TEAEs from 2 or more of 4 categories of AEs as described by Sampson et al. (2006). Occurrence of these events should be nearly coincident and develop rapidly after exposure to the most recent injection; based on recording of events on CRFs, all qualifying events must be within 1 day of study drug injection. The 4 categories to be considered in Criterion 2 are: • Category A: Involvement of the skin-mucosal tissue • Category B: Respiratory compromise • Category C: Reduced blood pressure or associated symptoms • Category D: Persistent gastrointestinal symptoms The specific MedDRA PTs covered by each of these Criterion 2 categories are shown in Appendix 8.	**Period 2, Period 3, and Combined Periods 2 and 3:** **Period 3 randomized withdrawal safety population (Fisher's exact test)**: TEAE by PT within Category, TEAE by maximum severity by PT within Category, SAE by PT within Category, AE leading to treatment discontinuation by PT within Category **Listing:** TEAE

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	Summaries of Criterion 2 anaphylactic TEAEs will be provided by the specific combination of categories as follows: • AB: events based on meeting Category A and Category B (but no other category) • AC: events based on meeting Category A and Category C (but no other category) • AD: events based on meeting Category A and Category D (but no other category) • BC: events based on meeting Category B and Category C (but no other category) • BD: events based on meeting Category B and Category D (but no other category) • CD: events based on meeting Category C and Category D (but no other category) • ABC: events based on meeting Category A, Category B and Category C (but no other category) • ABD: events based on meeting Category A, Category B and Category D (but no other category) • ACD: events based on meeting Category A, Category C and Category D (but no other category) • BCD: events based on meeting Category B, Category C and Category D (but no other category) • ABCD: events based on meeting each of the 4 Criterion 2 categories Summaries of treatment-emergent anaphylactic AEs will be provided for patients meeting each of the 2 criteria and for patients who meet either criteria overall. Severity of treatment-emergent Criterion 2 anaphylactic AEs will be based on the maximum severity of the specific events met by the patient. Maximum severity of an (or overall) treatment-emergent anaphylactic AE will be based on the maximum severity within Criterion 1 and/or Criterion 2. Allergic Reactions/Hypersensitivity Events, Non-Anaphylaxis: TEAEs of allergic reaction/hypersensitivity categorized as non-anaphylaxis events are defined by the narrow terms within Hypersensitivity SMQ (20000214) excluding the PTs noted in Appendix 9 and excluding the anaphylactic events as defined above.	
	A by-patient listing will be provided for all patients experiencing TEAE of allergic reactions/hypersensitivities at any time, including status/criterion of anaphylaxis or non-anaphylaxis, and the associated information collected on *Allergic/Hypersensitivity Reaction Follow-Up* eCRF page if identified by the investigator.	**Listing:** TEAE including information collected on *Allergic/Hypersensitivity Reaction Follow-Up* eCRF page
Injection Site	Injection site reaction is defined using the PTs from the MedDRA HLT of Injection site	**Period 2, Period 3, and Combined Periods**

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
Reactions	reactions as specified by MedDRA excluding the following 10 PTs: 1) Embolia cutis medicamentosa 2) Injection site joint discomfort 3) Injection site joint effusion 4) Injection site joint inflammation 5) Injection site joint movement impairment 6) Injection site joint pain 7) Injection site joint redness 8) Injection site joint swelling 9) Injection site joint warmth 10) Injection site joint infection The *Injection Site Reaction* eCRF page captures the injection site reactions identified by the investigator. These TEAEs will be summarized within the MedDRA HLT by maximum severity or category. If more than 1 TEAE of injection site reaction occurs, the event with the worst value (within the individual categories: redness, swelling and pain) will be used. Redness (Scored 0-4) [0] Subject's normal skin color, no increased redness [1] Noticeable, but very mild redness [2] Clearly red [3] Bright red [4] Dark with some scar formation Swelling (Scored 0-4 after running a finger over injected area) [0] No bump [1] Barely noticeable [2] Clear bump but very thin [3] Clear bump 1 mm thick [4] Clear bump 2 mm thick or more Pain (including burning) (Scored 0-3) [0] None [1] Mild [2] Moderate [3] Severe	**2 and 3: (Summary):** **Period 3 randomized withdrawal safety population (Fisher's exact test)**: TEAE by maximum severity by PT within HLT, SAE by PT within HLT, AE leading to treatment discontinuation by PT within HLT TEAE identified by the investigator PT within HLT: by maximum severity, by maximum redness category, by maximum swelling category, by maximum pain category **Listing:** TEAE including information collected on *Injection Site Reaction* eCRF page

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
Cerebro-cardiovascular Events	Cerebro-cardiovascular events will be externally adjudicated by the CEC at the Cleveland Clinic, as outlined in the Manual of Operations. The CEC will adjudicate investigator-reported events selected for adjudication and render an assessment as to whether the event represents a confirmed event (meeting the event definition with all necessary documentation), a non-event (does not meet the event definition and likely represents an alternative or nonevent diagnosis), or lacks sufficient documentation for confirmation of an event. All events which qualify for CEC adjudication will be used for the analysis of cerebro-cardiovascular events. The categories and subcategories of adjudicated events used for the analysis will include the following: • Cardiovascular o Death (Cardiovascular) o Cardiac Ischemic Event: Myocardial Infarction and Hospitalization for Unstable Angina o Serious Arrhythmia o Hospitalization for Heart Failure o Hospitalization for Hypertension o Resuscitated Sudden Death o Cardiogenic Shock o Coronary Revascularization • Neurologic o Cerebrovascular Event: Transient Ischemic Attack or Stroke (Haemorrhagic, Ischemic and Undetermined) • Peripheral Vascular Events o Peripheral Arterial Event o Peripheral Revascularization Events will be analyzed using MedDRA PT nested within the CEC assessment (confirmed event, no event, or insufficient documentation for event determination) and the subcategory. Subtypes of stroke (Hemorrhagic Stroke, Ischemic Stroke, and Undetermined Stroke Type) will be displayed in the analyses nested within Cerebrovascular Event. Subtypes of Serious Arrhythmia (Atrial Arrhythmia, Ventricular Arrhythmia, Heart Block, Other, Unknown) will be displayed nested within Serious Arrhythmia.	**Period 2, Period 3, and Combined Periods 2 and 3 (Summary):** **Period 3 randomized withdrawal safety population (Fisher's exact test)**: TEAE by PT within Subcategory, **Listing:** TEAE
Major Adverse	MACE (requiring adjudication as defined above) is defined as: • Vascular Death (including cardiovascular and cerebro-vascular causes excluding	**Period 2, Period 3, and Combined Periods 2 and 3 (Summary):**

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
Cerebro-Cardiovascular Events (MACE)	hemorrhagic deaths outside of the central nervous system) • Non-fatal myocardial infarction • Non-fatal stroke (subtypes: hemorrhagic stroke, ischemic stroke, undetermined stroke type) Where, • Vascular death should be captured as an Event on Adjudication - Death eCRF page with Adjudication Death Type = 'Cardiovascular'. • Non-fatal myocardial infarction should be captured as an Event on Adjudication - Cardiac Ischemic Event eCRF page with Type of Ischemic Event = "Myocardial Infarction" and the Event is NOT on Adjudication - Death eCRF page. • Non-fatal strokes (ischemic, hemorrhagic) should be captured as an Event on Adjudication - Cerebrovascular Event eCRF page with Stroke Cerebrovascular Event Subtype in one of the following categories: hemorrhagic stroke, ischemic stroke, undetermined stroke type, and the Event is NOT on Adjudication - Death eCRF page. Subcategories of non-fatal stroke (Hemorrhagic Stroke, Ischemic Stroke, and Undetermined Stroke Type) will be displayed nested within non-fatal stroke category.	**Period 3 randomized withdrawal safety population (Fisher's exact test)**: TEAE by maximum severity by PT within Category **Listing:** TEAE
Malignancies	Malignancy is defined using PTs from the Malignant or unspecified tumors SMQ as specified in MedDRA (SMQ: 20000091, which includes the sub-SMQs: • 20000195 [Tumors of unspecified malignancy], including sub-SMQs of 20000229 [Haematological tumours of unspecified malignancy] and 20000230 [Non-haematological tumours of unspecified malignancy] and • 20000194 [Malignant tumors], including sub-SMQs of 20000227 [Haematological malignant tumours] and 20000228 [Non-haematological malignant tumours]). Events will be summarize by the following categories: • Nonmelanoma Skin Cancer (NMSC) o Basal Cell Carcinoma, PTs include: ▪ Basal cell carcinoma ▪ Basosquamous carcinoma ▪ Basosquamous carcinoma of skin o Squamous Cell Carcinoma, PTs include: ▪ Squamous cell carcinoma of skin ▪ Bowen's disease ▪ Lip squamous cell carcinoma	**Period 2, Period 3, and Combined Periods 2 and 3 (Summary):** **Period 3 randomized withdrawal safety population (Fisher's exact test)**: TEAE by PT within Category, SAE by PT within Category, AE leading to treatment discontinuation by PT within Category **Listing:** TEAE

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
	▪ Skin squamous cell carcinoma metastatic ▪ Keratoacanthoma • Malignancies excluding NMSC: all PTs in the Malignant or unspecified tumors SMQ excluding the 8 defined NMSC PTs.	
Depression and Suicide/self-injury	Depression and suicide/self-injury is defined using the PTs from the Depression and suicide/self-injury SMQ as specified in MedDRA (SMQ: 20000035, which includes the sub-SMQs: 20000037 [Suicide/self-injury] and 20000167 [Depression (excluding suicide and self injury)]).	**Period 2, Period 3, and Combined Periods 2 and 3 (Summary):** **Period 3 randomized withdrawal safety population (Fisher's exact test)**: TEAE by PT within SMQ and sub-SMQ, SAE by PT within SMQ and sub-SMQ, AE leading to treatment discontinuation by PT within SMQ and sub-SMQ **Listing:** TEAE (including QIDS-SR16 total scores)
	The Quick Inventory of Depressive Symptomology-Self Report 16 items (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 (APA's) Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (APA 1994). Refer to Table RHBF.6.11 and Table RHBF.6.12 for further details. The following groups are based upon the maximum post-baseline QIDS-SR16 total score category (none, mild, moderate, severe, very severe) score: ▪ Improved; maximum post-baseline < baseline ▪ Worsened; post-baseline > baseline ▪ Same; post-baseline = baseline	**Period 2, Period 3, and Combined Periods 2 and 3** **Period 3 randomized withdrawal safety population** Shift in QIDS-SR16 total score categories
Inflammatory Bowel Disease	Inflammatory Bowel Disease (IBD) will be identified by medical review using the following Category and MedDRA PTs. The narrow terms are considered IBD. Medical reviews of patients with identified broad terms are needed for final determination of patients with IBD. IBD Specific Terms (Narrow terms) • Inflammatory Bowel Disease: Inflammatory bowel disease • Crohn's Disease: Crohn's disease • Ulcerative Colitis: Acute haemorrhagic ulcerative colitis; Colitis ulcerative; Proctitis ulcerative IBD Non-Specific Terms: The PTs in this category are listed in Appendix 11	**Period 2, Period 3, and Combined Periods 2 and 3 (Summary):** **Period 3 randomized withdrawal safety population (Fisher's exact test)**: TEAE by PT by maximum severity by PT within Category **Listing:** TEAE

Special Safety Topic	Definition / Derivation	Analysis / Summary / Listing
Interstitial Lung Disease	Interstitial lung disease is defined using the following terms: • Narrow terms in the interstitial lung disease SMQ (20000042) • The following 6 PTs from eosinophilic pneumonia SMQ (20000157): o Angiolymphoid hyperplasia with eosinophilia (Narrow) o Eosinophilic bronchitis (Narrow) o Hypereosinophilic syndrome (Narrow) o Loeffler's syndrome (Narrow) o Pulmonary eosinophilia (Narrow) o Pulmonary vasculitis (Narrow)	**Listing**: TEAE

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CEC = Central Events Committee; eCRF = electronic case report form; eDISH = Evaluation of Drug-Induced Serious Hepatotoxicity; HLT = High Level Term; MedDRA = Medical Dictionary for Regulatory Activities; OI = opportunistic infection; PT = preferred term; SAE = serious adverse event; SMQ = standardized MedDRA query; SOC = System Organ Class; TB = tuberculosis; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.

6.13.8. Immunogenicity

6.13.8.1. Definitions and Terms

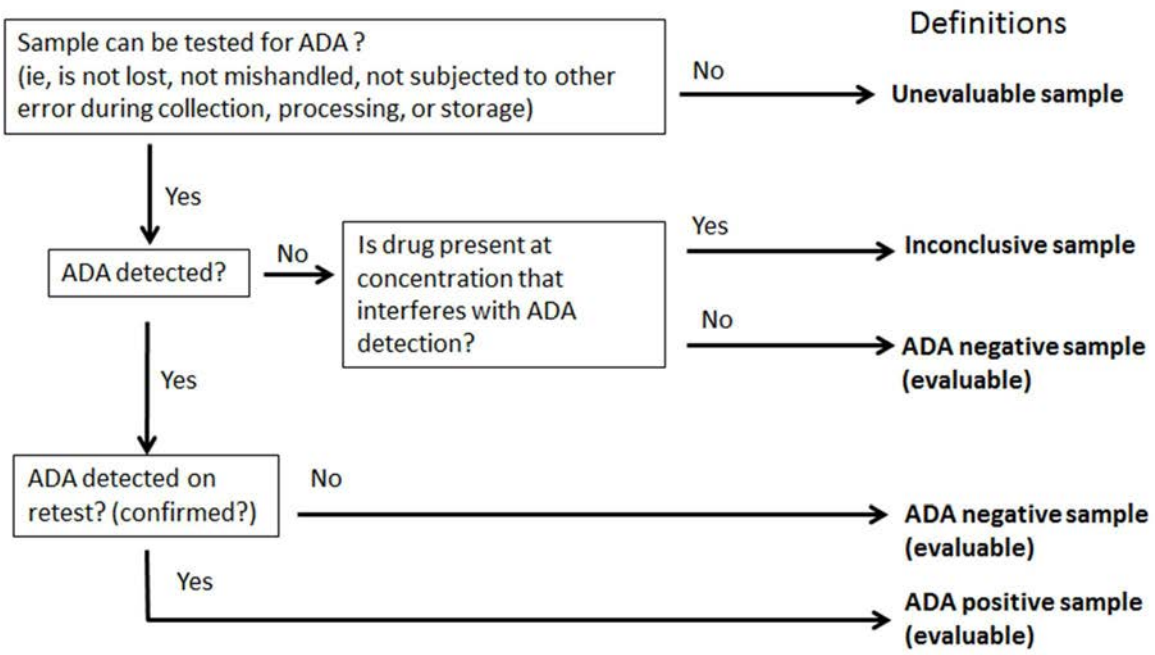
The following sample- and patient-related definitions and parameters will be used to describe the immunogenicity data.

6.13.8.1.1. Sample Category Definitions

Samples are classified into the following categories:

- **Unevaluable sample:** Sample could not be tested for anti-drug antibody (ADA) due to sample loss, mishandling, or errors in collection, processing, storage, etc.
- **Antidrug antibody (ADA) Positive sample:** The presences of ADA is detected and confirmed. The samples are reported as positive. If the sample is positive, a titer value is reported.
- **Neutralizing anti-drug antibody (NAb) Positive sample:** NAb are reported as detected.
- **Antidrug antibody (ADA) Negative sample:** The presence of ADA is not detected and the assay drug tolerance level is not exceeded.
- **Neutralizing anti-drug antibody (Nab) Negative sample:** The presence of NAb is not detected and the assay drug tolerance level is not exceeded.
- **Inconclusive sample:** when ADA/NAb is not detected in a sample but drug is present in the same sample at a level that can cause interference in the ADA/NAb detection method. The negative ADA/NAb result cannot be confirmed and the sample was considered inconclusive.
    - Confirmation of a negative ADA result was based on ixekizumab concentrations.

Figure RHBF.6.1 illustrates the relationship of some of the above terms.



Abbreviation: ADA = anti-drug antibody.

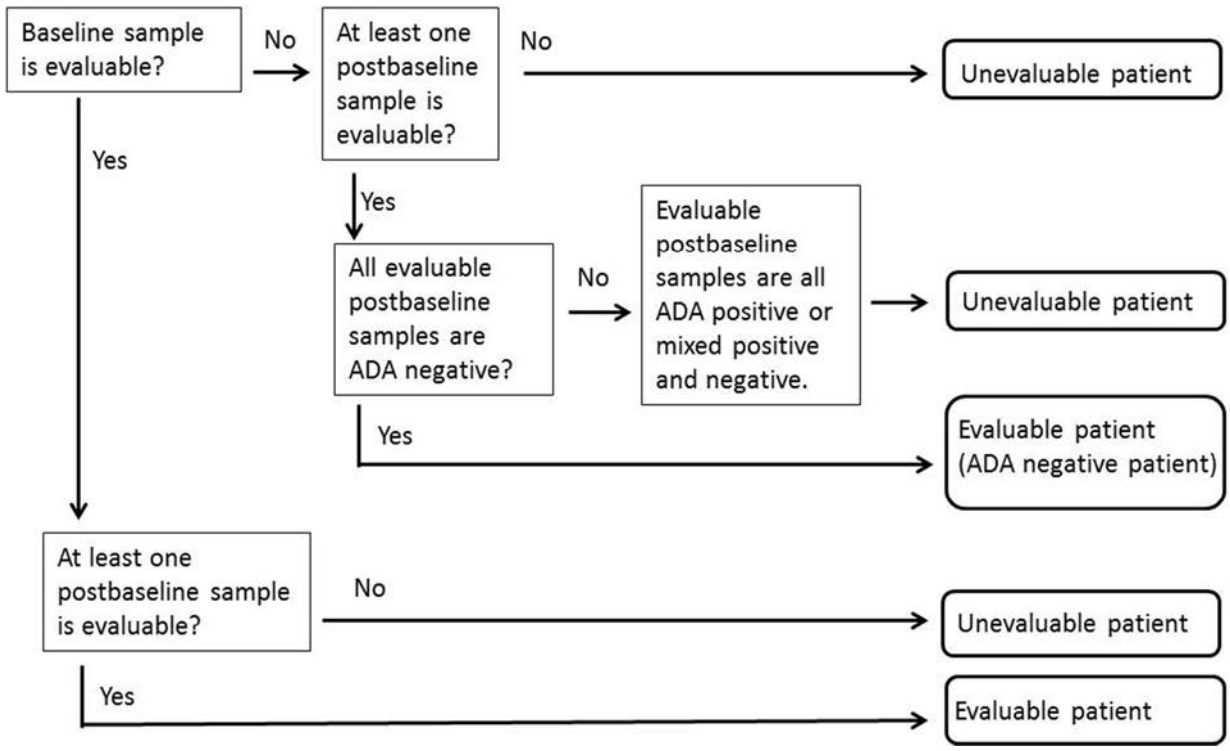
Figure RHBF.6.1. Sample definitions.

6.13.8.1.2. Patient Category Definitions

The following categories are applied to patients based on the classification of their samples:

- **Unevaluable patient:** a) a patient with no evaluable baseline sample and/or no evaluable postbaseline samples; b) a patient with an evaluable baseline sample but no evaluable postbaseline sample; c) a patient with no evaluable baseline sample, but whose evaluable postbaseline values are all ADA positive or a mix of positive and negative. (Note: If all post-baseline samples are negative, the patient is considered 'evaluable' and will be classified as ADA-negative.)
- **Evaluable patient:** a) Patient with an evaluable baseline sample and at least 1 evaluable post-baseline sample (that is, sample after administration of study drug); b) patient with no evaluable baseline sample whose evaluable post-baseline samples are all ADA negative.

Figure RHBF.6.2 illustrates the relationship of the above terms.



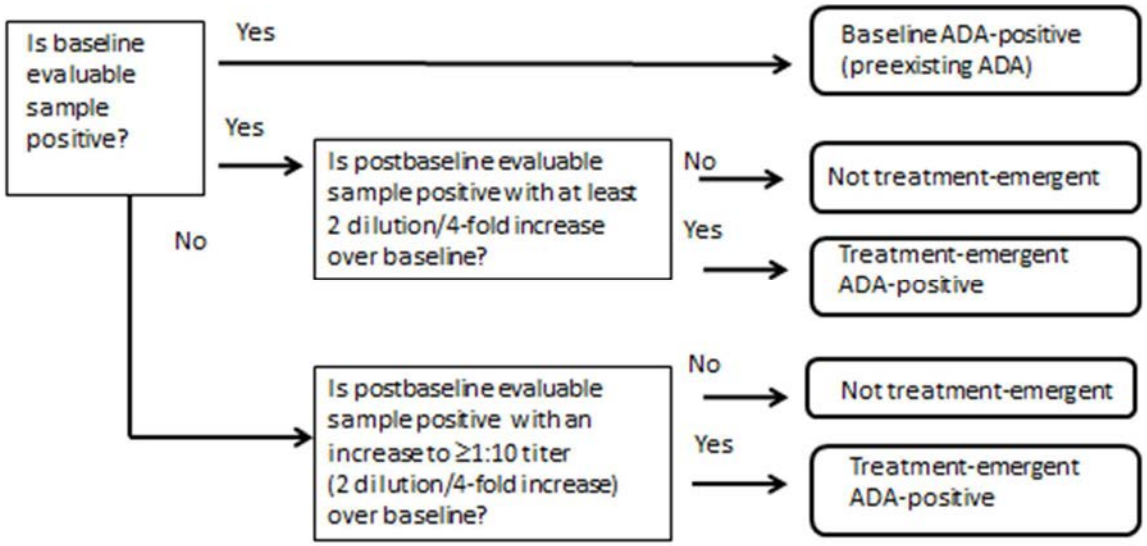
Abbreviation: ADA = anti-drug antibody.

Figure RHBF.6.2. Patient categories (evaluable/unevaluable) based on sample status at baseline and post-baseline.

6.13.8.1.3. Definitions for Clinical Interpretation of Assay Results

- **Baseline:** For immunogenicity analyses during Period 2, Period 3, and Period 4, baseline is the last nonmissing observation on, or prior to, the date of the first injection of study treatment of ixekizumab (Week 0).
- **Baseline ADA positive (preexisting antibody):** ADA detected in a sample collected at baseline.
- **Treatment-emergent antidrug antibody positive:** a) a patient with a ≥4-fold increase over a positive baseline antibody titer (Tier 3); or b) for a negative baseline titer, a patient with an increase from the baseline to a level of ≥1:10.
- **Baseline ADA-negative:** ADA is not detected in a sample collected at baseline.
- **Treatment-emergent antidrug antibody inconclusive patient:** A patient without a TE-ADA positive sample and with at least one sample for which drug levels may interfere with the ADA assay.
- **Treatment-emergent antidrug antibody negative patient:** A patient who is evaluable for TE-ADA and is not either TE-ADA positive or TE-ADA inconclusive.

Figure RHBF.6.3 illustrates the relationship of some of these terms.



Abbreviation: ADA = anti-drug antibody.

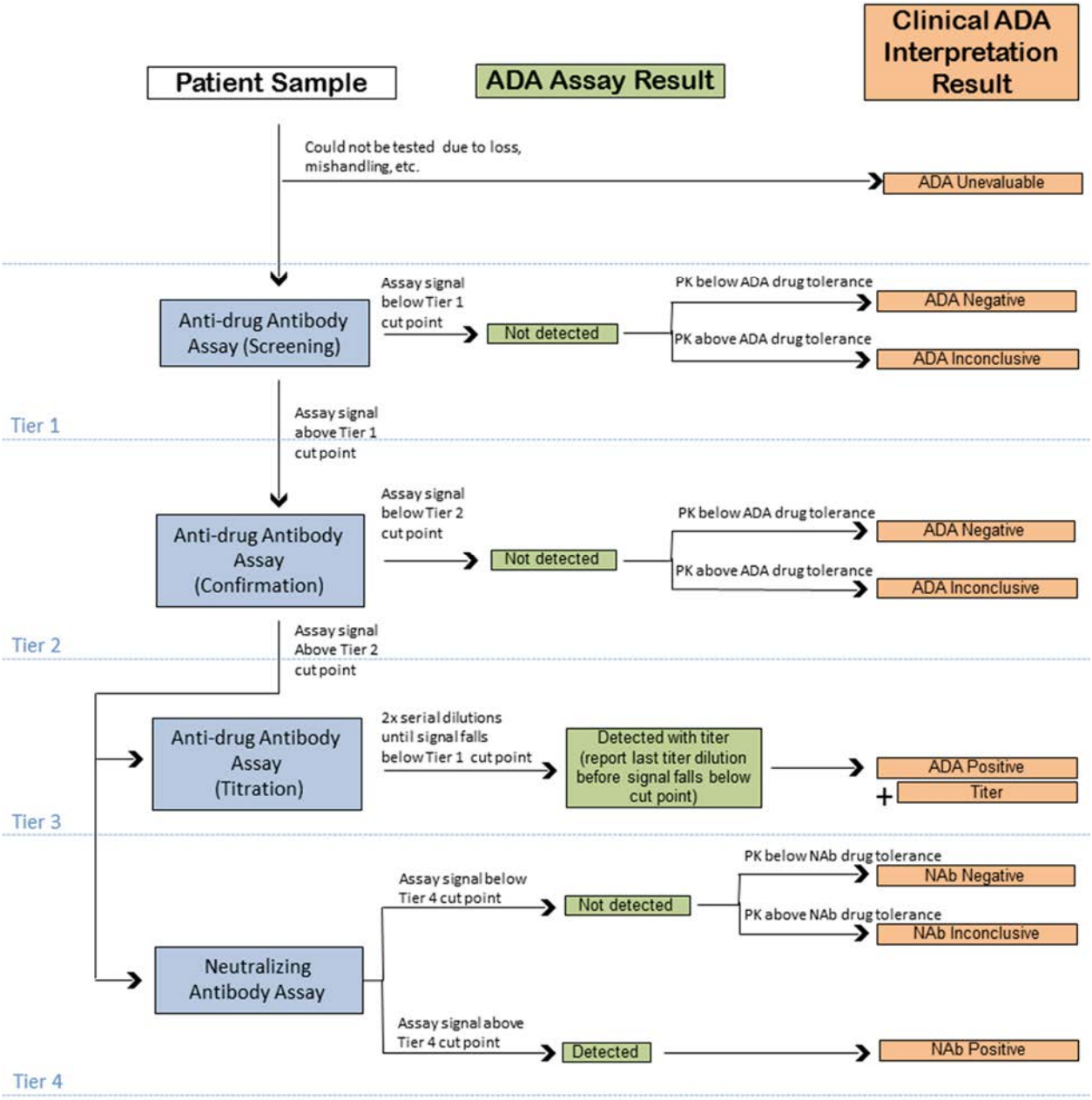
Figure RHBF.6.3. Relationship of terms for clinical interpretation of assay results for evaluable patients.

- **Incidence of TE-ADA:** Patients with TE-ADA as a proportion of the evaluable patient population during the treatment period. This excludes unevaluable patients.

All ADA positive samples will be evaluated for NAb. Definitions for NAb patient status will be defined as follows:

- **Neutralizing anti-drug antibody-positive patient:** A patient where a NAb positive result is detected for ≥1 TE-ADA positive samples.
- **Neutralizing anti-drug antibody-inconclusive patient:** A patient without a NAb positive sample and with at least one sample for which drug levels may interfere with the NAb assay.
- **Neutralizing anti-drug antibody-negative patient:** A patient who is evaluable for NAb and is not either NAb positive or NAb inconclusive.

A flow chart that reflects the connection between the analytical test results and the clinical interpretation based on the definitions is shown in Figure RHBF.6.4.



Abbreviation: ADA = anti-drug antibody; NAb = neutralizing anti-drug antibody; PK = pharmacokinetic.

Figure RHBF.6.4. Flow chart of ADA assessment with clinical interpretation of the various result possibilities.

6.13.8.2. Immunogenicity Analyses

Immunogenicity will be summarized for evaluable patients for (unless otherwise noted):

- Period 2 (initial open-label treatment period population)
- Period 3 (randomized withdrawal safety population)
- Relapse period (relapse population)

- Combined Period 2 and Period 3 (ixekizumab 80 mg Q2W-treated patients from the randomized withdrawal safety population and nonrandomized population)
- Period 4 (post-treatment follow-up period population).

Immunogenicity evaluable patients will be identified as TE-ADA positive, TE-ADA negative, or TE-ADA inconclusive, according to the definitions provided in Section 6.13.8.1.2 and further grouped into TE-ADA status groups and time-varying TE-ADA status groups:

TE-ADA Status Groups:

- **Treatment-emergent antidrug antibody** status (positive, negative, or inconclusive);
- Neutralizing anti-drug antibody status (positive, negative, or inconclusive) for TE-ADA positive patients
- **Treatment-emergent antidrug antibody** titer groups for TE-ADA positive patients:
  - Low Titer: TE-ADA titer value (LOCF) < 1:160
  - Moderate Titer: TE-ADA titer value (LOCF) ≥1:160 and < 1:1,280
  - High Titer: TE-ADA titer value (LOCF) ≥1:1,280

Time-varying TE-ADA Status Groups:

Individual ADA samples will be ascribed into 3 different dichotomous variables as explained in Table RHBF.6.7. Each variable has possible values of a 'greater-TE-ADA status' or a 'lesser-TE-ADA status,' in the sense that the level of TE-ADA detected in the greater-TE-ADA category is higher than in the lesser-TE-ADA category.

Table RHBF.6.7. TE-ADA Status Dichotomous Variables for AE analysis

TE-ADA Status Dichotomous Variable	Greater-TE-ADA Status	Lesser-TE-ADA Status
TE-ADA positive	TE-ADA positive	not TE-ADA positive
TE-ADA moderate-to-high	TE-ADA positive with moderate titer or high titer	not TE-ADA positive, or TE-ADA positive with low titer
TE-ADA high status	TE-ADA positive with high titer	not TE-ADA positive, or TE-ADA positive with low or moderate titer

TE-ADA Status Dichotomous Variables for AE analysis (Abbreviations and Footnotes)
Abbreviations: AE = adverse events; ADA = antidrug antibody; TE-ADA = treatment-emergent antidrug antibody.
Note: For purpose of this analysis, TE-ADA Inconclusive is taken to be "not TE-ADA positive."
Note: A TE-ADA low is defined as a TE-ADA positive with a titer value < 1:160; a TE-ADA moderate is defined as a TE-ADA positive with a titer value ≥1:160 and < 1:1,280; and a TE-ADA high is defined as a TE-ADA positive with a titer value ≥1:1,280.

For each TE-ADA status dichotomous variable, a time-varying TE-ADA status will be computed. At time *t* the TE-ADA status is taken to be the highest of the TE-ADA values bracketing time *t*. More formally, the TE-ADA status at time *t* is given by the greater of (a) the TE-ADA status at the most-recent postbaseline measurement prior to *t*, and (b) the TE-ADA status at the first TE-ADA postbaseline measurement at or after time *t*. In this computation, 'greater' is given by the greater-TE-ADA status of Table RHBF.6.7. If there is no value satisfying criterion (a), then the value (b) is used. Similarly, if there is no value (b), then the value (a) is used.

For each TE-ADA status dichotomous variable, patients will be categorized according to whether they were (i) always in lesser-TE-ADA status postbaseline or (ii) at some point postbaseline, were in greater-TE-ADA status.

6.13.8.2.1. Analyses of Characteristics of ADA Immune Response

The analyses of characteristics of ADA response will be conducted on all immunogenicity evaluable patients within the Initial Open-Label Treatment, Randomized Double-Blind Withdrawal Period, Combined Open-Label Treatment Period and Randomized Double-Blind Withdrawal Periods, Relapse Period, and the Post-Treatment Follow-up Period. Patients will be analyzed according to the treatment to which they were assigned.

The overall frequency and percentage (incidence) of patients will be summarized for the TE-ADA status groups and the time-varying TE-ADA status groups. Scheduled visits, unscheduled visits, and repeat measurements will be included.

The time to the development of TE-ADAs (TE-ADA positive, low titer, moderate titer, high titer, and NAb positive) will be calculated as follows:

Time to development of TE-ADAs/NAb (in weeks) = (Date of development of TE-ADAs/NAb – Date of first injection of study treatment + 1) / 7.

If a patient has not developed TE-ADAs/NAbs, they will be censored at the date of the last immunogenicity assessment. If a patient does not have any postbaseline assessments for immunogenicity, they will be censored at the date of randomization.

Descriptive statistics, including 25th percentile, 50th percentile (median), 75th percentile, and corresponding 95% CIs as well as probability of TE-ADA/NAb positive by endpoint summarized by treatment group, will also be provided if sufficient data is present. A Kaplan-Meier plot of the time to development of treatment-emergent ADA/NAb will be presented by treatment group, also if sufficient data is present. The log-rank test will be used to test the null

hypothesis against the alternate hypothesis that the time to TE-ADA/NAb is not equal between ixekizumab and placebo. Caution should be exercised in the interpretation of time-to event analyses, and related statistics, given the limited sampling scheme for immunogenicity testing.

For each TE-ADA status dichotomous variable (as defined in Table RHBF.6.7), summaries will be provided of the total postbaseline time in the greater-TE-ADA status for patients who were at some point postbaseline in the greater-TE-ADA status group. Postbaseline time in greater-TE-ADA status for each patient will be aggregated.

A by-patient listing to include treatment, visit date, visit, ADA result, TE-ADA result, NAb result, ADA titer value, ixekizumab concentration, ADA and NAb inconclusive results will also be provided, for patients with any one sample of ADA (or NAb) positive or inconclusive.

6.13.8.2.2. Analyses of Treatment-Emergent ADA Effects on Efficacy

Analyses will be performed to examine how patient TE-ADA effects time-to relapse in the randomized withdrawal ITT population by the TE-ADA status groups. The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to relapse. A Cox-proportional hazards model with treatment group, TE-ADA status group and the interaction of treatment group-by-TE-ADA status group included as factors in the model will be used to test the interaction of treatment group-by-TE-ADA status group. Additionally, the Kaplan-Meier product limit method will be used to estimate the survival curves for time-to relapse.

Analyses will also be performed to examine how patient TE-ADA effects the proportion of patients who relapse by 40 weeks of randomized treatment in the randomized withdrawal ITT population by the TE-ADA status groups. A logistic regression model with treatment group, TE-ADA status group and the interaction of treatment group-by-TE-ADA status group included as factors in the model will be used to test the interaction of treatment group-by-TE-ADA status group.

Analyses will also be performed to examine how patient TE-ADA effects the proportion of patients with 20% and 50% improvement in American College of Rheumatology criteria (ACR20 and ACR50) at the last observation in the initial open-label treatment period population and at 40 weeks of randomized treatment in the randomized withdrawal ITT population by the TE-ADA status groups. For the initial open-label treatment period population, the TE-ADA status groups will be summarized for the ixekizumab 80 mg Q2W treatment group. For the randomized withdrawal ITT population, a logistic regression model with treatment group, TE-ADA status group and the interaction of treatment group-by-TE-ADA status group included as factors in the model will be used to test the interaction of treatment group-by-TE-ADA status group.

The p-value associated with the interaction terms will be used to assess if the treatment group effect is consistent across TE-ADA status group. When the interaction term is statistically significant, the association between responder status and the treatment group depends, in some manner, on the status group. The interaction will be tested at the 10% significance level. If any group within the subgroup (for example, yes, no) is <10% of the total population, only

descriptive statistics will be provided for that subgroup (that is, no inferential testing). Treatment group differences will be evaluated within each subgroup regardless of whether the interaction is statistically significant.

6.13.8.2.3. Analyses of Treatment-Emergent ADA on Specific Adverse Events

The analyses of TE-ADA effects on safety will be conducted on all immunogenicity evaluable patients within the Initial Open-Label Treatment Period, Randomized Double-Blind Withdrawal Period, and the Combined Open-Label Treatment and Randomized Double-Blind Withdrawal Periods. Patients will be analyzed according to the treatment to which they were assigned.

Adverse events of special interest of allergic reaction/hypersensitivity (anaphylaxis and nonanaphylaxis) and of injection-site reactions will be included in an assessment of AE to TE-ADA over time. See Table RHBF.6.6 for the definitions of the AESIs. Timing of an AE will be taken to be the reported AE start date.

For each TE-ADA status dichotomous variable (as defined in Table RHBF.6.7), patients will be categorized according to whether they were (i) always in lesser-TE-ADA status postbaseline or (ii) at some point postbaseline, were in greater-TE-ADA status. For each AESI, within the time-varying TE-ADA status groups, a summary will be provided of the number of patients who had no event, events only while in lesser-TE-ADA status for group (i), or – for group (ii) – at least one event while in greater-TE-ADA status.

Additionally, summaries will be provided of the total number of AESI events (with unique start dates) by time-varying TE-ADA status groups at the event date. The summaries will aggregate time respectively in greater-TE-ADA status and in lesser-TE-ADA status, along with the event rates (rates per 100 patient-years) relative to those aggregate times.

By-patient listings will be provided of patients with TE-ADA who experience a treatment-emergent allergic reaction/hypersensitivity reaction or an injection site reaction.

6.14. Subgroup Analyses

6.14.1. Efficacy Subgroup Analysis

Subgroup analyses will be conducted for time-to relapse and the proportion of patients who relapse by 40 weeks of randomized treatment in the randomized withdrawal ITT population during Period 3.

For the time-to-relapse, the Kaplan-Meier product limit method will be used to estimate the survival curves for time-to relapse. Analyses will be performed using a Cox-proportional hazards model with treatment group, subgroup, and the interaction of treatment group-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 group-by-subgroup included as factors will be used.

The treatment group-by-subgroup interactions will be tested at the significance level of 0.10. If any group within the subgroup (for example, yes, no) is <10% of the total population, only

descriptive statistics will be provided for that subgroup (that is, no inferential testing). Treatment group differences will be evaluated within each category of the subgroup using log-rank test without stratifications or Fisher's exact test, regardless of whether the interaction is statistically significant.

Subgroups to be evaluated include:

- Demographic subgroups:
    - Age group: <65 years, ≥65 years to <75 years, ≥75 years
    - Age group: <40 years, ≥40 years
    - Gender (male, female)
    - Race: AI, AS, BL, NH, WH, MU
    - Ethnicity: Hispanic or Latino, Not Hispanic or Latino
    - Weight category: <100 kg, ≥100 kg
    - Weight category: <80 kg, ≥80 kg to <100 kg, ≥100 kg
    - BMI category: underweight (<18.5 kg/m^2); normal (≥18.5 to <25 kg/m^2); overweight (≥25 to <30 kg/m^2); obese (≥30 to 40 kg/m^2); extreme obese (≥40 kg/m^2)
- Geographic region subgroups:
    - Geographic region: US, Europe, Rest of the World
- Baseline severity subgroups:
    - C-reactive protein (mg/dL): ≤6, >6
    - Duration of PsA (years): 0 to <5, ≥5
    - Baseline psoriatic lesion(s) involving BSA ≥3%: yes or no)
    - Moderate to severe psoriasis (defined as PASI ≥12, sPGA ≥3, and BSA ≥10%): yes, no
    - Enthesitis (LEI score >0 or SPARCC >0): yes or no
    - Dactylitis (LDI-B score >0): yes or no
- Psoriatic arthritis therapy subgroups:
    - Previous cDMARD use at the time of randomization (past use, current use) for the randomized withdrawal ITT population
    - Methotrexate use at the time of randomization (none, past use, current use) for the randomized withdrawal ITT population

Additional subgroup analyses on efficacy may be performed as deemed appropriate and necessary.

6.14.2. Safety Subgroup Analysis

Subgroup analyses will be conducted for common TEAEs and AESIs of allergy/hypersensitivity, infections, and injection site reactions for the initial open-label treatment period population during Period 2 and the randomized withdrawal safety population during Period 3.

The most common TEAEs and AESIs will be presented by MedDRA PT nested within SOC (SMQ or High Level Term where specified in Section 6.13.7). A logistic regression model will be used to test the treatment group-by-subgroup interaction for the randomized withdrawal safety population. The model will include explanatory variables of treatment group, subgroup, and treatment group by-subgroup interaction. The interaction test will be evaluated at the 0.10 significance level. If any group within the subgroup (for example, yes, no) is <10% of the total population, only descriptive statistics will be provided for that subgroup (that is, no inferential testing). Treatment group differences will be evaluated within each category of the subgroup, regardless of whether the interaction is statistically significant. Treatment differences will be assessed within the subgroups using the Fisher's exact test.

Subgroups to be evaluated include:

- Demographic subgroups:
  - Age group: <65 years, ≥65 years to <75 years, ≥75 years
  - Age group: <40 years, ≥40 years
  - Gender (male, female)
  - Race: AI, AS, BL, NH, WH, MU
  - Ethnicity: Hispanic or Latino, Not Hispanic or Latino
  - Weight category: <100 kg, ≥100 kg
  - Weight category: <80 kg, ≥80 kg to <100 kg, ≥100 kg
  - Body mass index category: underweight (<18.5 kg/m^2); normal (≥18.5 and <25 kg/m^2); overweight (≥25 to <30 kg/m^2); obese (≥30 to 40 kg/m^2); extreme obese (≥40 kg/m^2)
- Geographic region subgroups:
  - Geographic region at baseline for the initial open-label treatment period population: Europe, US, Rest of the World
- Psoriatic arthritis therapy subgroups:
  - Previous cDMARD use at the time of randomization (past use, current use) for the randomized withdrawal safety population
  - Methotrexate use at the time of randomization (none, past use, current use) for the randomized withdrawal safety population.

6.15. Analysis for Australian Submission

Efficacy analysis may be conducted if needed to meet the Pharmaceutical Benefits Advisory Commission (PBAC) criteria for a regulatory submission or request. The time-to relapse and proportion of patients with relapse will be analyzed using a PBAC randomized withdrawal ITT population for Period 3. Data will be analyzed using the analysis methods defined in Section 6.1.2.1 for the time-to analysis and categorical analyses.

The PBAC randomized withdrawal ITT population is a subset of the randomized withdrawal population and is defined as all randomized patients in Period 3 with:

1. An elevated CRP >15 mg/L
2. An active joint count of at least 20 active (swollen and tender) joints or at least 4 major active joints: elbow, wrist, knee, ankle, shoulder and/or hip
3. Psoriatic arthritis that has not responded to adequate trials of at least 2 cDMARDs, administered either individually or in combination for a minimum of 3 months

6.16. Analysis for United Kingdom National Institute for Health and Care Excellence Submission

Efficacy analysis will be conducted to meet the UK's National Institute for Health and Care Excellence (NICE) criteria. The time-to relapse and proportion of patients with relapse will be analyzed using a NICE randomized withdrawal ITT population for Period 3. Data will be analyzed using the analysis methods defined in Section 6.1.2.1 for the time-to analysis and categorical analyses.

The NICE randomized withdrawal ITT population is a subset of the randomized withdrawal population and is defined as all randomized patients in Period 3 with:

1. Peripheral arthritis with ≥3 tender joints and ≥3 swollen joints
2. Psoriatic arthritis that has not responded to adequate trials of at least 2 cDMARDs, administered either individually or in combination.

6.17. Protocol Deviations

Protocol deviations will be identified throughout the study. Important protocol deviations are defined as those deviations from the protocol likely to have a significant impact on the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. All important protocol deviations identified are reviewed by the study team prior to database lock.

Table RHBF.6.8 includes the categories and subcategories of important protocol deviations, the source of identification for the deviation, and the statistical programming guidance for the CSR.

A by-patient listing of important protocol deviations will be provided for all entered patients.

The number and percentage of patients having important protocol deviation(s) will be summarized within category and subcategory of deviations by treatment group for:

- Period 2 (initial open-label treatment period population)
- Period 3 (randomized withdrawal ITT population).

In addition, other protocol deviations considered important for reporting purposes derived from manual review of study records as recorded via monitoring reports or other site compliance monitoring will be summarized. These may include

- Ethics review board (ERB) approval not obtained
- Follicle-stimulating hormone (FSH) not assessed
- Good Clinical Practice guidelines not followed by principal investigator (PI)
- Hepatitis monitoring not done
- Improper consent/re-consent (not timely, wrong version, not signed)
- Physical examination not performed
- Postbaseline pregnancy test not performed
- Quick Inventory of Depressive Symptomatology not assessed
- Serious adverse events not reported on time
- Tuberculosis test collected late
- Tuberculosis test not performed
- Temperature excursion at site
- Unqualified study personnel performing procedures
- One hour post-dose vitals not performed at Visit 2
- Assessment not performed by Independent Assessor
- Unauthorized use of electronic patient reported outcomes (ePRO) device credentials
- Vital signs not performed.

This list is not conclusive and additional other important protocol deviations may be identified.

Table RHBF.6.8. Identification and Action of Important Protocol Deviations

Important Protocol Deviation Category/Subcategory	Source to Identify Protocol Deviation	Statistical Programming Guidance for Clinical Study Report	Exclude from the PPS?
Patient did not give written consent			
Informed consent form must be signed before any protocol procedures begin (Proper order of informed consent signature, randomization, and therapy start dates).	Monitor and Stats	Either from monitor's list, or, If patient informed consent date is after Visit 1 date	Yes
Failed to meet study inclusion criteria but was enrolled into the study			
[1] Age <18 years	Monitor and Stats	From monitor's list. Stats may program preliminarily based on data for age <18 at Visit 1, but deviation must be confirmed and sourced by monitor. This is because only birth year is collected, and age is calculated by imputation.	Yes
[1a] Male patients did not use a reliable method of birth control	Monitor	From monitor's list.	Yes
[1b] Lack of confirmation of non-pregnant status prior to randomization at visit 2	Monitor	From monitor's list.	Yes
[2] No confirmed diagnosis of PsA of at least 6 months prior to baseline or did not meet CASPAR criteria	Monitor and Stats	Review monitor's list. Check time since PsA diagnosis and CASPAR criteria.	Yes
[3] <3 tender or <3 swollen joints at Visit 1 or Visit 2	Monitor and Stats	Review monitor's list. Check if TJC68 <3 or SJC66 <3 either at Visit 1 or at Visit 2	Yes
[4] Never been treated with a cDMARD or has been treated with a cDMARD and no documentation of inadequate response with a minimum of 12 weeks or intolerance	Monitor	From monitor's list.	Yes
[5] No active or history of plaque psoriasis	Monitor and Stats	Review monitor's list. Check if the answer to current Psoriasis is No AND patient contains no record in medical history where: 1. (the reported term for medical history = "PSORIASIS DISEASE" and category for medical history = "PRIMARY DIAGNOSIS") or 2. (the dictionary derived term = "PSORIASIS" and category for medical history = "PRE-EXISTING	Yes

Important Protocol Deviation Category/Subcategory	Source to Identify Protocol Deviation	Statistical Programming Guidance for Clinical Study Report	Exclude from the PPS?
		CONDITION") or 3. (reported term for medical history ="PLAQUE PSORIASIS" and category for medical history = "PRE-EXISTING CONDITION")]	
Met study exclusion criteria but was enrolled into the study			
[7] Prior or current use of bDMARDs or biologics	Monitor	Monitor's list	Yes
[8] Previous or current medication exposure at Visit 1 to LY2439821 or IL-17 antagonists or previous participation in the current study. *(Note: See protocol for patients who may be allowed to re-screen.)*	Monitor	Monitor's list	Yes
[9] Have history of drug-induced Ps	Monitor	Monitor's list	Yes
[10] Inadequate response to ≥4 cDMARDs prescribed alone or in combination for 3 months	Monitor and Stats	Either from monitor's list, or, If a patient used for least 90 days any 4 or more of the following previous therapies category or non-biologic systemic agent subcategory: MTX, Leflunomide, Azathioprine, Cyclosporine, Hydroxychloroquine, Gold Salts, Sulfasalazine	Yes
[11] & [12] Use of cDMARDs within the washout periods or using >1 at entry into the study, or using DMARDs at doses outside of specified range	Monitor	Monitor's list	Yes
[13] Have discontinued leflunomide within 4 weeks prior to baseline or from 4 to 12 weeks prior without drug elimination procedure	Monitor and Stats	Monitor's list, or, If the difference between Visit 2 date and medication end date <28 days for previous therapy, Leflunomide	Yes
[14] Use of oral corticosteroids >10 mg/day of prednisone or equivalent, use of variable doses within 4 weeks prior to baseline	Monitor	Monitor's list	Yes
[15] Have received parenteral glucocorticoids within 6 weeks prior to baseline or if use is anticipated during initial open-label treatment period (Period 2) of the study	Monitor and Stats	Monitor's list, or, If a patient has a reported previous therapy of parenteral glucocorticoids with and end date <42 days prior to the Visit 2 date	Yes
[16] Concomitant use of NSAIDs or	Monitor	Monitor's list	Yes

Important Protocol Deviation Category/Subcategory	Source to Identify Protocol Deviation	Statistical Programming Guidance for Clinical Study Report	Exclude from the PPS?
cyclooxygenase -2 inhibitors unless on a stable dose for at least 2 weeks prior to baseline			
[17] Use of opiate analgesics >30 mg/day of morphine or equivalent or variable doses within 6 weeks prior to baseline	Monitor and Status	Monitor's list, or, If a patient has either a reported previous therapy of opiate analgesics or a concomitant medication with ATC codes of N02AA with a start or end date of <42 days prior to Visit 2 date.	Yes
[18] Received systemic non-biologic psoriasis therapy (including, but not limited to, oral psoralens and ultraviolet A [PUVA] light therapy; cyclosporine; corticosteroids; MTX; oral retinoids; mycophenolate mofetil; thioguanine; hydroxyurea; sirolimus; azathioprine; fumaric acid derivatives; or 1, 25 dihydroxy vitamin D3 and analogues) or phototherapy (including either oral and topical PUVA light therapy, ultraviolet B [UVB] or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to baseline (Visit 2). or had topical psoriasis treatment (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, emollients and other non-prescription topical products containing urea, >3% salicylic acid, or alpha- or beta-hydroxyl acids, and medicated shampoos [for example those that contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues]) within the previous 2 weeks prior to baseline (Week 0; Visit 2). Note WHO Group 1weak potency (such as hydrocortisone) topical TRT are allowed.	Monitor and Stats	Monitor's list, or, If the patient has any record with an end date ≤28 days of the Visit 2 date for Phototherapy for previous therapy If the patient has any concomitant medications with an end date that is on or prior to Visit 2 date, and ≤28 days prior to the Visit 2 date for oral medications with the following ATC codes: D05B, D05BA, D05BB, D05BX). If the patient has any concomitant medications with an end date that is on or prior to Visit 2 date, and ≤14 days prior to the Visit 2 date for topical medications with the following ATC codes: D07AC, D07AD, D07BC, D07BD, D07CC, D07CD, D07XC, D07XD, A11CC, D05AA, D05AC, D05AD, D05AX, D05BB, L04AD, D11AC, D07AB, D02AF, D02BB.	Yes

Important Protocol Deviation Category/Subcategory	Source to Identify Protocol Deviation	Statistical Programming Guidance for Clinical Study Report	Exclude from the PPS?
[19] Use of tanning beds/booths for at least 4 weeks (or 28 days) prior to Visit 2 for patients with plaque psoriasis.	Monitor	Monitor's list	Yes
[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.	Monitor	Monitor's list	Yes
[21] Ever received natalizumab or other agents that target alpha-4-integrin	Monitor	Monitor's list	Yes
[22] Have been exposed to a live vaccine within 12 weeks prior to Visit 2 or intend to have a live vaccination during the course of the study, or participated in a BCG (12 months prior to baseline) or other vaccine clinical study within 12 weeks prior to Visit 2	Monitor	Monitor's list	Yes
[23] Had a BCG (12 months prior to baseline), or intent to have this vaccine during the study or within 12 months of completion of the study	Monitor	Monitor's list	Yes
[24] Have diagnosis of other inflammatory arthritic syndrome	Monitor	Monitor's list	Yes
[25] Have active Crohn's disease or active ulcerative colitis	Monitor	Monitor's list	Yes
[26] Have current diagnosis of fibromyalgia	Monitor	Monitor's list	Yes
[27] Have a chronic pain condition what would confound evaluation of the patient	Monitor	Monitor's list	Yes
[28] Evidence of active vasculitis or uveitis	Monitor	Monitor's list	Yes
[29] Surgical treatment of joint within 8 weeks prior to baseline or will require such up to Week 24	Monitor	Monitor's list	Yes
[30] Had any major surgery within 8 weeks prior to baseline (Week 0; Visit 2), or will require such during the study that, in the opinion of the	Monitor	Monitor's list	Yes

Important Protocol Deviation Category/Subcategory	Source to Identify Protocol Deviation	Statistical Programming Guidance for Clinical Study Report	Exclude from the PPS?
investigator in consultation with Lilly or its designee, would pose an unacceptable risk to the patient.			
[31] Have current or a history of lymphoproliferative disease	Monitor	Monitor's list	Yes
[32] Have active or history of malignant disease within the 5 years prior to baseline (Visit 2). Patients with successfully treated basal-cell carcinoma [no more than 3], squamous-cell carcinoma of the skin (no more than 2), within the 5 years prior to Visit 2 may participate in the study.	Monitor	Monitor's list	Yes
[33] Presence of significant uncontrolled cerebro-cardiovascular (for example, MI, unstable angina, unstable arterial hypertension, moderate-to-severe NYHA class III/IV heart failure, or cerebrovascular accident [CVA]), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic or neuropsychiatric disorders, or abnormal laboratory values at screening that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.	Monitor	Monitor's list	Yes
[34] Have had fluid overload, MI, or new-onset ischemic heart disease, uncompensated heart failure, or in the opinion of the investigator other serious cardiac disease within 12 weeks prior to Visit 2.	Monitor	Monitor's list	Yes
[35] Have history of a suicide attempt, have a score of 3 on Item 12 (Thoughts of Death or Suicide) of the QIDS-SR16 at screening (Visit 1)	Monitor and Stats	Monitor's list, or, If a patient has a score of 3 for the 'thoughts of death or suicide' on the QIDS-SR16 at Visits 1 or 2.	Yes

Important Protocol Deviation Category/Subcategory	Source to Identify Protocol Deviation	Statistical Programming Guidance for Clinical Study Report	Exclude from the PPS?
or baseline (Week 0; Visit 2), or are clinically judged by the investigator to be at risk for suicide.			
[36] Have serious infection (for example, pneumonia, cellulitis), been hospitalized, received IV antibiotics for an infection within 12 weeks of Visit 2, or had a serious bone or joint infection within 24 weeks prior to baseline, or have ever had an infection of an artificial joint, or are immunocompromised to an extent such that participation in the study would pose an unacceptable risk to the patient.	Monitor	Monitor's list	Yes
[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 jirovecii* pneumonia, histoplasmosis, coccidioidomycosis, or cryptococcosis) or have a known immunodeficiency	Monitor	Monitor's list	Yes
[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)	Monitor	Monitor's list	Yes
[39] Evidence or suspicion of active or latent TB (refer to Protocol Section 10.3.2.2 for details on determining full TB exclusion criteria).	Monitor	Monitor's list	Yes
[40] within 4 weeks of baseline (Week 0, Visit 2), have any active or recent infection other than those mentioned in exclusion criteria 36-39 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	Monitor	Monitor	Yes

Important Protocol Deviation Category/Subcategory	Source to Identify Protocol Deviation	Statistical Programming Guidance for Clinical Study Report	Exclude from the PPS?
symptoms			
[41] Body temperature ≥38 degrees Celsius (100.5°F) at Visit 2 or at rescreen (1 time) ≥4 weeks after documented resolution of elevated temperature	Monitor and Stats	Monitor's list, or, If a patient's temperature is ⩾38 digress Celsius at Visit 2	Yes
Important Protocol Deviation Category/Subcategory	**Source to Identify Protocol Deviation**	**Statistical Programming Guidance for Clinical Study Report**	**Exclude from the PPS?**
[42] Have uncontrolled arterial hypertension characterized by a systolic blood pressure (BP) >160 mm Hg or diastolic BP >100 mm Hg. *Determined by 2 consecutive elevated readings*	Monitor and Stats	Monitor's list, or, If a patients SBP >160 or DBP >100 mmHg at Visit 1	Yes
[43] Are positive for human immunodeficiency virus (HIV) serology (positive for HIV antibody)	Monitor and Stats	Monitor's list, or, If a patients laboratory tests at Visit 1 indicate they are positive for HIV antibody	Yes

Important Protocol Deviation Category/Subcategory	Source to Identify Protocol Deviation	Statistical Programming Guidance for Clinical Study Report	Exclude from the PPS?
[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 anti-hepatitis B core antibody (HBcAb+) and positive for anti-hepatitis B surface antibody (HBsAb+) with a 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 will be identified by the central laboratory and monitored during the study as detailed in Section 10.3.3.3 of the RHBF protocol).*	Monitor and Stats	Monitor's list, or, If a patients laboratory tests at Visit 1 indicate they are positive for hepatitis B	Yes
[45] Have evidence of or test positive for hepatitis C virus (HCV). A positive test for HCV is defined as: 1) positive for hepatitis C antibody (anti-HCV Ab), and 2) positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction).	Monitor and Stats	Monitor's list, or, If a patient's laboratory tests at Visit 1 indicate they are positive for hepatitis C virus	Yes
[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:	Monitor and Stats	Monitor's list, or, If a patients laboratory tests at Visit 1 indicate any of the following: 1. Neutrophil count <1500 cells/μL 2. Lymphocyte count <800 cells/μL	Yes

Important Protocol Deviation Category/Subcategory	Source to Identify Protocol Deviation	Statistical Programming Guidance for Clinical Study Report	Exclude from the PPS?
[46a] Neutrophil count <1500 cells/µL [46b]Lymphocyte count <800 cells/µL [46c] Platelet count <100,000 cells/µL [46d]Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN) [46e] Total white blood cell (WBC) count <3000 cells/µL [46f] Hemoglobin <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 >2.0 mg/dL.		3. Platelet count <100,000 cells/µL 4. AST or ALT >2.5 times the ULN 5. Total WBC <3000 cells/µL 6. Hemoglobin <8.5 g/dL for male patients and <8 g/dL for female patients 7. Serum creatinine >2 mg/dL	
[47] Have electrocardiogram (ECG) abnormalities that are considered clinically significant and would pose an unacceptable risk to the patient if participating in the study	Monitor	Monitor's list	Yes
[48] Have any other condition that precludes the patient from following and completing the protocol.	Monitor	Monitor's list	Yes
[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	Monitor	Monitor's list	Yes
[50] Are women who are lactating or breastfeeding	Monitor	Monitor's list	Yes
[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.	Monitor	Monitor's list	Yes
[52] are employees of Lilly or its designee or are employees of third-party organizations (TPOs)	Monitor	Monitor's list	Yes

Important Protocol Deviation Category/Subcategory	Source to Identify Protocol Deviation	Statistical Programming Guidance for Clinical Study Report	Exclude from the PPS?
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	Monitor	Monitor's list	Yes
[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	Monitor	Monitor's list	Yes
Met study discontinuation criteria but continued to receive study medication			
[D1] Neutrophil (segmented) counts: <500 cells/μL; or ≥500 and <1000 cells/μL (from 2 test results; the second test must be performed within 1 week from knowledge of the initial result); or ≥1000 and <1500 cells/μL (from 3 test results) and an infection that is not fully resolved	Monitor and Stats	Monitor's list, or, If a patient still receives study treatment after 10 days with confirmed segmented neutrophil counts <500 cells/μL; ≥500 and <1000 cells/μL (from a test and a re-test result; the re-test must be performed within 1 week from knowledge of the initial result); or ≥1000 and <1500 cells/μL (from a test and 2 re-test results) and an infection that is not fully resolved If there are missing re-test results, use the non-missing results	Yes
[D2] Total WBC count <2000 cells/μL	Monitor and Stats	Monitor's list, or, If a patient still receives study treatment after 10 days with confirmed total WBC count <2000 cells/μL (defined as a test and a retest within 10 days); If no retest, use the test results	Yes
[D3] Lymphocyte count <500 cells/μL	Monitor and Stats	Monitor's list, or, If a patient still receives study treatment after 10 days with confirmed lymphocyte count <500 cells/μL (defined as a test and a retest within 10 days)	Yes

Important Protocol Deviation Category/Subcategory	Source to Identify Protocol Deviation	Statistical Programming Guidance for Clinical Study Report	Exclude from the PPS?
		If no retest, use the test results	
[D4] Platelet count <50,000 cells/μL	Monitor and Stats	Monitor's list, or, If a patient still receives study treatment after 10 days with confirmed platelet count <50,000 cells/μL (defined as a test and a re-test within 10 days) If no retest, use the test results	Yes
[D5] Patient has a clinically significant systemic hypersensitivity reaction after subcutaneous (SC) administration of investigational product	Monitor	Monitor's list	Yes
[D6] Patient becomes pregnant	Monitor	Monitor's list	Yes
[D7] The patient develops a malignancy. (No more than 2 nonmelanoma skin cancers over any 12-month period during the study.)	Monitor	Monitor's list	Yes
[D8] The result of the TB test is positive at Week 52 (Visit 16) or later AND the patient is diagnosed with active infection	Monitor	Monitor's list	Yes
[D9] Patient develops symptoms suggestive of a lupus-like syndrome or is positive for antibodies against double-stranded DNA	Monitor	Monitor's list	Yes
[D10] 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 post-treatment follow-up period.	Monitor	Monitor's list	Yes
[D11] 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	Monitor	Monitor's list	Yes
[D12] The patient scores a 3 for Item 12 (Thoughts of Death or Suicide) on the QIDS-SR16 at any time in the study.	Monitor and Stats	Monitor's list, or, If patient still receives study treatment on the same day or after the date with a score of 3 for Item 12 on the QIDS-SR16	Yes

Important Protocol Deviation Category/Subcategory	Source to Identify Protocol Deviation	Statistical Programming Guidance for Clinical Study Report	Exclude from the PPS?
[D13] 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	Monitor and Stats	Monitor's list, or, If a patients has <20% improvement from baseline in both TJC and SJC at either Week 24 or any other subsequent visit through Week 104, with the exception of randomization through the following visit after relapse for those patients who are randomized.	Yes
[D14] 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	Monitor	Monitor's list	Yes
[D15] The patient becomes HBV DNA positive.	Monitor	Monitor's list	Yes
Missing Data/Assessments not Done			
MDA missing due to missing values of MDA components at baseline or any visit.	Stats	If missing any individual component of MDA at baseline or any visit from Weeks 24 through 104.	No
Missing ECG: missing baseline	Monitor	Monitor listing	No
Missing C-SSRS while on study medication	Monitor	If missing C-SSRS at any Visit From Week 2 through Week 104 after Amendment A implemented at site	No
Patient was inadvertently randomized. Due to a discrepancy in recorded ePRO data versus the IWRS data for meeting Coates Criteria for MDA.	Monitor	Monitor listing	Yes
Patient started on ixekizumab 80 mg Q2W after randomization to placebo and prior to experiencing a relapse (no longer meeting Coates criteria for MDA in Period 3).	Monitor and Stats	Monitor listing, or, programming for exposure to ixekizumab 80 mg Q2W after randomization and exposure to placebo in period 3 and prior to relapse.	Yes
Patient took incorrect medication	Monitor and Stats	Monitor's list, or, If patient randomized and exposure data shows the patient took incorrect study medication	No
Patient did not take any study medication	Monitor and Stats	Monitor's list, or, If patient randomized and exposure data shows the patient took no study medication	Yes
Patient non-compliant with study medication	Monitor and Stats	Monitor's list, or,	Yes

Important Protocol Deviation Category/Subcategory	Source to Identify Protocol Deviation	Statistical Programming Guidance for Clinical Study Report	Exclude from the PPS?
regimen. Patient missing 2 consecutive doses or take 2 doses of study medication on the same day (i.e. double-dosing) are considered to be non-compliant.		Study drug exposure is reported as missing more than 20% of expected doses for a study period or is missing 2 consecutive doses.	
Patient took prohibited concomitant medication	Monitor and Stats	Monitor's list, or, If patient takes prohibited concomitant medication. *(Note: Prohibited concomitant medication will be provided by medical in a separate file.)*	Yes
Unblinding is considered unjustified if the unblinding occurred on a patient where the patient's wellbeing was not dependent upon knowing their treatment assignment.	Monitor	Monitor's list	Yes

Abbreviations: ATC = anatomical therapeutic chemical; BCG = Bacille de Calmette et Guérin; bDMARD = biologic disease-modifying antirheumatic drug; bHCG = beta human chorionic gonadotropin; ; CASPAR = classification for psoriatic arthritis; cDMARD = conventional disease-modifying antirheumatic drug; DBP = diastolic blood pressure; ePRO = electronic patient reported outcomes; GCP = good clinical practice; IV = intravenous; IWRS = interactive web-response system; MDA = minimal disease activity; MI = myocardial infarction; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; NYHA = New York Heart Association; PPS = per protocol set; PsA = psoriatic arthritis; QIDS-SR16 = quick inventory of depressive symptomatology–self-report 16 items; SBP = systolic blood pressure; SJC = swollen joint count; TB = tuberculosis; TJC = tender joint count; WHO = World Health Organization.

The term "Monitor" indicates the protocol deviation will be identified by site monitors and entered into monitor's list using a spreadsheet. The spreadsheet will be exported as Study Data Tabulation Model (SDTM) DV domain.

The term "Stats" indicates the protocol deviation will be programmed based on data in clinical database by statistical programmers with the statistical programming guidance provided as the last column. The detailed programming specification will be documented in Analysis Data Model (ADaM) specification.

The terms "Monitor and Stats" indicates the protocol deviation will be a combination of monitor's list (SDTM.DV domain) and statistical programming from clinical database, the deviation will show if either source identifies.

6.18. Interim Analyses and Data Monitoring

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 open-label treatment period the visit of randomization or Week 64 for patients who do not meet the randomization criteria); only data from the open-label treatment period will be summarized. 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. The second interim lock and final database lock may be combined depending upon the timing of last patient visit. 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.

6.19. Planned Exploratory Analyses

6.19.1. Planned Exploratory Efficacy Analysis

Table RHBF.6.9 includes the description and derivation of the exploratory outcomes.

Table RHBF.6.10 provides the detailed analyses including analysis type, method and imputation, population, time point, and comparisons for exploratory analyses.

Table RHBF.6.9. Description and Derivation of Additional Exploratory Outcomes

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
Physician's Global Assessment of Disease Activity Visual Analog Scale (VAS)	Physician Global VAS: overall assessment of the severity of the patient's current PsA activity using a 100-mm horizontal VAS. The investigator making the assessment must be a rheumatologist or medically qualified physician.	Change from baseline in Physician Global VAS Percent improvement in Physician Global VAS	Range: 0 to 100 mm 0 represents no disease activity 100 represents extremely active disease activity	single measure, missing if missing missing if baseline or observed value are missing
Leeds Enthesitis Index (LEI)	LEI: For patients with enthesitis, an assessment that consists of 18 entheseal points is performed by site personnel. The LEI has been developed specifically for use in PsA and 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).	Change from baseline in LEI Percent Improvement in LEI	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).	if one or more sites are missing, then set to missing missing if baseline or observed value are missing
		Proportion of patients with resolution in enthesitis (LEI score = 0)	For patients with baseline enthesitis (LEI ≥1), number of patients LEI score of 0	if one or more sites are missing, then set to missing missing if baseline or observed value are missing
Leeds Dactylitis Index-Basic (LDI-B)	LDI-B: measure of severity of dactylitis for patients with dactylitis. Each dactylic 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.	Change from baseline in LDI-B Percent improvement in LDI-B	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). If the circumference of the affected digit ratio is 10% greater than the contra digit, the calculated ratio is minus 1 and	

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
			then multiplied 100 and 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 (Healy and Helliwell 2007).	
		Proportion of patients with resolution of dactylitis (LDI-B score =0)	For patients with baseline dactylitis (LDI-B score >0), number of patients with resolution of dactylitis (LDI-B score = 0)	NA
Spondyloarthritis Research Consortium of Canada (SPARCC)	SPARCC: For patients with enthesitis, an assessment that consists of 18 entheseal points is performed by site personnel. From this assessment the SPARCC 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 epicondyles (right and left), lateral epicondyles (right and left), and the supraspinatus insertion (right and left) (Mease 2011).	Change from baseline in SPARCC Percent improvement in SPARCC Proportion of patients with resolution of enthesitis (SPARCC >0)	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).	if one or more sites are missing, then set to missing. missing if baseline or observed value are missing
Disease Activity Score	DAS28-CRP: is a measure of disease activity in 28 joints that consists of a	Change from baseline in DAS28-CRP	The following equation will be used to calculate the DAS28-	if one or more component are missing, then set to

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
(28 diathrodial joint count) based on C-reactive protein (DAS28-CRP)	composite numerical score using the following measures: TJC, SJC, C-reactive protein (mg/L), and patient's global assessment of disease activity recorded by patients in a 100-mm VAS. The 28 joints to be examined and assessed as tender or not tender and as swollen or not swollen 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).	Percent improvement in DAS-CRP	CRP (Vander Cruyssen et al. 2005) See Appendix 3 for further details on calculating joint counts. Sum of the following: 1. $0.56\left(\sqrt{TJC28}\right)$ 2. $0.28\left(\sqrt{SJC28}\right)$ 3. $0.36\left(\ln\left[CRP+1\right]\right)$ 4. $0.014\left(PatientGlobalVAS\right)$ 5. 0.96 Higher DAS28-CRP scores indicate more severe symptoms and greater functional impairment.	missing. missing if baseline or observed value are missing
Psoriatic Arthritis Disease Activity Score (PASDAS)	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 (0 mm to 10 mm). The TJC is 68 joints, the SJC is 66 joints. Worse disease activity is represented by higher scores (Helliwell et al. 2013).	PASDAS	Sum the following: 1. $0.18\left(\sqrt{PhysicianGlobalVAS}\right)$ 2. $0.159\left(\sqrt{PatientGlobalVAS}\right)$ 3. $-0.253\left(\sqrt{PCS}\right)$ 4. $0.101*\left[\ln\left(SJC+1\right)\right]$ 5. $0.048*\left[\ln\left(TJC+1\right)\right]$ 6. $0.23*\left[\ln\left(LEI+1\right)\right]$ 7. $0.377*\left[\ln\left(TDC+1\right)\right]$ 8. $0.102*\left[\ln\left(CRP+1\right)\right]+2$ Then multiply by 1.5	if one or more components are missing, then set to missing.
Composite Psoriatic Disease Activity Index	CPDAI is a validated instrument to assess composite psoriatic disease activity and response to therapy (Mumtaz et al. 2011). This instrument assesses individual	Change from baseline in CPDAI Percent improvement in CPDAI	Each domain is scored from 0–3. Individual domain scores are summed to give an overall composite score (range 0–12).	if one or more domains are missing, then set to missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
(CPDAI)	domains: • 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.		The composite scores range from 0 to 12 for assessment excluding spinal disease, with a higher score indicating higher disease activity. See Appendix 10 for further details.	missing if baseline or observed value are missing
Psoriasis Area and Severity Index (PASI)	PASI improvement from baseline	PASI 75 Flag PASI 90 Flag PASI 100 Flag	Defined as at least a 75%, 90%, or 100% improvement from baseline in PASI score See Table RHBF.6.3 for details on the calculation of PASI	Single item, missing if missing
Psoriatic Arthritis Response Criteria (PsARC)	PsARC is a composite criteria reported in terms of the percentage of patients achieving response according to the following criteria: 1. Physician Global Assessment of Disease Activity, 2. Patient Global Assessment of Disease Activity, 3. TJC, and	PsARC responder Flag	Response is defined by improvement from baseline assessment in 2 of the 4 criteria, 1 in which must be a joint count; and there must not be worsening of any of the 4 criteria: 1. ≥30% reduction in TJC, 2. ≥30% reduction in SJC,	If one or more criteria are missing then missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	4. SJC		3. ≥20 mm reduction in the physician's assessment (VAS), and 4. ≥20 mm reduction in the patient's assessment (VAS) (Clegg et al. 1996)	
Static Physician's Global Assessment (sPGA) (0,1) and (0)	sPGA (0,1)	sPGA (0,1) Flag	Defined as plaques that are either clear or minimal (0,1)	Single item, missing if missing
	sPGA (0)	PGA (0) Flag	Defined as plaques that are clear (0)	Single item, missing if missing
Disease Activity index for PSoriatic Arthritis (DAPSA)	Composite score that includes at least one variable from each factor to cover all important domains of the multifaceted systemic disease with a main focus on the musculoskeletal system and excludes the skin domain (Smolen et al. 2015).	Change from baseline in DAPSA score Percent improvement in DAPSA score	Sum of the following: 1. SJC 2. TJC 3. patient pain VAS score 4. patient global VAS score 5. CRP (mg/L)	If any item is missing, then missing
		DAPSA Low Disease Activity (LDA)	4 < DAPSA ≤14	If DAPSA is missing, missing
		DAPSA Remission	DAPSA ≤4	If DAPSA is missing, missing
		DAPSA ≤14	DAPSA ≤14	If DAPSA is missing, missing

Abbreviations: NA = not applicable; PsA = psoriatic arthritis; SJC = swollen joint count; TJC = tender joint count.

Table RHBF.6.10. Description of Planned Exploratory Efficacy Analyses

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point
Coates criteria for minimal disease activity (MDA)	Time-to achieve sustained Coates Criteria for MDA (MDA for 12 consecutive months)	Descriptive Statistics for ixekizumab 80 mg Q2W (including Kaplan Meier estimates of the survival curve)	Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and 3 combined
Disease Activity Score (28 arthrodial joint count) based on CRP (DAS28-CRP)	Time-to achieve DAS28-CRP low disease activity (score ≤2.8) (Helliwell et al. 2014)	Descriptive Statistics for ixekizumab 80 mg Q2W (including Kaplan Meier estimates of the survival curve)	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Periods 2 and 3 combined
	Change from baseline in DAS28-CRP Percent improvement in DAS28-CRP	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Periods 2 and 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assess during Period 3, patients with 40 Weeks of Randomized Treatment
Psoriatic Arthritis Disease Activity Score (PASDAS)	Time-to achieve PASDAS low disease activity (score ≤3.2) (Helliwell et al. 2014)	Descriptive Statistics for ixekizumab 80 mg Q2W (including Kaplan Meier estimates of the survival curve)	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Periods 2 and 3 combined
	Change from baseline in PASDAS	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point
	Percent improvement in PASDAS		Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Periods 2 and 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assess during Period 3 through 40 Weeks of Randomized Treatment
Composite Psoriatic Disease Active Index (CPDAI)	Time-to achieve modified CPDAI low disease activity (score ≤3)	Descriptive Statistics for ixekizumab 80 mg Q2W (including Kaplan Meier estimates of the survival curve)	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Periods 2 and 3 combined
	Change from baseline in CPDAI domain scores Change from baseline in CPDAI composite scores	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Periods 2 and 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assess during Period 3 through 40 Weeks of Randomized Treatment
Psoriatic Arthritis Response Criteria (PsARC)	PsARC responder	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Periods 2 and 3 combined
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population	Assess during Period 3 through 40 Weeks of Randomized Treatment

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point
Psoriasis Area and Severity Index (PASI) 75, 90, and 100	Proportion of patients with PASI 75 Proportion of patients with PASI 90 Proportion of patients with PASI 100	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment population with baseline psoriatic lesions involving BSA ≥3%	Assessed during Period 2
			Ixekizumab-treated patients with baseline psoriatic lesions involving BSA ≥3%: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population with baseline psoriatic lesions involving BSA ≥3%	Assess during Period 3 through 40 Weeks of Randomized Treatment
	Change from baseline in PASI Total Score Percent Improvement in Total Score	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment population with baseline psoriatic lesions involving BSA ≥3%	Assessed during Period 2
			Ixekizumab-treated patients with baseline psoriatic lesions involving BSA ≥3%: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population with baseline psoriatic lesions involving BSA ≥3%	Assess during Period 3 through 40 weeks of Randomized Treatment
Static Physician's Global Assessment sPGA of Psoriasis (0,1) and (0)	Proportion of patients with sPGA (0,1) Proportion of patients with sPGA(0)	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment population with sPGA ≥3 at baseline	Assessed during Period 2
			Ixekizumab-treated patients with sPGA ≥3 at baseline: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population with sPGA ≥3 at baseline	Assess during Period 3 through 40 weeks of Randomized Treatment
Body surface area (BSA)	Change from baseline in percent involvement of BSA	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment population with baseline Psoriatic Lesions Involving ≥3% BSA	Assessed during Period 2
			Ixekizumab-treated patients with baseline Psoriatic Lesions Involving ≥3% BSA: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population with baseline Psoriatic Lesions Involving ≥3% BSA	Assess during Period 3 through 40 weeks of Randomized Treatment
Patient's Assessment of Pain Visual Analog Scale (VAS)	Change in baseline in Patient Pain VAS Percent improvement in Patient Pain VAS	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assess during Period 3 through 40 weeks of Randomized Treatment
Patient's Global Assessment of Disease Activity VAS	Change in baseline in patient global VAS Percent improvement in patient global VAS	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assess during Period 3 through 40 weeks of Randomized Treatment

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point
Physician's Global Assessment of Disease Activity VAS	Change in baseline in physician global VAS Percent improvement in physician global VAS	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assess during Period 3 through 40 weeks of Randomized Treatment
Spondyloarthritis Research Consortium of Canada (SPARCC)	Change from baseline in SPARCC Percent improvement in SPARCC	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population with baseline enthesitis (SPARCC >0)	Assessed during Period 2
			Ixekizumab-treated patients with baseline enthesitis (SPARCC >0): nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population with Baseline Enthesitis (SPARCC >0)	Assess during Period 3 through 40 weeks of Randomized Treatment

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point
	Proportion of patients with resolution in enthesitis (SPARCC =0)	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population with Baseline Enthesitis (SPARCC >0)	Assessed during Period 2
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population with Baseline Enthesitis (SPARCC >0)	Assess during Period 3 through 40 weeks of Randomized Treatment
Leeds Dactylitis Index - Basic (LDI-B)	Change from baseline in LDI-B Percent improvement in LDI-B	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population with baseline dactylitis (LDI-B Score >0)	Assessed during Period 2
			Ixekizumab-treated patients with baseline dactylitis (LDI-B Score >0): nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population with baseline dactylitis (LDI-B Score >0)	Assess during Period 3 through 40 weeks of Randomized Treatment
	Proportion of patients with improvement in dactylitis (≥1 digit resolved) Proportion of patients with resolution of dactylitis (LDI-B = 0)	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population with baseline dactylitis (LDI-B Score >0)	Assessed during Period 2
			Ixekizumab-treated patients with baseline dactylitis (LDI-B Score >0): nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population with baseline dactylitis (LDI-B Score >0)	Assess during Period 3 through 40 weeks of Randomized Treatment
Leeds Enthesitis Index (LEI)	Change from baseline in LEI	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population with baseline enthesitis (LEI Score >0)	Assessed during Period 2

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point
	Percent improvement in LEI		Ixekizumab-treated patients with baseline enthesitis (LEI Score >0): nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population with baseline enthesitis (LEI Score >0)	Assess during Period 3 through 40 weeks of Randomized Treatment
	Proportion of patients with resolution in enthesitis (LEI =0)	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population with baseline enthesitis (LEI Score >0)	Assessed during Period 2
			Ixekizumab-treated patients with baseline enthesitis (LEI Score >0: nonrandomized population and randomized withdrawal ITT population)	Assessed during Period 2 and Period 3 combined
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population with baseline enthesitis (LEI Score >0)	Assess during Period 3 through 40 weeks of Randomized Treatment
Enthesitis, 18 entheseal points (as measured by a combination of the LEI and the SPARCC)	Change from baseline in Enthesitis, 18 entheseal points Percent improvement in Enthesitis, 18 entheseal points	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population with baseline enthesitis (18 entheseal point score >0)	Assessed during Period 2
			Ixekizumab-treated patients with baseline enthesitis (18 entheseal point score >0): nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population with baseline enthesitis (18 entheseal points score >0)	Assess during Period 3 through 40 weeks of Randomized Treatment
	Proportion of patients with resolution in enthesitis (18 entheseal	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population with baseline enthesitis (18 entheseal points score >0)	Assessed during Period 2

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point
	points score =0)		Ixekizumab-treated patients with baseline enthesitis (18 entheseal points score >0: nonrandomized population and randomized withdrawal ITT population)	Assessed during Period 2 and Period 3 combined
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population with baseline enthesitis (18 entheseal points score >0)	Assess during Period 3 through 40 Weeks of Randomized Treatment
Swollen joint count (SJC)	Change from baseline in SJC Percent improvement in SJC	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assess during Period 3 through 40 weeks of Randomized Treatment
Tender joint count (TJC)	Change from baseline in TJC Percent improvement in TJC	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assess during Period 3 through 40 weeks of Randomized Treatment
Disease Activity index for PSoriatic Arthritis (DAPSA)	Change from baseline in DAPSA score Percent improvement in DAPSA score	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assess during Period 3 through 40 weeks of Randomized Treatment
	Proportion of patients with DAPSA LDA (DAPSA >4 and DAPSA ≤14)	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients (nonrandomized population and randomized withdrawal ITT population)	Assessed during Period 2 and Period 3 combined
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population	Assess during Period 3 through 40 Weeks of Randomized Treatment
	Proportion of patients with DAPSA remission (DAPSA ≤4)	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients (nonrandomized population and randomized withdrawal ITT population)	Assessed during Period 2 and Period 3 combined
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population	Assess during Period 3 through 40 Weeks of Randomized Treatment
	Proportion of patients with DAPSA ≤14	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients (nonrandomized population and randomized withdrawal ITT population)	Assessed during Period 2 and Period 3 combined
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population	Assess during Period 3 through 40 Weeks of Randomized Treatment

Abbreviations: ANCOVA = analysis of covariance; ITT = intent-to-treat; mBOCF = modified baseline observation carried forward; MMRM = mixed-effects model of repeated measures; NRI = nonresponder imputation; Q2W = every 2 weeks.

6.19.2. Planned Exploratory Health Outcomes/Quality-of-Life Analyses

The health outcomes and quality of life (QOL) measures are Itch NRS, Fatigue Severity NRS, DLQI, SF-36 Mental and Physical Component Summary Scores, EQ-5D-5L, Work Productivity and Activity Impairment Questionnaire-Specific Health Problem, and the QIDS-SR16. There will be no adjustment for multiple comparisons.

Table RHBF.6.11 includes the description and derivation of the health outcomes and QOL measures.

Table RHBF.6.12 provides the detailed analyses including analysis type, method and imputation, population, time point, and comparisons for health outcomes and QOL analyses.

Table RHBF.6.11. Description and Derivation of Health Outcomes and Quality-of-Life Measures

Measure	Description	Variable	Derivation / Comment	Missing Items
Itch Numeric Rating Scale (NRS)	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 selecting the integer that best describes the worst level of itching in the past 24 hours on an 11-point NRS anchored at 0 representing "no itching" and 10 representing "worst itch imaginable."	Itch NRS score	Range from 0 to 10.	Single item, missing if missing
		Itch NRS change from baseline	Calculated as: 1. observed Itch NRS – baseline Itch NRS 2. mBOCF Itch NRS	1. Missing if baseline or observed value is missing 2. Missing if baseline is missing
		Itch NRS ≥3 improvement from baseline	Reduced/decreased of ≥3 point from baseline	Missing if baseline or observed value is missing
		Itch NRS =0	Defined as a post-baseline Itch NRS score of 0	Missing if Itch NRS score is missing
Fatigue Severity Numeric Rating Scale	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 selecting the single number that describes their worst level of fatigue during the past 24 hours.	Fatigue Severity NRS	Range from 0 to 10.	Single item, missing if missing
		Fatigue Severity NRS change from baseline	Calculated as: 1. observed Fatigue Severity NRS – baseline Fatigue Severity NRS 2. mBOCF Fatigue Severity	1. Missing if baseline or observed value is missing 2. Missing if baseline is missing
		Fatigue Severity NRS = 0	Defined as a post-baseline Fatigue Severity NRS score of 0	Missing if Fatigue Severity NRS score is missing
		Improvement in 2 points and 3 points in Fatigue Severity NRS	Defined as a change from baseline in Fatigue Severity NRS score of ≥2; and Defined as a change from baseline in Fatigue Severity NRS score of ≥3	Missing if Fatigue Severity NRS score is missing

Measure	Description	Variable	Derivation / Comment	Missing Items
Dermatology Life Quality Index (DLQI)	DLQI: is a validated, dermatology-specific, patient-reported measure that evaluates patient's health-related quality of life. This questionnaire has 10 items that are grouped in 6 domains, including 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 and corresponding scores are: Very much = 3 A lot = 2 A little = 1 Not at all = 0 Not relevant = 0	DLQI symptoms and feelings domain	Sum of responses of questions #1 and #2: #1. How itchy, sore, painful or stinging has your skin been? #2. How embarrassed or self-conscious have you been because of your skin?	If one question in a domain is missing, that domain is missing.
		DLQI daily activities domain	Sum of responses of questions #3 and #4: #3. How much has your skin interfered with you going shopping or looking after your home or garden? #4. How much has your skin influenced the clothes you wear?	If one question in a domain is missing, that domain is missing.
		DLQI leisure domain	Sum of responses of questions #5 and #6: #5. How much has your skin affected any social or leisure activities? #6. How much has your skin make it difficult for you to do any sport?	If one question in a domain is missing, that domain is missing.
		DLQI work and school domain	Sum of responses of questions question #7A and #7B: #7A. Has your skin prevented you from working or studying? #7B. If No: how much has your skin been a problem at work or studying?	If the answer to question #7A is missing, this domain is missing. If #7A is No, and #7B is missing, this domain is missing.

Measure	Description	Variable	Derivation / Comment	Missing Items
		DLQI personal relationships domain	Sum of responses of questions #8 and #9: #8. How much has your skin created problems with your partner or any of your close friends or relatives? #9. How much has your skin caused any sexual difficulties?	If one question in a domain is missing, that domain is missing.
		DLQI treatment	Response of question #10: #10. How much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	If one question in a domain is missing, that domain is missing.
		DLQI total score	A DLQI total score is calculated by summing all 10 question responses, and has a range of 0 to 30 (less to more impairment) (Finlay and Khan 1994; Basra et al. 2008).	If two or more questions are missing, the total score is missing. *(Note: #7B could be a valid missing while #7A is not "No." That is, #7 should be considered as one question.)*
		DLQI (0,1)	A DLQI (0,1) response is defined as a post-baseline DLQI total score of 0 or 1. A DLQI total score of 0 to 1 is considered as having no effect on a patient's HRQoL (Khilji et al. 2002; Hongbo et al. 2005).	Missing if DLQI total score is missing
		DLQI total score ≥5 improvement from baseline	Reduction/decrease of ≥5 points from baseline. A 5-point change from baseline is considered as the minimal clinically important difference threshold.	Missing if baseline or observed value is missing
		DLQI total score and domain scores change from baseline	Calculated as: observed DLQI (total score or domain scores) – baseline DLQI (total score or domain scores)	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation / Comment	Missing Items
Medical Outcomes Study 36-item Short-Form Health Survey (SF-36)	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 (MCS) and Physical Component Summary (PCS) 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) health survey will be used, which has a 1-week recall period (Brazier et al. 1992; Ware and Sherbourne 1992).	8 associated domain scores: • Physical Functioning, • Role Physical, • Bodily Pain, • General Health, • Vitality, • Social Functioning, • Role Emotional, and Mental Health 2 component Scores: • MCS Score • PCS Score	Per copyright owner, the QualityMetric Health Outcomes™ Scoring Software 4.5 will be used to derive SF-36 domain and component scores. After data quality-controls, the SF-36 software will re-calibrate the item-level responses for calculation of the domain and component scores. These raw scores will be transformed into the domain scores (t-scores) using the 1-week recall period. The procedure to derive the SF-36 scores is described in Appendix 6. It entails exporting the patient data in a CSV or tab-delimited file for import, generation of the SF-36 scores and reports, and export of the calculated scores in a CSV or tab-delimited file for integration into SDTM/ADaM datasets. The summary scores range from 0 to 100.	Missing data handling offered by SF-36 software will not be used.
Work Productivity and Activity Impairment–Specific Health Problem	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.	percentage of absenteeism	Percent work time missed due to problem: (Q2/(Q2 + Q4))*100	if Q2 or Q4 is missing, then missing
		percentage of presenteeism (reduced productivity while at work)	Percent impairment while working due to problem: (Q5/10)*100	if Q5 is missing, then missing
		overall work impairment score that combines absenteeism and presenteeism	Percent overall work impairment due to problem: (Q2/(Q2+ Q4) + [(1-Q2/(Q2+Q4))*(Q5/10)])*100	if Q2, Q4, or Q5 is missing, then missing

Measure	Description	Variable	Derivation / Comment	Missing Items
	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]).	percentage of impairment in activities performed outside of work	Percent activity impairment due to problem: (Q6/10)*100	if Q6 is missing, then missing
European Quality of Life – 5 Dimensions 5 Level (EQ-5D-5L)	EQ-5D-5L is a standardized measure of health status used to provide 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 0- to 100-mm VAS. The descriptive system comprises the following 5 dimensions: item 1: mobility item 2: self-care item 3: usual activities item 4: pain/discomfort item 5: anxiety/depression 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.	EQ-5D mobility, EQ-5D self-care, EQ-5D usual activities, EQ-5D pain/ discomfort, EQ-5D anxiety/ depression	Five health profile dimensions, each dimension has 5 levels: 1 = no problems 2 = slight problems 3 = moderate problems 4 = severe problems 5 = extreme problems It should be noted that the numerals 1 to 5 have no arithmetic properties and should not be used as a primary score.	Each dimension is a single item, missing if missing. *(Note: Score of 9 is missing.)*
		EQ-5D-5L UK Population-based index score	Uses the concatenation of the value of each EQ-5D-5L dimension score in the order: item1; item2; item3; item4; item5. Derive EQ-5D-5L UK Population-based index score according to the link by using the UK algorithm (Szende et al. 2007) to produce a patient-level index score between -0.59 and 1.0 (continuous variable): http://www.euroqol.org/fileadmin/user_upload/Documenten/Excel/Cross	If any of the items is missing or equal to 9, the index score is missing

Measure	Description	Variable	Derivation / Comment	Missing Items
			walk_5L/EQ-5D-5L_Crosswalk_Value_Sets.xls	
	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 (EuroQol Group 2013 [WWW]). The VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labeled 100 = "best imaginable health state" and 0 = "worst imaginable health state." This information can be used as a quantitative measure of health outcome.	EQ-5D VAS	Range from 0 = "worst imaginable health state" to 100 = "best imaginable health state". *(Note: Higher value indicates better health state.)*	Single item, missing if missing
Quick Inventory of Depressive Symptoma-tology-Self Report (16	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	Sleep disturbance (initial, middle, and late insomnia or hypersomnia) Change from baseline in sleep disturbance	the highest score recorded for the 4 sleep items: #1 (falling asleep), #2 (sleep during the night), #3 (waking up too early) and #4 (sleeping too much).	Domain is missing if all items are missing.

Measure	Description	Variable	Derivation / Comment	Missing Items
		Sad mood Change from baseline in sad mood	Score recorded for item #5	Domain is missing if the item is missing.
		Decrease/increase in appetite/weight Change from baseline in decrease/increase in appetite/weight	the highest score recorded for the appetite/weight items (items #6 to #9)	Domain is missing if all items are missing or not applicable.
		Concentration Change from baseline in concentration	Score recorded for item #10 (concentration/ decision making)	Domain is missing if the item is missing.
		Self-criticism Change from baseline in self-criticism	Score recorded for item #11 (view of myself)	Domain is missing if the item is missing.
		Suicidal ideation Change from baseline in suicidal ideation	Score recorded for item #12 (thoughts of death or suicide)	Domain is missing if the item is missing
		Interest Change from baseline in interest	Score recorded for item #13 (general interest)	Domain is missing if the item is missing.
		Energy/fatigue Change from baseline in energy/fatigue	Score recorded for item #14 (energy level)	Domain is missing if the item is missing.
		Psychomotor agitation/ retardation Change from baseline in	The highest score recorded for the two psychomotor items: #15 (feeling slowed down) and #16 (feeling restless).	Domain is missing if all items are missing.

Measure	Description	Variable	Derivation / Comment	Missing Items
		psychomotor agitation/ retardation		
		QIDS-SR16 total score Change from baseline in QIDS-SR16 total score	QIDS-SR16 total score is the sum of the domain scores. The range for total score is 0 to 27.	The total score will be missing if any domain score is missing.
		Proportion of patients with at least a 50% decrease in QIDS-SR16 total score	QIDS-SR16 total score at each post-baseline visit is at least a 50% reduction of the patient's baseline QIDS-SR16 total score	The total score will be missing if any domain score is missing

Abbreviations: ADaM = Analysis Data Model; mBOCF = modified baseline observation carried forward; PsA = psoriatic arthritis; SDTM = Study Data Tabulation Model; UK = United Kingdom.

Table RHBF.6.12. Description of Planned Exploratory Health Outcomes and Quality-of-Life Analyses

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point
Itch Numeric Rating Scale (NRS)	Itch NRS ≥3 improvement from baseline	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population with baseline psoriatic lesions involving ≥3% BSA and baseline Itch NRS score ≥3	Assessed during Period 2
			Ixekizumab-treated patients with baseline psoriatic lesions involving ≥3% BSA and baseline Itch NRS score ≥3: nonrandomized and Randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population with baseline psoriatic lesions involving ≥3% BSA and baseline Itch NRS score ≥3	Assessed during Period 3 through 40 weeks of Randomized Treatment
	Itch NRS =0	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population with baseline psoriatic lesions involving ≥3% BSA and baseline Itch NRS score >0	Assessed during Period 2
			Ixekizumab-treated patients with baseline psoriatic lesions involving ≥3% BSA and baseline Itch NRS score >0: nonrandomized and Randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population with baseline psoriatic lesions involving ≥3% BSA and baseline Itch NRS score >0	Assessed during Period 3 through 40 weeks of Randomized Treatment
	Itch NRS change from baseline	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population with baseline psoriatic lesions involving BSA ≥3%	Assessed during Period 2
			Ixekizumab-treated patients with baseline psoriatic lesions involving BSA≥3%: nonrandomized population and Randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population with baseline psoriatic lesions involving BSA ≥3%	Assessed during Period 3 through 40 weeks of Randomized Treatment

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point
Fatigue Severity NRS	Fatigue Severity NRS =0	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and Randomized withdrawal ITT population	Assessed during Period 2 and Periods 3 combined
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population	Assessed during Period 3 through 40 weeks of Randomized Treatment
	Fatigue Severity NRS change from baseline	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and Randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assessed during Period 3 through 40 weeks of Randomized Treatment
Dermatology Life Quality Index (DLQI)	DLQI (0,1),	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population with baseline psoriatic lesions involving BSA≥3%	Assessed during Period 2
			Ixekizumab-treated patients with baseline psoriatic lesions involving BSA≥3%: nonrandomized population and Randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population with baseline psoriatic lesions involving BSA≥3%	Assessed during Period 3 through 40 weeks of Randomized Treatment
	DLQI total score and domain scores change from baseline	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population with baseline psoriatic lesions involving BSA ≥3%	Assessed during Period 2
			Ixekizumab-treated patients with baseline psoriatic lesions involving BSA ≥3%: nonrandomized population and Randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population with baseline psoriatic lesions involving BSA ≥3%	Assessed during Period 3 through 40 weeks of Randomized Treatment
36 item Short Form Health Survey	8 associated domain scores: • Physical Functioning • Role Physical • Bodily Pain • General Health, • Vitality • Social Functioning • Role Emotional • Mental Health	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and Randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assessed during Period 3 through 40 weeks of Randomized Treatment
	MCS Score	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and Randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assessed during Period 3 through 40 weeks of Randomized Treatment
	PCS Score	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and Randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assessed during Period 3 through 40 weeks of Randomized Treatment
Work Productivity and Activity Impairment–Specific	Change from baseline in the following: • percentage of absenteeism • percentage of presenteeism (reduced	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point
Health Problem	productivity while at work) • overall work impairment score that combines absenteeism and presenteeism • percentage of impairment in activities performed outside of work	MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assessed during Period 3 through 40 weeks of Randomized Treatment
European Quality of Life – 5 dimensions 5 level (EQ-5D)	EQ-5D mobility, EQ-5D self-care, EQ-5D usual activities, EQ-5D pain/discomfort, EQ-5D anxiety/depression	For each EQ-5D dimension, the proportion of patients with "no problems" will be summarized using descriptive statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		For each EQ-5D dimension, the proportion of patients with "no problems" will be analyzed by: Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population	Assessed during Period 3 through 40 weeks of Randomized Treatment
	EQ-5D-5L UK Population-based index score, EQ-5D VAS	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assessed during Period 3 through 40 weeks of Randomized Treatment
Quick Inventory of Depressive Symptoma-tology-Self	Observed and change from baseline in the following QIDS-SR16 domains: (1) sad mood (2) concentration	Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients : nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point
Report 16 Items (QIDS-SR16)	(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 (9) psychomotor agitation/retardation Observed and change from baseline in QIDS-SR16 total score	MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population	Assessed during Period 3 through 40 weeks of Randomized Treatment
		Descriptive Statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population with baseline QIDS-SR16 total score of ≥11	Assessed during Period 2
			Ixekizumab-treated patients with baseline QIDS-SR16 total score of ≥11: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		MMRM; ANCOVA with mBOCF	Randomized withdrawal ITT population with baseline QIDS-SR16 total score of ≥11	Assessed during Period 3 through 40 weeks of Randomized Treatment
	QIDS-SR16 total score categories: • None (no depression): 0–5 • Mild: 6-10 • Moderate: 11 – 15 • Severe: 16 – 20 • Very severe: 21 – 27.	Descriptive Statistics for ixekizumab 80 mg Q2W Shift table from maximum baseline for ixekizumab 80 mg Q2W Descriptive statistics on the category based on the maximum post-baseline: for ixekizumab 80 mg Q2W ○ Improved; maximum post-baseline category < maximum baseline category. ○ Worsened; maximum post-baseline category > maximum baseline category. ○ Same; maximum post-baseline category = maximum baseline category.	Initial open-label treatment period population	All post-baseline visits in Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	All post-baseline visits in Period 2 and Period 3 combined
			Randomized withdrawal ITT population	Assessed during Period 3 through 40 weeks of Randomized Treatment

Measure	Variable	Analysis Method (Section 6.1)	Population (Section 6.6.1)	Comparison/Time Point
	Proportion of patients with at least a 50% decrease in QIDS-SR16 total score	Descriptive statistics for ixekizumab 80 mg Q2W	Initial open-label treatment period population	Assessed during Period 2
			Ixekizumab-treated patients: nonrandomized population and randomized withdrawal ITT population	Assessed during Period 2 and Period 3 combined
		Logistic regression analysis with NRI; Fisher's exact test with NRI	Randomized withdrawal ITT population	Assessed during Period 3 through 40 Weeks of Randomized Treatment

Abbreviations: ANCOVA = analysis of covariance; ITT = intent-to-treat; mBOCF = modified baseline carried forward; MCS = Mental Component Summary; MMRM = mixed-effects model of repeated measures; NRI = nonresponder imputation; PCS = Physical Component Summary; Q2W = every 2 weeks; UK = United Kingdom; VAS = visual analog scale.

6.20. Annual Report Analyses

Annual report analyses will be documented in a separate document.

6.21. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include summary of AEs, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by treatment group and MedDRA PT.

- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- Adverse event reporting is consistent with other document disclosures for example, the clinical study report (CSR), manuscripts, and so forth.

7. Unblinding Plan

Refer to the I1F-MC-RHBF Blinding and Unblinding plan.

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9. Appendices

Appendix 1. Algorithm for Calculating Classification for Psoriatic Arthritis (CASPAR) Total Score

The classification for psoriatic arthritis (CASPAR) total score is defined as the summation of the following 5 categories in patients with inflammatory articular disease (joint, spine, or entheseal):

- Either:
  - Evidence of current psoriasis **(2 points)** or
  - a personal history of psoriasis or a family history of psoriasis **(1 point)**
- 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)**

If any of the above individual categories have a missing score, then the CASPAR total score will be the sum of the non-missing categories. If all of the above categories are missing then the CASPAR total score will equal 0.

Note the following:

- 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.

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.

Appendix 2. Algorithm for Calculating Coates Criteria for Minimal Disease Activity (MDA)

Coates criteria for MDA defines a state of disease activity and not a change in disease and includes all attributes of PsA. Coates criteria for MDA uses a composite of 7 key outcome measures. A patient is considered as achieving MDA if they fulfill 5 of the following 7 outcome criterion (Coates et al. 2010; Coates and Helliwell 2010):

- TJC $\leq$ 1;
- SJC $\leq$ 1;
- PASI total score $\leq$ 1 or BSA $\leq$ 3;
- Patient pain VAS score of $\leq$ 15;
- Patient global VAS score of $\leq$ 20;
- HAQ-DI score $\leq$ 0.5;
- Tender entheseal points (of 18 entheseal points) $\leq$ 1.

The modified Coates criteria for MDA is calculated in the same manner as the Coates criteria for MDA substituting sPGA for PASI. Therefore, a patient is considered as achieving modified MDA if they fulfill 5 of the following 7 outcome criterion (Mease et al. 2013):

- TJC $\leq$ 1;
- SJC $\leq$ 1;
- sPGA (0,1) or BSA $\leq$ 3;
- Patient pain VAS score of $\leq$ 15;
- Patient global VAS score of $\leq$ 20;
- HAQ-DI score $\leq$ 0.5;
- Tender entheseal points (of 18 entheseal points) $\leq$ 1.

Note the 18 tender entheseal points are measured from combining the unique entheseal sites from the LEI and the SPARCC. The LEI consists of 6 entheseal sites and the SPARCC consists of 16 entheseal sites.

Appendix 3. Algorithm for Calculating Joint Counts

Joints are evaluated and recorded as either non-evaluable, or if evaluable, then if tenderness is present or absent, and if swelling is present or absent. In total, 68 joints are assessed for tenderness and 66 are assessed for swelling. Hips are not assessed for swelling.

The number of tender/swollen joints will be calculated by summing all joints checked to have tenderness/swelling present. If at least half but not all of the joints are evaluable, then the observed prorated joint count will be calculated instead. The prorated scores for TJC will be adjusted based upon the number of evaluable joints: the counted score will be multiplied by 68 then divided by the number of joints evaluated (excluding non-evaluable joints and any joints with a missing response). For example: if only 60 of the 68 joints are assessed to be evaluable at a visit, and 32 of those 60 are tender, the prorated joint count is $(32/60)\times 68=36.27$ (not 32). The prorated joint count will be rounded up to the next integer and be used in calculating the percent change from baseline in TJC. The same algorithm will be applied to the calculation of percent change from baseline in SJC with the exception that the counted score will be multiplied by 66 then divided by the number of joints evaluated. If less than half of the joints are evaluable, the number of tender/swollen joints is missing.

This same algorithm will be used for the calculation of TJC and SJC based on 28 joints, which is part of the 28 diarthrodial joint count, based on C-reactive protein (DAS28-CRP) score.

Appendix 4. Algorithm for Calculating the Health Assessment Questionnaire–Disability Index (HAQ-DI)

The Health Assessment Questionnaire–Disability Index (HAQ-DI) is a patient-reported questionnaire 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 activities (Fries et al. 1980, 1982).

- Dressing and grooming (C1. Dress yourself, including tying shoelaces and doing buttons, C2. Shampooing your Hair)
    - Includes 2 component questions, 1 device checkbox (devices used for dressing), 1 help checkbox
- Arising (C1. Stand up from straight chair, C2. Get in and out of bed)
    - Includes 2 component questions, 1 device checkbox (built-up or special chair), 1 help checkbox
- Eating (C1. Cut your meat, C2. Lift a cup or glass to your mouth, C3. Open a new carton of milk)
    - Includes 3 component questions, 1 device checkbox (build-up or special utensils), 1 help checkbox)
- Walking (C1. Walk outdoors on flat ground, C2. Climb up 5 steps)
    - Includes 2 component questions, 4 device checkboxes (cane, walker, crutches, wheelchair), 1 help checkbox
- Hygiene (C1. Wash and dry your body, C2. Take a tub bath, C3. Gen on and off the toilet)
    - Includes 3 component questions, 4 device checkboxes (raised toilet seat, bathtub seat, bathtub bar, long-handled appliances in bathroom), 1 help checkbox.
- Reach (C1. Reach and get down a 5 pound object (such as a bag of sugar) from just above your head, C2. Bend down to pick up clothing from the floor)
    - Includes 2 component questions, 1 device checkbox (long-handled appliances for reach), 1 help checkbox
- Grip (C1. Open car doors, C2. Open jars which have been previously opened, C3. Turn faucets on and off)
    - Includes 3 component questions, 1 device checkbox (jar opener), 1 help checkbox
- Activities (C1. Run errands and shop, C2. Get in and out of a car, C3. Do chores such as vacuuming or yard work)
    - Includes 3 component questions, 1 help checkbox

In order to compute the HAQ-DI (Standard Disability Index) score, the following scores are assigned to the responses:

- Without any difficulty = 0
- With some difficulty = 1

- With much difficulty = 2
- Unable to do = 3.

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) when dressing and grooming, arising, eating, walking, hygiene, reach, grip, and performing other daily activities. 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.

Calculating the HAQ-DI:

The patient must have a score for at least 6 of the 8 categories. If there are <6 categories completed, a HAQ-DI cannot be computed.

- A category score is determined from the highest score of the subcategories, or components, in that category. (For example, in the category ARISING there are 3 sub-category items. If a patient responds with a 1, 2, and 0, respectively; the category score is 2.)
- Adjust for use of aids/devices and/or help from another person when indicated:
    - When there are no aids or devices or help indicated for a category, the category's score is not modified.
        - When aids or devices or help ARE indicated by the patient, adjust the score for a category by increasing a 0 or a 1 to a 2. If a patient's highest score for that sub-category is a 2 it remains a 2, and if a 3, it remains a 3.
    - Sum the 8 category scores
    - Divide the sum by the number of categories answered (range 6-8).

The scale is not truly continuous but has 25 possible values (that is, 0, 0.125, 0.250, 0.375 … 3). The mapping of the aids or devices to the categories is the following:

HAQ-DI Category	**Companion aids or devices item**
Dressing and Grooming	Devices used for dressing (button hook, zipper pull, long handled shoe horn, etc.)
Arising	Built up or special chair
Eating	Built up or special utensils
Walking	Cane, walker, crutches, wheelchair
Hygiene	Long handled appliances in bathroom; bathtub seat; raised toilet seat; bathtub bar
Reach	Long handled appliances for reach
Grip	Jar opener (for jars previously opened)

Abbreviations: HAQ-DI = Health Assessment Questionnaire–disability index.

Appendix 5. Algorithm for Determining American College of Rheumatology (ACR) Response

Details presented in this appendix will use "*x*" as a generic symbol, and the appropriate number (either 20, 50, or 70) is to be filled in when implementing in dataset programming code.

American College of Rheumatology (ACRx) response is defined as ≥*x*% improvement from baseline in tender joint count (68 counts) and ≥*x*% improvement in swollen joint count (66 counts), and ≥*x*% improvement in at least 3 of the following 5 items:

- Patient's global assessment of arthritis pain
- Patient's global assessment of disease activity
- Physician's global assessment of disease activity
- Health Assessment Questionnaire–Disability Index (HAQ-DI)
- C-reactive protein (CRP)

The following abbreviations will be used throughout this appendix to refer to the items needed in the algorithm definitions:

Parameter	Abbreviation for the Parameter
% improvement in tender joint count	TJC68
% improvement in swollen joint count	SJC66
% improvement in patient's assessment pain	PATPAIN
% improvement in patient's global assessment of disease activity	PATGA
% improvement in physician's global assessment of disease activity	PHYGA
% improvement in HAQ-DI	HAQ
% improvement in CRP	CRP

For all 7 parameters mentioned above, % improvement at a visit is calculated as:

(baseline value – value at visit) * 100 / baseline value.

To calculate the *observed* ACR*x* response at a visit:

- Step1: If the patient discontinued from the study prior to reaching the visit, then STOP – assign ACR*x* response as blank (that is, missing). Otherwise, calculate the % improvement at the visit for all 7 parameters as described above.
- Step2:
  - If 68 total joint count score (TJC68) AND 66 swollen joint count score (SJC66) are BOTH ≥*x*%, then proceed to Step 3.
  - If both are non-missing but one or both is <x%, then STOP – assign the patient as a nonresponder for ACR*x*.
  - If either or both are missing, proceed as follows:

a. If both are missing, then STOP – assign ACR*x* response as blank (that is, missing).
b. If one of TJC68 or SJC66 is missing and the non-missing value is <*x*%, then STOP – assign the patient as a nonresponder for ACR*x*.
c. If one of TJC68 or SJC66 is missing and the non-missing value is ≥*x*%, then STOP – assign ACR*x* response as blank (that is, missing).

- Step3: Consider the following 5 variables: patient's assessment pain (PATPAIN), patient's global assessment of disease activity (PATGA), physician's global assessment of disease activity (PHYGA), HAQ, and CRP.
  - If 3 or more items are missing, then STOP – assign ACR*x* response as blank (that is, missing).
  - If 3 or more items are non-missing, then proceed with the following order:
    d. If at least 3 items are ≥*x*%, then STOP – assign the patient as a responder for ACRx.
    e. If at least 3 items are <*x*%, then STOP – assign the patient as a nonresponder for ACRx.
    f. If <3 items are ≥*x*%, then STOP – assign ACR*x* response as blank (that is, missing).

To calculate the ACR*x* response at *post-baseline visits up to Week 104 using NRI*:

- Step 1: Calculate the % improvement at the visit for all 7 parameters as described above.
- Step 2: If all 7 parameters are missing at the visit, or if the patient discontinued from the study prior to reaching the visit, then STOP – assign the patient as a nonresponder for ACR*x*.
- Step 3: If at least 1 of the 7 parameters is non-missing at the visit and the patient is still enrolled in the study, then use LOCF to fill in any missing values.
- Step 4: If TJC68 AND SJC66 are BOTH ≥*x*%, then proceed to Step 5. If both are non-missing but one or both is <*x*%, then STOP – assign the patient as a nonresponder for ACR*x*. If either or both are missing, then STOP – assign the patient as a nonresponder for ACR*x*.
- Step 5: Consider the following 5 variables: PATPAIN, PATGA, PHYGA, HAQ, CRP.
  - If 3 or more of the 5 items are non-missing, then:
    - If 3 or more of the 5 items are ≥*x*%, then STOP – assign the patient as a responder for ACR*x*.
    - If <3 of those 5 items are ≥*x*%, then STOP – assign the patient as a nonresponder for ACR*x*.
  - If ≥3 of the 5 items are missing, then STOP – assign the patient as a nonresponder for ACR*x*.

Appendix 6. Derivation of SF-36v2® Health Survey, Acute Version Scores

The SF-36v2® Health Survey Scoring Software (QualityMetric Health Outcomes™ Scoring Software 4.5) will be used to calculate the SF-36v2® 8-domain and 2-component summary scores (Saris-Baglama et al. 2004). The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) is a 36-item, patient-completed 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 dimensions of mental well-being and physical well-being are captured by the Physical Component Summary (PCS) and Mental Component Summary (MCS) 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. In this study, the SF-36 acute version will be used, which has a 1-week recall.

The Scoring Software performs a 4-step process to calculate raw domain scores and t-scores consisting of

1. Data Cleaning and Item recording: First, data are checked for out of range values, converting invalid items to missing values. Next, items (BP01, BP02, GH01, GH03, GH05, VT01, VT02, SF01, MH03, MH05) are reverse scored, so that higher scores denote better health for all SF-36 items.
2. Although current research indicates a linear relationship between the SF-36 items and the underlying health concept, empirical research suggests that items GH01 and BP01 require recalibration to satisfy important scaling assumptions. Item GH01 will be rescored according to the following table:

Response to GH01	Recommended Value / Recalibrated Value
Excellent	5.0
Very Good	4.4
Good	3.4
Fair	2.0
Poor	1.0

The BP01 will be rescored with

Response Choices	Final Item Value
None	6.0
Very mild	5.4
Mild	4.2
Moderate	3.1
Severe	2.2
Very severe	1.0

Item 08 (BP02) will be rescored if BP01 and BP02 were answered

Response Choices	If BP02 Pre-coded Item Value	and BP01 Pre-coded Item Value	Then Final Item 08 (BP02) Value
Not at all	1	1	6
Not at all	1	2-6	5
A little bit	2	1-6	4
Moderately	3	1-6	3
Quite a bit	4	1-6	2
Extremely	5	1-6	1

Scoring of BP02 if BP01 is not answered:

Response Choices	Final Item Value
Not at all	6.0
A little bit	4.75
Moderately	3.5
Quite a bit	2.25
Extremely	1.0

3. After this rescoring, the raw domain scores will be calculated for the scale. Domain scores are the simple algebraic sum of the final values for all items in that scale.
4. All raw domain scores will be transformed to a 0-100 scale, with 0 being the lowest and 100 the highest possible score.
5. Finally, the 0-100 scores will be transformed to t-score based scores. First, a z-score transformation using the mean for the respective recall period, here 1 week recall, of the 1998 general U.S. population will be used. Then the distribution of z-score is linearly transformed to have a mean of 50 and a SD of 10 by multiplying each z-score with 10 and adding 50.

The calculation of component scores is a 3-step process using the domain scores, calculated as described above:

1. The standardized scores from Step 5, depending on the chosen recall period, are calculated.
2. These standardized Physical and Mental component scores are calculated as the weighted sums by the factor score coefficients, derived from the 1990 general US population, with the domain scores. If any domain score is missing then the aggregate Physical or Mental score will not be calculated.
3. The PCS and MCS are linearly transformed by multiplying by 10 and adding 50 to obtain the aggregate t-score based scoring.

To run the scoring algorithm, the SF-36 items recorded in the study database will be exported into a comma- or tab-separated values file (*.csv, *.tab). This file will then be loaded into the Scoring Software to perform the calculations described above. The resulting raw domain scores and t-scores (domain scores) will then be exported into a comma- or tab-separated values file and imported into SAS for storage in the Study Data Tabulation Mode/Analysis Data Model (SDTM/ADaM) datasets.

The comma- or tab-separated values file, each row will be one patient record and the first row will comprise the header columns, will have the following column specification: (to comply with the Scoring Software requirements)

eCRF Row #	**Column label for export to comma- or tab-separated values file [*.csv, *.tab]**	**Annotated SF-36 eCRF Variable** [Format: SF36V2RXX_SF36V2F1]	**Item Number, Score range**	**eCRF question / Specification**
1	GH01	[SF36V2R01_SF36V2F1]	Item # 1, Range 1-5	In general, would you say your health is:
2	HT	[SF36V2R02_SF36V2F1]	Item # 2, Range 1-5	Compared to one week ago, how would you rate your health in general now?
3	PF01	[SF36V2R03_SF36V2F1]	Item # 3a, Range 1-3	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
4	PF02	[SF36V2R04_SF36V2F1]	Item # 3b, Range 1-3	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
5	PF03	[SF36V2R05_SF36V2F1]	Item # 3c, Range 1-3	Lifting or carrying groceries
6	PF04	[SF36V2R06_SF36V2F1]	Item # 3d, Range 1-3	Climbing several flights of stairs
7	PF05	[SF36V2R07_SF36V2F1]	Item # 3e, Range 1-3	Climbing one flight of stairs
8	PF06	[SF36V2R08_SF36V2F1]	Item # 3f, Range 1-3	Bending, kneeling, or stooping
9	PF07	[SF36V2R09_SF36V2F1]	Item # 3g, Range 1-3	Walking more than a mile
10	PF08	[SF36V2R10_SF36V2F1]	Item # 3h,	Walking several hundred yards

eCRF Row #	Column label for export to comma- or tab-separated values file [*.csv, *.tab]	Annotated SF-36 eCRF Variable [Format: SF36V2RXX_SF36V2F1]	Item Number, Score range	eCRF question / Specification
			Range 1-3	
11	PF09	[SF36V2R11_SF36V2F1]	Item # 3i, Range 1-3	Walking one hundred yards
12	PF10	[SF36V2R12_SF36V2F1]	Item # 3j, Range 1-3	Bathing or dressing yourself
13	RP01	[SF36V2R13_SF36V2F1]	Item # 4a, Range 1-5	Cut down the amount of time you spent on work or other activities
14	RP02	[SF36V2R14_SF36V2F1]	Item # 4b, Range 1-5	Accomplished less than you would like
15	RP03	[SF36V2R15_SF36V2F1]	Item # 4c, Range 1-5	Were limited in the kind of work or other activities
16	RP04	[SF36V2R16_SF36V2F1]	Item # 4d, Range 1-5	Had difficulty performing the work or other activities (for example, it took extra effort)
17	RE01	[SF36V2R17_SF36V2F1]	Item # 5a, Range 1-5	Cut down the amount of time you spent on work or other activities
18	RE02	[SF36V2R18_SF36V2F1]	Item # 5b, Range 1-5	Accomplished less than you would like
19	RE03	[SF36V2R19_SF36V2F1]	Item # 5c, Range 1-5	Did work or other activities less carefully than usual
20	SF01	[SF36V2R20_SF36V2F1]	Item # 6, Range 1-5	During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
21	BP01	[SF36V2R21_SF36V2F1]	Item # 7, Range 1-6	How much bodily pain have you had during the past week?
22	BP02	[SF36V2R22_SF36V2F1]	Item # 8, Range 1-5	During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?
23	VT01	[SF36V2R23_SF36V2F1]	Item # 9a, Range 1-5	Did you feel full of life?
24	MH01	[SF36V2R24_SF36V2F1]	Item # 9b, Range 1-5	Have you been very nervous?
25	MH02	[SF36V2R25_SF36V2F1]	Item # 9c, Range 1-5	Have you felt so down in the dumps that nothing could cheer you up?
26	MH03	[SF36V2R26_SF36V2F1]	Item # 9d, Range 1-5	Have you felt calm and peaceful?
27	VT02	[SF36V2R27_SF36V2F1]	Item # 9e, Range 1-5	Did you have a lot of energy?
28	MH04	[SF36V2R28_SF36V2F1]	Item # 9f, Range 1-5	Have you felt downhearted and depressed?

eCRF Row #	Column label for export to comma- or tab-separated values file [*.csv, *.tab]	Annotated SF-36 eCRF Variable [Format: SF36V2RXX_SF36V2F1]	Item Number, Score range	eCRF question / Specification
29	VT03	[SF36V2R29_SF36V2F1]	Item # 9g, Range 1-5	Did you feel worn out?
30	MH05	[SF36V2R30_SF36V2F1]	Item # 9h, Range 1-5	Have you been happy?
31	VT04	[SF36V2R31_SF36V2F1]	Item # 9i, Range 1-5	Did you feel tired?
32	SF02	[SF36V2R32_SF36V2F1]	Item # 10, Range 1-5	During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?
33	GH02	[SF36V2R33_SF36V2F1]	Item # 11a, Range 1-5	I seem to get sick a little easier than other people
34	GH03	[SF36V2R34_SF36V2F1]	Item # 11b, Range 1-5	I am as healthy as anybody I know
35	GH04	[SF36V2R35_SF36V2F1]	Item # 11c, Range 1-5	I expect my health to get worse
36	GH05	[SF36V2R36_SF36V2F1]	Item # 11d, Range 1-5	My health is excellent
	SUBJID			Subjects ID
	VISID			Visid ID
	Gender			Sex coded as: f/m
	DateOfBirth			Date of birth formatted as: mm/dd/yyyy (when scoring software is run in US), or dd/mm/yyyy (when scoring software is run in non-US)
	RecordID			Running number for the exported records

Abbreviations: eCRF = electronic case report form; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey.

The SF-36 Scoring Software will derive raw domain scores and t-scores that can be exported into a comma- or tab-separated values file (*.csv, *.tab) with the following columns added:

Column label added to comma- or tab-separated values file from export [*.csv, *.tab]	**Scoring Software specification**
PF	Physical Functioning domain score
RP	Role Limitations Due To Physical Health domain score
BP	Bodily Pain domain score
GH	General Health Perceptions domain score
VT	Vitality domain score
SF	Social Functioning domain score
RE	Role Limitations Due To Emotional Problems domain score
MH	Mental Health domain score
PCS	Physical Component score
MCS	Mental health Component score

For scoring the trial data, the Missing Data Estimator option will not be selected. If an item is missing, there will be no imputation conducted by the Scoring Software. Only complete questionnaire data will be scored.

The Scoring Software also allows for calculating domain and component scores from weights derived from an oblique factor solution for comparative purposes. This option will not be used.

The SF-36 scoring using the Scoring Software will be conducted by a 2 person team overseeing each other in a single scoring session. In case of relevant observations during the scoring, those will be documented in pertinent meeting minutes and filed as part of the study documentation.

Appendix 7. Anti-infective Medications and Anatomical Therapeutic Chemical (ATC) Code List and Programming Guide

This appendix provides the code list of Anatomical Therapeutic chemical (ATC) of anti-infective medications and the programming guidance.

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18Jan2016)
A01AB	4	ANTIINFECTIVES AND ANTISEPTICS FOR LOCAL ORAL TREA
A02BD	4	COMBINATIONS FOR ERADICATION OF HELICOBACTER PYLOR
A07A	3	INTESTINAL ANTIINFECTIVES
A07AA	4	ANTIBIOTICS
A07AB	4	SULFONAMIDES
A07AC	4	IMIDAZOLE DERIVATIVES
A07AX	4	OTHER INTESTINAL ANTIINFECTIVES
B05CA	4	ANTIINFECTIVES
C05AB	4	ANTIBIOTICS
D01	2	ANTIFUNGALS FOR DERMATOLOGICAL USE
D01A	3	ANTIFUNGALS FOR TOPICAL USE
D01AA	4	ANTIBIOTICS
D01AC	4	IMIDAZOLE AND TRIAZOLE DERIVATIVES
D01AE	4	OTHER ANTIFUNGALS FOR TOPICAL USE
D01B	3	ANTIFUNGALS FOR SYSTEMIC USE
D01BA	4	ANTIFUNGALS FOR SYSTEMIC USE
D06	2	ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGIC
D06A	3	ANTIBIOTICS FOR TOPICAL USE
D06AA	4	TETRACYCLINE AND DERIVATIVES
D06AX	4	OTHER ANTIBIOTICS FOR TOPICAL USE
D06B	3	CHEMOTHERAPEUTICS FOR TOPICAL USE
D06BA	4	SULFONAMIDES
D06BB	4	ANTIVIRALS
D06BX	4	OTHER CHEMOTHERAPEUTICS
D06C	3	ANTIBIOTICS AND CHEMOTHERAPEUTICS, COMBINATIONS
D07C	3	CORTICOSTEROIDS, COMBINATIONS WITH ANTIBIOTICS
D07CA	4	CORTICOSTEROIDS, WEAK, COMBINATIONS WITH ANTIBIOTICS
D07CB	4	CORTICOSTEROIDS, MODERATELY POTENT, COMBINATIONS WITH ANTIBIOTICS
D07CC	4	CORTICOSTEROIDS, POTENT, COMBINATIONS WITH ANTIBIOTICS
D07CD	4	CORTICOSTEROIDS, VERY POTENT, COMBINATIONS WITH ANTIBIOTICS
D09AA	4	MEDICATED DRESSINGS WITH ANTIINFECTIVES
D10AF	4	ANTIINFECTIVES FOR TREATMENT OF ACNE
G01AA	4	ANTIBIOTICS
G01AC	4	QUINOLINE DERIVATIVES
G01AE	4	SULFONAMIDES
G01AF	4	IMIDAZOLE DERIVATIVES

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18Jan2016)
G01AG	4	TRIAZOLE DERIVATIVES
G01AX	4	OTHER ANTIINFECTIVES AND ANTISEPTICS
G01BA	4	ANTIBIOTICS AND CORTICOSTEROIDS
G01BC	4	QUINOLINE DERIVATIVES AND CORTICOSTEROIDS
G01BE	4	SULFONAMIDES AND CORTICOSTEROIDS
G01BF	4	IMIDAZOLE DERIVATIVES AND CORTICOSTEROIDS
G04AB	4	QUINOLONE DERIVATIVES (EXCL. J01M)
G04AC	4	NITROFURAN DERIVATIVES
G04AG	4	OTHER URINARY ANTISEPTICS AND ANTIINFECT
G04AH	4	SULFONAMIDES IN COMBINATION WITH OTHER DRUGS
G04AK	4	URINARY ANTISEPT&ANTIINF, COMB EXCL SULFONAMIDES
J01	2	ANTIBACTERIALS FOR SYSTEMIC USE
J01A	3	TETRACYCLINES
J01AA	4	TETRACYCLINES
J01B	3	AMPHENICOLS
J01BA	4	AMPHENICOLS
J01C	3	BETA-LACTAM ANTIBACTERIALS, PENICILLINS
J01CA	4	PENICILLINS WITH EXTENDED SPECTRUM
J01CE	4	BETA-LACTAMASE SENSITIVE PENICILLINS
J01CF	4	BETA-LACTAMASE RESISTANT PENICILLINS
J01CG	4	BETA-LACTAMASE INHIBITORS
J01CR	4	COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE
J01D	3	OTHER BETA-LACTAM ANTIBACTERIALS
J01DA	4	CEPHALOSPORINS AND RELATED SUBSTANCES
J01DB	4	FIRST-GENERATION CEPHALOSPORINS
J01DC	4	SECOND-GENERATION CEPHALOSPORINS
J01DD	4	THIRD-GENERATION CEPHALOSPORINS
J01DE	4	FOURTH-GENERATION CEPHALOSPORINS
J01DF	4	MONOBACTAMS
J01DH	4	CARBAPENEMS
J01DI	4	OTHER CEPHALOSPORINS
J01E	3	SULFONAMIDES AND TRIMETHOPRIM
J01EA	4	TRIMETHOPRIM AND DERIVATIVES
J01EB	4	SHORT-ACTING SULFONAMIDES
J01EC	4	INTERMEDIATE-ACTING SULFONAMIDES
J01ED	4	LONG-ACTING SULFONAMIDES
J01EE	4	COMBINATIONS OF SULFONAMIDES AND TRIMETHOPRIM, INC
J01F	3	MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS
J01FA	4	MACROLIDES
J01FF	4	LINCOSAMIDES
J01FG	4	STREPTOGRAMINS
J01G	3	AMINOGLYCOSIDE ANTIBACTERIALS
J01GA	4	STREPTOMYCINS
J01GB	4	OTHER AMINOGLYCOSIDES
J01M	3	QUINOLONE ANTIBACTERIALS
J01MA	4	FLUOROQUINOLONES

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18Jan2016)
J01MB	4	OTHER QUINOLONES
J01R	3	COMBINATIONS OF ANTIBACTERIALS
J01RA	4	COMBINATIONS OF ANTIBACTERIALS
J01WA	4	HERBAL ANTIBACTERIALS FOR SYSTEMIC USE
J01WB	4	HERBAL URINARY ANTISEPTICS AND ANTIINFECTIVES
J01X	3	OTHER ANTIBACTERIALS
J01XA	4	GLYCOPEPTIDE ANTIBACTERIALS
J01XB	4	POLYMYXINS
J01XC	4	STEROID ANTIBACTERIALS
J01XD	4	IMIDAZOLE DERIVATIVES
J01XE	4	NITROFURAN DERIVATIVES
J01XX	4	OTHER ANTIBACTERIALS
J02	2	ANTIMYCOTICS FOR SYSTEMIC USE
J02A	3	ANTIMYCOTICS FOR SYSTEMIC USE
J02AA	4	ANTIBIOTICS
J02AB	4	IMIDAZOLE DERIVATIVES
J02AC	4	TRIAZOLE DERIVATIVES
J02AX	4	OTHER ANTIMYCOTICS FOR SYSTEMIC USE
J04AA	4	AMINOSALICYLIC ACID AND DERIVATIVES
J04AB	4	ANTIBIOTICS
J04AC	4	HYDRAZIDES
J04AK	4	OTHER DRUGS FOR TREATMENT OF TUBERCULOSIS
J04AM	4	COMBINATIONS OF DRUGS FOR TREATMENT OF TUBERCULOSI
J04B	3	DRUGS FOR TREATMENT OF LEPRA
J04BA	4	DRUGS FOR TREATMENT OF LEPRA
J05	2	ANTIVIRALS FOR SYSTEMIC USE
J05A	3	DIRECT ACTING ANTIVIRALS
J05AA	4	THIOSEMICARBAZONES
J05AB	4	NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRI
J05AC	4	CYCLIC AMINES
J05AD	4	PHOSPHONIC ACID DERIVATIVES
J05AE	4	PROTEASE INHIBITORS
J05AF	4	NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE IN
J05AG	4	NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS
J05AH	4	NEURAMINIDASE INHIBITORS
J05AR	4	ANTIVIRALS FOR TREATMENT OF HIV INFECTIONS, COMBIN
J05AX	4	OTHER ANTIVIRALS
P01A	3	AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOAL DISE
P01AA	4	HYDROXYQUINOLINE DERIVATIVES
P01AB	4	NITROIMIDAZOLE DERIVATIVES
P01AC	4	DICHLOROACETAMIDE DERIVATIVES
P01AR	4	ARSENIC COMPOUNDS
P01AX	4	OTHER AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOA
P01BA	4	AMINOQUINOLINES
P01BC	4	METHANOLQUINOLINES
P01BD	4	DIAMINOPYRIMIDINES

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18Jan2016)
P01BE	4	ARTEMISININ AND DERIVATIVES, PLAIN
P01BF	4	ARTEMISININ AND DERIVATIVES, COMBINATIONS
P01BX	4	OTHER ANTIMALARIALS
P01C	3	AGENTS AGAINST LEISHMANIASIS AND TRYPANOSOMIASIS
P01CA	4	NITROIMIDAZOLE DERIVATIVES
P01CB	4	ANTIMONY COMPOUNDS
P01CC	4	NITROFURAN DERIVATIVES
P01CD	4	ARSENIC COMPOUNDS
P01CX	4	OTHER AGENTS AGAINST LEISHMANIASIS AND TRYPANOSOMI
P02	2	ANTHELMINTICS
P02B	3	ANTITREMATODALS
P02BA	4	QUINOLINE DERIVATIVES AND RELATED SUBSTANCES
P02BB	4	ORGANOPHOSPHOROUS COMPOUNDS
P02BX	4	OTHER ANTITREMATODAL AGENTS
P02C	3	ANTINEMATODAL AGENTS
P02CA	4	BENZIMIDAZOLE DERIVATIVES
P02CB	4	PIPERAZINE AND DERIVATIVES
P02CC	4	TETRAHYDROPYRIMIDINE DERIVATIVES
P02CE	4	IMIDAZOTHIAZOLE DERIVATIVES
P02CF	4	AVERMECTINES
P02CX	4	OTHER ANTINEMATODALS
P02D	3	ANTICESTODALS
P02DA	4	SALICYLIC ACID DERIVATIVES
P02DW	4	HERBAL ANTICESTODALS
P02DX	4	OTHER ANTICESTODALS
P02WA	4	HERBAL ANTHELMINTICS
P03A	3	ECTOPARASITICIDES, INCL. SCABICIDES
P03AA	4	SULFUR CONTAINING PRODUCTS
P03AB	4	CHLORINE CONTAINING PRODUCTS
P03AC	4	PYRETHRINES, INCL. SYNTHETIC COMPOUNDS
P03AX	4	OTHER ECTOPARASITICIDES, INCL. SCABICIDES
P03BA	4	PYRETHRINES
R02AB	4	ANTIBIOTICS
S01A	3	ANTIINFECTIVES
S01AA	4	ANTIBIOTICS
S01AB	4	SULFONAMIDES
S01AD	4	ANTIVIRALS
S01AE	4	FLUOROQUINOLONES
S01AX	4	OTHER ANTIINFECTIVES
S01C	3	ANTIINFLAMMATORY AGENTS AND ANTIINFECTIVES IN COMB
S01CA	4	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION
S01CB	4	CORTICOSTEROIDS/ANTIINFECTIVES/MYDRIATICS IN COMBI
S01CC	4	ANTIINFLAMMATORY AGENTS, NON-STEROIDS AND ANTIINFECTIVES
S02A	3	ANTIINFECTIVES
S02AA	4	ANTIINFECTIVES
S02C	3	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18Jan2016)
S02CA	4	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION
S03A	3	ANTIINFECTIVES
S03AA	4	ANTIINFECTIVES
S03C	3	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION
S03CA	4	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION

Abbreviation: ATC = World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC) Anatomical Therapeutic Chemical (ATC) classification system.

For the above list, the higher level of ATC includes all the lower levels under that level, for example, level 2 term includes all the level 3 terms under it, level 3 term includes all the level 4 terms under it. Therefore, for programming simplicity, the table below provides all the required ATC codes by highest level.

ATC Level 2	ATC Level 3	ATC Level 4
		A01AB
		A02BD
	A07A	
		B05CA
		C05AB
D01		
D06		
	D07C	
		D09AA
		D10AF
		G01AA
		G01AC
		G01AE
		G01AF
		G01AG
		G01AX
		G01BA
		G01BC
		G01BE
		G01BF
		G04AB
		G04AC
		G04AG
		G04AH
		G04AK
J01		
J02		
		J04AA
		J04AB
		J04AC
		J04AK

ATC Level 2	ATC Level 3	ATC Level 4
		J04AM
	J04B	
J05		
	P01A	
		P01BA
		P01BC
		P01BD
		P01BE
		P01BF
		P01BX
	P01C	
P02		
	P03A	
		P03BA
		R02AB
	S01A	
	S01C	
	S02A	
	S02C	
	S03A	
	S03C	

Abbreviation: ATC = World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC) Anatomical Therapeutic Chemical (ATC) classification system.

Appendix 8. MedDRA Preferred Terms for Each Category Associated with Criterion 2 for Anaphylactic Allergic Reactions/Hypersensitivity Events

Preferred Terms (MedDRA Version 21.0)	
Category A: Involvement of the Skin/Mucosal Tissue	
Administration site hypersensitivity	Localised oedema
Administration site rash	Mouth swelling
Administration site urticarial	Nasal obstruction
Allergic oedema	Nodular rash
Allergic otitis externa	Ocular hyperaemia
Angioedema	Oedema
Circumoral oedema	Oedema mouth
Drug eruption	Oedema mucosal
Erythema	Orbital oedema
Eye allergy	Palatal oedema
Eye oedema	Palatal swelling
Eye pruritus	Perineal rash
Eye swelling	Periorbital oedema
Eyelid oedema	Pruritus
Face oedema	Pruritus allergic
Flushing	Pruritus generalised
Generalised erythema	Rash
Gingival oedema	Rash erythematous
Gingival swelling	Rash generalised
Idiopathic urticaria	Rash pruritic
Injection site dermatitis	Skin oedema
Injection site hypersensitivity	Skin swelling
Injection site rash	Swelling
Injection site urticaria	Swelling face
Injection site vasculitis	Swollen tongue
Lip oedema	Tongue oedema
Lip swelling	Urticaria
	Urticaria papular
Category B: Respiratory Compromise	
Acute respiratory failure	Laryngotracheal oedema
Allergic cough	Oropharyngeal spasm
Allergic pharyngitis	Oropharyngeal swelling
Asthma	Pharyngeal oedema
Asthmatic crisis	Respiratory arrest
Bronchial hyperreactivity	Respiratory distress
Bronchial oedema	Respiratory failure
Bronchospasm	Respiratory tract oedema
Cardio-respiratory distress	Reversible airways obstruction
Chest discomfort	Sensation of foreign body
Choking	Sneezing

Preferred Terms (MedDRA Version 21.0)	
Choking sensation	Spasmodic dysphonia
Cough	Status athmaticus
Cyanosis	Stridor
Dyspnoea	Tachypnea
Epiglottic oedema	Throat tightness
Hyperventilation	Tracheal obstruction
Hypoxia	Tracheal oedema
Laryngeal dyspnoea	Upper airway obstruction
Laryngeal obstruction	Wheezing
Laryngeal oedema	
Laryngitis allergic	
Laryngospasm	
Category C: Reduced Blood Pressure or Associated Symptoms	
Blood pressure decreased	Hypoperfusion
Blood pressure diastolic decreased	Hypotension
Blood pressure systolic decreased	Hypovolaemic shock
Cardiac arrest	Incontinence
Cardiopulmonary failure	Mean arterial pressure decreased
Cardio-respiratory arrest	Peripheral circulatory failure
Cardiovascular insufficiency	Presyncope
Circulatory collapse	Shock
Diastolic hypotension	Shock symptom
Distributive shock	Syncope
Dizziness	Urinary Incontinence
Category D: Persistent Gastrointestinal Symptoms	
Abdominal discomfort	Gastrointestinal pain
Abdominal pain	Intestinal angioedema
Abdominal pain lower	Nausea
Abdominal pain upper	Retching
Diarrhoea	Visceral pain
Epigastric discomfort	Vomiting
Gastrointestinal oedema	

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.

Appendix 9. Allergic Reactions/Hypersensitivity MedDRA Preferred Terms

Allergic reactions/hypersensitivities will be defined using the following MedDRA Preferred Terms as defined in MedDRA:

- Broad and narrow terms in the Anaphylactic reaction SMQ (20000021)
- Broad and narrow terms in the Angioedema SMQ (20000024)
- Broad and narrow terms in the Severe cutaneous adverse reactions SMQ (20000020)
- Broad and narrow terms in the Hypersensitivity SMQ (20000214) excluding the preferred terms as noted below.

The following Preferred Terms (based on review of MedDRA Version 21.0) from the Hypersensitivity SMQ will be excluded from the analysis:

Administration site dermatitis	Injection site rash
Administration site eczema	Injection site recall reaction
Administration site rash	Injection site urticaria
Administration site recall reaction	Injection site vasculitis
Allergic otitis externa	Instillation site hypersensitivity
Allergic otitis media	Instillation site rash
Allergic sinusitis	Instillation site urticaria
Allergic transfusion reaction	Iodine allergy
Allergy alert test positive	Mast cell degranulation present
Allergy test positive	Medical device site dermatitis
Allergy to surgical sutures	Medical device site eczema
Allergy to vaccine	Medical device site hypersensitivity
Anaphylactic transfusion reaction	Medical device site rash
Antiallergic therapy	Medical device site recall reaction
Application site dermatitis	Medical device site urticaria
Application site eczema	Nodular rash
Application site hypersensitivity	Pathergy reaction
Application site rash	Radioallergosorbent test positive
Application site recall reaction	Reaction to azo-dyes
Application site urticaria	Reaction to colouring
Application site vasculitis	Rhinitis allergic
Arthritis allergic	Shock
Aspirin-exacerbated respiratory disease	Shock symptom
Asthma-chronic obstructive pulmonary disease overlap syndrome	Skin test positive
	Solvent sensitivity
Blepharitis allergic	Stoma site hypersensitivity
Blood immunoglobulin E abnormal	Stoma site rash
Blood immunoglobulin E increased	Urticaria contact
Bromoderma	Urticarial vasculitis
Catheter site dermatitis	Vaccination site dermatitis
Catheter site eczema	Vaccination site exfoliation

Catheter site hypersensitivity	Vaccination site eczema
Catheter site rash	Vaccination site hypersensitivity
Catheter site urticaria	Vaccination site rash
Catheter site vasculitis	Vaccination site recall reaction
Chronic eosinophilic rhinosinusitis	Vaccination site urticaria
Chronic hyperplastic eosinophilic sinusitis	Vaccination site vasculitis
Circulatory collapse	Vaccination site vesicles
Conjunctivitis allergic	Vessel puncture site rash
Contact stomatitis	Vessel puncture site vesicles
Complement factor decreased	Vulvovaginal rash
Complement factor increased	Acute respiratory failure
Complement factor C1 decreased	Allergy to chemicals
Complement factor C1 increased	Allergy to fermented products
Complement factor C2 decreased	Anti-insulin antibody increased
Complement factor C2 increased	Anti-insulin antibody positive
Complement factor C3 decreased	Anti-insulin receptor antibody increased
Complement factor C3 increased	Anti-insulin receptor antibody positive
Complement factor C4 decreased	Blood immunoglobulin A abnormal
Complement factor C4 increased	Blood immunoglobulin A increased
Complement fixation abnormal	Blood immunoglobulin D increased
Complement fixation test positive	Blood immunoglobulin G abnormal
Contrast media allergy	Blood immunoglobulin G increased
Contrast media reaction	Blood immunoglobulin M abnormal
Dennie-Morgan fold	Blood immunoglobulin M increased
Dermatitis acneiform	Immune complex level increased
Dermatitis contact	Immunoglobulins abnormal
Dermatitis herpetiformis	Immunoglobulins increased
Dermatitis infected	Immunology test abnormal
Device allergy	Haemolytic transfusion reaction
Dialysis membrane reaction	Infantile asthma
Distributive shock	Fixed eruption
Drug cross-reactivity	Rhinitis perennial
Drug provocation test	Seasonal allergy
Eczema infantile	
Eczema vaccinatum	
First use syndrome	
Fixed drug eruption	
Giant conjuctivitis	
Hand dermatitis	
Heparin-induced thrombocytopenia	
Hereditary angioedema	
Implant site dermatitis	
Implant site hypersensitivity	
Implant site rash	
Implant site urticaria	
Immune-mediated adverse reaction	
Incision site dermatitis	
Incision site rash	
Infusion site dermatitis	

Infusion site eczema Infusion site hypersensitivity Infusion site rash Infusion site recall reaction Infusion site urticaria Infusion site vasculitis Injection site dermatitis Injection site eczema Injection site hypersensitivity	

Appendix 10. Algorithm for Calculating Composite Psoriatic Disease Activity Index (CPDAI)

Composite Psoriatic Disease Activity Index (CPDAI) is a validated instrument to assess composite psoriatic disease activity and response to therapy (Mumtaz et al. 2011). This instrument assesses individual domains:

- peripheral arthritis as assessed by the number of tender and swollen joints and the Health Assessment Questionnaire–Disability Index(HAQ-DI)
- skin as assessed by the Psoriasis Area and Severity Index (PASI) and the Dermatology Life Quality Index (DLQI)
- enthesitis as assessed by the number of sites with enthesitis and the HAQ-DI
- dactylitis as assessed by the number of digits affected and the HAQ-DI
- Spinal disease as assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Quality of Life (ASQoL)

The table below shows the instruments for each domain and the range in their total score:

Domain	Instrument	Total Score Range
Peripheral arthritis	TJC/SJC	0-68/0-66
	HAQ-DI	0-3
Skin disease	PASI	0-72
	DLQI	0-30
Enthesitis	LEI	0-6
	HAQ-DI	0-3
Dactylitis	Digit Score	0-20
	HAQ-DI	0-3
Spinal disease	BASDAI	0-10
	ASQoL	0-18

Abbreviations: ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; DLQI = Dermatology Life Quality Index; HAQ-DI = Health Assessment Questionnaire–Disability Index; LEI = Leeds Enthesitis Index; PASI = Psoriasis Area and Severity Index; SJC = swollen joint count; TJC = tender joint count.

Each domain is scored from 0 to 3. Individual domain scores are summed to give an overall composite CPDAI score. The composite scores range from 0 to 15 for the assessment, with a higher score indicating higher disease activity. See the table below for details:

Domain	**Not involved (0)**	**Mild (1)**	**Moderate (2)**	**Severe (3)**
Peripheral arthritis	TJC and SJC = 0	TJC or SJC ≤ 4; and HAQ-DI < 0.5	TJC or SJC ≤ 4 and HAQ-DI ≥ 0.5; or TJC or SJC > 4 and HAQ-DI < 0.5	TJC or SJC > 4 and HAQ-DI ≥0.5
Skin disease	Absence of plaque psoriasis as defined PASI = 0	PASI ≤ 10 and DLQI ≤ 10	PASI ≤ 10 and DLQI > 10; or PASI > 10 and DLQI ≤ 10	PASI > 10 and DLQI > 10
Enthesitis	Absence of enthesitis as defined (LEI = 0	LEI ≤ 3 sites; HAQ-DI < 0.5	LEI ≤ 3 sites and HAQ-DI ≥ 0.5; or LEI > 3 sites and HAQ-DI < 0.5	LEI > 3 and HAQ-DI ≥0.5
Dactylitis	Absence of dactylitis as defined by the Digit score = 0	Digit score ≤ 3 digits; HAQ-DI < 0.5	Digit score ≤ 3 and HAQ-DI ≥ 0.5; or Digit score > 3 and HAQ-DI < 0.5	Digit score > 3 and HAQ-DI ≥0.5
Spinal disease	BASDAI = 0 and ASQoL = 0	BASDAI < 4; ASQoL < 6	BASDAI < 4 and ASQoL ≥ 6; or BASDAI ≥ 4 and ASQoL < 6	BASDAI > 4 and ASQol ≥ 6

Abbreviations: BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; DLQI = Dermatology Life Quality Index; HAQ-DI = ; LEI = Leeds Enthesitis Index; PASI = Psoriasis Area and Severity Index; SJC = swollen joint count; TCJ = tender joint count;

The modified CPDAI will sum up each domain with the exception of spinal disease. The composite scores range from 0 to 12 for the assessment, with a higher score indicating higher disease activity.

Appendix 11. Lilly-defined MedDRA V21.0 Preferred Terms for Inflammatory Bowel Disease (IBD)

Condition	Preferred Term (MedDRA version 21.0)	Lilly Defined Classification
Inflammatory bowel disease	Inflammatory bowel disease	Narrow
Crohn's disease	Crohn's disease	Narrow
Ulcerative colitis	Acute haemorrhagic ulcerative colitis	Narrow
	Colitis ulcerative	Narrow
	Proctitis ulcerative	Narrow
Non-specific terms	Abscess intestinal	Broad
	Anal abscess	Broad
	Anal fistula	Broad
	Anal fistula excision	Broad
	Anal fistula infection	Broad
	Anovulvar fistula	Broad
	Aorto-duodenal fistula	Broad
	Colitis	Broad
	Colon fistula repair	Broad
	Colonic fistula	Broad
	Diverticular fistula	Broad
	Duodenal fistula	Broad
	Enterocolitis haemorrhagic	Broad
	Enterocolonic fistula	Broad
	Enterocutaneous fistula	Broad
	Enterovesical fistula	Broad
	Gastrointestinal fistula	Broad
	Gastrointestinal fistula repair	Broad
	Fistula of small intestine	Broad
	Intestinal fistula	Broad
	Intestinal fistula infection	Broad
	Intestinal fistula repair	Broad
	Jejunal fistula	Broad

Condition	Preferred Term (MedDRA version 21.0)	Lilly Defined Classification
	Large intestinal ulcer perforation	Broad
	Rectal fistula repair	Broad
	Faecal calprotectin abnormal	Broad
	Faecal calprotectin increased	Broad
	Proctitis haemorrhagic	Broad
	Pseudopolyposis	Broad
	Rectoprostatic fistula	Broad
	Rectourethral fistula	Broad

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.

Appendix 12. Lilly-defined MedDRA V21.0 Preferred Terms for Opportunistic Infections (OI)

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
Pneumocystis jirovecii (II)	Pneumocystis jirovecii pneumonia Pneumocystis jirovecii infection	Narrow
	Pneumocystis test positive Blood beta-D-glucan Blood beta-D-glucan abnormal Blood beta-D-glucan increased Gomori methenamine silver stain Carbon monoxide diffusing capacity decreased Carbon monoxide diffusing capacity	Broad
Human polyomavirus infection including BK virus disease including PVAN (V), and Progressive Multifocal Leukoencephalopathy (IV)	Human polyomavirus infection Polyomavirus-associated nephropathy BK virus infection Progressive multifocal leukoencephalopathy JC virus infection JC virus granule cell neuronopathy	Narrow
	Anti-JC virus antibody index Polyomavirus test Polyomavirus test positive Giant papillary conjuctivitis JC virus test JC virus test positive JC polyomavirus test	Broad
Cytomegalovirus disease (V)	Cytomegalovirus chorioretinitis Cytomegalovirus colitis Cytomegalovirus duodenitis Cytomegalovirus enteritis Cytomegalovirus enterocolitis Cytomegalovirus gastritis Cytomegalovirus gastroenteritis Cytomegalovirus gastrointestinal infection Cytomegalovirus gastrointestinal ulcer Cytomegalovirus hepatitis Cytomegalovirus infection Cytomegalovirus mononucleosis Cytomegalovirus mucocutaneous ulcer Cytomegalovirus myelomeningoradiculitis Bartonellosis (disseminated disease only) (V) Cytomegalovirus nephritis Cytomegalovirus oesophagitis Cytomegalovirus pancreatitis Cytomegalovirus pericarditis Cytomegalovirus syndrome Cytomegalovirus urinary tract infection Cytomegalovirus viraemia	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Disseminated cytomegaloviral infection Encephalitis cytomegalovirus Pneumonia cytomegaloviral	
	Cytomegalovirus test Cytomegalovirus test positive	Broad
Post-transplant lymphoproliferative disorder (EBV) (V)	Epstein-Barr virus associated lymphoma Epstein-Barr virus associated lymphoproliferative disorder Epstein-Barr virus positive mucocutaneous ulcer Post transplant lymphoproliferative disorder	Narrow
	Epstein-Barr viraemia Epstein-Barr virus infection Lymphoproliferative disorder Lymphoproliferative disorder in remission Oral hairy leukoplakia	Broad
Bartonellosis (disseminated disease only) (V)	Bacillary angiomatosis Peliosis hepatis Splenic peliosis Systemic bartonellosis Trench fever	Narrow
	Bartonella test Bartonella test positive Bartonellosis Cat scratch disease	Broad
Blastomycosis (IV)	Blastomycosis Epididymitis blastomyces Osteomyelitis blastomyces Pneumonia blastomyces	Narrow
	N/A	Broad
Toxoplasmosis (myocarditis, pneumonitis, or characteristic retinochoroiditis only) (IV)	Cerebral toxoplasmosis Eye infection toxoplasmal Hepatitis toxoplasmal Meningitis toxoplasmal Myocarditis toxoplasmal Pneumonia toxoplasmal	Narrow
	Toxoplasma serology Toxoplasma serology positive Toxoplasmosis	Broad
Coccidioidomycosis. (II)	Coccidioides encephalitis Coccidioidomycosis Cutaneous coccidioidomycosis Meningitis coccidioides	Narrow
	N/A	Broad
Histoplasmosis (II)	Acute pulmonary histoplasmosis Chronic pulmonary histoplasmosis Endocarditis histoplasma Histoplasmosis Histoplasmosis cutaneous Histoplasmosis disseminated Meningitis histoplasma Pericarditis histoplasma Retinitis histoplasma	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Presumed ocular histoplasmosis syndrome	Broad
Aspergillosis (invasive disease only) (II)	Aspergillosis oral Cerebral aspergillosis Meningitis aspergillus Oro-pharyngeal aspergillosis	Narrow
	Aspergillus infection Aspergillus test Aspergillus test positive Bronchopulmonary aspergillosis Sinusitis aspergillus	Broad
Candidiasis (invasive disease or oral not limited to the tongue) (II)	Candida endophthalmitis Candida osteomyelitis Candida pneumonia Candida retinitis Candida sepsis Cerebral candidiasis Endocarditis candida Fungal oesophagitis Gastrointestinal candidiasis Hepatic candidiasis Hepatosplenic candidiasis Meningitis candida Oesophageal candidiasis Oropharyngeal candidiasis Peritoneal candidiasis Splenic candidiasis Systemic candida	Narrow
	Bladder candidiasis Candida infection Candida test Candida test positive Mucocutaneous candidiasis Oral candidiasis Oral fungal infection Respiratory moniliasis	Broad
Cryptococcosis (II)	Cryptococcal cutaneous infection Cryptococcal fungaemia Cryptococcosis Disseminated cryptococcosis Gastroenteritis cryptococcal Meningitis cryptococcal Neurocryptococcosis Osseous cryptococcosis Pneumonia cryptococcal	Narrow
	Cryptococcus test Cryptococcus test positive	Broad
Other invasive fungi: Mucormycosis (=zygomycosis) [Rhizopus, Mucor, and Lichtheimia], *Scedosporum/Pseudallescheria boydii*, *Fusarium* (II)	Allescheriosis Fusarium infection Mucormycosis Scedosporium infection Phaeohyphomycosis Phaeohyphomycosis brain abscess	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Pseudallescheria infection Pseudallescheria sepsis	
	See "Non-specific terms" below	Broad
Legionellosis (II)	Legionella infection Pneumonia legionella Pontiac fever	Narrow
	Legionella test Legionella test positive	Broad
Listeria monocytogenes (invasive disease only) (II)	Listeria encephalitis Listeria sepsis Meningitis listeria	Narrow
	Listeriosis Listeria test Listeria test positive Listeraemia	Broad
Tuberculosis (I)	Adrenal gland tuberculosis Bone tuberculosis Choroid tubercles Conjunctivitis tuberculous Cutaneous tuberculosis Disseminated Bacillus Calmette-Guerin infection Disseminated tuberculosis Ear tuberculosis Epididymitis tuberculous Extrapulmonary tuberculosis Immune reconstitution inflammatory syndrome associated tuberculosis Intestinal tuberculosis Joint tuberculosis Lymph node tuberculosis Male genital tract tuberculosis Meningitis tuberculous Oesophageal tuberculosis Oral tuberculosis Pericarditis tuberculous Peritoneal tuberculosis Prostatitis tuberculous *Pulmonary tuberculoma* Pulmonary tuberculosis Renal tuberculosis Salpingitis tuberculous Silico tuberculosis Spleen tuberculosis Thyroid tuberculosis Tuberculid Tuberculoma of central nervous system Tuberculosis Tuberculosis bladder Tuberculosis gastrointestinal Tuberculosis liver Tuberculosis of central nervous system Tuberculosis of eye	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Tuberculosis of genitourinary system Tuberculosis of intrathoracic lymph nodes Tuberculosis of peripheral lymph nodes Tuberculosis ureter Tuberculous abscess central nervous system Tuberculous endometritis Tuberculous laryngitis Tuberculous pleurisy Tuberculous tenosynovitis	
	Interferon gamma release assay Interferon gamma release assay positive Mycobacterium tuberculosis complex test Mycobacterium tuberculosis complex test positive Tuberculin test Tuberculin test false negative Tuberculin test positive	Broad
Nocardiosis (II)	Cutaneous nocardiosis Nocardia sepsis Nocardiosis Pulmonary nocardiosis	Narrow
	Nocardia test positive	Broad
Nontuberculous mycobacterium disease (II)	Atypical mycobacterial infection Atypical mycobacterial lower respiratory tract infection Atypical mycobacterial lymphadenitis Atypical mycobacterial pneumonia Atypical mycobacterium pericarditis Borderline leprosy Bovine tuberculosis Indeterminate leprosy Leprosy Lepromatous leprosy Mycobacterial infection Mycobacterial peritonitis Mycobacterium abscessus infection Mycobacterium avium complex immune restoration disease Mycobacterium avium complex infection Mycobacterium chelonae infection Mycobacterium fortuitum infection Mycobacterium kansasii infection Mycobacterium marinum infection Mycobacterium ulcerans infection Superinfection mycobacterial Tuberculoid leprosy Type 1 lepra reaction Type 2 lepra reaction	Narrow
	Atypical mycobacterium test positive Mycobacterial disease carrier Mycobacterium leprae test positive Mycobacterium test Mycobacterium test positive	Broad
Salmonellosis (invasive disease	Aortitis salmonella	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
only) (II)	Arthritis salmonella Meningitis salmonella Osteomyelitis salmonella Paratyphoid fever Pneumonia salmonella Salmonella sepsis Salmonella bacteraemia Typhoid fever	
	Salmonella test positive Salmonellosis	Broad
HBV reactivation (IV)	Hepatitis B reactivation	Narrow
	Asymptomatic viral hepatitis Chronic hepatitis B HBV-DNA polymerase increased Hepatitis B Hepatitis B DNA assay Hepatitis B DNA assay positive Hepatitis B DNA increased Hepatitis B antigen Hepatitis B antigen positive Hepatitis B core antigen Hepatitis B core antigen positive Hepatitis B e antigen Hepatitis B e antigen positive Hepatitis B surface antigen Hepatitis B surface antigen positive Hepatitis B virus test Hepatitis B virus test positive Hepatitis infectious Hepatitis post transfusion Hepatitis viral Withdrawal hepatitis	Broad
Herpes simplex (invasive disease only) (IV)	Colitis herpes Gastritis herpes Herpes oesophagitis Herpes sepsis Herpes simplex colitis Herpes simplex encephalitis Herpes simplex gastritis Herpes simplex hepatitis Herpes simplex meningitis Herpes simplex meningoencephalitis Herpes simplex meningomyelitis Herpes simplex necrotising retinopathy Herpes simplex oesophagitis Herpes simplex pneumonia Herpes simplex sepsis Herpes simplex visceral Herpes simplex viraemia Meningitis herpes Meningoencephalitis herpetic Meningomyelitis herpes	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Pneumonia herpes viral	
	Eczema herpeticum Herpes ophthalmic Herpes simplex Herpes simplex DNA test positive Herpes virus infection Herpes virus test abnormal Herpes simplex virus test positive Ophthalmic herpes simplex	Broad
Herpes zoster (any form) (II)	Disseminated varicella zoster vaccine virus infection Encephalitis post varicella Genital herpes zoster Herpes zoster Herpes zoster cutaneous disseminated Herpes zoster disseminated Herpes zoster infection neurological Herpes zoster meningitis Herpes zoster meningoencephalitis Herpes zoster meningomyelitis Herpes zoster meningoradiculitis Herpes zoster necrotising retinopathy Herpes zoster oticus Herpes zoster pharyngitis Necrotising herpetic retinopathy Ophthalmic herpes zoster	Narrow
	Varicella zoster virus infection Varicella virus test Varicella virus test positive	Broad
Stronglyoides (hyperinfection syndrome and disseminated forms only) (IV)	Strongyloidiasis	Narrow
	N/A	Broad
Paracoccidioides infections (V)	Paracoccidioides infection Pulmonary paracoccidioidomycosis	Narrow
	N/A	Broad
Penicillium marneffei (V)	Penicillium infection	Narrow
	Penicillium test positive	Broad
Sporothrix schenckii (V)	Cutaneous sporotrichosis Pulmonary sporotrichosis Sporotrichosis	Narrow
	N/A	Broad
Cryptosporidium species (chronic disease only) (IV)	Biliary tract infection cryptosporidial	Narrow
	Cryptosporidiosis infection Gastroenteritis cryptosporidial	Broad
Microsporidiosis (IV)	Microsporidia infection	Narrow
	N/A	Broad
Leishmaniasis (Visceral only) (IV)	Visceral leishmaniasis	Narrow
	Leishmaniasis	Broad
Trypanosoma cruzi infection (Chagas' Disease) (disseminated disease only) (V)	Chagas' cardiomyopathy Meningitis trypanosomal	Narrow
	American trypanosomiasis Trypanosomiasis	Broad

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Trypanosoma serology positive	
Campylobacteriosis (invasive disease only) (V)	Campylobacter sepsis	Narrow
	Campylobacter infection Campylobacter test positive	Broad
Shigellosis (invasive disease only) (V)	Shigella sepsis	Narrow
	Shigella infection Shigella test positive	Broad
Vibriosis (invasive disease due to *V. vulfnificus*) (V)	N/A	Narrow
	Vibrio test positive Vibrio vulnificus infection	Broad
HCV progression (V)	N/A	Narrow
	Chronic hepatitis C Hepatitis C Hepatitis C RNA Hepatitis C virus test Hepatitis C RNA increased Hepatitis C RNA positive Hepatitis C RNA fluctuation Hepatitis C virus test positive	Broad
Non-specific terms	N/A	Narrow
	Abscess fungal Alternaria infection Arthritis fungal Biliary tract infection fungal Central nervous system fungal infection Cerebral fungal infection Encephalitis fungal Erythema induratum Eye infection fungal Fungaemia Fungal abscess central nervous system Fungal endocarditis Fungal labyrinthitis Fungal peritonitis Fungal pharyngitis Fungal retinitis Fungal sepsis Hepatic infection fungal Meningitis fungal Mycotic endophthalmitis Myocarditis mycotic Oropharyngitis fungal Osteomyelitis fungal Otitis media fungal Pancreatitis fungal Parasitic lung infection Parasitic pneumonia Pericarditis fungal Phaehyphomycosis Pneumonia fungal Pulmonary mycosis Pulmonary trichosporonosis	Broad

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Sinusitis fungal Splenic infection fungal Systemic mycosis	

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.

Leo Document ID = e23de465-31a7-4763-9651-e1da7e0a70e4

Approver: PPD
Approval Date & Time: 25-Oct-2018 18:34:52 GMT
Signature meaning: Approved