Statistical Analysis Plan I1F-MC-RHCF (v2)

A 52-Week Multicenter, Randomized, Open-Label, Parallel-Group Study Evaluating the Efficacy and Safety of Ixekizumab versus Adalimumab in Patients with Psoriatic Arthritis Who Are Biologic Disease-Modifying Anti-Rheumatic Drug Naïve

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1. Statistical Analysis Plan: I1F-MC-RHCF: A 52-Week Multicenter, Randomized, Open-Label, Parallel-Group Study Evaluating the Efficacy and Safety of Ixekizumab versus Adalimumab in Patients with Psoriatic Arthritis Who Are Biologic Disease-Modifying Anti-Rheumatic Drug Naive

Ixekizumab (LY2439821) Psoriatic Arthritis

Study I1F-MC-RHCF is a Phase 3b/4, multicenter, randomized, open-label, parallel-group study with blinded outcomes assessments evaluating the efficacy and safety of ixekizumab versus adalimumab in patients with psoriatic arthritis who are biologic disease-modifying anti-rheumatic drug naive during a 52-week treatment period.

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Protocol I1F-MC-RHCF
Phase 3b/4

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly on Aug 21, 2017.
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 03-Dec-2018 GMT

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to first patient visit (FPV).

Statistical Analysis Plan (SAP) Version 2 was approved prior to interim 1 database lock (24 week).

Revisions since Version 1:

Section	Action
Section 6.1 General Considerations	Updated p-values to 3 decimal places. Corrected typo.
Section 6.1.1 General Considerations for Open-Label Treatment Period (Period 2)	Revised baseline definition to last available value "on or prior to" the first injection of the study drug.
Section 6.7 Methodology for Noninferiority Test	Updated references.
Section 6.9.1 Demographics and Baseline Characteristics	Removed Composite Psoriatic Disease Activity Index (CPDAI).
Section 6.9.3 Historical Illness and Pre-existing Conditions	Clarified definitions of historical illness and pre-existing conditions.
Section 6.11 Concomitant Therapy	Removed unnecessary analyses for concomitant therapy.
Section 6.12 Efficacy Analyses Table 6.3	Updated imputation mehods for MDA, LEI and LDI-B.
Section 6.12 Efficacy Analyses Table 6.4	Added Kaplan-Meier plots for time to first simultaneous ACR50 and PASI 100 response. Updated time points of Kaplan Meier plots.
Section 6.12.1.3 Other Secondary Outcomes	Removed by-patient listings for secondary efficacy measure.
Section 6.13 Health Outcomes/Quality-of-Life Analyses	Removed by-patient listings for health outcome measure.
Section 6.13 Health Outcomes/Quality-of-Life Analyses Table 6.6	Update analysis population for analyses regrading to Itch NRS = 0.
Section 6.15.1 Extent of Exposure	Removed by-patient listing for extent of exposure.
Section 6.15.3.1 Special Safety Topics Including Adverse Events of Special Interest Table 6.7	Text updates for definition/derivation of AESIs to be consistent with PSAP V8 Removed duplicated or unnecessary analyses Changed Covance to performing lab reference range Wording updates per most recent PSAP for Infections, Allergic Reactions/Hypersensitivities, Injection Site Reactions, CV, IBD, ILD.
Section 6.15.4 Clinical Laboratory Evaluation	Updated population for laboratory analyses. Removed by-patient listings.
Section 6.15.5 Vital Signs and Other Physical Findings	Updated population for vital signs analyses. Removed by-patient listing.

Section	Action
Section 6.15.6 Columbia-Suicide Severity Rating Scale	Updated C-SSRS analyses.
Section 6.16.1 Efficacy Subgroup Analyses	Added additional exploratory subgroup analyses.
Section 6.17 Protocol Violations	Added potential additional analyses.
Section 6.17 Protocol Violations Table 6.9	Updated important protocol violations per most recent Trial Issue Management Plan.
Section 6.19 Planned Exploratory Analyses	Removed exploratory subgroup analyses.
Appendix 1	Updated NNT CI calculation method.
Appendix 2	Removed Appendix 2.
Appendix 4	Clarified the algorithm for calculating Joint Counts.
Appendix 7	Updated norms to 2009.
Appendices 9-12	Updated per PSAP V8.

4. Study Objectives

Table RHCF.4.1 shows the objectives and endpoints of the study.

Table RHCF.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary To assess whether ixekizumab is superior to adalimumab at Week 24 in the treatment of patients with active PsA as measured by American College of Rheumatology 50 (ACR50) and Psoriasis Area and Severity Index 100 (PASI 100)	• Proportion of patients simultaneously achieving ACR50 and PASI 100 at Week 24
Major Secondary Objectives: To assess whether ixekizumab is noninferior to adalimumab at Week 24 in the treatment of patients with active PsA as measured by ACR50 To assess whether ixekizumab is superior to adalimumab at Week 24 in the treatment of patients with active PsA as measured by PASI 100	• Proportion of patients achieving ACR50 in each treatment group at Week 24 • Proportion of patients achieving PASI 100 in each treatment group at Week 24
Other Secondary Objectives: To assess the effect of treatment with ixekizumab compared with adalimumab as measured by efficacy and quality of life outcomes	<u>PsA Endpoints</u> Time course of response to treatment over 52 weeks as measured by: • Proportion of patients achieving ACR20, ACR50, and ACR70 responses • Change from baseline in individual components of the American College of Rheumatology (ACR) Core Set - tender joint count, swollen joint count, patient's pain assessment, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, C-reactive protein (CRP), and Health Assessment Questionnaire–Disability Index (HAQ-DI) score • Proportion of patients simultaneously achieving ACR50 and PASI 100 response • Change from baseline in the Disease Activity Score (28 diarthrodial joint count) based on C-reactive protein (DAS28-CRP) • Proportion of patients achieving Minimal Disease Activity (MDA) • Proportion of patients achieving Psoriatic Arthritis Response Criteria (PsARC) • Change from baseline in Modified Composite Psoriatic Disease Activity Index (CPDAI) score • Proportion of patients achieving low disease activity or remission according to the Modified Composite Psoriatic Disease Activity Index definition

Objectives	Endpoints
	• Proportion of patients with HAQ-DI improvement ≥0.35 • Change from baseline in the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index score in patients with enthesitis at baseline (ie, baseline SPARCC Enthesitis Index score >0) • Change from baseline in the Leeds Enthesitis Index (LEI) score in patients with enthesitis at baseline (ie, baseline LEI score >0) • Proportion of patients with resolution in enthesitis in the subgroup of patients with enthesitis at baseline as measured by the SPARCC Enthesitis Index (ie, baseline SPARCC Enthesitis Index score >0) • Proportion of patients with resolution in enthesitis in the subgroup of patients with enthesitis at baseline as measured by the LEI (ie, baseline LEI score >0) • Change from baseline in the Leeds Dactylitis Index-Basic (LDI-B) score in patients with dactylitis at baseline (ie, baseline LDI-B score >0) • Proportion of patients with resolution in dactylitis in the subgroup of patients with dactylitis at baseline as measured by the LDI-B (ie, baseline LDI-B score >0) <u>Psoriasis/Nail Endpoints</u> Time course of response to treatment over 52 weeks as measured by: • Change from baseline in body surface area (BSA) • Proportion of patients who achieve the following PASI scores: PASI 75, PASI 90, or PASI 100 (defined as 75%, 90%, and 100% improvement from baseline in PASI criteria, respectively) • Proportion of patients achieving an absolute PASI score ≤1 or ≤2 or ≤3 • Change from baseline in the Nail Psoriasis Severity Index (NAPSI) Fingernails score in the subgroup of patients with fingernail involvement at baseline (ie, baseline NAPSI Fingernails score >0) <u>QoL Endpoints</u> Time course of response to treatment over 52 weeks as measured by: • Change from baseline in the Itch Numeric Rating Scale (NRS) score • Proportion of patients with Itch NRS score equal to 0 • Change from baseline in Fatigue Severity NRS score • Change from baseline in Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) • Physical Component Summary score • Mental Component Summary score • Change from baseline in measures of health utility (European Quality of Life–5 Dimensions 5 Level health outcomes instrument [EQ-5D-5L]) • Change from baseline in Dermatology Life Quality Index (DLQI) total score • Change from baseline in Treatment Satisfaction Questionnaire <u>Safety</u> • Change from baseline in Columbia–Suicide Severity Rating Scale (C-SSRS)

Abbreviations: ACR50 = American College of Rheumatology 50; BSA = body surface area; CPDAI = Composite Psoriatic Disease Activity Index; CRP = C-reactive protein; C-SSRS = Columbia–Suicide Severity Rating Scale; DAS28-CRP = Disease Activity Score (28 diarthrodial joint count) based on C-reactive protein; DLQI = Dermatology Life Quality Index; EQ-5D-5L = European Quality of Life–5 Dimensions 5 Level health outcomes instrument; HAQ-DI = Health Assessment Questionnaire–Disability Index; LDI-B = Leeds Dactylitis Index-Basic; LEI = Leeds Enthesitis Index; MDA = Minimal Disease Activity; NAPSI = Nail Psoriasis Severity Index; NRS = Numeric Rating Scale; PASI 100 = Psoriasis Area and Severity Index 100; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; SF-36 = 36-Item Short Form Health Survey; SPARCC = Spondyloarthritis Research Consortium of Canada.

5. Study Design

5.1. Summary of Study Design

Study I1F-MC-RHCF (RHCF) is a Phase 3b/4, multicenter, randomized, open-label, parallel-group study with blinded outcomes assessments evaluating the efficacy and safety of ixekizumab versus adalimumab in patients with active psoriatic arthritis (PsA) who are naive of biologic disease-modifying anti-rheumatic drug (bDMARD) during a 52-week treatment period.

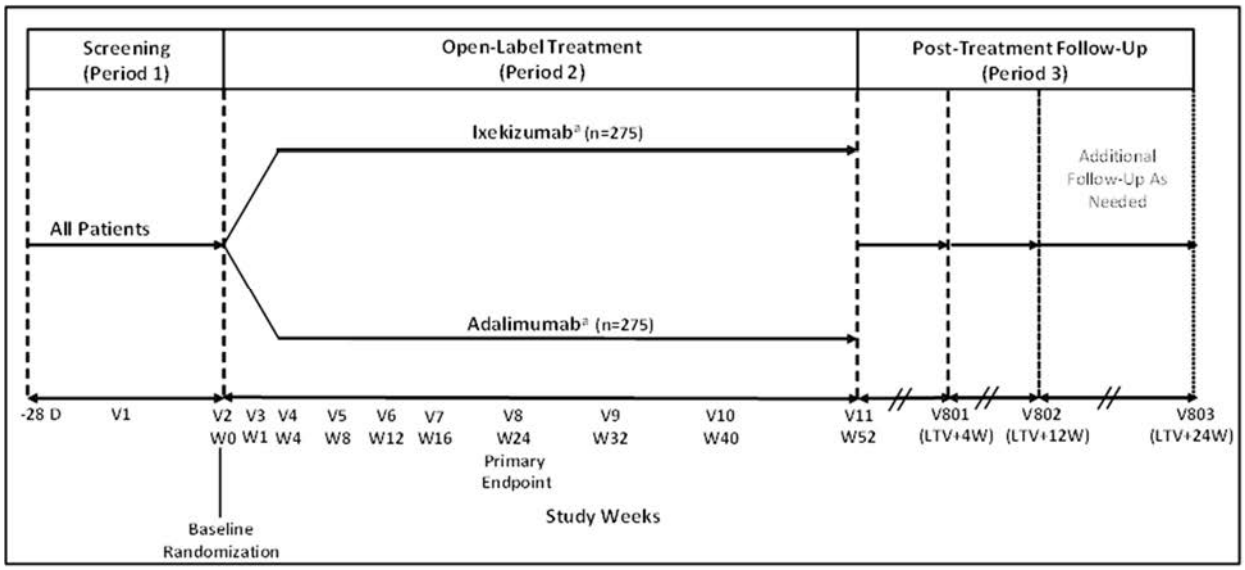
The study will consist of 3 periods:

- Period 1: Screening Period (Visit 1) up to 28 days before randomization (Visit 2)
- Period 2: Open-Label Treatment Period (Visit 2 through Visit 11) from Week 0 to Week 52
- Period 3: Post-Treatment Follow-Up Period occurring from the last treatment visit during Period 2 or Early Termination Visit (ETV) up to a minimum of 12 weeks after that visit

All patients randomized to ixekizumab will receive a starting dose of 160 mg at randomization (Visit 2 [Week 0]). Patients with moderate-to-severe plaque psoriasis will receive ixekizumab 80 mg every 2 weeks (Q2W) from Week 2 to Week 12 and every 4 weeks (Q4W) thereafter. Patients not meeting criteria for moderate-to-severe plaque psoriasis at randomization will receive ixekizumab 80 mg Q4W starting at Week 4.

Patients randomized to adalimumab with moderate-to-severe plaque psoriasis will receive a starting dose of 80 mg at randomization (Visit 2 [Week 0]) followed by 40 mg Q2W starting at Week 1. Patients not meeting criteria for moderate-to-severe plaque psoriasis will receive a starting dose of 40 mg at randomization (Visit 2) followed by 40 mg Q2W starting at Week 2 (see Section 7.1 of study protocol for details regarding treatments administered).

Figure RHCF.5.1 illustrates the study design.



Abbreviations: D = days; LTV = last treatment visit during Period 2 or Early Termination Visit; n = number of subjects; V = visit; W = week.
[a] See Section 7.1 of RHCF Study Protocol for dosing details.

Figure RHCF.5.1. Illustration of study design for Clinical Protocol I1F-MC-RHCF.

5.2. Determination of Sample Size

Approximately 550 patients who meet all criteria for enrollment at Visits 1 and 2 will be randomized in a 1:1 ratio at Week 0 (Visit 2) in Period 2 to ixekizumab or adalimumab (275 patients per treatment group).

Sample size was calculated assuming the proportion of patients simultaneously achieving 50% improvement in American College of Rheumatology criteria (ACR50) and 100% improvement from baseline in Psoriasis Area and Severity Index criteria (PASI 100) as 13.6% and 31.3% in the adalimumab and ixekizumab treatment groups, respectively, as observed in the conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD)-experienced population from Study I1F-MC-RHAP (RHAP). According to the nQuery software, a total sample size of 550 (ie, 275 per treatment group) using a 2-sided Fisher's exact test at 0.05 level of significance would yield approximately 99% power for testing ixekizumab versus adalimumab.

This sample size would yield 78% power for testing the noninferiority of ixekizumab to adalimumab at a 1-sided 0.025 level of significance based on a noninferiority margin of -12% and using ACR50 response rates of 43.8% and 44.1% as observed for the ixekizumab and adalimumab treatment groups, respectively, in the csDMARD-experienced population from Study RHAP. For testing superiority of ixekizumab to adalimumab based on PASI 100 response rates of 46.9% and 23.7% as observed for ixekizumab and adalimumab in the csDMARD-experienced population from Study RHAP, this sample size would yield approximately 99% power using a 2-sided Fisher's exact test at 0.05 level of significance.

5.3. Method of Assignment to Treatment

Patients who meet all Visit 1 and Visit 2 eligibility criteria for enrollment will be randomized at Visit 2 (Week 0) in a 1:1 ratio to open-label treatment with ixekizumab or adalimumab at Week 0 (Visit 2). Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign investigational product to each patient. Site personnel will confirm that they have located the correct investigational product by entering a confirmation number found on the investigational product into the IWRS. The randomization will be stratified by concomitant csDMARD use at baseline (Yes, No) and moderate-to-severe plaque psoriasis involvement (Yes, No).

6. A Priori Statistical Methods

6.1. General Considerations

This plan describes a priori statistical analyses that will be performed. 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. Lilly will be responsible for producing the tables, figures, and listings, unless otherwise specified. All tables, figures, and listings will be checked independently for consistency and integrity by Lilly. This analysis plan also includes exploratory analyses that are intended to be produced separately from the clinical study report (CSR) outputs, as noted below.

Additional efficacy, health outcomes, and safety analyses for Health Technology Assessment (HTA) purposes will be described in a separate document, and results will be reported separately from the CSR.

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD) and/or standard error of the mean (SEM), if applicable, median, minimum, 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 and SEM will be reported to 2 more decimal places than the raw data. 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 with non-missing data at the relevant time point, frequency counts, and the percentages based on 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 post-baseline means improvement from baseline. Similarly, percent improvement from baseline is calculated as the negative percent change from baseline if a lower value at post-baseline means improvement from baseline. If the baseline value is missing for a particular variable, then the change from baseline and the percent improvement from baseline will not be calculated.

Data collected at early termination visits will be mapped to the next planned visit number for that patient. For by-visit 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; such analyses include, but are not limited to, shift analyses and modified baseline observation carried forward (mBOCF) endpoint analyses.

All confidence intervals (CIs) and statistical tests will be 2-sided with an α level of 0.05 unless specified otherwise. 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 that 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 1 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).

Table RHCF.6.1 gives the treatment groups to be displayed for each treatment period and analysis population. Analysis populations are defined in Section 6.1.3. Note: "IXE" and "ADA" will be included in treatment group names for ixekizumab and adalimumab, respectively, in the statistical reports where applicable.

Table RHCF.6.1. Treatment Groups for Each Treatment Period and Analysis Population

Treatment Period	Analysis Population	Treatment Groups	Abbreviation	Comparison
Open-Label Treatment Period (Period 2)	Intent-to-Treat Population; Safety Population	Ixekizumab 80 mg Q4W (or Q2W/Q4W) Adalimumab 40 mg Q2W	IXE ADA	IXE vs ADA
Post-Treatment Follow-up Period (Period 3)[a]	Follow-up Population	Ixekizumab 80 mg Q4W (or Q2W/Q4W) Adalimumab 40 mg Q2W	IXE ADA	Not applicable

Abbreviations = ADA = adalimumab; IXE = ixekizumab; Q2W = every 2 weeks; Q4W = every 4 weeks.

[a] Treatment group refers to the dosage regimen that the patient received immediately prior to entering the Post-Treatment Follow-up Period.

6.1.1. General Considerations for the Open-Label Treatment Period (Period 2)

Baseline will be defined as the last available value on or prior to the first injection of the study drug for both efficacy, health outcomes, and safety analyses. In most cases, this will be the measurement recorded at Week 0 (Visit 2).

Categorical and continuous data will be summarized as described in Section 6.1.

Comparisons of ixekizumab versus adalimumab will be performed for all outcome variables in Period 2, as deemed appropriate, using methods described in Section 6.2.

Safety will be assessed by summarizing and analyzing adverse events (AEs), laboratory analytes including neutrophil counts, vital signs, and concomitant medications. The duration of exposure will also be summarized.

6.1.2. General Considerations for the Post-Treatment Follow-Up Period (Period 3)

Unless otherwise specified, the baseline for the safety analyses in Period 3 is defined as the last nonmissing assessment on or prior to entering Period 3, that is on or prior to Week 52 (Visit 11) or ETV.

The categorical safety measures will be summarized with incidence rates. The mean change of the continuous safety measures will be summarized by visits.

6.1.3. Analysis Populations

The follow analysis populations will be used:

Intent to Treat Population (ITT): The ITT Population consists of all randomized patients. Even if the patient does not take the assigned treatment, does not receive the correct treatment, does not receive any medication, or otherwise does not follow the protocol, the patients will be analyzed according to the treatment to which they were assigned at Week 0. Unless otherwise specified, all efficacy and health outcomes analyses for the Open-Label Treatment Period (Period 2) will be conducted on the ITT population.

Safety Population: The Safety Population is defined as all randomized patients who received at least 1 dose of study treatment. Patients will be analyzed according to the treatment to which they were assigned at Week 0. Unless otherwise specified, all safety analyses for the Open-Label Treatment Period will be conducted on the Safety Population.

Post-Treatment Follow-Up Population: The Post-Treatment Follow-Up Population consists of all randomized patients who received at least 1 dose of study treatment during Period 2 and have entered the Post-Treatment Follow-Up Period. Safety analyses for Period 3 (Post-Treatment Follow-Up Period) will be conducted on this population. Patients will be analyzed according to the last treatment they received before entering Period 3 (see treatment groups defined in Table RHCF.6.1).

Table RHCF.6.2 gives the description of each of the population sets in the study as well as their intended analysis purposes.

Table RHCF.6.2. Efficacy, Health Outcomes, and Safety Measures Summarized and/or Analyzed for Each Analysis Population

Population Name	Measurement Summarization of Population
All Patients Entered	Tables for patient allocation and analysis populations, patient disposition
Intent-to-Treat Population	Tables, listings and/or figures for the following: patient disposition, important protocol deviations, patient characteristics, historical diagnoses, pre-existing conditions, previous therapies, concomitant medications, primary and secondary efficacy measures, health outcomes, exploratory measures for the Open-Label Treatment Period (Period 2)
Safety Population	Tables, listings and/or figures for safety assessments, treatment compliance, duration of exposure for the Open-Label Treatment Period (Period 2)
Follow-Up Population	Tables, listings and/or figures for the following: patient disposition, concomitant medications, and safety assessments for the Post-Treatment Follow-Up Period (Period 3)

6.2. Analysis Methods

6.2.1. Categorical

Unless specified otherwise, the primary analysis method for the binary categorical efficacy and health outcome variables will be a logistic regression model with treatment, concomitant csDMARD use at baseline, and moderate-to-severe plaque psoriasis involvement as factors. The odds ratios and the corresponding 95% CIs will be reported. Fisher's exact test will be used as the secondary analysis method.

For ordinal categorical variables, a logistic regression model using cumulative logits will be used.

Treatment differences (Absolute Risk Reductions [ARR]), Relative Risks (RR), Numbers Needed to Treat (NNT) estimates, and their corresponding 95% CIs (using normal approximation) will also be reported. See Appendix 1 for more details.

The statistical methodology for assessing noninferiority of ixekizumab to adalimumab for ACR50 is described in Section 6.7.

6.2.2. Continuous Endpoints

Unless specified otherwise, the primary analysis method for all continuous efficacy and health outcome variables will be a MMRM analysis. The model will include treatment group, concomitant csDMARD use at baseline, moderate-to-severe plaque psoriasis involvement, visit-as-fixed factors, baseline value as covariate and baseline-by-visit and treatment-by-visit interaction terms. The MMRM analyses will be conducted using a restricted maximum likelihood (REML)-based repeated measures approach. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack

of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by the compound symmetry structure will be used. The first structure to yield convergence will be used for inference. The Newton-Raphson with ridging optimization technique will be used to aid with convergence. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom and adjust standard errors. Type III tests for the least squares (LS)Means will be used for the statistical comparison; the 95% CI will also be reported.

An analysis of covariance (ANCOVA) model and mBOCF imputation method as detailed in Section 6.4.2 will be used as the secondary analysis method for treatment comparisons on continuous efficacy and health outcome variables. The ANCOVA model will include treatment, concomitant csDMARD use at baseline, moderate-to-severe plaque psoriasis involvement, and baseline value in the model. Type III sums of squares for the LSMeans will be used for the statistical comparison; the 95% CI will be reported.

6.3. Adjustments for Covariates

The randomization at the beginning of Open-Label Treatment Period (Period 2) is stratified by concomitant csDMARD use at baseline (Yes, No) and moderate-to-severe plaque psoriasis involvement (Yes, No). Unless otherwise specified, all efficacy and health outcome analyses during Period 2 will include the concomitant csDMARD use at baseline and moderate-to-severe plaque psoriasis involvement in the model. In general, when an MMRM is to be used for analyses, baseline value and baseline-by-visit interactions will be included as covariates; when an ANCOVA is to be used for analyses, baseline value will be included as a covariate.

The OBSMARGINS/OM option will be used in the LSMEANS statement in SAS to account for imbalance in the stratification variables.

6.4. Handling of Dropouts or Missing Data

6.4.1. Non-Responder Imputation (NRI) for Clinical Response

Analysis of categorical efficacy and health outcome variables will be based on treatment success/failure. This approach yields results numerically identical to non-responder imputation (NRI), but it is interpreted differently. Patients will be considered treatment failures (or non-responders) if they do not meet the clinical response criteria or have missing clinical response data at a particular time point of analysis.

6.4.2. Modified Baseline Observation Carried Forward (mBOCF)

Missing data for continuous efficacy and health outcomes variables will be imputed using a mBOCF method. For patients discontinuing investigational product due to an AE, including death , the baseline observation will be carried forward to the corresponding primary endpoint for evaluation. For patients discontinuing investigational product for any other reason, the last non-missing post-baseline observation before discontinuation will be carried forward to the corresponding time point of evaluation. Randomized patients without at least 1 post-baseline

observation will not be included for evaluation with the exception of patients discontinuing study treatment due to an AE (including death).

6.4.3. Missing Data Imputation for Adverse Event and Concomitant Medication Dates

If a medication date (prior therapy or concomitant medication) or event (historical event, pre-existing condition, or AE) date is completely or partially missing, the following imputation rules should be utilized in the analysis unless otherwise stated:

- For the start date:
  - If year, month, and day are missing, then use the earlier of the patient's first visit date or 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.
  - The imputed date should not be before the minimum of the patient's first visit or consent date.
- 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 should not be beyond the patient's last visit date.
- For the end time:
  - Impute as 23:59.

If there is any doubt for the start and end date/times for events, the event will be flagged as treatment-emergent or follow-up emergent according to 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. For medications, the medication will be flagged as concomitant.

6.5. Multicenter Studies

This study will be conducted by multiple investigators at multiple sites internationally. The primary endpoint at Week 24 will be summarized by sites using descriptive statistics only.

6.6. Multiple Comparisons/Multiplicity

A multiple testing procedure for the primary and major secondary endpoints will be implemented to control the family-wise type I error rate at a 2-sided α level of 0.05. The primary and major secondary endpoints will be sequentially tested in the following order to compare ixekizumab versus adalimumab, using the primary analysis method.

1. Test 1 for Primary Endpoint – Proportion of patients simultaneously achieving ACR50 and PASI 100 at Week 24: A superiority test of the primary endpoint will be performed at an overall 2-sided $\alpha = 0.05$ using the methods described in Section 6.2.1.
2. Test 2 for Major Secondary Endpoint #1 – Proportion of patients achieving ACR50 at Week 24: If the test for the primary endpoint is significant, then a noninferiority test for the major secondary endpoint #1 will be performed using the methods described in Section 6.7.
3. Test 3 for Major Secondary Endpoint #2 – Proportion of patients achieving PASI 100 at Week 24: If the test for major secondary endpoint #1 is significant, then a superiority test for major secondary endpoint #2 will be performed using the methods described in Section 6.2.1.

If a test in this sequence is not significant, all subsequent tests will be considered nonsignificant.

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

6.7. Methodology for Noninferiority Test

For assessing noninferiority of ixekizumab to adalimumab, missing data will be imputed using the NRI method. Noninferiority analysis will be performed on the ITT population using a prespecified fixed margin approach. There is no universally accepted value for what is considered to be a clinically unimportant difference between 2 treatments for a particular efficacy measure. We will consider the points from EMEA Committee for Medicinal Products for Human Use (CHMP) (CHMP 2005) and FDA guidance (2016) which state that an appropriate noninferiority margin should be based on both clinical and statistical grounds.

The null hypothesis will be rejected if the lower bound of the 2-sided 95% CI for the difference in proportions of responders on ixekizumab minus adalimumab is greater than the prespecified margin, meaning ixekizumab will be deemed noninferior to adalimumab. If the lower bound of the CI exceeds 0 (the corresponding p-value from the logistic regression model will also be produced), and ixekizumab will be deemed superior to adalimumab based on the p-value. The 95% CIs for the difference in proportions will be calculated using the simple asymptotic method, without continuity correction (that is, normal approximation to the binomial distribution).

Based on EMEA CHMP (CHMP [WWW]), FDA guidance (FDA [WWW]), and Weinblatt et al. (2013), a noninferiority margin of -12.0% for ACR50 between ixekizumab and adalimumab (ie, response rate of ixekizumab – response rate of adalimumab) is considered appropriate. This noninferiority margin represents an approximately 50% preservation of the adalimumab treatment effect (based on the difference between adalimumab and placebo) observed in a historical Phase 3 study for adalimumab 40 mg twice weekly compared with placebo (Mease et al. 2005) and Study RHAP (Mease et al. 2016).

6.8. Patient Disposition

Patient flow will be summarized from entered to randomized to completion, and analysis populations will be listed and summarized by treatment group.

The following patient disposition summaries will be provided for Open-Label Treatment Period (Period 2):

- The number and percentage of patients in the ITT population completing the Open-Label Treatment Period or prematurely discontinuing from the Open-Label Treatment Period, by treatment group and primary reason for discontinuation.
  Fisher's exact test will be used to test for treatment differences between treatment groups in the percentage of patients discontinuing from the Open-Label Treatment Period, and in the percentage of patients discontinuing for each reason.
- The number and percentage of patients in the ITT population completing the Open-Label Treatment Period or prematurely discontinuing from the Open-Label Treatment Period, by treatment group, visit, and primary reason for discontinuation.
- The time to discontinuation from the Open-Label Treatment Period due to any reason (in weeks).
  Time to discontinuation due to any reason (in weeks) and due to an AE (in weeks) will be summarized graphically for the ITT population by treatment group using Kaplan-Meier techniques. The time to discontinuation (in weeks) from the Open-Label Treatment Period will be calculated as:

  (Date of discontinuation from Open-Label Treatment Period – Date of randomization + 1)/7

  Patients completing the Open-Label Treatment Period will be censored at the date of completion (ie, the date of Visit 11 [Week 52]). Patients without a date of Open-Label Treatment Period completion or discontinuation will be censored at the last nonmissing date out of the following dates: date of last dose and date of last study visit up to and including Visit 11 (Week 52) (scheduled or unscheduled). Descriptive statistics including 25th percentile, median, 75th percentile, and corresponding 95% CIs, as well as probability of discontinuation by Week 52 will be summarized by treatment group. The log-rank test will be used to test for differences in the time to discontinuation between the treatment groups.

The following patient disposition summary will be provided for the Post-Treatment Follow-Up Period (Period 3):

- The number and percentage of patients in the Post-Treatment Follow-Up Population completing each follow-up visit or prematurely discontinuing from the Post-Treatment Follow-Up Period, by treatment group, visit, and primary reason for discontinuation.

Patient allocation by region, country, and center/site will be summarized with number of patients who entered the study, number of ITT patients for each treatment group, number of patients discontinued from study treatment, and number of patients discontinued from study.

6.9. Patient Characteristics

6.9.1. Demographics and Baseline Characteristics

Demographic variables and baseline characteristics (including baseline clinical measures) will be summarized for the ITT population. For weight, body mass index (BMI), tobacco use and alcohol consumption, baseline is defined in the same manner as the safety baseline (as defined in Section 6.15).

The continuous variables will be summarized using descriptive statistics, and the categorical variables will be summarized using frequency counts and percentages. The comparisons among treatment groups will be conducted using an ANOVA model with treatment as a factor for continuous data and using a 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 demographic variables to be presented include the following:

- Age (in years)
- Age group: <65 years or ≥65 years
- Sex
- Age group within sex
- Ethnicity: Hispanic or Latino, Non-Hispanic and Non-Latino
- Race
- Country
- Geographic Regions:
    - Europe, Rest of the World
- Height (cm)
- Weight (kg)
- Weight category: <100 kg or ≥100 kg
- Weight category: <80 kg, ≥80 kg and <100 kg, or ≥100 kg
- Body mass index (BMI, kg/m^2)
- Body mass index 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); or extremely obese (≥40 kg/m^2)
- Tobacco use: never, current, or former
- Alcohol use: never, current, or former
- Other baseline characteristics to be presented include the following:
    - 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 these 2 date components are missing.

  - Time since PsA onset (years): <5 or ≥5
  - Time since PsA diagnosis (years): ≤2 or >2

- Time since 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 these 2 date components are missing.

- Tender Joint Counts (TJC) based on 68 joints
- Swollen Joint Counts (SJC) based on 66 joints
- Physician's global assessment of disease activity (mm)
- Patient's Global Assessment (PatGA) of Disease Activity (mm)
- Patient's assessment of joint pain (mm)
- Health Assessment Questionnaire–Disability Index (HAQ-DI) total score
- C-reactive protein (CRP) (mg/L)
- CRP categories; >6 mg/L or ≤6 mg/L
- Rheumatoid Factor Positive (RF+); yes or no
- Disease Activity Score-C-Reactive Protein (DAS28-CRP)
- DAS28-CRP; <2.6, ≥2.6 and <3.2, ≥3.2 and <5.1, ≥5.1
- Enthesitis (LEI >0); yes or no
- Enthesitis (SPARCC >0); yes or no
- Leeds Enthesitis Index (LEI) for patients with baseline enthesitis (LEI >0)
- Spondyloarthritis Research Consortium of Canada (SPARCC) for patients with baseline enthesitis (SPARCC >0)
- Dactylitis (LDI-B score >0); yes or no
- Leeds Dactylitis Index – Basic (LDI-B) for patients with baseline dactylitis (LDI-B score >0)

- Modified CPDAI without the spinal disease assessment (Ankylosing Spondylitis Quality of Life Questionnaire [AsQoL] and BASDAI)
- Psoriasis Area and Severity Index (PASI) total score
- PASI total score: <12, ≥12
- Static Physician Global Assessment of Psoriasis (sPGA) score
- sPGA score: <3, ≥3
- Moderate to Severe Psoriasis (defined as PASI ≥12, sPGA ≥3, and BSA ≥10); yes or no
- Percentage of Body Surface Area (BSA)
- BSA: <10%, ≥10%
- Itch Numeric Rating Scale (Itch NRS) score
- Itch NRS score; 0, >0 and ≤3, >3
- Nail Psoriasis (NAPSI > 0): yes or no
- Nail Psoriasis Severity Index (NAPSI) score for patients with baseline fingernail involvement (NAPSI >0)
- Fatigue Severity Numeric Rating Scale (Fatigue NRS) score
- SF-36 Physical Component Summary score
- SF-36 Mental Component Summary score
- Dermatology Life Quality Index (DLQI) total score
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Self-Harm Supplement Form
- Self-Harm Follow-Up Form
- Concomitant Glucocorticoids use at baseline; yes or no
- Concomitant Glucocorticoids mean daily dose at baseline
- Concomitant Methotrexate use at baseline; yes or no
- Concomitant Methotrexate mean weekly dose at baseline
- Concomitant Conventional disease-modifying antirheumatic drugs (csDMARD) use at baseline; yes or no
- Number of prior csDMARD therapies: 1, 2, 3, or >3
- European Quality of Life – 5 dimensions 5 level (EQ-5D 5L)
- Latent TB; yes or no.

By-patient listings of demographic and baseline characteristics, respectively, for the ITT population will be provided.

6.9.2. 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* electronic case report form [eCRF] page) will be summarized by treatment group, overall, and preferred name. 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 ITT population.

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

Listing of previous therapy for PsA will be provided for the ITT population.

6.9.3. Historical Illness and Pre-existing Conditions

Historical illnesses and pre-existing conditions will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Historical illness/condition is defined as the condition/event recorded on the *Pre-Existing Conditions and Medical History* eCRF page or on the *Prespecified Medical History* eCRF page with an end date prior to the date of informed consent. Pre-existing conditions for the Open-Label Treatment Period (Period 2) are defined as those conditions recorded on the *Pre-Existing Conditions and Medical History* eCRF page or on the *Prespecified Medical History* eCRF pages with a start date prior to the date of informed consent, and no end date (ie, 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 for the open-label treatment period (Period 2). If a pre-existing condition worsens in severity on or after the date of informed consent, it will be considered an AE from the date of worsening onwards. Patients will only be counted once, regardless of how many conditions are included under the same System Organ Class (SOC) and Preferred Term (PT).

The number and percentage of patients with historical illnesses, pre-existing conditions and adverse events occurring prior to the first dose will be provided by treatment group, overall, and by SOC and PT for the Open-Label Treatment Period for the ITT population. For condition/event that is gender specific (as defined by MedDRA), the denominator and computation of the percentage will include only patients from the given gender.

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

Listing of historical illnesses and pre-existing conditions will be provided for ITT population.

6.10. Treatment Compliance

Study treatment dispensed will be listed (including the CT Lot number) for all entered patients. Study treatment administration and compliance will be listed for all entered patients.

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) is 17 injections for patients on ixekizumab with moderate-to-severe plaque psoriasis. Patients will receive 2 ixekizumab 80 mg injections at Week 0, 1 ixekizumab 80 mg injection every 2 weeks from Week 2 to Week 12, and 1 ixekizumab 80 mg injection every 4 weeks from Week 16 to Week 48.

- Number of injections prescribed (that is, expected) is 14 injections for patients on ixekizumab without moderate-to-severe plaque psoriasis. Patients will receive 2 ixekizumab 80 mg injections at Week 0 and 1 ixekizumab 80 mg injection every 4 weeks from Week 4 to Week 48.
- Number of injections prescribed (that is, expected) is 28 injections for patients on adalimumab with moderate-to-severe plaque psoriasis. Patients will receive 2 adalimumab 40 mg injections at Week 0 and 1 adalimumab 40 mg injection every 2 weeks from Week 1 to Week 51.
- Number of injections prescribed (that is, expected) is 26 injections for patients on adalimumab without moderate-to-severe plaque psoriasis. Patients will receive 1 adalimumab 40 mg injection every 2 weeks from Week 0 to Week 50.
- For patients who discontinue during Period 2, 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.

Overall compliance for the Open-Label Treatment Period will be considered if the patient misses 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 study period.

Treatment compliance with investigational product will be summarized for the Open-Label Treatment Period (ITT population).

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

6.11. Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) drug dictionary.

Medication start and stop dates will be compared to the date of first dose of treatment in the treatment period to allow medications to be classified as either Prior or Concomitant for the Open-Label Treatment Period and Post-Treatment Follow-Up period.

Prior medications are those medications that start and stop prior to the date of first dose of treatment in corresponding treatment period. Concomitant therapy for Period 2 is defined as a therapy that starts before, on, or after the first day of study treatment in Period 2 and before the last visit date in Period 2 and continues into Period 2, that is, either no end date (the therapy is ongoing) or an end date on or after the first day of study treatment in Period 2. Note that a concomitant therapy will belong to Period 2 if the therapy starts and ends on the exact same day as the first day of study treatment in Period 2. Concomitant therapy for the Post-Treatment Follow-Up Period (Period 3) is defined as a therapy that starts before, on, or after the last visit date in Period 2 and continues into Period 3, that is, either no end date (the therapy is ongoing) or

an end date after the last visit date in Period 2. A concomitant therapy will belong to Period 2 if the therapy starts and ends on the exact same day as the last visit date in Period 2.

Concomitant therapies and prior therapies will both be summarized for the following periods and populations:

- Open-Label Treatment Period (ITT Population)
- Post-Treatment Follow-Up Period (Post-Treatment Follow-Up Population).

The comparisons will be conducted using Fisher's exact test.

The following summaries will be provided:

- Concomitant therapy by WHO ATC Level 4 and WHO PT

A by-patient listing of all concomitant and prior medications will be provided for the ITT Population.

6.12. Efficacy Analyses

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

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

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

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
American College of Rheumatology (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.	ACR20/50/70 Time to first ACR20/50/70 response	See Appendix 2 for details.	See Appendix 2 for details.
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 very 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% to 100% involvement): 0 = 0% (clear)	PASI total score Total PASI score ≤ 1, ≤ 2, or ≤ 3	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,	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
	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.		upper limb, trunk, and lower limb, respectively. PASI scores are treated as a continuous score, with 0.1 increments within these values.	
		• Change from baseline in PASI total score	Calculated as: observed PASI score – baseline PASI score	Missing is baseline or observed value is missing
		• PASI 75/90/100	Defined as at least 75%, 90%, or 100% improvement in PASI total score from baseline	Single item, missing if PASI total score is missing
ACR50 and PASI 100	Patients who achieve ACR50 and PASI 100 simultaneously.	• Simultaneous ACR50 and PASI 100		Missing if either ACR score or PASI score is missing.
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 item on the eCRF. Range from 0% to 100%	Single item, missing if missing.
		• Change from baseline in BSA	Calculated as: observed BSA – baseline BSA	Missing is baseline or observed value is missing

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
Nail Psoriasis Severity Index (NAPSI)	NAPSI will be used if the patient has fingernail psoriasis at baseline. The NAPSI is a numeric, reproducible, objective tool for evaluation of fingernail psoriasis. This scale is used to evaluate the severity of fingernail bed psoriasis and fingernail matrix psoriasis by area of involvement in the fingernail unit. In this study, only fingernail involvement will be assessed. The fingernail is divided with imaginary horizontal and longitudinal lines into quadrants. Each fingernail is given a score for fingernail bed psoriasis (0-4) and fingernail matrix psoriasis (0-4), depending on the presence (score of 1) or absence (score of 0) of any of the features of fingernail bed and fingernail matrix psoriasis in each quadrant: 0 = None 1 = present in one quadrant of nail 2 = present in two quadrants of nail 3 = present in three quadrants of nail 4 = present in four quadrants of nail	• NAPSI score	The NAPSI score of a fingernail is the sum of scores in fingernail bed and fingernail matrix from each quadrant (maximum of 8). Each fingernail is evaluated, and the sum of all the fingernails is the total NAPSI score (range, 0 to 80), usually indicated as NAPSI score.	For each fingernail, if either the bed or matrix score is missing or not done, then the score for that finger is missing. If <50% of the finger scores from 10 fingers are missing, the imputation will be performed by using the average score of the remaining fingernails. If ≥50% of the finger scores are missing, the NAPSI score will be left as missing
		• Change from baseline in NAPSI score	Calculated as: observed NAPSI – baseline NAPSI	Missing if baseline or observed value is missing
		• NAPSI = 0	NAPSI score equals to 0, indicating resolution of nail psoriasis.	Single item, missing if observed NAPSI score missing.
Tender Joint Count (TJC) (68 joint count)	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	• TJC score	Adjusted sum of the painful/tender joints for all 68 joints: *(sum of the evaluable individual joint*	If more than half of the joint scores are nonevaluable, the total score will be missing.

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
	as tender or not tender.		*scores)/(number of evaluable joints)×68* See Appendix 3 for complete details.	
		• Change from baseline in TJC score	Calculated as: observed TJC score – baseline TJC score	Missing if baseline or observed value is missing
Swollen Joint Count (SJC) (66 joint count)	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 score	Adjusted sum of the swollen joints for all 66 joints: *(sum of the evaluable individual joint scores)/(number of evaluable joints)×66* See Appendix 3 for complete details.	If more than half of the joint scores are nonevaluable, the total score will be missing.
		• Change from baseline in SJC score	Calculated as: observed SJC score – baseline SJC score	Missing if baseline or observed value is 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's pain VAS score	Range: 0 to 100 mm 0 represents no joint pain 100 represents the worst joint pain	Single item, missing if missing
		• Change from baseline in patient's pain VAS score	Calculated as: observed patient's pain VAS– baseline patient's pain VAS	Missing if baseline or observed value is 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's global assessment VAS score	Range: 0 to 100 mm 0 represents no disease activity 100 represents extremely active disease activity	Single item, missing if missing

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
		• Change from baseline in patient's global assessment VAS score	Calculated as: observed patient's global assessment VAS– baseline patient's global assessment VAS	Missing if baseline or observed value is missing
Physician's Global Assessment of Disease Activity Visual Analog Scale (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.	• Physician's global assessment VAS score	Range: 0 to 100 mm 0 represents no disease activity 100 represents extremely active disease activity	Single measure, missing if missing.
		• Change from baseline in physician's global assessment VAS score	Calculated as: observed physician's global assessment VAS– baseline physician's global assessment VAS	Missing if baseline or observed value is missing
Patient's Assessment of Physical Function Health Assessment Questionnaire–Disability Index (HAQ-DI)	Patient-reported standardized questionnaire that is commonly used in PsA to measure disease-associated disability (assessment of physical function). It consists of 24 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other daily activities	• 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 domains. If there are <6 domains completed, a HAQ-DI will be missing.
		• Change from baseline in HAQ-DI score	Calculated as: observed HAQ-DI score– baseline HAQ-DI score	Missing if baseline or observed value is missing
		• HAQ-DI improvement $\geq$0.35	Change from baseline $\leq$ –0.35 in HAQ-DI score	Missing if baseline or observed value is missing
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)	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

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
		• Change from baseline in CRP (mg/L)	Calculated as: observed CRP – baseline CRP	Missing if baseline or observed value is missing
Psoriatic Arthritic Response Criteria (PsARC)	PsARC is a composite criteria reported in terms of the percentage of patients achieving response according to the following criteria: PGA, PatGA, TJC, and SJC. Overall response is defined by improvement from the baseline assessment in 2 of the 4 criteria, 1 of which must be a joint count; there must not be worsening in any of the 4 criteria: At least 30% reduction in TJC At least 30% reduction in SJC At least a 1-point reduction in physician's assessment At least a 1-point reduction in patient's assessment The PsARC response was modified in this study by using the PGA and the PatGA on a 100-mm VAS instead of a 5-point Likert scale in the original criteria. The results from the 2 VAS measures were assessed as a difference from baseline (in mm), and criteria 3 and 4, above, were changed to "at least a 20 mm reduction" (Clegg 1996).	PsARC	Overall response is defined by improvement from the baseline assessment in 2 of the 4 criteria, 1 of which must be a joint count; there must not be worsening in any of the 4 criteria: At least 30% reduction in TJC At least 30% reduction in SJC At least a 20-mm reduction in physician's assessment At least a 20-mm reduction in patient's assessment	If the patient achieves PsARC with the non-missing measures, then impute as achieving PsARC; otherwise, the result is missing.
Coates criteria for Minimal Disease Activity (MDA) (6 entheseal points)	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	Coates criteria for MDA (6 entheseal points)	Patients are classified as achieving Coates criteria for MDA (6 entheseal points) if they fulfill 5 of 7 outcome	If the patient achieves MDA with the non-missing measures, then impute as achieving MDA; otherwise,

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
	a patients' disease (Coates et al. 2010a; Coates and Helliwell 2010b). The LEI is used to assess tender entheseal points.		measures: TJC ≤1 SJC ≤1 PASI total score ≤1 or BSA ≤3 patient pain VAS score of ≤15 patient global assessment VAS score of ≤20 HAQ-DI score ≤0.5 tender entheseal points (6 entheseal points) ≤1	the result is missing.
Coates criteria for Minimal Disease Activity (MDA) (18 entheseal points)	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. 2010a; Coates and Helliwell 2010b). The LEI and SPARCC are used to assess tender entheseal points.	Proportion of patients achieving Coates criteria for MDA (18 entheseal points)	Patients are classified as achieving Coates criteria for MDA (18 entheseal points) if they fulfill 5 of 7 outcome measures: TJC ≤1 SJC ≤1 PASI total score ≤1 or BSA ≤3 patient pain VAS score of ≤15 patient global VAS score of ≤20 HAQ-DI score ≤0.5 tender entheseal points ≤1 (based on 18 entheseal points)	If the patient achieves MDA with the non-missing measures, then impute as achieving MDA; otherwise, the result is missing.
Leeds Enthesitis Index (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],	LEI score	Each of the 6 sites is assigned a score of 0 (absent) or 1 (present) and the results are added to produce a total score (range: 0-6).	If one or more of the 6 sites are missing, then set LEI score to missing.
		Change from baseline in LEI	Calculated as: observed LEI score – baseline LEI score	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
	medial femoral condyle [left and right], and Achilles tendon insertion [left and right]) (Healy and Helliwell 2008).	• LEI score = 0	LEI score equals to 0, indicating complete resolution in enthesitis.	Missing if observed value are missing
Spondyloarthritis Research Consortium of Canada (SPARCC)	If the patient has enthesitis, the SPARCC will be administered by a blinded assessor. The SPARCC enthesitis index evaluates tenderness in a total of 16 enthesitis sites: the greater trochanter (right/left [R/L]), quadriceps tendon insertion into the patella (R/L), patellar ligament insertion into the patella and tibial tuberosity (R/L), Achilles tendon insertion (R/L), plantar fascia insertion (R/L), medial and lateral epicondyles (R/L), and the supraspinatus insertion (R/L) (Mease 2011).	• SPARCC enthesitis score	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 1 or more sites are missing, then set to missing.
		• Change from baseline in SPARCC enthesitis score	Calculated as: observed SPARCC enthesitis score – baseline SPARCC enthesitis score	Missing if baseline or observed value is missing
		• SPARCC enthesitis score = 0	SPARCC enthesitis score equals to 0, indicating complete resolution in enthesitis.	Missing if observed value is missing
Leeds Dactylitis Index-Basic (LDI-B)	If the patient has dactylitis, the LDI-B will be administered by a blinded assessor. The LDI-B has been developed to measure the severity of dactylitis. Once the presence of dactylitis is established in each digit, the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot is measured (Helliwell et al. 2005).	• LDI-B score	Each dactylitic digit is defined by a minimum increase of 10% in circumference over the contralateral digit. If the same digits on each hand or foot are thought to be involved, the clinician will refer to a table of normative values (provided to study sites) for a value that will be used to provide the comparison. If the ratio is >1.1, then subtract 1 from the calculated ratio and multiply it by 100 and the tenderness	If 1 or more sites are missing, then set to missing.

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
			score of 0 (not tender) or 1 (tender). Otherwise, if the ratio of the circumference of the digit is ≤1.1, then the LDI-B score is set to 0. 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).	
		• Change from baseline in LDI-B	Calculated as: observed LDI-B score – baseline LDI-B score	Missing if baseline or observed value are missing
		• LDI-B score = 0	LDI-B score equals to 0, indicating complete resolution in dactylitis.	Missing if observed value is missing
Disease Activity Score based on C-Reactive Protein (DAS28-CRP)	The DAS28-CRP is a measure of disease activity in 28 joints that consists of a composite numerical score utilizing the following variables: TJC, SJC, hs-CRP (measured in mg/L), and PatGA recorded by patients on a 0- to 100-mm VAS. For DAS28-CRP, the 28 joints to be examined and assessed as tender or not tender for TJC (TJC 28) and as swollen or not swollen for SJC (SJC 28) 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,	• DAS28-CRP score	The following equation will be used to calculate the DAS28 (Vander Cruyssen et al. 2005): $DAS28 - CRP = 0.56(\sqrt{TJC\ 28}) + 0.28(\sqrt{SJC\ 28}) + 0.36(\ln(CRP + 1)) + 0.014(VAS) + 0.96$ Where TJC 28 is calculated as: *(sum of the evaluable individual joint scores)/(number of evaluable joints)×28;* SJC 28 is calculated as: *(sum of the evaluable individual joint*	If one or more variables are missing, then set to missing.

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
	the 8 proximal interphalangeal joints, and the 2 knees (Smolen et al. 1995).		*scores)/(number of evaluable joints)×28* See Appendix 3 for complete details.	
		• DAS28-CRP <2.6 • DAS28-CRP ≥2.6 and <3.2 • DAS28-CRP ⩾3.2 and <5.1 • DAS28-CRP ⩾5.1	DAS28-CRP score falls in intervals <2.6 ≥2.6 and <3.2 ≥3.2 and <5.1 ≥5.1	Missing if DAS28-CRP score is missing
		• Change from baseline in DAS28-CRP	Calculated as: observed DAS28-CRP score – baseline DAS28-CRP score	Missing if baseline or observed value are missing
Modified Composite Psoriatic Disease Activity Index (mCPDAI)	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 HAQ-DI • skin as assessed by the PASI and the Dermatology Life Quality Index (DLQI)	• mCPDAI total score	Each domain with the exception of spinal disease is scored from 0-3. Individual domain scores are summed to give an overall composite score (range 0-12) with a higher score indicating higher disease activity (see Appendix 5).	If 1 or more components are missing, then set to missing.

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
		• Change from baseline in mCPDAI total score	Calculated as: observed mCPDAI score – baseline mCPDAI score	Missing if baseline or observed value are missing
		• mCPDAI $\leq$5	mCPDAI score $\leq$5, indicating low disease activity or remission in modified CPDAI (Salaffi et al. 2014)	Missing if observed mCPDAI is missing

Abbreviations: BSA = body surface area; eCRF = electronic case report form; PsA = psoriatic arthritis.

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

Measure	Variable	Analysis Method (Section 6.2)	Population (Section 6.1.3)	Comparison/Time Point	Analysis Type
Composite endpoint of American College of Rheumatology (ACR) 50 and Psoriasis Area and Severity Index (PASI) 100	• Proportion of patients with ACR50 and PASI 100 simultaneously (Primary Endpoint at Week 24)	Logistic regression using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at Week 24 and all other post-baseline visits	Primary analysis (IXE vs ADA at Week 24) Secondary analysis
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at Week 24 and all other post-baseline visits	Secondary analysis
	• Time to first simultaneous ACR50 and PASI 100 response	Log-rank Test Kaplan-Meier product limit method	ITT population	IXE vs ADA up to Week 24 and Week 52	Exploratory analysis
		Kaplan-Meier plots (survival curve)	ITT population	IXE vs ADA up to Week 24 and Week 52	Exploratory analysis
American College of Rheumatology (ACR) Responder Index 20, 50, and 70	• Proportion of patients with ACR20 • Proportion of patients with ACR50 (Major Secondary Endpoint at Week 24) • Proportion of patients with ACR70	Logistic regression using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at Week 24 and all other post-baseline visits	Major secondary analysis (ACR50: IXE vs ADA at Week 24) Secondary analysis
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at Week 24 and all other post-baseline visits	Secondary analysis
	• Time to first ACR20 response	Log-rank Test Kaplan-Meier product limit method	ITT population	IXE vs ADA up to Week 24 and Week 52	Exploratory analysis

Measure	Variable	Analysis Method (Section 6.2)	Population (Section 6.1.3)	Comparison/Time Point	Analysis Type
	• Time to first ACR50 response • Time to first ACR70 response	Kaplan-Meier plots (survival curve)	ITT population	IXE vs ADA up to Week 24 and Week 52	Exploratory analysis
Tender Joint Count (TJC) (68 joint count)	• Change from baseline in TJC Score	MMRM	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
Swollen Joint Count (SJC) (66 joint count)	• Change from baseline in SJC Score	MMRM	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
Patient's Assessment of Pain Visual Analog Scale (VAS)	• Change from baseline in patient's pain VAS score	MMRM	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
Patient's Global Assessment of Disease Activity Visual Analog Scale (VAS)	• Change from baseline in patient's global assessment VAS score	MMRM	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
Physician's Global Assessment of Disease Activity Visual Analog Scale	• Change from baseline in physician's global	MMRM	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		ANCOVA model using mBOCF (see Section	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis

Measure	Variable	Analysis Method (Section 6.2)	Population (Section 6.1.3)	Comparison/Time Point	Analysis Type
(VAS)	assessment VAS score	6.4.2)			
Patient's Assessment of Physical Function Health Assessment Questionnaire–Disability Index (HAQ-DI)	• Change from baseline in HAQ-DI score	MMRM	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
	• Proportion of patients with HAQ-DI improvement ⩾0.35	Logistic regression using the NRI method (see Section 6.4.1)	ITT population - patients with HAQ-DI ≥0.35 at baseline	IXE vs ADA at each post-baseline visit	Secondary analysis
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population - patients with HAQ-DI ≥0.35at baseline	IXE vs ADA at each post-baseline visit	Secondary analysis
C-Reactive Protein (CRP)	• Change from baseline in CRP (mg/L)	MMRM	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
Disease Activity Score based on C-Reactive Protein (DAS28-CRP)	• Change from baseline in DAS28-CRP	MMRM	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
	Proportion of patients with DAS28-CRP categories:	Logistic regression using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at each post-baseline visit	Exploratory analysis

Measure	Variable	Analysis Method (Section 6.2)	Population (Section 6.1.3)	Comparison/Time Point	Analysis Type
	<2.6 ≥2.6 and <3.2 ≥3.2 and <5.1 ≥5.1	Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at each post-baseline visit	Exploratory analysis
Psoriatic Arthritic Response Criteria (PsARC)	Proportion of patients achieving PsARC	Logistic regression using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
Psoriasis Area and Severity Index (PASI)	• Proportion of patients with PASI 75 • Proportion of patients with PASI 90 • Proportion of patients with PASI 100 (major secondary endpoint at Week 24)	Logistic regression using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at each post-baseline visit	Major secondary analysis (PASI 100: IXE vs ADA at Week 24) Secondary Analysis (other visits)
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis

Measure	Variable	Analysis Method (Section 6.2)	Population (Section 6.1.3)	Comparison/Time Point	Analysis Type
	• Change from baseline in PASI score	MMRM	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
	• Proportion of patients with absolute PASI score ≤1 or ≤2 or ≤3	Logistic regression using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
	• Time to first PASI 75 response • Time to first PASI 90 response • Time to first PASI 100 response	Log-rank Test Kaplan-Meier product limit method	ITT population	IXE vs ADA up to Week 24 and Week 52	Exploratory analysis
		Kaplan-Meier plots (survival curve)	ITT population	IXE vs ADA up to Week 24 and Week 52	Exploratory analysis
Coates criteria for Minimal Disease Activity (MDA) (6 entheseal points)	Proportion of patients achieving MDA (6 entheseal points)	Logistic regression using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
Coates criteria for Minimal Disease Activity (MDA) (18 entheseal points)	Proportion of patients achieving Coates criteria for MDA (18 entheseal points)	Logistic regression using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis

Measure	Variable	Analysis Method (Section 6.2)	Population (Section 6.1.3)	Comparison/Time Point	Analysis Type
Leeds Enthesitis Index (LEI)	• Change from baseline in LEI score	MMRM	ITT population - patients with baseline enthesitis (LEI >0)	IXE vs ADA at each post-baseline visit	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population - patients with baseline enthesitis (LEI >0)	IXE vs ADA at each post-baseline visit	Secondary analysis
	Proportion of patients with complete resolution in enthesitis (LEI score = 0)	Logistic regression using the NRI method (see Section 6.4.1)	ITT population - patients with baseline enthesitis (LEI >0)	IXE vs ADA at each post-baseline visit	Secondary analysis
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population for patients with baseline enthesitis (LEI >0)	IXE vs ADA at each post-baseline visit	Secondary analysis
Leeds Dactylitis Index-Basic (LDI-B)	• Change from baseline in LDI-B score	MMRM	ITT population - patients with baseline dactylitis (LDI-B >0)	IXE vs ADA at or after Week 12	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population - patients with baseline dactylitis (LDI-B >0)	IXE vs ADA at or after Week 12	Secondary analysis
	Proportion of patients with complete resolution in dactylitis (LDI-B score = 0)	Logistic regression using the NRI method (see Section 6.4.1)	ITT population - patients with baseline dactylitis (LDI-B >0)	IXE vs ADA at or after Week 12	Secondary analysis
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population for patients with baseline dactylitis (LDI-B >0)	IXE vs ADA at or after Week 12	Secondary analysis
Spondyloarthritis Research Consortium of	• Change from baseline in SPARCC	MMRM	ITT population - patients with baseline enthesitis (SPARCC >0)	IXE vs ADA at each post-baseline visit	Secondary analysis

Measure	Variable	Analysis Method (Section 6.2)	Population (Section 6.1.3)	Comparison/Time Point	Analysis Type
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population - patients with baseline enthesitis (SPARCC >0)	IXE vs ADA at each post-baseline visit	Secondary analysis
	Proportion of patients with complete resolution in enthesitis (SPARCC enthesitis score = 0)	Logistic regression using the NRI method (see Section 6.4.1)	ITT population - patients with baseline enthesitis (SPARCC >0)	IXE vs ADA at each post-baseline visit	Secondary analysis
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population for patients with baseline enthesitis (SPARCC >0)	IXE vs ADA at each post-baseline visit	Secondary analysis
Modified Composite Psoriatic Disease Activity Index (mCPDAI)	• Change from baseline in modified CPDAI total scores	MMRM	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
	Proportion of patients with low disease activity or remission (mCPDAI ≤5)	Logistic regression using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
Body Surface Area (BSA)	• change from baseline in BSA	MMRM	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population	IXE vs ADA at each post-baseline visit	Secondary analysis
Nail Psoriasis Severity Index (NAPSI)	• Change from baseline in NAPSI score	MMRM	ITT population - patients with baseline fingernail involvement (NAPSI >0)	IXE vs ADA at or after Week 12	Secondary analysis

Measure	Variable	Analysis Method (Section 6.2)	Population (Section 6.1.3)	Comparison/Time Point	Analysis Type
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population - patients with baseline fingernail involvement (NAPSI >0)	IXE vs ADA at or after Week 12	Secondary analysis
	Proportion of patients with complete resolution in nail psoriasis (NAPSI = 0)	Logistic regression using the NRI method (see Section 6.4.1)	ITT population - patients with baseline fingernail involvement (NAPSI >0)	IXE vs ADA at each post-baseline visit at or after Week 12	Exploratory analysis
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population - patients with baseline fingernail involvement (NAPSI >0)	IXE vs ADA at each post-baseline visit at or after Week 12	Exploratory analysis

Abbreviations: ADA = adalimumab; ANCOVA = analysis of covariance; ITT = intent to treat; IXE = ixekizumab; mBOCF = modified baseline observation carried forward; MMRM = mixed-effects model of repeated measures; NRI = non-responder imputation.

6.12.1. Analysis Methodology for Primary and Major Secondary Outcomes

6.12.1.1. Primary Outcome and Methodology

The primary efficacy endpoint is the proportion of patients simultaneously achieving both ACR50 and PASI 100 responses at Week 24.

ACR50 response is an efficacy measure for which a patient must satisfy the following:

1. ≥50% improvement from baseline in TJC and
2. ≥50% improvement from baseline in SJC and
3. ≥50% improvement from baseline in at least 3 of the following 5 ACR Core Set criteria:
   a. Patient's Assessment of Pain Visual Analog Scale (VAS)
   b. PatGA VAS
   c. PGA VAS
   d. patient's assessment of physical function as measured by the HAQ-DI
   e. acute-phase reactant as measured by high sensitivity (assay) CRP (hs-CRP)

Full details of the algorithm to calculate ACR Response can be found in Appendix 2.

PASI 100 is an efficacy measure for which a patient must meet an improvement of 100% in the PASI compared to baseline.

The primary analysis for comparison of ixekizumab with adalimumab at Week 24 using the primary efficacy endpoint will be a logistic regression analysis as described in Section 6.2.1 based on the ITT population in the Open-Label Treatment Period (Period 2). Missing data will be imputed using the NRI method described in Section 6.4.1.

6.12.1.2. Methodology for Major Secondary Outcomes

The major secondary endpoints are as follows:

1. Proportion of patients achieving ACR50 in each treatment group at Week 24
2. Proportion of patients achieving PASI 100 in each treatment group at Week 24

The analyses of the secondary endpoints will be based on the ITT population in the Open-Label Treatment Period (Period 2) comparing ixekizumab versus adalimumab at Week 24 using methods described in Section 6.7 for the major secondary endpoint #1 and using methods from Section 6.2.1 for the major secondary endpoint #2. Missing data will be imputed using the NRI method described in Section 6.4.1.

A multiple testing procedure, as described in Section 6.6, will be used for testing the primary and major secondary endpoints.

6.12.1.3. Other Secondary Outcomes

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

By-patient listings for primary efficacy measurements ACR and PASI will be provided.

6.13. Health Outcomes/Quality-of-Life Analyses

The health outcomes and quality of life (QOL) measures are Itch NRS, Fatigue Severity NRS, SF-36, EQ-5D-5L, DLQI, and Treatment Satisfaction Questionnaire. Table RHCF.6.5 includes the description and derivation of the health outcomes and QOL measures.

The analyses of health outcome variables for Period 2 will be based on the ITT population.

Table RHCF.6.6 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment group comparisons for health outcomes and QOL analyses.

Table RHCF.6.5. Description and Derivation of Health Outcomes and Quality-of-Life Measures

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
Itch Numeric Rating Scale (NRS)	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
		• Change from baseline in Itch NRS score	Calculated as: observe Itch NRS score – baseline Itch NRS score	Missing is 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 (NRS)	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
		• Change from baseline in Fatigue severity NRS	Calculated as: observe Fatigue NRS score – baseline Fatigue NRS score	Missing is baseline or observed value is missing
Medical Outcomes Study 36-item Short Form Health Survey (SF-36)	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.	Observed and change from baseline in: 8 associated domain scores: • Physical Functioning • Role Physical • Bodily Pain • General Health • Vitality • Social Functioning • Role Emotional • Mental Health	Per copyright owner, the Quality Metric 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)	Missing data handling offered by SF-36 software will not be used

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
	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).	2 component Scores: • MCS Score • PCS Score	using the 1-week recall period. The procedure to derive the SF-36 scores is described in Appendix 6. The summary scores range from 0 to 100. 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.	

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
European Quality of Life – 5 Dimensions – 5 Level (EQ-5D-5L)	The 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 or 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 or her health state by ticking (or placing a cross) in the box associated with the most appropriate statement in each of the 5 dimensions. 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 [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	• EQ-5D mobility, • EQ-5D self-care, • EQ-5D usual activities, • EQ-5D pain/discomfort, • EQ-5D anxiety/depression,	5 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.)*

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
		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
		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/Crosswalk_5L/EQ-5D-5L_Crosswalk_Value_Sets.xls	If any of the items is missing or equal to 9, the index score is missing

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
Dermatology Life Quality Index (DLQI)	The 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 1 question in a domain is missing, that domain is missing.

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
		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 1 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 made it difficult for you to do any sport?	If 1 question in a domain is missing, that domain is missing.
		DLQI work and school domain	Sum of responses of questions #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.
		DLQI personal and 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 1 question in a domain is missing, that domain is missing.
		DLQI treatment	Response of question #10: #10. How much of a problem	If 1 question in a domain is missing, that domain is

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
			has the treatment for your skin been, for example by making your home messy, or by taking up time?	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 2 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 1 question.
		Change from baseline in DLQI total score	Calculated as observed DLQI – baseline DLQI	Missing if baseline or observed value are missing
		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
Treatment Satisfaction Questionnaire (TSQ)	The TSQ is a clinician-administered questionnaire that provides an assessment of the patient's opinion of the effectiveness, safety, and overall satisfaction of the study medication. Patients will be asked to respond to questionnaire items using a 4-point	Question #1 = "mostly satisfied"	Patient's answer to Question #1: Please tell me whether you are mostly satisfied, somewhat satisfied, somewhat dissatisfied, or mostly dissatisfied with the effectiveness of this medication is mostly satisfied.	Single item, missing if missing

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
		Question #2 = "mostly satisfied"	Patient's answer to Question #2: Please tell me whether you are mostly satisfied, somewhat satisfied, somewhat dissatisfied, or mostly dissatisfied with the effectiveness over time of this medication is mostly satisfied.	Single item, missing if missing
		Question #3 = "mostly satisfied"	Patient's answer to Question #3: Please tell me whether you are mostly satisfied, somewhat satisfied, somewhat dissatisfied, or mostly dissatisfied with the long term safety of this medication is mostly satisfied.	Single item, missing if missing
		Question #4 = "mostly satisfied"	Patient's answer to Question #4: How would you rate your overall satisfaction with this medication is mostly satisfied.	Single item, missing if missing

Table RHCF.6.6. Description of Health Outcomes and Quality-of-Life Analyses

Measure	Variable	Analysis Method (Section 6.2)	Population (Section 6.1.3)	Comparison/Time Point	Analysis Type
Itch NRS	• Change in baseline for Itch NRS	MMRM	ITT population	At each post-baseline visit	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population	At each post-baseline visit	Secondary analysis
	Itch NRS = 0	Logistic regression using the NRI method (see Section 6.4.1)	ITT population for patients with baseline Itch NRS >0	At each post-baseline visit	Secondary analysis
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population for patients with baseline Itch NRS >0	At each post-baseline visit	Secondary analysis
Fatigue Severity NRS	• Change from baseline in fatigue severity NRS score	MMRM	ITT population	At Week 4, 12, 16, 24, 32, and 52	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population	At Week 4, 12, 16, 24, 32, and 52	Secondary analysis
Medical Outcomes Study 36-item Short-Form Health Survey	Change from baseline in: • Mental component summary score • Physical component summary score	MMRM	ITT population	At Week 4, 12, 16, 24, 32, and 52	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population	At Week 4, 12, 16, 24, 32, and 52	Secondary analysis
	Change from baseline in 8 domain scores	MMRM	ITT population	At Week 4, 12, 16, 24, 32, and 52	Exploratory analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population	At Week 4, 12, 16, 24, 32, and 52	Exploratory analysis

Measure	Variable	Analysis Method (Section 6.2)	Population (Section 6.1.3)	Comparison/Time Point	Analysis Type
DLQI	• Change from baseline in DLQI total score	MMRM	ITT population	At each post-baseline visit	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT population	At each post-baseline visit	Secondary analysis
	• DLQI (0,1)	Logistic regression using the NRI method (see Section 6.4.1)	ITT population	At each post-baseline visit	Exploratory analysis
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population	At each post-baseline visit	Exploratory analysis
EQ-5D-5L	• Change from baseline in EQ-5D VAS	MMRM	ITT Population	At Week 4, 12, 16, 24, 32, and 52	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT Population	At Week 4, 12, 16, 24, 32, and 52	Secondary analysis
	Change from baseline in EQ-5D-5L UK Population-based index score	MMRM	ITT Population	At Week 4, 12, 16, 24, 32, and 52	Secondary analysis
		ANCOVA model using mBOCF (see Section 6.4.2)	ITT Population	At Week 4, 12, 16, 24, 32, and 52	Secondary analysis
TSQ	Proportion of patients answering "mostly satisfied" to • Question #1 • Question #2 • Question #3 • Question #4	Logistic regression using the NRI method (see Section 6.4.1)	ITT population	At Week 12, 24, and 52	Secondary analysis
		Fisher's exact test using the NRI method (see Section 6.4.1)	ITT population	At Week 12, 24, and 52	Secondary analysis

Abbreviations: ANCOVA = analysis of covariance; EQ-5D-5L = European Quality of Life-5 Dimensions 5 Level Health Outcomes Instrument; DLQI = Dermatology Life Quality Index; ITT = intent-to-treat; mBOCF = modified baseline observation carried forward; MMRM = mixed-effects model of repeated measures; NRI = non-responder imputation; NRS = Numeric Rating Scale; TSQ = Treatment Satisfaction Questionnaire; UK = United Kingdom; VAS = Visual Analog Scale.

6.14. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

N/A.

6.15. Safety Analyses

The primary safety analyses will focus on comparisons of ixekizumab versus adalimumab in the Open-Label Treatment Period (Period 2). Fisher's exact test will be used for all AEs and other categorical safety data. Continuous vital sign and laboratory values will be analyzed by an ANCOVA with treatment and baseline value in the model. Type 3 sums of squares will be used. The significance of within-treatment group changes from baseline will be evaluated by testing whether the treatment group LSMean changes from baseline are different from zero using a t-statistic. In addition to the LSMeans and tests, the standard deviation, minimum, median, and maximum will be displayed. Unless otherwise specified, change from baseline will include only those subjects with both baseline and post-baseline measures.

For safety analyses, p-values should be interpreted with caution as the analyses are intended to be descriptive and should not be thought of as hypothesis testing, unless there is a prespecified hypothesis. P-values and CIs, if reported, provide some evidence of the strength of the finding and are only useful as a flagging mechanism.

Summaries of safety data collected during the Post-Treatment Follow-Up Period will be presented separately. The categorical safety measures will be summarized with incidence rates. The continuous safety measures will be summarized using mean changes.

6.15.1. Extent of Exposure

Duration of exposure to study drug will be summarized by treatment group using descriptive statistics; the summary will also include the total exposure in patient years, mean, and median total dose. Exposure of safety population in the Open-Label Treatment Period (Period 2) will be summarized.

The duration of exposure will be calculated as follows:

- $Duration\ of\ exposure\ (days) =$
  $Date\ of\ last\ visit\ (scheduled\ or\ unscheduled)\ during$ the $treatment\ period\ -$
  $Date\ of\ first\ injection\ for\ the\ treatment\ period\ + 1$
- Total exposure in patient years will be calculated as follows:

$$Total\ exposure\ in\ patient\ years = \frac{Sum\ of\ duration\ (days)\ of\ exposures\ for\ all\ patients\ in\ treatment\ group}{365.25}$$

- Total dose (in mg) is calculated by the summation of dose for each active injection taken during the treatment period.
- Note that the total number of injections received will be calculated using the response to the question "Was the injection given?" on the *Study administration* electronic eCRF page.

Descriptive statistics will be provided for patient days of exposure and the frequency of patients falling into the following different exposure ranges (that is, only the exposure ranges that fall within the treatment period will be presented) will be summarized:

- >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥90 days, ≥120 days, ≥183 days, ≥365 days.
- >0 to <7 days, ≥7 to <14 days, ≥14 to <30 days, ≥30 to <60 days, ≥60 to <90 days, ≥90 to <120 days, ≥120 to <183 days, ≥183 to <365 days, and ≥365 days.

6.15.2. Adverse Events

6.15.2.1. Analyses of Adverse Events

Adverse events are classified based on MedDRA. A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after the first dose of the study medication and on or prior to the date of the last visit within the treatment period. Both the date/time of the event and the date/time of the dose (that is, injection) are considered when determining TEAEs. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. The maximum severity for each LLT during the baseline period will be used as baseline severity (in some cases baseline period is a single time point). Events with a missing severity during the treatment period will be considered treatment emergent. The treatment period will be included as post-baseline for the analysis. If an event is pre-existing during the baseline period but it 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. Adverse events with a particular LLT will be classified as treatment-emergent if they first start on or after the first dose date in the treatment period (ie, a patient has no pre-existing conditions with that LLT) or if the severity is greater than the pre-treatment 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 Week 52 (Visit 11) or the ETV. The MedDRA LLT will be used when classifying FEAEs as follow-up emergent. For AEs that are ongoing at the date of Week 52 (Visit 11) or ETV, the maximum severity recorded for each LLT on the date of Week 52 (Visit 11) 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 earlier of the patient's first visit date or 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.
  - The imputed date should not be before the minimum of the patient's first visit or consent date.
- 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 in the follow-up period.
  - 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.
- For the end time:
  - Impute as 23:59.
- If there is any doubt, the event will be flagged as treatment-emergent or follow-up emergent according to 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.

An overview table will be provided and will include the frequency and percentage of patients who experienced a TEAE, TEAE by maximum severity, a treatment-emergent adverse events of special interest (AESI), serious adverse event (SAE), death, or discontinued from the study due to an AE (including death) will be summarized by treatment group for the Open-Label Treatment Period.

In general, for all AE-related summaries, the number and percentage of patients experiencing the events will be presented by dosing regimen. When the SOC is presented, events will be ordered by decreasing frequency in the ixekizumab treatment group within SOC. When the SOC is not presented, the events will be ordered by decreasing frequency in the ixekizumab treatment group. For incidence counts, each patient will be counted only once within each PT and within each SOC. Percentages will be based on the number of patients in a particular treatment group. For events that are gender specific, the denominator and computation of the percentage will include only patients from the given gender.

The following summary tables will be provided for the Open-Label Treatment Period (Safety Population):

- An overview summary of AEs
- TEAEs, by SOC and PT
- TEAEs, by PT
- TEAEs by maximum severity, by SOC and PT

The following summary tables will be provided for the Post-Treatment Follow-Up Period (Follow-Up Population):

- FEAEs, by maximum severity, by SOC and PT

By-patient listing of all TEAEs will be provided.

6.15.2.2. Common Adverse Events

The number and percentages of patients with common TEAEs will be summarized by treatment group for each treatment period using similar methods described in Section 6.15.2.1. Common

TEAEs will be defined as those TEAEs that occurred in ≥1% before rounding of total treated patients including all ixekizumab dose regimens. Events will be ordered by decreasing frequency within SOC or PT in the combined ixekizumab dose group.

The following summary tables will be provided for the Open-Label Treatment Period (Safety Population):

- TEAEs, by PT

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

By-patient listings of deaths, SAEs, and AEs leading to discontinuation will be provided, respectively.

All deaths will be included, regardless of the investigator's or the sponsor's judgment about causality, including the following:

- any deaths occurring during participation in the study in the database for which data are being presented
- any deaths occurring after a patient leaves (is discontinued from or completed) the study in the database for which data are being presented if the death is:
  - the result of a process initiated during the study, regardless of when it actually occurred, or
  - occurs during Period 3 after discontinuation of study drug

An SAE is any AE that results in one 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.

The following summary tables (including treatment group comparison for Period 2) will be provided for the Safety Population during the Open-Label Treatment Period (Period 2):

- SAEs by SOC and PT
- AEs that lead to treatment discontinuation (including death) by SOC and PT

The following summary tables (by treatment group during Period 2) will be provided for the Post-Treatment Follow-Up Population during the Post-Treatment Follow-Up Period (Period 3):

- Follow-up emergent SAEs (FESAEs) by SOC and PT
- FEAEs that lead to treatment discontinuation (including death) by SOC and PT

6.15.3.1. Special Safety Topics Including Adverse Events of Special Interest

Safety information on special topics including AESI will be presented by treatment group and by study period. Table RHCF.6.7 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 or 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 RHCF.6.7. Definitions and Analyses of Special Safety Topics

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 SMQ or sub-SMQ 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)	**Open-Label Treatment Period (Safety Population):** TEAE by PT within SMQ or sub-SMQ
	Elevations in hepatic laboratory tests (ALT, AST, ALP, total bilirubin) using Performing Laboratory Reference Ranges are defined as: • Include scheduled visits, unscheduled visits, and repeat measurements. • ALT or AST: maximum post-baseline measurement ≥3 times (3×), 5 times (5×), 10 times (10×), and 20 times (20×) the Performing Lab 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, patients whose maximum baseline is >1× ULN but <3× ULN, patients whose maximum baseline value is ≥3× ULN, and patients whose baseline values are missing. o The analysis of 5× ULN will contain 5 subsets: patients whose non-missing maximum baseline value is ≤ to 1× ULN, patients whose maximum baseline is >1× ULN but <3× ULN, patients whose maximum baseline is ≥3× ULN but <5× ULN, patients whose maximum baseline value is ≥5× ULN, and patients whose baseline values are missing. o The analysis of 10× ULN will contain 6 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, patients whose maximum baseline is >1× ULN but <3× ULN, patients whose maximum baseline is ≥3× ULN but <5X ULN, patients whose maximum baseline is ≥5× ULN but <10× ULN, patients whose maximum baseline value is ≥10× ULN, and patients whose baseline values are missing. o The analysis of 20× ULN will contain 7 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, patients whose maximum baseline is >1× ULN but <3× ULN, patients whose maximum baseline is ≥3× ULN but <5× ULN, patients whose maximum baseline is ≥5× ULN but <10× ULN, patients whose maximum baseline is ≥10× ULN but <20× ULN, patients whose maximum baseline value is ≥20× ULN, and patients whose baseline values are missing. 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.	**Open-Label Treatment Period (Safety Population):** Elevations in hepatic laboratory tests: maximum baseline category to abnormal maximum post-baseline category

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
	○ 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. ○ 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. ○ 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: The number and percentages of patients with a total bilirubin measurement ≥1.5 times (1.5×), and ≥2 times (2×) the Performing Lab ULN during the treatment period will be summarized for all patients with a post-baseline value. ○ The analysis of 1.5× ULN will contain 4 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, patients whose maximum baseline is >1× ULN but <1.5× ULN, patients whose maximum baseline value is ≥1.5× ULN, and patients whose baseline values are missing. ○ The analysis of 2× ULN will contain 5 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, patients whose maximum baseline is >1× ULN but <1.5× ULN, patients whose maximum baseline is ≥1.5× ULN but <2× ULN, patients whose maximum baseline value is ≥2× ULN, and patients whose baseline values are missing. • ALP: The number and percentages of patients with an ALP measurement >1.5× the Performing Lab ULN during the treatment period will be summarized for all patients with a post-baseline value, and divided into 4 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, patients whose maximum baseline is >1× ULN but ≤1.5× ULN, patients whose maximum baseline value is >1.5× ULN, and patients whose baseline values are missing. • The number and percentages of patients meeting the following elevated hepatic criteria: maximum ALT ≥3× ULN and maximum Total Bilirubin ≥2× ULN during the treatment period will be summarized.	
	Shift for ALT, AST, and total bilirubin from maximum baseline to maximum post-baseline will be produced with the requirements using Performing Lab Reference Ranges: • 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:	**Open-Label Treatment Period (Safety Population):** Shifts from maximum baseline to maximum post-baseline category

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
	○ ALT: ≤1× ULN, >1 to <3× ULN, ≥3 to <5× ULN, ≥5 to <10× ULN, ≥10 to <20× ULN, and ≥20× ULN ○ AST: ≤1× ULN, >1 to <3× ULN, ≥3 to <5× ULN, ≥5 to <10× ULN, ≥10× to <20× ULN, and ≥20× ULN ○ Total bilirubin: ≤1× ULN, >1 to <1.5× ULN, ≥1.5 to <2× ULN, and ≥2× ULN ○ ALP: ≤1× ULN, >1 to ≤1.5× ULN, and >1.5× ULN • With additional categories: ○ Decreased: post-baseline category < baseline category ○ Increased: post-baseline category > baseline category ○ Same: post-baseline category = baseline category	
	Elevated hepatic criteria: maximum ALT ≥3× ULN and maximum total bilirubin ≥2× ULN. Listing of patients who meet any of the following criteria: • Elevated hepatic criteria: defined as maximum ALT ≥3× ULN, maximum total bilirubin ≥2× ULN • An ALT or AST ≥3× ULN • An ALP ≥1.5× ULN • A total bilirubin ≥2× ULN The listing will include patient demographics, concomitant medications, ALT/AST/ALP/total bilirubin/GGT by visit, treatment start and stop dates, and reason for treatment discontinuation	**Open-Label Treatment Period (Safety Population):** Elevated hepatic criteria
	eDISH plot: Use maximum ALT measurement and maximum total bilirubin measurement with patients having at least 1 post-baseline ALT and total bilirubin, which contributes 1 point to the plot. The measurements do not need to be taken at the same blood draw.	**Open-Label Treatment Period (Safety Population):** eDISH plot (to be prepared in spotfire)
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)	**Open-Label Treatment Period (Safety Population):** TEAE by PT within sub-SMQ
Infections	Infections are events including all infections (defined using all the MedDRA PTs from the Infections and infestations SOC), serious infections, potential opportunistic infections, and infections resulting in anti-infective medication administration (i.e., antibacterial, antiviral, antifungal, antiparasitic treatment.). The relationship between TEAE infections and other clinical, laboratory, and hematology parameters will be examined using Spotfire tool.	**Open-Label Treatment Period (Safety Population):** TEAE by PT TEAE by maximum severity by PT* SAE by PT*

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
		AEs leading to discontinuation of study drug* *Included in overall TEAE by maximum severity, SAE and DCAE.
	Anti-infective medications are defined in Appendix 8 including antibiotics, antifungals, antivirals, or antiprotozoals.	
	The OIs are defined in Appendix 9. This list contain PTs as contained within Categories (narrow or broad) from the Infections and Infestations SOC and from the Investigations SOC that can assist in identifying potential OIs. The narrow terms are considered OIs unless medical review 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 definition of OIs. The number and percentage of patients with TEAEs that represent potential OIs and as potential OIs will be summarized by treatment group using MedDRA PT nested within categories. Events will be ordered by decreasing frequency in the ixekizumab group nested within categories.	**Open-Label Treatment Period (Safety Population):** TEAE of OIs by PT within category **Listing:** TEAE of OIs
	The duration of each common TEAE PT of Infections and narrow terms for OIs is defined as: Duration of treatment-emergent AE Infections (in weeks) = (End date of AE – Start date of AE + 1) / 7 Patients who do not have the PT will not be included in the analysis. If the TEAE has not been reported as ended by the date of completion from the study, or date of early discontinuation, it will be censored as of that date. 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.	**Open-Label Treatment Period (Safety Population):** Duration of Common TEAE Duration of OIs (narrow terms) (to be prepared in spotfire) Duration of Candida infections (to be prepared in spotfire)

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
Allergic Reactions/ Hypersensitivities	Allergic reactions/hypersensitivity events will be categorized as either anaphylaxis or non-anaphylaxis events (these will refer to events that are not localized to the site of injection) and summarized separately. Allergic Reactions/Hypersensitivity Events, 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 two screening 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 • Kounis Syndrome • Type 1 hypersensitivity 2) to identify possible cases, following Criterion 2 as defined by Sampson et al. (2006). Criterion 2 for anaphylaxis requires having TEAEs from two or more of four categories of AEs as described by Sampson et al. (2006). Occurrence of these events should be nearly coincident; based on recording of events or 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 10. 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)	**Open-Label Treatment Period (Safety Population):** TEAE by PT within Category TEAE by maximum severity by PT SAE by PT within Category AE leading to discontinuation of study drug within Category

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
	• 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. Separate summaries will be provided for TEAEs by maximum severity, SAEs, and AEs resulting in study drug discontinuation. 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 (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 11 and excluding the anaphylactic events as defined above.	

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
Injection Site Reactions	Injection site reaction is defined using the PTs from the MedDRA HLT of Injection site reactions as defined 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 redness 5) Injection site joint infection 6) Injection site joint inflammation 7) Injection site joint movement impairment 8) Injection site joint pain 9) Injection site joint swelling 10) Injection site joint warmth.	**Open-Label Treatment Period (Safety Population)**: TEAE by PT within HLT TEAE by maximum severity by PT within HLT AE leading to discontinuation of study drug within HLT
	The *Injection Site Reaction* eCRF page captures the injection site reactions identified by the investigator. Patients with TEAE of injection site reactions will be categorized into 3 groups: patients with 1 TEAE of injection site reaction event, patients with 2 or 3 events, and patients with ≥4 events. 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) • [1] Mild • [2] Moderate • [3] Severe	**Open-Label Treatment Period (Safety Population):** TEAE identified by the investigator by PT within HLT TEAE identified by the investigator by maximum severity by PT within HLT TEAE identified by the investigator by max redness category within HLT TEAE identified by the investigator by max swelling category within HLT TEAE identified by the investigator by max pain category within HLT

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 MI
	  o Hospitalization for Unstable Angina
	  o Hospitalization for Heart Failure
	  o Serious Arrhythmia
	  o Hospitalization for Hypertension
	  o Resuscitated Sudden Death
	  o Cardiogenic Shock due to Myocardial Infarction
	  o Coronary Revascularization
	• Neurologic
	  o Cerebrovascular Event: Transient Ischemic Attack or Stroke (Hemorrhagic, 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. Subcategories of stroke (Hemorrhagic Stroke, Ischemic Stroke, and Unknown Stroke Type) will be displayed in the analyses nested within stroke. Subcategories of Serious Arrhythmia (Atrial Arrhythmia, Ventricular Arrhythmia, Heart Block, Other, Unknown) will be displayed nested within Serious Arrhythmia.
		Open-Label Treatment Period (Safety Population): TEAE by PT within Subcategory

MACE	MACE (requiring adjudication as defined above) is defined as: • Vascular death (including cardiovascular and cerebro-vascular causes excluding hemorrhagic deaths outside of the central nervous system) • Non-fatal myocardial infarction	**Open-Label Treatment Period (Safety Population):** TEAE by maximum severity PT within Category

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
	• Non-fatal stroke (subcategories: ischemic, hemorrhagic, unknown 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.	
Malignancies	Malignancy is defined using PTs from the Malignant or unspecified tumors SMQ as defined in MedDRA (SMQ: 20000091, which includes the sub-SMQs: (1) 20000194 [Malignant tumours], including sub-SMQs of 20000227 [Haematological malignant tumours] and 20000228 [Non-haematological malignant tumours]; (2) 20000195 [Tumours of unspecified malignancy], including sub-SMQs of 20000229 [Haematological tumours of unspecified malignancy] and 20000230 [Non-haematological tumours of unspecified malignancy]. Events will be summarized by the following categories: • 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 ▪ Skin squamous cell carcinoma metastatic ▪ Keratoacanthoma • Malignancies excluding NMSC: all PTs in the Malignant or unspecified tumors SMQ excluding the 8 defined NMSC PTs.	**Open-Label Treatment Period (Safety Population):** TEAE by PT within Category
Depression	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	**Open-Label Treatment Period (Safety Population):**

Special Safety Topic	Definition/Derivation	Analysis/Summary/Listing
	[Suicide/self-injury] and 20000167 [Depression (excluding suicide and self-injury)]).	TEAE by PT within SMQ
IBD	IBD will be identified using the following subcategory and MedDRA PTs. The narrow terms are considered IBD. Medical reviews of patients identified with 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 hemorrhagic ulcerative colitis; Colitis ulcerative; Proctitis ulcerative IBD Non-Specific Terms: The PTs in this category are listed in Appendix 11.	**Open-Label Treatment Period (Safety Population):** TEAE by PT within subcategory
ILD	ILD is defined using the following terms: • Narrow terms in the Interstitial lung disease SMQ (20000042) • Additional 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)	**Open-Label Treatment Period (Safety Population):** TEAE by PT by maximum severity by PT within interstitial lung disease

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CEC = Central Events Committee; eCRF = electronic case report form; eDISH = Evaluation of Drug-Induced Serious Hepatotoxicity; GGT = gamma-glutamyltransferase; HLT = High Level Term; IBD = inflammatory bowel disease; ILD = Interstitial Lung Disease; ITT = intent-to-treat; MACE = Major Adverse Cerebro-Cardiovascular Events; MedDRA = Medical Dictionary for Regulatory Activities; MI = myocardial infarction; NMSC = Nonmelanoma Skin Cancer; OI = opportunistic infection; PsA = psoriatic arthritis; 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.

6.15.4. Clinical Laboratory Evaluation

Laboratory evaluations will be summarized and analyzed for the following periods:

- Open-Label Treatment Period (Safety Population)
- Post-Treatment Follow-Up Period (Post-Treatment Follow-Up Population)

Laboratory analyses will include planned analytes only. Planned analytes are those specified in the protocol. However, unplanned/unscheduled measurements of planned analytes will be included/ excluded as specified in the relevant sections. Examples of unplanned/unscheduled measurements include those that the clinical investigator orders as a repeat test or "retest" of a laboratory test if he or she has received an abnormal value, and those the investigator orders for a "follow-up visit" due to clinical concerns.

Laboratory test observed values at each visit (starting at baseline) and change from baseline to each visit will be displayed in box plots (with outliers displayed) for patients who have both a baseline and at least 1 post-baseline result for Period 2 and Period 3, respectively. Baseline will be the last nonmissing observation in the baseline period. Original-scale data will be used for the display. Unscheduled visits and repeat measurements will be excluded. In each of the plots displaying values at each visit, lines indicating the performing lab reference ranges will be added. Displays using both standard (SI) and conventional (CN) units will be provided (when different). The following summary statistics will be included in a table below the box plot: N, mean, standard deviation, minimum, Q1, median, Q3, and maximum. P-values and confidence limits will not be included in the summary statistics at the bottom of the box plot. Box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries.

The number and percentages of patients with treatment-emergent abnormal, high, or low laboratory results at any time will be summarized by treatment for the treatment period. Scheduled visits, unscheduled visits, and repeat measurements will be included. Performing lab reference ranges will be used to define the low and high limits.

- Categorical laboratory tests:
    - A treatment-emergent **abnormal** result is defined as a change from normal at all baseline visits to abnormal at any time during the treatment period.
- Numerical laboratory tests:
    - A treatment-emergent **high** result is defined as a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time 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 all baseline visits to a value less than the low limit at any time during the treatment period.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP), neutrophils, leukocytes, platelets, and lymphocytes will not be included in this treatment-emergent abnormal, high, or low laboratory results analysis. A separate analysis

to address the risk of liver injury is described in Table RHCF.6.7 in which performing lab reference ranges will be used.

By-patient listing of abnormal laboratory test results (criteria defined in the shift tables excluding the normal category) for parameters of special interest (hepatic, leukocytes, and platelets) will be provided.

6.15.4.1. Leukocytes (White Blood Cells) and Platelets

Further analyses will be conducted for total leukocytes, neutrophils, platelets, lymphocytes, monocytes, eosinophils, and basophils. Neutrophils will include both segmented neutrophils and absolute neutrophils (derived by adding segmented neutrophils and band neutrophil). The segmented neutrophils and absolute neutrophils will be summarized using the same categories.

Shift tables will be produced showing the number and percentage of patients with a minimum post-baseline result for neutrophils, lymphocytes (including Th17 lymphocytes), platelets, and leukocytes, and will be summarized overall and by treatment group and baseline result. Unless otherwise specified, neutrophils will be summarized for absolute neutrophils. Scheduled visits, unscheduled visits, and repeat measurements will be included. Baseline is defined as the minimum result during the defined baseline period.

The following LLNs will be defined for the 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

Such 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 ×109/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).

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 within the following group 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 the Open-Label Treatment Period (Period 2) and Post-Treatment Follow-Up Period (Period 3). 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.

The change from minimum baseline to minimum post-baseline result for each of these leukocytes and platelets will be summarized graphically using a box plot for Safety Population in Period 2.

6.15.4.2. Neutrophil Follow-Up

Neutrophil counts will be followed throughout the study. Patients will continue to be followed in Period 3 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: $<1.5 \times 10^9$/L) at the last scheduled visit or early termination visit prior to entering the Post-Treatment Follow-Up Period (Period 3) 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 3 until neutrophil recovery.

Neutrophil clinical recovery is defined as an absolute neutrophil count ≥1500 cells/μL (SI units: $\geq 1.5 \times 10^9$/L) or greater than or equal to a patient's minimum 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 dosing regimen and week interval for Neutrophil Follow-Up Population in the Post-Treatment Follow-Up Period (Period 3). 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.

6.15.5. Vital Signs and Other Physical Findings

Vital signs and physical characteristics will be summarized and analyzed for the following periods:

- Open-Label Treatment Period (Safety Population)
- Post-Treatment Follow-up Period (Post-Treatment Follow-Up Population)

For vital signs and physical characteristics, the observed values at each visit (starting at baseline) and change from baseline to each scheduled visit, respectively, will be displayed in box plots for patients who have both baseline and at least 1 post-baseline result. Baseline will be the last nonmissing observation in the baseline period. Original-scale data will be used for the display. Unscheduled visits and repeat measurements will be excluded. Reference limits will not be displayed. The following summary statistics will be included in a table below the box plot: N, mean, standard deviation, minimum, Q1, median, Q3, and maximum. P-values and confidence limits will not be included in the summary statistics at the bottom of the box plot. Box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries.

The frequency and percentages of patients with treatment-emergent high or low vital signs and physical characteristics results at any time will be summarized by treatment group for Period 2 and Period 3, respectively.

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

Table RHCF.6.8 will be used to define the low and high baseline values as well as the limits that are specified as treatment emergent. Note: Weight does not have an abnormal baseline; therefore, the treatment-emergent values are determined by change from baseline. For categorical variables, scheduled visits, unscheduled visits, and repeat measurements will be included.

Table RHCF.6.8. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight and Changes for Adults

Parameter	Low	High
Systolic BP (mm Hg) [1] (supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) [1] (supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) [1] (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.

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

6.15.6. Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) is an assessment tool that evaluates suicidal ideation and behavior. Information on the C-SSRS scale can be found through the following link: http://www.cssrs.columbia.edu.

Specifically, the following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale to facilitate the definitions of the composite and comparative endpoints and to enable clarity in the presentation of the results.

Category 1 – Wish to be Dead
Category 2 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5 – Active Suicidal Ideation with Specific Plan and Intent
Category 6 – Preparatory Acts or Behavior
Category 7 – Aborted Attempt
Category 8 – Interrupted Attempt
Category 9 – Actual Attempt (non-fatal)
Category 10 – Completed Suicide.
Self-injurious behavior without suicidal intent is also a C-SSRS outcome (although not suicide related) and has a binary response (yes/no).

Composite endpoints based on the above categories are defined below.

- **Suicidal ideation:** A "yes" answer at any time during treatment to any 1 of the 5 suicidal ideation questions (Categories 1-5) on the C-SSRS.
- **Suicidal behavior:** A "yes" answer at any time during treatment to any 1 of the 5 suicidal behavior questions (Categories 6-10) on the C-SSRS.

- **Suicidal ideation or behavior:** A "yes" answer at any time during treatment to any 1 of the 10 suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

The Self-Harm Supplement Form is a 1-question form that is completed, at any visit, including baseline visit, that asks for the number of suicidal behaviors, possible suicidal behaviors, 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) that collects supplemental information on the self-injurious behavior is to be completed.

Change from baseline to each post-baseline visit in C-SSRS total score will be analyzed using MMRM methods for the safety population during Period 2. If the number of patients in analysis is less than 10% of patients in total, only a by-patient listing will be provided.

The 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's 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 ideation and behavior for that patient will be displayed, even if not positive. Note, missing data should not been imputed.

The Self-Harm data will be listed by patient and visit if number of events on Self-Harm Supplement Form is not zero in the CRF "*Self-Harm Questionnaire Supplement.*"

6.15.7. Immunogenicity

Not applicable.

6.15.8. Electrocardiograms

Not applicable.

6.16. Subgroup Analyses

6.16.1. Safety Subgroup Analyses

Safety subgroup analysis for common TEAEs and AESIs of allergy/hypersensitivity, infections, and injection site reactions will be summarized by treatment and overall, during the Open-Label Treatment Period for the safety population.

Subgroups to be evaluated include the following:

- Patient Demographic Subgroups:
  - Sex: female or male
  - Age group: <65 years, or ≥65 years
- Geographic Region Subgroups:
  - Geographic region: Europe, Rest of the World
- Concomitant Therapy:
  - Concomitant csDMARD use at baseline: yes or no
  - Concomitant methotrexate use at baseline: yes or no

    - Concomitant glucocorticoids use at baseline: yes or no
- Baseline Severity Groups:
    - Moderate-to-severe plaque psoriasis involvement: yes or no

Treatment effects will be assessed within the subgroups using the Fisher's exact test. The most common TEAEs and AESI will be presented by MedDRA PT nested within SOC (SMQ or High Level Term where specified). A logistic regression model will be used to test the treatment-by-subgroup interaction. The response variable will be each AE. The explanatory variables will be treatment, subgroup, and treatment by-subgroup interaction. The interaction test will be evaluated at the 0.10 significance level. If any of the subgroups (for example, the age <65 group or the age ≥65 group) is less than 10% of the total population, only descriptive statistics will be provided for that subgroup (that is, no inferential testing).

6.16.2. Efficacy Subgroup Analyses

Subgroup analyses will be conducted for the following efficacy assessments:

- ACR50 and PASI 100 simultaneous response rate at Week 24 with ITT Population in the Open-Label Treatment Period

Subgroups to be evaluated include the following:

- Patient Demographic Subgroups:
    - Age group: <65 years or ≥65 years
    - Ethnicity: Hispanic or Latino, Non-Hispanic and Non-Latino
- Geographic Region Subgroups:
    - Geographic region: Europe, Rest of the World
- Concomitant Therapy:
    - Concomitant csDMARD use at baseline: yes or no
    - Concomitant methotrexate use at baseline: yes or no
    - Concomitant glucocorticoids use at baseline: yes or no
    - Number of prior csDMARD therapies: 1, 2, 3, or >3
- Baseline Severity Groups:
    - Moderate-to-severe plaque psoriasis involvement: yes or no

Additional exploratory subgroup analyses will be conducted for the following efficacy assessments:

- ACR20, 50, and 70 response rates at Week 24 with ITT population in the Open-Label Treatment Period
- PASI 75, 90, and 100 response rates at Week 24 with ITT population in the Open-Label Treatment Period

Subgroup to be evaluated includes:

- Concomitant Therapy:
    - Concomitant csDMARD use at baseline: yes or no
    - Concomitant methotrexate use at baseline: yes or no

- Baseline Severity Groups:
    - Moderate-to-severe plaque psoriasis involvement: yes or no

A logistic regression model with treatment, subgroup, and the interaction of treatment-by-subgroup included as factors will be used. The treatment-by-subgroup interaction will be tested at the significance level of 0.10. Treatment group effects will be evaluated within each category of the subgroup using Fisher's exact test, regardless of whether the interaction is statistically significant. Missing data will be imputed using NRI, as described in Section 6.4.1. The treatment differences with 95% CIs by each subgroup category will be reported. If any of the subgroups (for example, the age <65 group or the age ≥65 group) is less than 10% of the total population, only descriptive statistics will be provided for that subgroup (that is, no inferential testing).

6.17. Protocol Violations

Protocol deviations will be identified throughout the study. Important protocol deviations are defined as those violations 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.

Table RHCF.6.9 includes the categories and subcategories of important protocol violations, the source of identification for the violation, 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 violation(s) will be summarized within category and subcategory of violations by treatment group for the following:

- Open-Label Treatment Period (ITT Population)

Additional analyses will be conducted on patients who don't have any or a subset of protocol violations for primary and/or major secondary endpoints.

Table RHCF.6.9. Identification and Action of Important Protocol Violations

Important Protocol Violation Category/Subcategory	Source to Identify Protocol Violation	Statistical Programming Guidance for Clinical Study Report
Category: Informed Consent		
Sub-Category: Informed Consent not Obtained/Missing/Late	Monitor and Stats	Either from monitor's list, or, If patient informed consent date is after Visit 1 date or missing informed consent
Subcategory: Improper Informed Consent	Monitor	Monitor's list
Category: Eligibility		
[1] Age <18 years	Monitor	Monitor's list
[1a] Male patients disagree to use a reliable method of birth control during the study.	Monitor	Monitor's list: male patients who disagree to use a reliable method of birth control during the study.
[1b] Pregnancy confirmation at Visit 1 and prior to randomization at Visit 2.	Monitor	Monitor's list: positive pregnancy test result from lab test at Visit 1, and check if patient was randomized and takes drug. Check Visit 2 urine pregnancy test.
[1b] Are women ≥40 and <60 years of age who have had a cessation of menses for at least 12 months, and FSH <40 mIU/mL	Monitor and Stats	Monitor's list: Women ≥40 and <60 years of age who do not have negative bHCG results and who have a FSH <40 mIU/mL at Visit 1.
[1b] Are women of non-childbearing potential, defined as either women who have had surgical sterilization or who are ≥60 years of age	Monitor	Monitor's list: women who have had surgical sterilization.
[2] No confirmed diagnosis of PsA of at least 6 months prior to baseline or did not meet CASPAR criteria	Monitor	Monitor's list
[3] <3 TJC or <3 SJC at Visit 1 or 2	Monitor	Monitor's list.
[4] BSA <3% at Visit 1 or 2	Monitor and Stats	Monitor's list. Check if BSA <3% either at Visit 1 or at Visit 2
[50] Have not been treated with 1 or more csDMARDs	Monitor and Stats	Monitor's list and stats programming. Check past or present use for MTX, sulfasalazine, leflunomide, or hydroxychloroquine

Important Protocol Violation Category/Subcategory	Source to Identify Protocol Violation	Statistical Programming Guidance for Clinical Study Report
[6] Currently enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study	Monitor	Monitor's list.
[7] Have received prior or currently receiving treatment with any biologic or small molecule therapy for PsA or Ps, including investigation therapies (such as, but not limited to, a TNF inhibitor, IL-1 receptor antagonists, IL-6 inhibitor; anti-IL-12/23p40, T cell or B cell targeted therapies, or Janus kinase inhibitors). Note: previous treatment of phosphodiesterase type 4 inhibitors will be permitted. Treatment with phosphodiesterase type 4 inhibitors must have been discontinued at least 8 weeks before randomization (Visit 2).	Monitor	Monitor's list
[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
[9] Have history of drug-induced Ps.	Monitor	Monitor's list
[10] Use of csDMARDs (other than MTX, leflunomide, sulfasalazine, or cyclosporinein) within 8 weeks prior to Visit 2; or have discontinued MTX, leflunomide, sulfasalazine, or cyclosporine within 12 weeks prior to Visit 2.	Monitor	Monitor's list
[11] Have discontinued leflunomide within 4 weeks prior to Visit 2 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
[12] Use of oral corticosteroids at average daily doses of >10 mg/day of prednisone or equivalent, use of variable doses within 4 weeks prior to Visit 2.	Monitor	Monitor's list

Important Protocol Violation Category/Subcategory	Source to Identify Protocol Violation	Statistical Programming Guidance for Clinical Study Report
[13] Have received parenteral glucocorticoids within 6 weeks prior to Visit 2 or if use is anticipated during the first 24 weeks of 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 either a start or end date <42 days prior to the Visit 2 date
[14] Concomitant use of NSAIDs or cyclooxygenase - 2 inhibitors unless on a stable dose for at least 2 weeks prior to Visit 2	Monitor	Monitor's list
[15] Use of opiate analgesics at average daily doses of >30 mg/day of morphine or equivalent or variable doses within 6 weeks prior to Visit 2	Monitor and Stats	Monitor's list, or, If a patient has either a reported previous therapy of opiate analgesics with average dose >30 mg/day or a concomitant medication with ATC codes of N02AA with a start or end date of <42 days prior to Visit 2 date.
[16] Have received systemic nonbiologic Ps therapy other than csDMARDs or corticosteroids as indicated above (including, but not limited to oral psoralens and ultraviolet A light therapy oral retinoids, thioguanine, hydroxyurea, sirolimus, azathioprine, fumaric acid derivatives, or 1, 25 dihydroxy vitamin D3 and analogs) or phototherapy (including either oral and topical ultraviolet A, ultraviolet B, or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to randomization (Visit 2); or had topical Ps treatment within the previous 2 weeks prior to randomization (Visit 2). Note WHO Group 1 weak potency topical steroids are allowed.	Monitor and Stats	Monitor's list, or, If the patient has any record with a start date or an end date <28 days of the Visit 2 date for phototherapy for previous therapy. If the patient has any concomitant medications with a start date or an end date that is on or prior to Visit 2 date, and <28 days prior to the Visit 2 date for oral medications. 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. Note: ATC codes will be provided by medical in a separate file.
[17] Use of tanning booths for at least 4 weeks prior to Visit 2 and during the study for patients with plaque psoriasis.	Monitor	Monitor's list
[18] 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

Important Protocol Violation Category/Subcategory	Source to Identify Protocol Violation	Statistical Programming Guidance for Clinical Study Report
[19] Ever received efalizumab or natalizumab or other agents that target alpha-4-integrin	Monitor	Monitor's list
[20] 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 within 12 weeks of completing treatment in this study, or participated in other vaccine clinical study within 12 weeks prior to Visit 2	Monitor	Monitor's list
[21] Had a BCG (12 months prior to Visit 2), or intent to have this vaccine with BCG during the study or within 12 months of completion of the study	Monitor	Monitor's list
[22] Have diagnosis of other inflammatory arthritic syndrome	Monitor	Monitor's list
[23] Have active Crohn's disease or active ulcerative colitis	Monitor	Monitor's list
[24] Have current diagnosis of fibromyalgia or other chronic pain condition that would confound evaluation of the patient	Monitor	Monitor's list
[25] Evidence of active vasculitis or uveitis	Monitor	Monitor's list
[26] Surgical treatment of joint within 8 weeks prior to Visit 2 or will require such up to Week 24	Monitor	Monitor's list
[27] Had any major surgery within 8 weeks prior to Visit 2, or will require such during the study that, in the opinion of the investigator in consultation with Lilly or its designee, would pose an unacceptable risk to the patient.	Monitor	Monitor's list
[28] Have active or history of malignant disease within the 5 years prior to Visit 2. Note: 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

Important Protocol Violation Category/Subcategory	Source to Identify Protocol Violation	Statistical Programming Guidance for Clinical Study Report
[29] Presence of significant uncontrolled cerebro-cardiovascular (for example, MI, unstable angina, unstable arterial hypertension, moderate-to-severe NYHA class III/IV heart failure, or CVA), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic, or neuropsychiatric disorders, or abnormal laboratory values, or illicit drug use (including cannabinoids, whether legalized or not) at screening that in the opinion of the investigator pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.	Monitor	Monitor's list
[30] Have had uncompensated heart failure, fluid overload, or MI, or evidence of new-onset ischemic heart disease or other serious cardiac disease within 12 weeks prior to Visit 2.	Monitor	Monitor's list
[31] Presence of significant uncontrolled neuropsychiatric disorder; have recent history (within 30 days prior to screening visit (Visit 1) and any time between screening visit (Visit 1) and randomization (Visit 2) of a suicide attempt; or develops active suicidal ideation with some intent to act with or without a specific plan (yes to question 4 or 5 on the "Suicidal Ideation" portion of the C-SSRS) or develops suicide-related behaviors as recorded on the C-SSRS at screening or randomization (Visit 2); or are clinically judged by the investigator to be at risk for suicide.	Monitor and Stats	Monitor's list, or, If a patient has a yes to question 4 or 5 on the "Suicidal Ideation" portion of the C-SSRS or develops suicide-related behaviors as recorded on the C-SSRS at Visits 1 or 2.
[32] Have presence or personal history or family history (first degree relative) of demyelinating disorder.	Monitor	Monitor's list

Important Protocol Violation Category/Subcategory	Source to Identify Protocol Violation	Statistical Programming Guidance for Clinical Study Report
[33] Have serious infection, 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 Visit 2, or have ever had an infection of an artificial joint, or an infection that occurs with increased incidence in an immunocompromised host (including, but not limited to, *Pneumocystis jirovecii* pneumonia, active histoplasmosis, or coccidioidomycosis), or have a known immunodeficiency.	Monitor	Monitor's list
[34] Have a known immunodeficiency or are immunocompromised to an extent such that participation in the study would pose an unacceptable risk to the patient.	Monitor	Monitor's list
[35] Have or had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 12 weeks prior to Visit 2.	Monitor	Monitor's list
[36] Evidence or suspicion of active or latent TB (refer to RHCF Protocol Section 9.4.4.2 for details on determining full TB exclusion criteria).	Monitor	Monitor's list
[37] Have any other active or recent infection other than mentioned above within 4 weeks of randomization (Visit 2) that, in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study. Note: These patients may be rescreened once ≥4 weeks after documented resolution of symptoms	Monitor	Monitor's list
[38] Sitting systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg. Note: Determined by 2 consecutive elevated readings.	Monitor and Stats	Monitor's list, or, If a patient's systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg at Visit 2 (pre-dose read)

Important Protocol Violation Category/Subcategory	Source to Identify Protocol Violation	Statistical Programming Guidance for Clinical Study Report
[39] Are positive for 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
[40] 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 positive for HBV DNA. Note: Patients who are HBsAg-, and HBcAb+ and HBV DNA negative may be enrolled in the study. Patients who meet these criteria at screening will be identified by the central laboratory and monitored during the study as detailed in Section 9.4.5.4 of the RHCF protocol.	Monitor and Stats	Monitor's list; or If test positive for HBV at Visit 1 by testing: 1) positive for hepatitis B surface antigen (HBsAg+), OR 2) positive for anti-hepatitis B core antibody (HBcAb+) AND are HBV DNA positive. Note: If multiple records at Visit 1, use the last observation. Patients who are HBsAg- AND HBcAb+ AND HBV DNA negative can be enrolled. This would not be a protocol violation.
[41] Have evidence of or test positive for 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 HCV.

Important Protocol Violation Category/Subcategory	Source to Identify Protocol Violation	Statistical Programming Guidance for Clinical Study Report
[42] The most recent lab panel meet any of the following criteria: [42a] Neutrophil count <1500 cells/µL [42b] Lymphocyte count <800 cells/µL [42c] Platelet count <100,000 cells/µL [42d] AST or ALT >2.5× ULN [42e] Total WBC count <3000 cells/µL [42f] Hemoglobin <8.5 g/dL (85.0 g/L) for male patients and <8.0 g/dL (80 g/L) for female patients [42g] Serum creatinine >2.0 mg/dL. [42h] Have clinical laboratory test results at screening that are outside the normal reference range for the population and are considered clinically significant, per investigator assessment. Note: Laboratory tests can be repeated a maximum of 1 time, and results must be received and reviewed prior to randomization (Visit 2).	Monitor and Stats	Monitor's list, or, If a patients laboratory tests at Visit 1 indicate any of the following: Neutrophil count <1500 cells/µL Lymphocyte count <800 cells/µL Platelet count <100,000 cells/µL AST or ALT >2.5× ULN Total WBC <3000 cells/µL Hemoglobin <8.5 g/dL for male patients and <8 g/dL for female patients Serum creatinine >2 mg/dL
[43] Have any condition or contraindication as addressed in the local labelling for adalimumab that would preclude the patient from participating in this protocol.	Monitor	Monitor's list
[44] Have any other condition that precludes the patient from following and completing the protocol.	Monitor	Monitor's list
[45] Are women who are breastfeeding	Monitor	Monitor's list
[46] Are study 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
[47] Are Lilly employees or its designee or are employees of third-party organizations involved in the study.	Monitor	Monitor's list

Important Protocol Violation Category/Subcategory	Source to Identify Protocol Violation	Statistical Programming Guidance for Clinical Study Report
[48] Are currently enrolled in, or discontinued from a clinical trial involving an investigational product or nonapproved use of a drug or device within the last 4 weeks or a period of at least 5 half-lives of the last administration of the drug, whichever is longer, or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.	Monitor	Monitor's list
[49] Are unwilling or unable to comply with the use of a data collection device to directly record data from the patient.	Monitor	Monitor's list
Category: Study Procedures		
Sub-Category: Violation of Discontinuation Criteria		
[D1] Discontinuation of the study drug after consultation with medical monitor for abnormal liver tests, defined as having 1 of the following: ALT or AST >8× ULN ALT or AST >5× ULN for more than 2 weeks ALT or AST >3× ULN and total bilirubin level >2× ULN or prothrombin time >1.5× ULN ALT or AST >3×ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) ALP >3× ULN ALP >2.5× ULN and TBL >2× ULN ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	Monitor	Monitor's list

Important Protocol Violation Category/Subcategory	Source to Identify Protocol Violation	Statistical Programming Guidance for Clinical Study Report
[D2] 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 of latest dose 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
[D3] Total WBC count <2000 cells/μL	Monitor and Stats	Monitor's list, or, If a patient still receives study treatment after 10 days of latest dose 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
[D4] Lymphocyte count <500 cells/μL	Monitor and Stats	Monitor's list, or, If a patient still receives study treatment after 10 days of latest dose with confirmed lymphocyte count <500 cells/μL (defined as a test and a retest within 10 days) If no retest, use the test results
[D5] Platelet count <50,000 cells/μL	Monitor and Stats	Monitor's list, or, If a patient still receives study treatment after 10 days of latest dose 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
[D6] Changes in BP defined as sitting systolic BP at ≥160 mm Hg plus ≥20 mm Hg increase from baseline (Week 0, Visit 2) and/or diastolic BP at ≥100 mm Hg plus ≥10 mm Hg increase from baseline that do not respond following maximal allowed intervention.	Monitor	Monitor's list

Important Protocol Violation Category/Subcategory	Source to Identify Protocol Violation	Statistical Programming Guidance for Clinical Study Report
[D7] If the investigator decides that the patient should be withdrawn because of a severe AE, an SAE, or a clinically significant change in a laboratory value, the investigational product is to be discontinued, and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately.	Monitor	Monitor's list
[D8] Patient has a clinically significant systemic hypersensitivity reaction after SC administration of investigational product	Monitor	Monitor's list
[D9] Patient becomes pregnant	Monitor	Monitor's list
[D10] The patient develops a malignancy. (No more than 2 nonmelanoma skin cancers over any 12-month period during the study.)	Monitor	Monitor's list
[D11] Patient develops symptoms suggestive of a lupus-like syndrome or is positive for antibodies against double-stranded DNA	Monitor	Monitor's list
[D12] If the patient for any reason requires treatment with another therapeutic agent that has been demonstrated to be effective for the treatment of PsA.	Monitor	Monitor's list
[D13] 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
[D14] The patient develops active suicidal ideation with some intent to act with or without a specific plan (yes to question 4 or 5 on the "Suicidal Ideation" portion of the C-SSRS) or develops suicide-related behaviors as recorded on the C-SSRS.	Monitor and Stats	Monitor's list, or, If patient still receives study treatment on the same day or after the date with a yes to question 4 or 5 on the "Suicidal Ideation" portion of the C-SSRS or develops suicide-related behaviors as recorded on the C-SSRS.
[D15] The patient develops any condition or contraindication as addressed in the local labelling for adalimumab that would preclude the patient from continuing in this study protocol.	Monitor	Monitor's list

Important Protocol Violation Category/Subcategory	Source to Identify Protocol Violation	Statistical Programming Guidance for Clinical Study Report
[D16] The investigator decides that the patient should be withdrawn from the study	Monitor	Monitor's list
[D17] The patient requests to be withdrawn from the study	Monitor	Monitor's list
[D18] The investigator or Lilly 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
[D19] The patient becomes HBV DNA positive.	Monitor	Monitor's list
[D20] The patient is diagnosed with an active TB infection.	Monitor	Monitor's list
Category: Study Procedures		
Sub-Category: Excluded Con-meds	Monitor and Stats	Either from monitor's list, or If patient takes prohibited concomitant medication. Note: Prohibited concomitant medication (with details of dose restrictions) will be provided by medical in a separate file.
Sub-Category: Lab/Imaging Criteria		
Missing lab chemistry and hematology: missing baseline or not having at least 1 post-baseline	Monitor and Stats	Monitor's list; or If missing lab chemistry and hematology baseline or not having at least 1 post-baseline
Sub-Category: Other		
Missing ACR or PASI	Monitor and Stats	Monitor's list; or If missing any ACR or PASI data at any visit (Weeks 0 through 52).
Missing C-SSRS any visit except Visit 1	Monitor and Stats	From monitor's list; if missing C-SSRS at any visit except Visit 1
Had unqualified site personnel perform clinical safety and/or efficacy assessments	Monitor	Monitor's list
Unblinding of the blinded rater at the site	Monitor	Monitor's list

Category: Investigational Product		
Sub-Category: Treatment Assignment/Randomization Error		
Took incorrect study medication	Monitor and Stats	Monitor's list; or If IWRS study drug dispense data not match with the treatment label identifier on the *Exposure as Collected* eCRF page
Sub-Category: Compliance	Monitor and Stats	Monitor's list; or If non-compliant with study medication regimen or over-dose during the treatment period. Note: Non-compliance with therapy is defined to be missing more than 20% of expected doses and missing 2 or more consecutive doses; over-dose is defined as to take more injections at the same time point than specified in the protocol.
Sub-Category: Patient took medication not fit for use	Monitor	Monitor's list
Sub-Category: Other		
Randomized but did not take any study medication	Monitor	Monitor's list
Sub-Category: Treatment Assignment /Randomization Error		
Stratification error leading to incorrect dosing regimen	Monitor and Stats	Monitor's list; or If IWRS stratification data does not match patients' severity of plaque psoriasis (PASI, sPGA and BSA)

Abbreviations: AE = adverse event; ACR = America College of Rheumatology; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATC = anatomical therapeutic chemical; BCG = Bacille de Calmette et Guérin; bDMARD = biologic disease-modifying antirheumatic drug; bHCG = beta-human chorionic gonadotropin; BP = blood pressure; BSA = body surface area; CASPAR = classification for psoriatic arthritis; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CVA = cerebrovascular accident; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic case report form; FSH = follicle-stimulating hormone; GCP = good clinical practice; HCV = hepatitis C virus; HIV= human immunodeficiency virus; IL = interleukin; IV = intravenous; IWRS = interactive web-response system; JAK = Janus kinase; MI = myocardial infarction; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; NYHA = New York Heart Association; PASI = Psoriasis Area and Severity Index; Ps = psoriasis; PsA = psoriatic arthritis; PUVA = psoralen ultraviolet A; SAE = serious adverse event; SC = subcutaneous; SJC = swollen joint count; TB = tuberculosis; TJC = tender joint count; TNF = tumor necrosis factor; ULN = upper limit of normal; UVB = ultraviolet B; WBC = white blood cell; 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 violation 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

An interim database lock will occur, and the analysis will be performed at the time (that is, a cutoff date) when the last patient completes Visit 8 (Week 24), completes ETV, or discontinues from Period 2. This database lock will include all data collected by the cutoff date including data after Week 24 from the Open-Label Treatment Period and follow-up data from patients who have begun Post-Treatment Follow-Up Period (Period 3).

This interim database lock at Week 24 will be considered the primary database lock for this study because all primary and major secondary study objectives will be assessed at this time.

A final database lock will occur after all enrolled patients have completed or discontinued the Post-Treatment Follow-Up Period.

There will be no data monitoring committee.

6.19. 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 the following:

Summary of adverse events, 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, by MedDRA PT.

- An adverse event is considered "Serious" whether or not it is a TEAE.
- An adverse event 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).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

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8. Appendices

Appendix 1. Definition of Numbers Needed to Treat (NNT)

Numbers needed to treat (NNT) is defined as reciprocal of the difference in response rate between active treatment and comparator (Absolute Risk Reductions [ARR]). For instance, if ADA and IXE had response rates of 30% and 60%, respectively, then NNT=1/(0.6-0.3)=3.3. As for the CI, we take the CI for NNT as the reciprocal of the CI for ARR. The NNT and its CI will not be reported if 0 is included in the CI for ARR, i.e. the superiority test for two treatment arms is not significant.

Reference Table: List of Topical Treatments that are Prescribed/Administered for Psoriasis or Psoriatic Arthritis Patients with Appropriate ATC Code

Topical Treatments	ATC Code
Topical corticosteroids: These powerful anti-inflammatory drugs are the most frequently prescribed medications for treating mild-to-moderate psoriasis. They slow cell turnover by suppressing the immune system, which reduces inflammation and relieves associated itching. Topical corticosteroids range in strength from mild to very strong. Low-potency corticosteroid ointments are usually recommended for sensitive areas, such as your face or skinfolds, and for treating widespread patches of damaged skin. Your doctor may prescribe stronger corticosteroid ointment for small areas of your skin, for persistent plaques on your hands or feet, or when other treatments have failed. Medicated foams and scalp solutions are available to treat psoriasis patches on the scalp. Long-term use or overuse of strong corticosteroids can cause thinning of the skin and resistance to the treatment's benefits. To minimize side effects and to increase effectiveness, topical corticosteroids are generally used on active outbreaks until they are under control.	D07-- (Level 2)
Vitamin D analogs: These synthetic forms of vitamin D slow down the growth of skin cells. Calcipotriene (Dovonex) is a prescription cream or solution containing a vitamin D analog that may be used alone to treat mild-to-moderate psoriasis or in combination with other topical medications or phototherapy. This treatment can irritate the skin. Calcitriol (Rocaltrol) is expensive, but may be equally effective and possibly less irritating than calcipotriene.	A11CC
Anthralin: This medication is believed to normalize DNA activity in skin cells. Anthralin (Dritho-Scalp) can also remove scale, making the skin smoother. However, anthralin can irritate skin, and it stains virtually anything it touches, including skin, clothing, countertops, and bedding. For that reason, doctors often recommend short-contact treatment – allowing the cream to stay on your skin for a brief time before washing it off. Anthralin is sometimes used in combination with ultraviolet light.	D05AC
Topical retinoids: These are commonly used to treat acne and sun-damaged skin, but tazarotene (Tazorac, Avage) was developed specifically for the treatment of psoriasis. Like other vitamin A derivatives, it normalizes DNA activity in skin cells and may decrease inflammation. The most common side effect is skin irritation. It may also increase sensitivity to sunlight, so sunscreen should be applied while using the medication. Although the risk of birth defects is far lower for topical retinoids than for oral retinoids, your doctor needs to know if you are pregnant or intend to become pregnant if you are using tazarotene.	D05BB
Calcineurin inhibitors: Currently, calcineurin inhibitors – tacrolimus (Prograf) and pimecrolimus (Elidel) – are approved only for the treatment of atopic dermatitis, but studies have shown them to be effective, at times, in the treatment of psoriasis. Calcineurin inhibitors are thought to disrupt the activation of T cells, which in turn reduces inflammation and plaque buildup. The most common side effect is skin irritation. Calcineurin inhibitors are not recommended for long-term or continuous use because of a potential increased risk of skin cancer and lymphoma. Calcineurin inhibitors are used only with your doctor's input and approval. They may be especially helpful in areas of thin skin, such as around the eyes, where steroid creams or retinoids are too irritating or may cause harmful effects.	L04AD
Salicylic acid: Available over-the-counter (nonprescription) and by prescription, salicylic acid promotes sloughing of dead skin cells, and reduces scaling. Sometimes it is combined with other medications, such as topical corticosteroids or coal tar, to increase its effectiveness. Salicylic acid is available in medicated shampoos and scalp solutions to treat scalp psoriasis.	D02AF
Coal tar: A thick, black byproduct of the manufacture of petroleum products and coal, coal tar is probably the oldest treatment for psoriasis. It reduces scaling, itching, and inflammation. Exactly how it works is not known. Coal tar has few known side effects, but it is messy, stains clothing and bedding, and has a strong odor. Coal tar is available in over-the-counter shampoos, creams, and oils. It is also available in higher concentrations by prescription.	D05AA

Topical Treatments	ATC Code
Moisturizers: By themselves, moisturizing creams will not heal psoriasis, but they can reduce itching and scaling and can help combat the dryness that results from other therapies. Moisturizers in an ointment base are usually more effective than are lighter creams and lotions.	D02A- (Level 3)
Calcipotriene	D05AX
Tazarotene	D05AX
Herbal and traditional preparations	V90

Note: ATC = WHOCC Anatomical Therapeutic Chemical classification system; WHOCC = World Health Organization Collaborating Centre for Drug Statistics Methodology.

Appendix 2. Algorithm for Determining ACR Responses

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.

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 three of the following five items:

- Patient's global assessment of arthritis pain;
- Patient's global assessment of disease activity;
- Physician's global assessment of disease activity;
- HAQ-DI;
- 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 seven 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 ACRx response as blank (ie, missing). Otherwise, calculate the % improvement at the visit for all seven parameters as described above.
- **Step2:**
  - If TJC68 AND SJC66 are BOTH ≥x%, then proceed to step3.
  - If both are nonmissing but one or both is <x%, then STOP – assign the patient as a non-responder for ACRx.
  - If either or both are missing, proceed as follows:
    a. If both are missing, then STOP – assign ACRx response as blank (ie, missing).
    b. If one of TJC68 or SJC66 is missing and the nonmissing value is <*x*%, then STOP – assign the patient as a non-responder for ACR*x*.

c. If one of TJC68 or SJC66 is missing and the nonmissing value is ≥*x*%, then STOP – assign ACRx response as blank (ie, missing).

- **Step3:** Consider the following five variables: PTPAIN, PTDISACT, PHYSDISACT, HAQ, and CRP.
  - If three or more items are missing, then STOP – assign ACRx response as blank (ie, missing).
  - If three or more items are nonmissing, then proceed with the following order:
    a. If at least three items are ≥*x*%, then STOP – assign the patient as a responder for ACR*x*.
    b. If at least three items are <*x*%, then STOP – assign the patient as a non-responder for ACR*x*.
    c. If less than three items are ≥*x*%, then STOP – assign ACR*x* response as blank.

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 HAQ-DI

The 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; Ramey et al. 1996).

- **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 five 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 less than six categories completed, a HAQ-DI cannot be computed.

- A category score is determined from the highest score of the sub-categories, or components, in that category. (For example, in the category ARISING there are three 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 zero or a one to a two. If a patient's highest score for that sub-category is a two it remains a two, and if a three, it remains a three.
    - Sum the eight 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 (i.e., 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	Raised toilet seat, bathtub seat, bathtub bar, long-handled appliances in bathroom
Reach	Long handled appliances for reach
Grip	Jar opener (for jars previously opened)

Appendix 5. Algorithm for Calculating CPDAI and mCPDAI

CPDAI is a validated composite instrument to assess 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 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
- dactylitis as assessed by the number of digits affected and the HAQ-DI
- spinal disease as assessed by the BASDAI and 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 HAQ-DI	0-68/0-66 0-3
Skin disease	PASI DLQI	0-72 0-30
Enthesitis	LEI HAQ-DI	0-6 0-3
Dactylitis	Digit Score HAQ-DI	0-20 0-3
Spinal disease	BASDAI ASQoL	0-10 0-18

Each domain is scored from 0–3. 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 by the eCRF or 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 by the eCRF	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 eCRF	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

The modified CPDAI will sum up each domain with the exception of spinal disease score (0–3). The composite scores range from 0 to 12 for the assessment, with a higher score indicating higher disease activity.

Appendix 6. Deviation 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 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 period (The SF Community – SF-36 Health Survey Update [WWW]).

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 2009 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 U.S. 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 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, Range 1-3	Walking several hundred yards
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

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
				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?
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

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
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
	Sex			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

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 a 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 Treatments and Anatomical Therapeutic Chemical (ATC) Code List

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
G01AG	4	TRIAZOLE DERIVATIVES
G01AX	4	OTHER ANTIINFECTIVES AND ANTISEPTICS
G01BA	4	ANTIBIOTICS AND CORTICOSTEROIDS

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18JAN2016)
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
J01MB	4	OTHER QUINOLONES
J01R	3	COMBINATIONS OF ANTIBACTERIALS
J01RA	4	COMBINATIONS OF ANTIBACTERIALS

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18JAN2016)
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
P01BE	4	ARTEMISININ AND DERIVATIVES, PLAIN
P01BF	4	ARTEMISININ AND DERIVATIVES, COMBINATIONS
P01BX	4	OTHER ANTIMALARIALS

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18JAN2016)
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
S02CA	4	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION
S03A	3	ANTIINFECTIVES
S03AA	4	ANTIINFECTIVES

ATC Code	ATC Level	ATC Description (Based on ATC Dictionary 18JAN2016)
S03C	3	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION
S03CA	4	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION

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

Appendix 8. Lilly-Defined MedDRA V21.0 Preferred Terms for Opportunistic Infections (OIs)

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
Pneumocystis jirovecii (II)	Pneumocystis jirovecii infection Pneumocystis jirovecii pneumonia	Narrow
	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 Pneumocystis test positive	Broad
Human Polyomavirus Infection including BK virus disease and PVAN (V), and Progressive Multifocal Leukoencephalopathy (IV)	BK virus infection Human polyomavirus infection JC virus granule cell neuronopathy JC virus infection Polyomavirus-associated nephropathy Progressive multifocal leukoencephalopathy	Narrow
	Anti-JC virus antibody index JC polyomavirus test JC virus test JC virus test positive Polyomavirus test Polyomavirus test positive	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 Cytomegalovirus myocarditis	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Cytomegalovirus oesophagitis Cytomegalovirus pancreatitis Cytomegalovirus pericarditis Cytomegalovirus syndrome Cytomegalovirus urinary tract infection Cytomegalovirus viraemia 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
	NA	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	Broad

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Toxoplasmosis	
Coccidioidomycosis (II)	Coccidioides encephalitis Coccidioidomycosis Cutaneous coccidioidomycosis Meningitis coccidioides	Narrow
	NA	Broad
Histoplasmosis (II)	Acute pulmonary histoplasmosis Chronic pulmonary histoplasmosis Endocarditis histoplasma Histoplasmosis Histoplasmosis cutaneous Histoplasmosis disseminated Meningitis histoplasma Pericarditis histoplasma Retinitis histoplasma	Narrow
	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	Broad

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Candida test Candida test positive Mucocutaneous candidiasis Oral candidiasis Oral fungal infection Respiratory moniliasis	
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 Phaeohyphomycotic brain abscess Pseudallescheria infection Pseudallescheria sepsis	Narrow
	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
	Listeria test Listeria test positive Listeraemia Listeriosis	Broad
Tuberculosis (I)	Adrenal gland tuberculosis Bone tuberculosis Choroid tubercles	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	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 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	Broad

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Mycobacterium tuberculosis complex test Mycobacterium tuberculosis complex test positive Tuberculin test Tuberculin test false negative Tuberculin test positive	
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 only) (II)	Aortitis salmonella Arthritis salmonella Meningitis salmonella Osteomyelitis salmonella	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Paratyphoid fever Pneumonia salmonella Salmonella bacteraemia Salmonella sepsis 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 antigen Hepatitis B antigen positive Hepatitis B core antigen Hepatitis B core antigen positive Hepatitis B DNA assay Hepatitis B DNA assay positive Hepatitis B DNA increased 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 viraemia	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
	Herpes simplex visceral Meningitis herpes Meningoencephalitis herpetic Meningomyelitis herpes 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 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
	NA	Broad
Paracoccidioides infections (V)	Paracoccidioides infection Pulmonary paracoccidioidomycosis	Narrow
	NA	Broad
Penicillium marneffei (V)	Penicilliosis	Narrow
	Penicillium test positive	Broad
Sporothrix schenckii (V)	Cutaneous sporotrichosis Pulmonary sporotrichosis Sporotrichosis	Narrow
	NA	Broad

Opportunistic Infection	Preferred Term (MedDRA Version 21.0)	Lilly Defined Classification
Cryptosporidium species (chronic disease only) (IV)	Biliary tract infection cryptosporidial	Narrow
	Cryptosporidiosis infection Gastroenteritis cryptosporidial	Broad
Microsporidiosis (IV)	Microsporidia infection	Narrow
	NA	Broad
Leishmaniasis (Visceral only) (IV)	Visceral leishmaniasis	Narrow
	Leishmaniasis	Broad
Trypanosoma cruzi infection (Chagas' Disease) (progression of chronic and disseminated disease only) (V)	 Chagas' cardiomyopathy Meningitis trypanosomal	Narrow
	American trypanosomiasis Trypanosomiasis Trypanosoma serology positive	Broad
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)	NA	Narrow
	Vibrio test positive Vibrio vulnificus infection	Broad
HCV progression (V)	 NA	Narrow
	Chronic hepatitis C Hepatitis C Hepatitis C RNA Hepatitis C RNA increased Hepatitis C RNA fluctuation Hepatitis C RNA positive Hepatitis C virus test Hepatitis C virus test positive	Broad
Non-specific terms	 NA	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	Broad

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

Abbreviations: EBV = Epstein-Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus; NA = not applicable; PVAN = polyomavirus-associated nephropathy.

Appendix 9. 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 asthmaticus
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 10. Allergic Reactions/Hypersensitivity MedDRA Preferred Term List

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.

Preferred Terms (MedDRA v.21.0) from Hypersensitivity SMQ Excluded from 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	Shock
Arthritis allergic	Shock symptom
Aspirin-exacerbated respiratory disease	Skin test positive
Asthma-chronic obstructive pulmonary disease overlap syndrome	Solvent sensitivity
	Stoma site hypersensitivity
Blepharitis allergic	Stoma site rash
Blood immunoglobulin E abnormal	Urticaria contact
Blood immunoglobulin E increased	Urticarial vasculitis
Bromoderma	Vaccination site dermatitis
Catheter site dermatitis	Vaccination site exfoliation
Catheter site eczema	Vaccination site eczema
Catheter site hypersensitivity	Vaccination site hypersensitivity
Catheter site rash	Vaccination site rash

Preferred Terms (MedDRA v.21.0) from Hypersensitivity SMQ Excluded from Analysis	
Catheter site urticaria	Vaccination site recall reaction
Catheter site vasculitis	Vaccination site urticaria
Chronic eosinophilic rhinosinusitis	Vaccination site vasculitis
Chronic hyperplastic eosinophilic sinusitis	Vaccination site vesicles
Circulatory collapse	Vessel puncture site rash
Conjunctivitis allergic	Vessel puncture site vesicles
Contact stomatitis	Vulvovaginal rash
Complement factor decreased	Acute respiratory failure
Complement factor increased	Allergy to chemicals
Complement factor C1 decreased	Allergy to fermented products
Complement factor C1 increased	Anti-insulin antibody increased
Complement factor C2 decreased	Anti-insulin antibody positive
Complement factor C2 increased	Anti-insulin receptor antibody increased
Complement factor C3 decreased	Anti-insulin receptor antibody positive
Complement factor C3 increased	Blood immunoglobulin A abnormal
Complement factor C4 decreased	Blood immunoglobulin A increased
Complement factor C4 increased	Blood immunoglobulin D increased
Complement fixation abnormal	Blood immunoglobulin G abnormal
Complement fixation test positive	Blood immunoglobulin G increased
Contrast media allergy	Blood immunoglobulin M abnormal
Contrast media reaction	Blood immunoglobulin M increased
Dennie-Morgan fold	Immune complex level increased
Dermatitis acneiform	Immunoglobulins abnormal
Dermatitis contact	Immunoglobulins increased
Dermatitis herpetiformis	Immunology test abnormal
Dermatitis infected	Haemolytic transfusion reaction
Device allergy	Infantile asthma
Dialysis membrane reaction	Fixed eruption
Distributive shock	Rhinitis perennial
Drug cross-reactivity	Seasonal allergy
Drug provocation test	
Eczema infantile	
Eczema vaccinatum	
First use syndrome	
Fixed drug eruption	
Giant papillary conjunctivitis	
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	

Preferred Terms (MedDRA v.21.0) from Hypersensitivity SMQ Excluded from Analysis	
Infusion site rash	
Infusion site recall reaction	
Infusion site urticaria	
Infusion site vasculitis	
Injection site dermatitis	
Injection site eczema	
Injection site hypersensitivity	

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
	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