Statistical Analysis Plan I1F-MC-RHBH (Version 2)

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

NCT03364309

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# 1. Statistical Analysis Plan:

# I1F-MC-RHBH: A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Maintenance Dosing Period to Evaluate the Efficacy and Safety of LY2439821 in Chinese Patients with Moderate-to-Severe Plaque Psoriasis

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Ixekizumab (LY2439821) Psoriasis

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

Statistical Analysis Plan Version 2 electronically signed and approved by Lilly: on date provided below.

Approval Date:

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# 2. Table of Contents

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# 3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to first unblinding.

SAP Version 2 was approved prior to final database lock. The major changes made in this revision are as follows:

- In section 6.1.2, added sensitivity analysis (categorical MMRM) for selected endpoints in the intent-to-treat population.
- In section 6.1.3.1, added sensitivity analysis (categorical MMRM) for selected endpoints in maintenance dosing period primary population.
- In section 6.4, added a listing for patient disposition from study and study treatment due to COVID-19, respectively.
- In section 6.5, added a listing of protocol deviations due to COVID-19.
- In section 6.10 Table RHBH. 6.7, MMRM analysis for Joint Pain VAS change from baseline will be based on 'ITT population - patients with baseline psoriatic arthritis' instead of 'ITT population - patients with baseline Joint Pain VAS >0'. The change was made so the anlaysis is consistent with the objective in section 4.2.2

# 4. Study Objectives

## 4.1. Primary Objectives

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

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

## 4.2. Secondary Objectives

### *4.2.1. Major Secondary Objectives*

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

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

### *4.2.2. Other Secondary Objectives*

The other secondary objectives of the study are as follows:

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

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

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

# 5. Study Design

This section contains the summary of study design, the method of treatment assignment, and the sample size determination from the protocol for Study I1F-MC-RHBH.

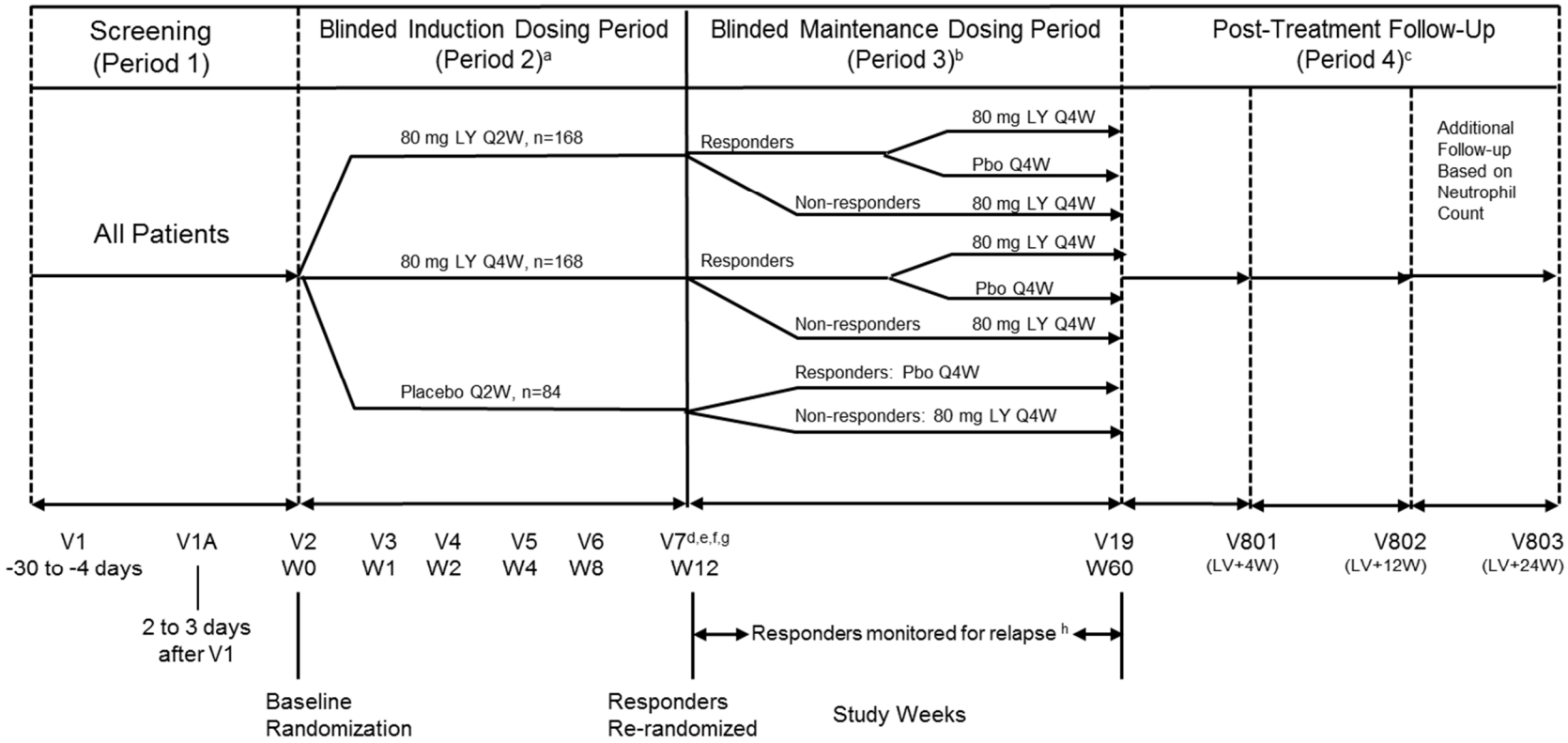
## 5.1. Summary of Study Design

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

The study consists of 4 periods:

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

Figure RHBH. 5.1. illustrates the study design.




Abbreviations: LV = last visit; n = sample size; Q2W = every 2 weeks; Q4W = every 4 weeks; V = visit; W = week.

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

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

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

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

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

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

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

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

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

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

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

## 5.2. Method of Assignment to Treatment

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

**At Week 12 (Visit 7)**, patients who enter Period 3 will be classified as a responder (sPGA score of 0 or 1) or non-responder (sPGA score of >1). Patients who received ixekizumab during Period 2 and who are responders will be re-randomized at a 2:1 ratio to 80 mg Q4W or placebo using the IWRS. Patients will be stratified by ixekizumab induction dosing regimen (80 mg Q2W or 80 mg Q4W). Patients who received placebo during Period 2 and who are responders will be assigned to continue to receive placebo until relapse occurs. Relapse (loss of response) is defined as an sPGA score of ≥3. Non-responders who received any investigational product (assigned to any treatment group) during Period 2 will be assigned to receive treatment with 80 mg ixekizumab Q4W. Assignment to treatment will be determined by the IWRS.

## 5.3. Determination of Sample Size

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

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

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

between the ixekizumab dosing interval and placebo within each original treatment group, assuming the proportions of patients maintaining a PASI 75 are 70% for 80 mg Q4W and 10% for placebo within each original treatment group. A 2-sided Fisher's exact test at the 0.025 significance level is assumed.

# 6. A Priori Statistical Methods

## 6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (hereafter Lilly). The statistical analyses will be performed using SAS® Version 9.2 or higher. The latest version of the Medical Dictionary for Regulatory Activities (MedDRA®) will be used.

Not all displays and analyses described in this SAP will necessarily be included in the CSR. Not all displays will necessarily be created as a "static" display. Some displays may be incorporated as interactive display tools such as Spotfire instead of or in addition to a static display. Any display described in this SAP and not provided in CSR would be available upon request.

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

### *6.1.1. Analysis Population*

The following major analysis populations will be used (additional analysis populations for specific analysis will be defined in the corresponding analysis section):

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

**Per Protocol Set (PPS):** In addition, the primary analysis will be repeated using the per protocol set (PPS), which is defined as all randomized patients who are compliant with therapy, who do not have a subset of important protocol deviations that impact the primary efficacy endpoint (Section 6.5), and whose investigator site does not have significant good clinical practice (GCP) issues that require a report to the regulatory agencies prior to Week 12 (Visit 7). Compliance with therapy is defined to be missing no more than 20% of expected doses, not missing 2 consecutive doses, and no double dosing (that is, taking more injections at the same time point than specified in the protocol) during the period that patients participated in the study and prior to Week 12 (Visit 7) (see Section 6.8). Patients will be analyzed according to the treatment to which they are assigned.

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

**Maintenance Dosing Period Primary population:** defined as all re-randomized patients (that is, patients randomized to ixekizumab in Period 2 who achieved an sPGA (0, 1) and were re-randomized at Week 12) who received at least 1 dose of study treatment during Period 3.

Patients will be analyzed according to the treatment to which they were re-randomized. Only information prior to relapse will be presented.

**Maintenance Dosing Period Secondary population:** defined as the ixekizumab patients who were not re-randomized at Week 12 or patients who were randomized to placebo at Week 0, who received at least 1 dose of study treatment during Period 3. Patients will be analyzed according to the treatment to which they were assigned upon entry into Period 3.

**Maintenance Dosing Period Relapse population:** defined as all patients who were responders at Week 12 (that is, patients who achieved an sPGA (0,1) at Week 12) who first experience a relapse (sPGA ≥3) at any point during the maintenance dosing period (that is, Period 3). Although all patients will receive 80 mg Q4W, patients will be analyzed according to the treatment to which they were re-randomized or assigned at Week 12 (see treatment groups defined in Table RHBH. 6.1.).

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

Table RHBH. 6.1. describes the treatment groups and the comparisons for each study period and the analysis population.

## Table RHBH. 6.1. Treatment Groups and Comparisons for Each Study Period and Analysis Population

| Study Period | Analysis Population | Treatment Group | Abbreviation | Comparison |
|---|---|---|---|---|
| Induction Dosing Period (Period 2) | Intent-to-Treat Population; Per Protocol Set; Safety Population | Placebo | PBO | IXE80Q4W vs. PBO; IXE80Q2W vs. PBO; Overall [a] |
| | | Ixekizumab 80 mg Q4W | IXE80Q4W | |
| | | Ixekizumab 80 mg Q2W | IXE80Q2W | |
| | | Total Ixekizumab | Total IXE | |
| | | Total | Total | |
| Maintenance Dosing Period (Period 3) | Maintenance Dosing Period Primary Population (by Individual Dose) | Ixekizumab 80 mg Q4W/Placebo | IXE80Q4W/PBO | IXE80Q4W/IXE80Q4W vs IXE80Q4W/PBO; IXE80Q2W/IXE80Q4W vs IXE80Q2W/PBO Overall [a] |
| | | Ixekizumab 80 mg Q4W/Ixekizumab 80 mg Q4W | IXE80Q4W/IXE80Q4W | |
| | | Ixekizumab 80 mg Q2W/Placebo | IXE80Q2W/PBO | |
| | | Ixekizumab 80 mg Q2W/ Ixekizumab 80 mg Q4W | IXE80Q2W/IXE80Q4W | |
| | | Total | Total | |
| | Maintenance Dosing Period Primary Population (by Pooled Dose) | Ixekizumab/Placebo | IXE/PBO | IXE/IXE vs IXE/PBO |
| | | Ixekizumab/Ixekizumab | IXE/IXE | |
| | | Total | Total | |
| | Maintenance Dosing Period Secondary Population [b] | PlaceboResp/Placebo | PBOResp/PBO | No Comparison |
| | | PlaceboNonR/Ixekizumab 80 mg Q4W | PBONonR/IXE80Q4W | |
| | | Ixekizumab 80 mg Q4WNonR/Ixekizumab 80 mg Q4W | IXE80Q4WNonR/IXE80Q4W | |
| | | Ixekizumab 80 mg Q2WNonR/Ixekizumab 80 mg Q4W | IXE80Q2WNonR/IXE80Q4W | |
| | | Total Ixekizumab | Total IXE | |
| | | Total | Total | |
| | Maintenance Dosing Period Relapse Population | PlaceboResp/Placebo | PBOResp/PBO | No Comparison |
| | | Ixekizumab 80 mg Q4W/Placebo | IXE80Q4W/PBO | |
| | | Ixekizumab 80 mg Q4W/Ixekizumab 80 mg Q4W | IXE80Q4W/IXE80Q4W | |
| | | Ixekizumab 80 mg Q2W/Placebo | IXE80Q2W/PBO | |
| | | Ixekizumab 80 mg Q2W/Ixekizumab 80 mg Q4W | IXE80Q2W/IXE80Q4W | |
| | | Total | Total | |
| Post-Treatment Follow-Up Period (Period 4) [c] | Follow-Up Population | Placebo | PBO | No Comparison |
| | | Ixekizumab 80 mg Q4W | IXE80Q4W | |
| | | Ixekizumab 80 mg Q2W | IXE80Q2W | |
| | | Total Ixekizumab | Total IXE | |
| | | Total | Total | |

Abbreviations: IXE = ixekizumab; Q2W = every 2 weeks; Q4W = every 4 weeks; vs. = versus.

[a] Overall comparison will be conducted for demographics, historical illness, medical history, preexisting condition, and previous therapy. The pairwise comparisons and the overall comparison will be conducted for concomitant therapy, compliance, disposition, and safety.

[b] For maintenance dosing secondary population, 'Total IXE' is the pooled group of PBONonR/IXE80Q4W, IXE80Q4WNonR/IXE80Q4W and IXE80Q2WNonR/IXE80Q4W.

[c] Treatment Group refers to the treatment regimen that the patient received prior to entering Period 4.

### 6.1.2. General Considerations for Analyese during Period 2 (Induction Dosing Period)

Period 2 starts after the first dose of study treatment (Visit 2, Week 0) and ends prior to the first injection of study treatment at Week 12 (Visit 7) or the early discontinuation visit (between Weeks 0 and 12). If a patient has Visit 7 but does not receive injection at Week 12 (Visit 7), the last recorded time for Visit 7 is used as the end time for Period 2.

Baseline for ITT and Safety Populations will be defined as the last available value before the first injection for efficacy, health outcomes, and safety analyses. In most cases, this will be the measure recorded at Week 0 (Visit 2). For efficacy/health outcome measures, if the patient does not take any injection, the last available value on or prior to randomization date will be used. Change from baseline (CFB) will be calculated as the visit value of interest minus the baseline value. For safety analyses using a baseline period, the baseline period is defined as the time from Visit 1 to the date/time of the first injection.

Comparisons between each ixekizumab treatment group (80 mg Q2W or 80 mg Q4W) and placebo will be performed for all analyses in Period 2.

The primary analysis method for treatment comparisons of categorical efficacy and health outcomes variables will be a logistic regression analysis with treatment as a factor using PROC Logistic. The odds ratio and the corresponding 95% CIs, as well as the treatment differences and the corresponding 95% CIs, will be reported. Secondary analysis will be conducted using a Fisher's exact test. In the case when logistic regression model does not produce statistical results due to sparse data, Fisher's exact test will be used.

For all categorical efficacy and health outcome variables that are collected at repeated visits, treatment group comparisons will be analyzed at each visit using the logistic regression model. Missing data will be imputed using the NRI method (Section 6.2.1).

As a sensitivity analysis for selected categorical efficacy measures e.g. sPGA (0,1), sPGA (0), PASI 75/90/100, a categorical, pseudo-likelihood based mixed-effects model of repeated measures (categorical mixed-effects model of repeated measures [MMRM]) estimating the percentage of patients achieving response across postbaseline visits will be used. The model will include treatment, baseline value, visit, treatment-by-visit and baseline-by-visit interactions as fixed factors. The binomial distribution and the logit link function will be used. The restricted maximum likelihood (REML) will be used. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The Newton-Raphson with ridging optimization technique will be used to aid with convergence. The probability of response, the corresponding 2-sided 95% CI, and the p-value for treatment comparisons at Week 12 (Visit 7) and all other postbaseline visits will be reported.

The primary analyses for the continuous efficacy and health outcomes variables will be made using mixed effects for repeated measures (MMRM) analysis. A secondary analysis for selected continuous efficacy and health outcomes variables will be made using analysis of covariance (ANCOVA).

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

When the ANCOVA model is used, the model includes treatment, and baseline value with the last observation carried forward (LOCF) (Section 6.2.2). Type III sums of squares for the LS means will be used for the statistical comparison; the 95% CI will be reported.

For variables that are not collected at each post-baseline visit, data may exist at visits where the variable was not scheduled to be collected, due to early discontinuation visits. In these situations, data from the early discontinuation visit that does not correspond to the planned collection schedule will be excluded from the MMRM analyses. However, the data will still be used in other analyses, including shift analyses, change from baseline to LOCF endpoint analyses, and other categorical analyses.

Time to first clinical response (e.g. sPGA (0,1)) on initially assigned treatment will be assessed based on the ITT Population in Period 2. Unless otherwise specified, time to first clinical response (e.g. sPGA (0,1)) is defined as:

*Time to first clinical response (days) = Date of first clinical response during Period 2 on initially assigned treatment – Date of Week 0 randomization + 1*

If a patient has not met the criteria for response by completion or early discontinuation of Period 2 on initially assigned treatment, the patient will be censored at the date of their last visit during Period 2.

A Kaplan-Meier plot of the time to first clinical response by treatment group will be provided. The number of patients at risk and experiencing a response by each scheduled visit during Period 2 will be presented by treatment group. Treatment group comparisons will be performed using the log-rank test.

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

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

Period 3 starts at the first injection of study treatment at Week 12 (Visit 7) and ends on the date of Week 60 (Visit 19) or the date of the ETV (if it occurs between Weeks 12 and 60).

For Period 3 efficacy and health outcomes analyses, baseline is defined as the last non-missing assessment recorded on or prior to the date of first injection of study treatment at Week 0 (Visit 2). In most cases, this will be the measure recorded at Week 0 (Visit 2).

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

For patients who met relapse criteria (loss of response; sPGA ≥3) and were retreated with ixekizumab, only data up to the time of relapse will be included in the maintenance of effect analyses. These patients will be considered non-responders to categorical assessments per the NRI imputation method (see Section 6.2.1).

#### 6.1.3.1. Maintenance Dosing Period Primary Population

Unless otherwise specified, treatment comparisons of categorical efficacy and health outcomes variables will be analyzed using a logistic regression model with treatment group fitted as an explanatory variable. The odds ratio and the corresponding 95% CIs, as well as the treatment differences and the corresponding 95% CIs, will be reported. Secondary analysis on the categorical efficacy and health outcome variables will be conducted using a Fisher's exact test.

As a sensitivity analysis for selected categorical efficacy measures e.g. sPGA (0,1), sPGA (0), PASI 75/90/100, a categorical, pseudo-likelihood based mixed-effects model of repeated measures (categorical mixed-effects model of repeated measures [MMRM]) estimating the percentage of patients achieving response across postbaseline visits will be used. The model will include treatment, baseline value, visit, treatment-by-visit and baseline-by-visit interactions as fixed factors. The binomial distribution and the logit link function will be used. The restricted maximum likelihood (REML) will be used. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The Newton-Raphson with ridging optimization technique will be used to aid with convergence. The probability of response, the corresponding 2-sided 95% CI, and the p-value for treatment comparisons at Week 60 (Visit 19) and all other postbaseline visits will be reported.

Treatment comparisons for continuous efficacy and health outcomes variables will be made using MMRM models. ANCOVA models will also be used for selected continuous efficacy and health outcomes variables.

When MMRM is used, the model will include treatment, baseline value, visit, treatment-by-visit, and baseline-by-visit interactions as fixed factors. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of

convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by compound symmetry will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least-squares (LS) means will be used for the statistical comparison; the 95% CI will be reported. Treatment arm comparisons with placebo at Week 60 (Visit 19) and all other visits will be tested.

When the ANCOVA model is used, the model includes treatment and baseline value in the model. Type III sums of squares for the LS means will be used for the statistical comparison. For each treatment comparison performed, the LS mean for each treatment group, an estimate of the difference between treatments, corresponding 95% CI and p-value will be presented.

The time to relapse (loss of response; sPGA ≥3) during Period 3 is defined as:

$$Time\ to\ relapse\ (days) = date\ of\ first\ sPGA\ \geq 3\ during\ Period\ 3 - date\ of\ Week\ 12\ re\text{-}randomization\ +\ 1.$$

If a patient has not experienced relapse by completion or early discontinuation of Period 3, the patient will be censored at the date of their last visit during Period 3.

For each treatment group, a Kaplan-Meier plot of the time to relapse will be provided. The number of patients at risk and experiencing a relapse event by each scheduled visit during Period 3 will be presented by treatment group. Within each induction treatment group, maintenance treatment group comparisons will be performed using the log-rank test.

For the safety analyses, treatment group comparisons will be performed. Fisher's exact test will be used for all AE, baseline, discontinuation, and other categorical data. The continuous baseline characteristics will be analyzed using an ANOVA model with treatment as a factor. Continuous vital sign, and laboratory values will be analyzed by an ANCOVA model with treatment and baseline value as independent variables.

#### 6.1.3.2. Maintenance Dosing Period Secondary Population

The number and percentage of patients achieving or maintaining a categorical efficacy and health outcome responses (that is, sPGA (0,1), sPGA (0), PASI 75, PASI 90, PASI 100, etc.) will be summarized by treatment group for all scheduled visits (NRI), including Week 60 (NRI).

Continuous efficacy and health outcomes measures will be summarized by treatment group at all scheduled visits during Period 3, including Week 60 (LOCF) using descriptive statistics (n, mean, SD, median, minimum and maximum).

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

#### 6.1.3.3. Maintenance Dosing Period Relapse Population

For patients who were retreated with ixekizumab following loss of response (relapse), the proportion of patients maintaining or achieving categorical efficacy and health outcome responses (that is, sPGA (0,1), sPGA (0), PASI 75, PASI 90, PASI 100) within 12 weeks after ixekizumab retreatment will be summarized by treatment group. For the safety analyses on the

Maintenance Dosing Period Relapse population with ixekizumab retreatment, baseline is defined as the last non-missing assessment on or prior to the first dose of re-treatment. The treatment period for the Maintenance Dosing Period Relapse population with ixekizumab retreatment starts at the time of the relapse visit (first dose of re-treatment) and ends on the date of Week 60 (Visit 19) or the ETV (if it occurs between the relapse visit and Week 60).

The categorical safety measures will be summarized with incidence rates.

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

For Period 4 safety analyese, baseline is defined as the last non-missing assessment on or prior to entering Period 4, i.e. on or prior to Week 60 (Visit 19) or ETV.

Selected safety data will be summarized using descriptive statistics.

## 6.2. Handling of Dropouts or Missing Data

The methods for imputation of missing data to be used in this study are in accordance with the precedent set in other Phase 3 psoriasis trials (Leonardi et al. 2008; Papp et al. 2008) and ixekizumab Phase 3 studies (RHAZ, RHBA, and RHBC).

### *6.2.1. Nonresponder Imputation (NRI)*

Analysis of categorical efficacy and health outcomes variables will be assessed using a NRI method. Patients will be considered a nonresponder for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data at the analysis time point. Randomized patients without at least 1 post-baseline observation will also be defined as nonresponders for the NRI analysis.

### *6.2.2. Last Observation Carried Forward (LOCF)*

A LOCF analysis will be performed on selected continuous efficacy and health outcomes variables as secondary analysis. For patients discontinuing investigational product for any reason, the last non-missing postbaseline observation before discontinuation will be carried forward to the corresponding endpoint for evaluation. Randomized patients without at least 1 post-baseline observation will not be included for evaluation.

## 6.3. Multiple Comparisons/Multiplicity

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

In order to reflect the test order and how the multiple doses will be analyzed, the doses have been renamed and the treatment comparisons to be performed in each dosing period are shown in Table RHBH. 6.2. (treatment groups will be presented as defined in Section 6.1.1).

**Table RHBH. 6.2. Treatment Comparisons during the Induction Dosing Period and Maintenance Dosing Period**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## 6.4. Patient Disposition

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

Patient disposition from study will be listed for the ITT population and summarized with reasons for disposition for the ITT population and the follow-up population, respectively. Patient disposition from study due to COVID-19 will also be listed.

Patient disposition from study treatment will be listed for the ITT population and summarized for the ITT population in Period 2 and the Maintenance Dosing Period Primary/Secondary/Relapse Population in Period 3 with reasons for disposition. Fisher's exact test will be used to test for a difference between and among treatment groups for the ITT population in Period 2 and the Maintenance Dosing Period Primary Population in Period 3. Patient disposition from study treatment due to COVID-19 will also be listed. The time to study treatment discontinuation due to any reason (in weeks) will be summarized by treatment group and graphically using Kaplan-Meier techniques, for each treatment period. The log-rank test will be used to compare time to study treatment discontinuation between treatment groups. The time to study treatment discontinuation will be calculated as:

$$\frac{Date\ of\ study\ treatment\ discontinuation\ in\ period - Date\ of\ first\ dose\ in\ period + 1}{7}$$

For Induction Dosing period, if the date of first dose is missing, the date of randomization will be used. Patients completing the study treatment will be censored at the date of completion (that is, the date of the last scheduled visit in the period). For the analyses of Period 3, if a patient

experiences relapse during the period, they will be censored at the date of relapse (Analysis populations: ITT Population, Maintenance Dosing Period Primary Population)

Patient allocation by 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.

## 6.5. Protocol Deviations

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

A separate document (known as the trial issue management plan) will be used to define the categories and subcategories of important protocol deviations, whether or not these deviations will result in the exclusion of patients from PPS, and the source of identification for the deviations.

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

- Period 2 (ITT population);
- Period 3 (Maintenance Dosing Period Primary/Secondary population).

A by-patient listing of important protocol deviations will be provided. A listing of protocol deviations due to COVID-19 will also be provided.

## 6.6. Patient Characteristics

### *6.6.1. Demographics and Baseline Characteristics*

Patient demographic variables and baseline characteristics will be summarized for Period 2 (ITT Population) and Period 3 (Maintenance Dosing Period Primary/Secondary/Relapse Population) by treatment group and overall. 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 for the ITT population and for Maintenance Dosing Period Primary Population will be conducted using an ANOVA model with treatment as a factor for continuous data, and using 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). Table RHBH. 6.3. shows the details of patient characteristics variables that will be summarized.

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

**Table RHBH. 6.3. Patient Characteristics (and Variables for Subgroup Analysis)**

| Variable | Summary | Efficacy Subgroup Analysis For Categories |
|---|---|---|
| Age [a] | quantitative summary (in years) | |
| | <65 years, ≥65 years to <75 years, ≥75 years | Yes |
| | <40 years, ≥40 years | |
| Sex | male, female | Yes |
| Age groups within Sex | Male: <40 years, ≥40 years | |
| | Female: <40 years, ≥40 years | |
| Race | Asian | |
| Height | quantitative summary (in cm) | |
| Weight | quantitative summary (in kg) | |
| | <60 kg, ≥60 kg and <100 kg, ≥100 kg | Yes |
| BMI [b] | quantitative summary (in $kg/m^2$) | |
| | underweight (<18.5 $kg/m^2$), normal (≥18.5 and <25 $kg/m^2$), overweight (≥25 and < 30 $kg/m^2$), obese (≥30 and < 40 $kg/m^2$), extreme obese (≥40 $kg/m^2$) | Yes |
| Waist circumference | quantitative summary (in cm) | |
| Alcohol use | never, current, former | |
| Caffeine use | never, current, former | |
| Tobacco use | never, current, former | |
| Previous systemic therapy [c,d] | never used, non-biologic only, biologic only, biologic and non-biologic | Yes |
| Previous non-biologic systemic therapy [c] | never used, ever used | |
| | never used, used 1 therapy, used 2 therapies, used ≥3 therapies | |
| | inadequate response, loss of response, intolerance, or contraindication: < 3 therapies, ≥3 therapies | Yes |
| Previous biologic therapy [d] | never used, ever used | Yes |
| | never used, used 1 therapy, used 2 therapies, used ≥3 therapies | Yes |
| Previous phototherapy (UVB or PUVA) | never used, ever used | Yes |
| Age at psoriasis onset | quantitative summary (in years) | |
| Age group at psoriasis onset | <40 years (Type 1 psoriasis), ≥40 years (Type 2 psoriasis) | |
| Duration of psoriasis [e] | quantitative summary (in years) | |
| Age at psoriasis diagnosis | quantitative summary (in years) | |
| Duration of psoriasis diagnosis [f] | quantitative summary (in years) | |
| Baseline sPGA | quantitative summary | |
| | category: 3, 4, 5 | Yes |
| | category: 3, combined 4 or 5 | Yes |
| Baseline PASI | quantitative summary | |
| | <20, ≥20 | Yes |
| Psoriatic arthritis | yes, no | |
| Finger nail psoriasis | yes, no | Yes |
| Baseline NAPSI | quantitative summary | |
| Scalp psoriasis | yes, no | Yes |
| Baseline PSSI | quantitative summary | |
| Palmoplantar psoriasis | yes, no | Yes |
| Baseline PPASI | quantitative summary | |

| | | |
|---|---|---|
| Baseline BSA (%) | quantitative summary | |
| | <20%, ≥20% | Yes |
| Baseline Itch NRS score | quantitative summary | |
| | <4, ≥4 | |
| | =0, >0 | |
| Baseline DLQI total score | quantitative summary | |
| | <5, ≥5 | |
| Baseline Joint Pain VAS (for patients with baseline PsA) | quantitative summary | |
| Baseline QIDS-SR16 | quantitative summary of total score | |
| | Item12: 0, 1, 2, 3 | |

Abbreviations: BMI = body mass index; UVB= ultraviolet B; PUVA= psoralen and ultraviolet A; QIDS-SR 16= Quick Inventory of Depressive Symptomatology–Self-Report 16 items.

[a] Age will be calculated as: Age = floor((intck('month', brthdtc, rfstdtc) – (day(rfstdtc) < day(brthdtc)))/12). Here brthdtc = Imputed date of birth (July 1st in the year of birth collected in the eCRF), and rfstdtc = subject reference start date (that is, the date when patient is first exposed to study treatment).

[b] BMI will be calculated as BMI ($kg/m^2$) = Weight (kg) / (Height (m))$^2$.

[c] Non-biologics are defined as: cyclosporine, methotrexate, corticosteroids, acitretin, fumaric acid derivatives, apremilast, other non-biologics, and psoralen and ultraviolet A (PUVA).

[d] Biologics are defined as: efalizumab, ustekinumab, infliximab, etanercept, alefacept, adalimumab, golimumab, certolizumab pegol, and other biologics.

[e] Duration of psoriasis = (date of informed consent – date of psoriasis onset)/365.25, where the date of psoriasis onset is recorded on the Prespecified Medical History – Psoriasis eCRF page.

[f] Duration of psoriasis diagnosis = (date of visit 2 – date of psoriasis diagnosis)/365.25, where the date of psoriasis diagnosis is recorded on the Prespecified Medical History – Psoriasis eCRF page.

### *6.6.2. Historical Illnesses and Preexisting Conditions*

Historical illnesses and preexisting conditions will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

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.

Preexisting conditions for Period 2 are defined as those conditions/events recorded on the *Pre-Existing Conditions and Medical History* eCRF page or on the *Prespecified Medical History* eCRF page with a start date prior to the date of informed consent, and no end date (that is, the event is ongoing) or an end date on or after the date of informed consent. Preexisting conditions and adverse events occurring prior to first dose will be reported for Period 2. Preexisting conditions for Period 3 are defined as those preexisting conditions and AEs which are ongoing at the treatment period baseline. Notice if a preexisting condition worsens in severity on or after the date of informed consent, it will be recorded as an AE on *AE* eCRF page from the date of worsening onwards.

The following summaries will be provided for Period 2 (ITT population), and Period 3 (Maintenance Dosing Period Primary Population):

- The number and percentage of patients with historical illnesses by treatment group and overall, by System Organ Class (SOC) and preferred term. (ITT Population in Period 2 only)

- The number and percentage of patients with preexisting conditions by treatment group and overall, by SOC and preferred term (Adverse events occurring prior to first dose will also be summarized for Period 2).
- The number and percentage of patients with prespecified medical history (hypertension; diabetes mellitus, Type I; diabetes mellitus, Type II insulin dependent; diabetes mellitus, Type II non-insulin dependent; coronary artery disease; history of stroke; dyslipidemia; psoriatic arthritis; Crohn's disease; ulcerative colitis) by treatment group and overall.

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.

## 6.7. Previous and Concomitant Therapy

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

### *6.7.1. Previous Therapy*

Previous therapy is defined as the therapy that starts and ends prior to the date of first dose of study treatment in Period 2. If therapy start and/or end dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study treatment in Period 2. If there is clear evidence to suggest that the therapy stopped prior to the first dose of study treatment in Period 2, the therapy will be assumed to be previous only.

The following summaries will be provided for Period 2 (ITT population), and Period 3 (Maintenance Dosing Period Primary Population):

- Previous therapy (captured in the *Prior Therapy: Psoriasis* eCRF page and *Concomitant Therapy* eCRF page) by WHO ATC Level 4 and WHO preferred term.
- Previous psoriasis therapy captured in the *Prior Therapy: Psoriasis* eCRF page to be summarized according to type (topical prescription therapy, topical non-prescription therapy, non-biologic systemic agent, biologic agent, non-biologic non-systemic agent, phototherapy) and therapy. The previous biologic agent will be further classified as TNF-α inhibitor (includes infliximab, etanercept, adalimumab, golimumab, certolizumab pegol), interleukin (IL) 12/23 inhibitor (includes ustekinumab), and other (includes efalizumab, alefacept, or other biological agent).
- The number and percentage of patients with each reason for discontinuation of previous psoriasis therapy to be summarized by type and therapy.

### *6.7.2. Concomitant Therapy*

Concomitant therapy for a treatment period is defined as the therapy that starts before, on, or after the first day of study treatment in the defined treatment period and before the last visit date of the defined treatment period, and continues into the defined treatment period, that is, either no end date (the therapy is ongoing) or an end date on or after the first day of study treatment in the defined treatment period. Note, concomitant therapy will belong to a treatment Period if the

therapy starts and ends on the exact same day as the first day of study treatment of the treatment period.

The following summaries will be provided for Period 2 (ITT population), and Period 3 (Maintenance Dosing Period Primary Population):

- Concomitant therapy by WHO ATC Level 4 and WHO preferred term (also for Maintenance Dosing Period Secondary/Relapse Population in Period 3)
- The number and percentage of patients taking concomitant therapy of topical product to be summarized for topical and topical steroid therapies, respectively, by WHO ATC Level 4 and WHO preferred term. The definition of concomitant topical therapy can be found in the LY2439821 Program Safety Analysis Plan version 8 (PSAP v8) Appendix 9 (or most current version).
- The number and percentage of patients who received premedication for allergic reaction/hypersensitivity captured in the *Allergic / Hypersensitivity Reaction Follow-Up* eCRF page.

## 6.8. Treatment Compliance

By-patient listings of randomization schedule for the ITT population and study drug dispensed (include the CT Lot number) for the Safety Population will be provided.

Throughout the treatment period, randomized patients will record information in a Study Drug Administration Log (captured in the *Exposure as Collected* 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:

$$Treatment\ compliance\ (\%) = 100\ \times \frac{Total\ number\ of\ injections\ administered}{Total\ number\ of\ injections\ prescribed}$$

- For patients who complete Period 2, the number of injections prescribed (that is, expected) during Period 2 will be equal to 7 (2 injections at Week 0 and 1 injection every 2 weeks from Week 2 to Week 10).
- For patients who complete Period 3, the number of injections prescribed (that is, expected) during Period 3 will be equal to 13 (2 injections at Week 12 and 1 injection every 4 weeks from Week 16 to Week 56).
- For patients who discontinue during the treatment period, 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 as Collected* eCRF page.

A patient will be considered overall compliant with study treatment during each treatment period if he/she 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).

Treatment compliance by treatment week and overall will be summarized for the Safety Population for Period 2 and for the Maintenance Dosing Period Primary/Secondary Population for Period 3.

## 6.9. Efficacy Analyses

Table RHBH. 6.4. includes the description and derivation of the coprimary and secondary efficacy outcomes.

Table RHBH. 6.5. provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment group comparisons for coprimary and secondary efficacy analyses.

**Table RHBH. 6.4. Description and Derivation of Coprimary and Secondary Efficacy Outcomes**

| Measure / Description | Variable | Derivation / Comment | Imputation Approach if with Missing Components |
|---|---|---|---|
| **Static Physician Global Assessment (sPGA):**<br>sPGA is the physician's global assessment of the patient's psoriasis (Ps) lesions at a given time point (European Medicines Agency [EMA] 2004 [WWW]). Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5). | sPGA score | Range from 0 to 5: clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5). | Single item, missing if missing |
| | sPGA (0,1) – **coprimary** | An sPGA assessed as either 0 or 1, which represents a clinically meaningful response of minimal plaque severity or complete resolution of plaque Ps. | Missing if sPGA is missing |
| | sPGA (0) | An sPGA assessed as 0, which represents a clinically important endpoint indicating complete resolution of plaque Ps. | Missing if sPGA is missing |
| **Psoriasis Area and Severity Index (PASI):**<br>PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head and neck, trunk, arms, and legs) and the severity of 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).<br>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):<br>0 = none<br>1 = slight<br>2 = moderate<br>3 = severe<br>4 = very severe<br>The body is divided into four anatomical regions comprising the head (h), upper limb (u), trunk (t), and lower limb (l). In each of these areas, the fraction of total body surface area affected is | PASI score | The composite PASI score is calculated by multiplying the sum of the individual-severity scores for each area by the weighted area-of-involvement score for that respective area, and then summing the four resulting quantities as follows:<br>$PASI = 0.1(R_h + T_h + S_h)A_h + 0.2(R_u + T_u + S_u)A_u + 0.3(R_t + T_t + S_t)A_t + 0.4(R_l + T_l + S_l)A_l$<br>Where,<br>$R_h$, $R_u$, $R_t$, $R_l$ = redness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively;<br>$T_h$, $T_u$, $T_t$, $T_l$ = thickness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively;<br>$S_h$, $S_u$, $S_t$, $S_l$ = scaliness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively;<br>$A_h$, $A_u$, $A_t$, $A_l$ = numerical value translation of % area of psoriatic involvement score for the head, upper limb, trunk, and lower limb, respectively.<br>PASI scores are treated as a continuous score, with 0.1 increments within these values. | If any individual score is missing, the PASI score will not be calculated, hence missing |
| | PASI change from baseline | Calculated as: observed PASI – baseline PASI | Missing if baseline or observed value is missing |

| Measure / Description | Variable | Derivation / Comment | Imputation Approach if with Missing Components |
|---|---|---|---|
| graded on a 0-6 scale (0 for no involvement; up to 6 for 90% - 100% involvement):<br>0 = 0% (clear)<br>1 = >0% to <10%<br>2 = 10% to <30%<br>3 = 30% to <50%<br>4 = 50% to <70%<br>5 = 70% to <90%<br>6 = 90% to 100%<br><br>The various body regions are weighted to reflect their respective proportion of body surface area. | PASI percent improvement from baseline | Calculated as:<br>$Percent\ improvement\ from\ baseline\ = 100 \times \frac{Baseline\ PASI - Observed\ PASI}{Baseline\ PASI}$<br>If a patient has experienced an improvement, this measure will be positive. If a patient has experienced a worsening in the condition, this measure will be negative. | Missing if baseline or observed value is missing |
| | PASI 50 | A minimum clinically meaningful response; at least a 50% improvement in PASI score from baseline | Missing if baseline or observed value is missing |
| | PASI 75 - **coprimary** | A clinically meaningful response; at least a 75% improvement in PASI score from baseline | Missing if baseline or observed value is missing |
| | PASI 90 | Higher level of clearance; at least a 90% improvement in PASI score from baseline | Missing if baseline or observed value is missing |
| | PASI 100 | Complete resolution of plaque Ps; a 100% improvement in PASI score from baseline | Missing if baseline or observed value is missing |
| **Percentage of Body Surface Area (BSA):**<br>The investigator will evaluate the percentage involvement of psoriasis on each patient's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), in which 1% corresponds to the size of the patient's hand (including the palm, fingers, and thumb) (National Psoriasis Foundation [NPF] 2009). | BSA | Collected as a single scale as part of *PASI* electronic case report form (eCRF) page. Range from 0% to 100%. | Single item, missing if missing |
| | BSA change from baseline | Calculated as: observed BSA – baseline BSA | Missing if baseline or observed value is missing |

| Measure / Description | Variable | Derivation / Comment | Imputation Approach if with Missing Components |
|---|---|---|---|
| **Nail Psoriasis Severity Index (NAPSI):**<br>NAPSI will be used if the patient has fingernail psoriasis at baseline. The NAPSI is a numeric, reproducible, objective tool for evaluation of fingernail Ps. 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 to 4) and fingernail matrix psoriasis (0 to 4), depending on the presence (score of 1) or absence (score of 0) of any of the features of fingernail bed and fingernail matrix psoriasis in each quadrant:<br>0 = None<br>1 = present in one quadrant of nail<br>2 = present in two quadrants of nail<br>3 = present in three quadrants of nail<br>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 bed or matrix score is missing or not done, 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. |
| | NAPSI score change from baseline | Calculated as: observed NAPSI – baseline NAPSI | Missing if baseline or observed value is missing |
| | NAPSI score =0 | A NAPSI response is defined as a NAPSI score of 0, which is also referred to as nail clearance. | Missing if NAPSI score is missing |
| **Psoriasis Scalp Severity Index (PSSI):**<br>PSSI will be used if the patient has scalp psoriasis at baseline. The scalp will be assessed for erythema (redness), induration (hardness), and desquamation (shedding of skin) and percentage of area affected as follows:<br>Erythema, Induration and Desquamation:<br>0 = Absent<br>1 = Slight<br>2 = Moderate | PSSI score | The PSSI score is a composite score derived from the sum of the scores for erythema, induration and desquamation multiplied by the score for the extent of scalp area involved (percent of scalp involved). The range is 0 to 72. | If any individual score is missing, the PSSI score will not be calculated, hence missing. |
| | PSSI score change from baseline | Calculated as: observed PSSI – baseline PSSI | Missing if baseline or observed value is missing |

| Measure / Description | Variable | Derivation / Comment | Imputation Approach if with Missing Components |
|---|---|---|---|
| 3 = Severe<br>4 = Severest Possible<br>Percent of Scalp Involved:<br>0 = none<br>1 = <10%<br>2 = 10 – 29%<br>3 = 30 – 49%<br>4 = 50 – 69%<br>5 = 70 – 89%<br>6 = 90 – 100% | PSSI score =0 | A PSSI response is defined as a PSSI score of 0, which is also referred to as scalp clearance. | Missing if PSSI score is missing |
| **Palmoplantar Psoriasis Area and Severity Index (PPASI):**<br>PPASI will be used if the patient has palmoplantar psoriasis at baseline. Both palms and soles on each hand and foot will be individually assessed for erythema, induration, desquamation and percentage of area affected as follows:<br>Erythema (E), Induration (I) and Desquamation (D):<br>0 = None<br>1 = Slight<br>2 = Moderate<br>3 = Severe<br>4 = Very Severe<br>Percent of Palm and Sole Area Covered:<br>0 = None<br>1 = <10%<br>2 = 10 – 29%<br>3 = 30 – 49%<br>4 = 50 – 69%<br>5 = 70 – 89% | PPASI score | The PPASI score is a composite score derived from the sum scores for erythema, induration, and desquamation multiplied by a score for the extent of palm and sole area involvement. The range is 0 to 72.<br>$PPASI = 0.2(E_{rp} + I_{rp} + D_{rp})A_{rp} + 0.2(E_{lp} + I_{lp} + D_{lp})A_{lp} + 0.3(E_{rs} + I_{rs} + D_{rs})A_{rs} + 0.3(E_{ls} + I_{ls} + D_{ls})A_{ls}$<br>Where,<br>$E_{rp}$, $E_{lp}$, $E_{rs}$, $E_{ls}$ = Erythema score of plaques on the right palm (rp), left palm (lp), right sole (rs), left sole (ls), scored 0-4 respectively;<br>$I_{rp}$, $I_{lp}$, $I_{rs}$, $I_{ls}$ = Induration score of plaques on the right palm (rp), left palm (lp), right sole (rs), left sole (ls), scored 0-4 respectively;<br>$D_{rp}$, $D_{lp}$, $D_{rs}$, $D_{ls}$ = Desquamation score of plaques on the right palm (rp), left palm (lp), right sole (rs), left sole (ls), scored 0-4 respectively;<br>$A_{rp}$, $A_{lp}$, $A_{rs}$, $A_{ls}$ = numerical value translation of % area covered for the right palm, left palm, right sole, and left sole, respectively. | If any individual score is missing, the PPASI score will not be calculated, hence missing. |
| | PPASI change from baseline | Calculated as: observed PPASI – baseline PPASI | Missing if baseline or observed value is missing |
| | PPASI 50 | At least a 50% improvement in PPASI score from baseline | Missing if baseline or observed value is missing |

| Measure / Description | Variable | Derivation / Comment | Imputation Approach if with Missing Components |
|---|---|---|---|
| 6 = 90 – 100% | PPASI 75 | at least a 75% improvement in PPASI score from baseline | Missing if baseline or observed value is missing |
| | PPASI 100 | a 100% improvement in PPASI score from baseline | Missing if baseline or observed value is missing |

## Table RHBH. 6.5. Description of Coprimary and Secondary Efficacy Analyses

| Variable | Analysis Method (Sections 6.1 and 6.2) | Population (Section 6.1.1) | Comparison/Time Point | Analysis Type |
|---|---|---|---|---|
| sPGA | | | | |
| sPGA (0,1) – **coprimary** | Logistic regression analysis with NRI; Fisher's exact test with NRI; Categorical MMRM | ITT Population | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 and all other postbaseline visits in Period 2 | Primary analysis is logistic regression analysis with NRI for ITT population comparing IXE80Q2W & IXE80Q4W vs. PBO at Week 12 (Section 6.9.1). Other analyses are additional analyses of coprimary outcomes (Section 6.9.3). |
| | Logistic regression analysis with NRI | Per-Protocol Set (PPS) | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 | Additional analyses of coprimary outcomes (Section 6.9.3). |
| | KM analysis of time to first sPGA(0,1) Response | ITT Population | IXE80Q2W & IXE80Q4W vs. PBO in Period 2 | Additional analyses of coprimary outcomes (Section 6.9.3). |
| | Logistic regression analysis with NRI; Fisher's exact test with NRI; Categorical MMRM | Maintenance Dosing Period Primary Population | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO and IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs. IXE/PBO at Week 60 and all other postbaseline visits in Period 3 | Major secondary analyses (Section 6.9.2); Additional analyses of coprimary outcomes (Section 6.9.3). |
| | Descriptive statistics of sPGA(0,1) response | Maintenance Dosing Period Secondary Population | By treatment group at Week 60 and all other postbaseline visits in Period 3 | Other secondary analysis (Section 6.9.4.2.2, Section 6.1.3.2) |

| Variable | Analysis Method (Sections 6.1 and 6.2) | Population (Section 6.1.1) | Comparison/Time Point | Analysis Type |
|---|---|---|---|---|
| | Descriptive statistics of sPGA(0,1) response | Maintenance Dosing Period Relapse Population with IXE Retreatment | By treatment group within 12 weeks after IXE retreatment | Other secondary analysis (Section 6.9.4.2.3, Section 6.1.3.3). |
| | Subgroup analyses | ITT Population | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 | Subgroup analyses (Section 6.14.1) |
| sPGA (0) | Logistic regression analysis with NRI; Fisher's exact test with NRI; Categorical MMRM | ITT Population | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 and all other post-baseline visits in Period 2 | Major secondary analysis (Section 6.9.2); Other secondary analysis (Section 6.9.4.1) |
| | Logistic regression analysis with NRI; Fisher's exact test with NRI; Categorical MMRM | Maintenance Dosing Period Primary Population | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO and IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs. IXE/PBO at Week 60 and all other postbaseline visits in Period 3 | Major secondary analysis (Section 6.9.2); Other secondary analysis (Section 6.9.4.2.1) |
| | Descriptive statistics of sPGA (0) response | Maintenance Dosing Period Secondary Population | By treatment group at Week 60 and all other postbaseline visits in Period 3 | Other secondary analysis (Section 6.9.4.2.2, Section 6.1.3.2) |
| | Descriptive statistics of sPGA (0) response | Maintenance Dosing Period Relapse Population with IXE Retreatment | By treatment group within 12 weeks after IXE retreatment | Other secondary analysis (Section 6.9.4.2.3, Section 6.1.3.3). |
| | Subgroup analyses | ITT Population | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 | Subgroup analyses (Section 6.14.1) |
| sPGA score | KM analysis of time to relapse (sPGA≥3) | Maintenance Dosing Period Primary Population | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO and IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO in Period 3 | Other secondary analysis (Section 6.9.4.2.1) |
| PASI | | | | |

| Variable | Analysis Method (Sections 6.1 and 6.2) | Population (Section 6.1.1) | Comparison/Time Point | Analysis Type |
|---|---|---|---|---|
| PASI 75 - **coprimary** | Logistic regression analysis with NRI; Fisher's exact test with NRI; Categorical MMRM | ITT Population | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 and all other postbaseline visits in Period 2 | Primary analysis is logistic regression analysis with NRI for ITT population comparing IXE80Q2W & IXE80Q4W vs. PBO at Week 12 (Section 6.9.1). Other analyses are additional analyses of coprimary outcomes (Section 6.9.3). |
| | Logistic regression analysis with NRI | Per-Protocol Set (PPS) | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 | Additional analyses of coprimary outcomes (Section 6.9.3). |
| | KM analysis of time to first PASI 75 Response | ITT Population | IXE80Q2W & IXE80Q4W vs. PBO in Period 2 | Additional analyses of coprimary outcomes (Section 6.9.3). |
| | Logistic regression analysis with NRI; Fisher's exact test with NRI; Categorical MMRM | Maintenance Dosing Period Primary Population | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO and IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs. IXE/PBO at Week 60 and all other postbaseline visits in Period 3 | Additional analyses of coprimary outcomes (Section 6.9.3). |
| | Descriptive statistics of PASI 75 response | Maintenance Dosing Period Secondary Population | By treatment group at Week 60 and all postbaseline visits in Period 3 | Other secondary analysis (Section 6.9.4.2.2, Section 6.1.3.2) |
| | Descriptive statistics of PASI 75 response | Maintenance Dosing Period Relapse Population with IXE Retreatment | By treatment group within 12 weeks after IXE retreatment | Other secondary analysis (Section 6.9.4.2.3, Section 6.1.3.3). |
| | Subgroup analyses | ITT Population | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 | Subgroup analyses (Section 6.14.1) |
| PASI 50, PASI 90, PASI 100 | Logistic regression analysis with NRI; Fisher's exact test with NRI; Categorical MMRM | ITT Population | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 and all other post-baseline visits in Period 2 | Major secondary analysis (Section 6.9.2); Other secondary analysis (Section 6.9.4.1) |

| Variable | Analysis Method (Sections 6.1 and 6.2) | Population (Section 6.1.1) | Comparison/Time Point | Analysis Type |
|---|---|---|---|---|
| PASI 90, PASI 100 | Logistic regression analysis with NRI; Fisher's exact test with NRI; Categorical MMRM | Maintenance Dosing Period Primary Population | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO and IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs. IXE/PBO at Week 60 and all other postbaseline visits in Period 3 | Other secondary analysis (Section 6.9.4.2.1, Section 6.1.3.1) |
| | Descriptive statistics | Maintenance Dosing Period Secondary Population | By treatment group at Week 60 and all postbaseline visits in Period 3 | Other secondary analysis (Section 6.9.4.2.2, Section 6.1.3.2) |
| | Descriptive statistics | Maintenance Dosing Period Relapse Population with IXE Retreatment | By treatment group within 12 weeks after IXE retreatment | Other secondary analysis (Section 6.9.4.2.3, Section 6.1.3.3). |
| PASI change from baseline, PASI percent improvement from baseline | MMRM; ANCOVA with LOCF | ITT Population | IXE80Q2W & IXE80Q4W vs PBO at Week 12 and all other post-baseline visits in Period 2 | Other secondary analysis (Section 6.9.4.1, Section 6.1.2) |
| | MMRM; ANCOVA with LOCF | Maintenance Dosing Period Primary Population | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO and IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs IXE/PBO at all postbaseline visits in Period 3 | Other secondary analysis (Section 6.9.4.2.1, Section 6.1.3.1) |
| | Descriptive statistics | Maintenance Dosing Period Secondary Population | By treatment group at Week 60 and all postbaseline visits in Period 3 | Other secondary analysis (Section 6.9.4.2.2, Section 6.1.3.2) |
| BSA | | | | |
| BSA change from baseline | MMRM | ITT Population | IXE80Q2W & IXE80Q4W vs PBO at Week 12 and all other post-baseline visits in Period 2 | Other secondary analysis (Section 6.9.4.1, Section 6.1.2) |

| Variable | Analysis Method (Sections 6.1 and 6.2) | Population (Section 6.1.1) | Comparison/Time Point | Analysis Type |
|---|---|---|---|---|
| | MMRM | Maintenance Dosing Period Primary Population | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO and IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs IXE/PBO at all postbaseline visits in Period 3 | Other secondary analysis (Section 6.9.4.2.1, Section 6.1.3.1) |
| NAPSI | | | | |
| NAPSI score change from baseline | MMRM; ANCOVA with LOCF | ITT Population - patients with baseline nail involvement | IXE80Q2W & IXE80Q4W vs PBO at Week 12 and all other post-baseline visits in Period 2 | Major secondary analysis (Section 6.9.2); Other secondary analyses (Section 6.9.4.1, Section 6.1.2) |
| | MMRM; ANCOVA with LOCF | Maintenance Dosing Period Primary Population with baseline nail involvement | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO and IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs IXE/PBO at all postbaseline visits in Period 3 | Other secondary analyses (Section 6.9.4.2.1, Section 6.1.3.1) |
| NAPSI score = 0 | Logistic regression analysis with NRI; Fisher's exact test with NRI | ITT Population - patients with baseline nail involvement | IXE80Q2W & IXE80Q4W vs PBO at Week 12 and all other post-baseline visits in Period 2 | Other secondary analyses (Section 6.9.4.1, Section 6.1.3.1) |
| | Logistic regression analysis with NRI; Fisher's exact test with NRI | Maintenance Dosing Period Primary Population with baseline nail involvement | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO and IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs IXE/PBO at all postbaseline visits in Period 3 | Other secondary analyses (Section 6.9.4.2.1, Section 6.1.3.1) |
| PSSI | | | | |
| PSSI score change from baseline | MMRM | ITT Population - patients with baseline scalp involvement | IXE80Q2W & IXE80Q4W vs PBO at Week 12 and all other post-baseline visits in Period 2 | Other secondary analyses (Section 6.9.4.1, Section 6.1.2) |

| Variable | Analysis Method (Sections 6.1 and 6.2) | Population (Section 6.1.1) | Comparison/Time Point | Analysis Type |
|---|---|---|---|---|
| | MMRM | Maintenance Dosing Period Primary Population with baseline scalp involvement | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO and IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs. IXE/PBO at all postbaseline visits in Period 3 | Other secondary analyses (Section 6.9.4.2.1, Section 6.1.3.1) |
| PSSI score = 0 | Logistic regression analysis with NRI; Fisher's exact test with NRI | ITT Population - patients with baseline scalp involvement | IXE80Q2W & IXE80Q4W vs PBO at Week 12 and all other post-baseline visits in Period 2 | Other secondary analyses (Section 6.9.4.1, Section 6.1.3.1) |
| | Logistic regression analysis with NRI; Fisher's exact test with NRI | Maintenance Dosing Period Primary Population with baseline scalp involvement | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO and IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs IXE/PBO at all postbaseline visits in Period 3 | Other secondary analyses (Section 6.9.4.2.1, Section 6.1.3.1) |
| PPASI | | | | |
| PPASI score change from baseline | MMRM | ITT Population - patients with baseline palmoplantar involvement | IXE80Q2W & IXE80Q4W vs PBO at Week 12 and all other post-baseline visits in Period 2 | Other secondary analyses (Section 6.9.4.1, Section 6.1.2) |
| | MMRM | Maintenance Dosing Period Primary Population with baseline palmoplantar involvement | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO and IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs IXE/PBO at all postbaseline visits in Period 3 | Other secondary analyses (Section 6.9.4.2.1, Section 6.1.3.1) |
| PPASI 50, PPASI 75, PPASI 100 | Logistic regression analysis with NRI; Fisher's exact test with NRI | ITT Population - patients with baseline palmoplantar involvement | IXE80Q2W & IXE80Q4W vs PBO at Week 12 and all other post-baseline visits in Period 2 | Other secondary analyses (Section 6.9.4.1, Section 6.1.2) |

| Variable | Analysis Method (Sections 6.1 and 6.2) | Population (Section 6.1.1) | Comparison/Time Point | Analysis Type |
|---|---|---|---|---|
| | Logistic regression analysis with NRI; Fisher's exact test with NRI | Maintenance Dosing Period Primary Population with baseline palmoplantar involvement | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO and IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs IXE/PBO at all postbaseline visits in Period 3 | Other secondary analyses (Section 6.9.4.2.1, Section 6.1.3.1) |

Abbreviations: ANCOVA = analysis of covariance; BSA = body surface area; ITT = intent-to-treat; IXE80Q2W = ixekizumab 80 mg every 2 weeks; IXE80Q4W = ixekizumab 80 mg every 4 weeks; LOCF = last observation carried forward; MMRM = mixed-effects model of repeated measures; NAPSI = Nail Psoriasis Severity Index; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PASI 50/75/90 = at least a 50%/75%/90% improvement from baseline in PASI score; PASI 100 = a 100% improvement from baseline in PASI score; PPASI = Palmoplantar Psoriasis Area and Severity Index; PPASI 50/75 = at least a 50%/75% improvement in PPASI score from baseline; PPASI 100 = a 100% improvement in PPASI score from baseline; PSSI = Psoriasis Scalp Severity Index; sPGA = static Physician Global Assessment; vs. = versus.

### 6.9.1. Coprimary Outcomes and Primary Analysis Methodology

The coprimary outcomes are:

- Proportion of patients achieving sPGA (0,1) at Week 12, and
- Proportion of patients achieving PASI 75 at Week 12.

The primary analysis will be based on the ITT population for the Induction Dosing Period (Period 2) comparing each ixekizumab dose regimen and placebo at Week 12 (Visit 7). The primary analysis is logistic regression analysis with treatment as a factor (Section 6.1.2). Missing data will be imputed using the NRI method (Section 6.2.1).

The coprimary comparisons will be tested based on the gatekeeping testing procedure detailed in Section 6.3.

### 6.9.2. Major Secondary Efficacy Analyses

The major secondary outcomes are:

- Proportion of patients achieving sPGA (0) at Week 12 (Visit 7)
- Proportion of patients achieving PASI 90 at Week 12 (Visit 7)
- Proportion of patients achieving PASI 100 at Week 12 (Visit 7)
- Change from baseline in NAPSI score at Week 12 (Visit 7)
- Proportion of patients maintaining an sPGA (0,1) from Week 12 (Visit 7) after re-randomization at start of Maintenance Dosing Period to Week 60 (Visit19) for ixekizumab-treated patients who had an sPGA (0,1) at Week 12 and were re-randomized
- Proportion of patients maintaining or achieving an sPGA (0) from Week 12 (Visit 7) after re-randomization at start of Maintenance Dosing Period to Week 60 (Visit 19) for ixekizumab-treated patients who had an sPGA (0,1) at Week 12 and were re-randomized

The major secondary analyses will be based on the ITT population for the Induction Dosing Period (Period 2) at Week 12 (Visit 7) and based on the Maintenance Dosing Period Primary population for the Maintenance Dosing Period (Period 3) at Week 60 (Visit 19). The analysis for categorical efficacy outcomes will be logistic regression analysis with treatment as a factor with NRI (Section 6.1.2, Section 6.1.3.1, Section 6.2.1). The analysis for continuous efficacy outcomes will use MMRM with treatment, baseline value, visit, treatment-by-visit, and baseline-by-visit interactions as fixed factors (Section 6.1.2).

The major secondary comparisons will be tested based on the gatekeeping multiple testing procedure detailed in Section 6.3.

### 6.9.3. Additional Analyses of Co-Primary Outcomes

There will be no adjustment for multiple comparisons for additional analyses of the co-primary outcomes.

To support the primary efficacy analysis, the coprimary outcomes, sPGA (0,1) and PASI 75, will be analyzed based on the PPS population for the Induction Dosing Period (Period 2) at Week 12

(Visit 7) using a logistic regression analysis with treatment as a factor (Section 6.1.2). Missing data will be imputed using the NRI method (Section 6.2.1). A categorical MMRM analysis with treatment, baseline value, visit, treatment-by-visit and baseline-by-visit interactions as fixed factors will be also be done (Section 6.1.2).

The time to first sPGA (0,1) response, and the time to first PASI 75 response will be assessed based on the ITT Population during Period 2 as described in Section 6.1.2. Figures showing the proportion of patients achieving an sPGA (0,1) response and a PASI 75 response at each scheduled visit during Period 2 within each treatment group in the ITT population (including Week 12, NRI) will be provided.

Figures showing the proportion of patients maintaining an sPGA (0,1) response and maintaining a PASI 75 response at each scheduled visit during Period 3 (including Week 60, NRI) within each treatment group in the Maintenance Dosing Period Primary Population will also be provided.

Please see Table RHBH. 6.5. for details of other additional analyses for co-primary outcomes.

### *6.9.4. Other Secondary Efficacy Analyses*

There will be no adjustment for multiple comparisons for other secondary efficacy analyses.

#### 6.9.4.1. Period 2 (Induction Dosing Period)

Other secondary analyses will be done on sPGA (0), PASI 50, PASI 90, PASI 100, NAPSI score = 0, PPSI score = 0, PPASI 50, PPASI 75, PPASI 100, PASI change from baseline, PASI percent improvement from baseline, BSA change from baseline, NAPSI change from baseline, PSSI change from baseline, PPASI change from baseline. Comparisons of Ixekizumab treatment groups and placebo will be provided for Week 12 and all other postbaseline visits in Period 2.

Table RHBH. 6.5. provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment comparisons for other secondary analyses.

#### 6.9.4.2. Period 3 (Maintenance Dosing Period)

##### *6.9.4.2.1. Maintenance Dosing Period Primary Population*

Other secondary analyses will be done on sPGA (0), PASI 90, PASI 100, NAPSI score = 0, PPSI score = 0, PPASI 50, PPASI 75, PPASI 100, PASI change from baseline, PASI percent improvement from baseline, BSA change from baseline, NAPSI change from baseline, PSSI change from baseline, PPASI change from baseline. Comparisons of ixekizumab treatment groups and placebo will be provided for Week 60 and all other postbaseline visits in Period 3. A categorical MMRM analysis for selected variables with treatment, baseline value, visit, treatment-by-visit and baseline-by-visit interactions as fixed factors will be also be done (Section 6.1.3.1).

The time to relapse (loss of response; sPGA ≥3) during Period 3 will be assessed based on the Maintenance Dosing Period Primary Population as described in Section 6.1.3.1.

The number and percentage of placebo patients experiencing disease rebound within 8 weeks (worsening of Ps severity over baseline sPGA score, ***or*** worsening of Ps severity over baseline PASI score by 125%, ***or*** change in Ps phenotype [for example, from plaque to pustular]) after re-randomization to placebo at Week 12 will be summarized.

Table RHBH. 6.5. provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment comparisons for other secondary analyses.

#### *6.9.4.2.2. Maintenance Dosing Period Secondary Population*

The number and percentage of patients achieving or maintaining categorical efficacy outcome responses (sPGA (0,1), sPGA (0), PASI 75, PASI 90, PASI 100, PPASI 50, PPASI 75, PPASI 100) will be summarized by treatment group for all scheduled visits during Period 3, including Week 60 (NRI).

The change from baseline and percent improvement in PASI scores, the change from baseline in BSA, NAPSI scores, PSSI scores and PPASI scores will be summarized using descriptive statistics.

#### *6.9.4.2.3. Maintenance Dosing Period Relapse Population*

For patients who were retreated with ixekizumab following loss of response (relapse), the proportion of patients regaining or achieving categorical efficacy outcome responses (that is, sPGA (0,1), sPGA (0), PASI 75, PASI 90, PASI 100) within 12 weeks after ixekizumab retreatment will be summarized using descriptive statistics by treatment group.

## 6.10. Health Outcomes/Quality of Life Analyses

The health outcomes and quality of life (QoL) measures are Itch NRS, DLQI, SF-36 MCS and PCS, patient's global assessment of disease severity (PatGA) and Joint Pain VAS.

Table RHBH. 6.6. includes the description and derivation of the health outcomes and QoL measures.

Table RHBH. 6.7. provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment group comparisons for health outcomes and QoL analyses.

**Table RHBH. 6.6. 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):**<br>Itch NRS is a single-item, patient-reported outcome (PRO) measure designed to capture information on the overall severity of a patient's itching due to their psoriatic skin condition by having the patient circle the integer that best describes the worst level of itching in the past 24 hours on an 11-point NRS anchored at 0 representing "no itching" and 10 representing "worst itch imaginable." | Itch NRS score | Range from 0 to 10. | Single item, missing if missing |
| | Itch NRS change from baseline | Calculated as: observed Itch NRS – baseline Itch NRS | Missing if baseline or observed value is missing |
| | Itch NRS ≥4 improvement from baseline | Reduced/decreased of ≥4 point from baseline | Missing if baseline or observed value is missing |
| | Itch NRS =0 | Defined as a post-baseline Itch NRS score of 0 | Missing if Itch NRS score is missing |
| **Dermatology Life Quality Index (DLQI):**<br>DLQI is a validated, dermatology-specific, patient-reported measure that evaluates patient's health-related QoL. 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:<br>Very much = 3<br>A lot = 2<br>A little = 1<br>Not at all = 0<br>Not relevant = 0 | DLQI symptoms and feelings domain | Sum of responses of questions #1 and #2:<br>#1. How itchy, sore, painful or stinging has your skin been?<br>#2. How embarrassed or self-conscious have you been because of your skin? | If one question in a domain is missing, that domain is missing. |
| | DLQI daily activities domain | Sum of responses of questions #3 and #4:<br>#3. How much has your skin interfered with you going shopping or looking after your home or garden?<br>#4. How much has your skin influenced the clothes you wear? | If one question in a domain is missing, that domain is missing. |
| | DLQI leisure domain | Sum of responses of questions #5 and #6:<br>#5. How much has your skin affected any social or leisure activities?<br>#6. How much has your skin make it difficult for you to do any sport? | If one question in a domain is missing, that domain is missing. |
| | DLQI work and school domain | Sum of responses of questions question #7A and #7B:<br>#7A. Has your skin prevented you from working or studying?<br>#7B. If No: how much has your skin been a problem at work or studying? | If the answer to question #7A is missing, this domain is missing. If #7A is No, and #7B is missing, this domain is missing. |

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

| Measure / Description | Variable | Derivation / Comment | Imputation Approach if with Missing Components |
|---|---|---|---|
| **Medical Outcomes Study 36-item Short-Form Health Survey (SF-36):**<br>The SF-36 is a 36-item patient-administered measure designed to be a short, multipurpose assessment of health in the areas of physical functioning, role–physical, role–emotional, bodily pain, vitality, social functioning, mental health, and general health. The 2 overarching domains of mental well-being and physical well-being are captured by the Mental Component Summary and Physical Component Summary scores. The summary scores range from 0 to 100; higher scores indicate better levels of function and/or better health. Items are answered on Likert scales of varying lengths. The SF-36 version 2 (acute version) will be used, which utilizes a 1-week recall period (Ware [2000]). | 8 associated domain scores (scaled score and t-score):<br>• Physical Functioning,<br>• Role Physical,<br>• Bodily Pain,<br>• General Health,<br>• Vitality,<br>• Social Functioning,<br>• Role Emotional,<br>• Mental Health<br><br>2 component Scores (t-score):<br>• MCS Score<br>• PCS Score | Per copyright owner, the QualityMetric Health Outcomes™ Scoring Software will be used to derive SF-36 domain and component scores. After data quality-controls, the SF-36 software will re-calibrate the item-level responses for calculation of the domain and component scores. These raw scores will be transformed into the domain scores (t-scores) using the 1-week recall period. The summary scores range from 0 to 100. | If an item is missing, there will be imputation conducted by the Scoring Software. |
| | PCS, MCS scores change from baseline | Calculated as: observed score – baseline score | Missing if baseline or observed value is missing |
| **Patient's Global Assessment of Disease Severity** | PatGA score | Range from 0 to 5. | Single item, missing if missing |

| Measure / Description | Variable | Derivation / Comment | Imputation Approach if with Missing Components |
|---|---|---|---|
| **(PatGA):**<br>PatGA is a single-item, patient-reported outcome (PRO) measure designed to capture information on the overall severity of a patient's psoriasis by having the patient circle the integer that best describes their disease 'today' on a 6-point NRS anchored at 0 (clear), 1, 2, 3, 4, or 5 (severe). | PatGA change from baseline | Calculated as: observed PatGA – baseline PatGA | Missing if baseline or observed value is missing |
| Joint Pain Visual Analog Scale (VAS): Joint Pain VAS is a patient-administered scale designed to measure current joint pain from psoriatic arthritis (PsA) using a 100-mm horizontal VAS. Overall severity of a patient's join pain from PsA at the present time is indicated by placing a single mark on the horizontal scale (0 = none; 100 = as severe as you can imagine). | Joint Pain VAS | Range from 0 to 100. Note: higher value indicates greater severity of illness. | Single item, missing if missing |
| | Joint Pain VAS change from baseline | Calculated as: observed Joint Pain VAS – baseline Joint Pain VAS | Missing if baseline or observed value is missing |
| | Joint Pain VAS =0 | Defined as a post-baseline Joint Pain VAS of 0 | Missing if Joint Pain VAS is missing |

Abbreviations: MCS = mental component summary; NRS = Numeric Rating Scale; PCS = physical component summary; PRO = patient reported outcome; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; VAS = visual analog scale.

**Table RHBH. 6.7. Description of Health Outcomes and Quality-of-Life Analyses**

| Variable | Analysis Method (Sections 6.1 and 6.2) | Population (Section 6.1.1) | Comparison / Time Point |
|---|---|---|---|
| Itch NRS | | | |
| Itch NRS ≥4 improvement from baseline **— Major secondary** | Logistic regression analysis with NRI; Fisher's exact test with NRI | ITT population - patients with baseline Itch NRS score ≥4 | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 and all other post-baseline visits in Period 2 |
| | Logistic regression analysis with NRI; Fisher's exact test with NRI | Maintenance Dosing Period Primary Population - patients with baseline Itch NRS score ≥4 | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO, IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs IXE/PBO at Week 60 and all other postbaseline visits in Period 3 |
| Itch NRS change from baseline | MMRM | ITT population | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 and all other post-baseline visits in Period 2 |
| | MMRM | Maintenance Dosing Period Primary Population | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO, IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs IXE/PBO at Week 60 and all other postbaseline visits in Period 3 |
| DLQI | | | |
| DLQI (0,1) | Logistic regression analysis with NRI; Fisher's exact test with NRI | ITT population | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 and all other post-baseline visits in Period 2 |
| | Logistic regression analysis with NRI; Fisher's exact test with NRI | Maintenance Dosing Period Primary Population | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO, IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs IXE/PBO at Week 60 and all other postbaseline visits in Period 3 |
| DLQI total score change from baseline **— Major secondary** DLQI domain scores change from baseline | MMRM; ANCOVA with LOCF | ITT population | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 and all other post-baseline visits |
| | MMRM; ANCOVA with LOCF | Maintenance Dosing Period Primary Population | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO, IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs IXE/PBO at Week 60 and all other postbaseline visits in Period 3 |
| 36 item Short Form Health Survey (SF-36) | | | |
| SF-36 PCS, MCS, domain scores change from baseline | MMRM | ITT Population | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 and all other post-baseline visits |
| | MMRM | Maintenance Dosing Period Primary Population | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO, IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and |

| Variable | Analysis Method (Sections 6.1 and 6.2) | Population (Section 6.1.1) | Comparison / Time Point |
|---|---|---|---|
| | | | IXE/IXE vs IXE/PBO at Week 60 and all other postbaseline visits in Period 3 |
| Patient's Global Disease Assessment (PatGA) | | | |
| PatGA score change from baseline | MMRM | ITT Population | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 and all other post-baseline visits |
| | MMRM | Maintenance Dosing Period Primary Population | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO, IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO and IXE/IXE vs IXE/PBO at Week 60 and all other postbaseline visits in Period 3 |
| Joint Pain VAS | | | |
| Joint Pain VAS change from baseline | MMRM | ITT population - patients with baseline psoriatic arthritis | IXE80Q2W & IXE80Q4W vs. PBO at Week 12 and all other post-baseline visits |
| | MMRM | Maintenance Dosing Period Primary Population - patients with baseline psoriatic arthritis | IXE80Q2W/IXE80Q4W vs. IXE80Q2W/PBO and IXE80Q4W/IXE80Q4W vs. IXE80Q4W/PBO at Week 60 and all other postbaseline visits in Period 3 |

Abbreviations: ANCOVA = analysis of covariance; DLQI = Dermatology Life Quality Index; ITT = intent-to-treat; LOCF = last observation carried forward; MMRM = mixed-effects model of repeated measures; NRI = nonresponder imputation; NRS = Numeric Rating Scale; VAS = visual analog scale.

## 6.11. Pharmacokinetic/Pharmacodynamic Methods

Details of pharmacokinetic/pharmacodynamic (PK/PD) analyses can be found in a separate PK/PD analysis plan.

## 6.12. Safety Analyses

Safety will be assessed by summarizing and analyzing AEs, laboratory analytes, vital signs, QIDS-SR16, and C-SSRS. The duration of treatment exposure will also be summarized.

Safety analyses will be conducted for each period separately, including Period 4 (Follow-up Period). Note that different baseline definitions will be used for each period (Section 6.1). All summaries of safety data for patients who experience relapse will use the relapse baseline (Section 6.1.3.3). Only treatment-emergent safety data will be summarized for the relapse population (that is, TEAEs including AESIs, SAEs, adverse events as reason for study treatment discontinuation, treatment-emergent clinical laboratory assessments, treatment-emergent vitals).

### *6.12.1. Extent of Exposure*

Duration of exposure to study treatment will be summarized by treatment group for each treatment period using descriptive statistics.

#### 6.12.1.1. Period 2 (Induction Dosing Period)

The duration of exposure on the induction dosing treatment for the Safety Population will be calculated as:

$$\begin{aligned} &Duration\ of\ induction\ exposure\ (days) \\ &\quad = Date\ of\ last\ visit\ (scheduled\ or\ unscheduled)\ in\ Period\ 2 \\ &\quad - Date\ of\ first\ dose\ in\ Period\ 2 + 1 \end{aligned}$$

The number and percentage of patients in each of the following categories will be summarized: >0 days, ≥7 days, ≥14 days, ≥30 days, ≥60 days, and ≥90 days. Note that patients may be included in more than one category. The number and percentage of patients falling into the following subcategories will also be summarized: >0 to <7 days, ≥7 to <14 days, ≥14 to <30 days, ≥30 to <60 days, ≥60 to <90 days and ≥90 days.

The summaries will also include the following information:

- Total exposure in patient years, calculated as:

$$\begin{aligned} &Induction\ exposure\ in\ patient\ years \\ &= \frac{Sum\ of\ duration\ of\ induction\ exposure\ for\ all\ patients\ in\ treatment\ group}{365.25} \end{aligned}$$

- Mean and median total dose. Total dose (in mg) is calculated by the number of active injections taken during the treatment period multiplied by dose. For those patients randomized to 80 mg (Q2W or Q4W), the total dose (in mg) taken during Period 2 will be calculated as follows:

$$\begin{aligned} &Total\ Period\ 2\ dose\ for\ patients\ on\ 80\ mg\ (Q2W\ or\ Q4W) \\ &= Total\ number\ of\ active\ injections\ (including\ loading\ doses)\ received\ in\ Period\ 2 \\ &\times 80 \end{aligned}$$

Note that the total number of active injections received will be calculated using the response to the question 'Was dose administered?' on the *Exposure as Collected* eCRF page and the actual dose description from IWRS study drug dispense dataset.

### 6.12.1.2. Period 3 (Maintenance Dosing Period)

#### *6.12.1.2.1. Maintenance Dosing Period Primary Population and Maintenance Dosing Period Secondary Population*

The duration of exposure on maintenance treatment will be calculated as:

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

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

The number and percentage of patients in each of the following categories will be summarized: >0 days, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥90 days, ≥120 days, ≥183 days, and ≥365 days. Note that patients may be included in more than one category. The number and percentage of patients falling into the following subcategories will also be summarized: >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.

The summaries will also include the following information:

- Total exposure in patient years, calculated as:

$$\begin{aligned} &Maintenance\ exposure\ in\ patient\ years \\ &= \frac{Sum\ of\ duration\ of\ maintenance\ exposure\ for\ all\ patients\ in\ treatment\ group}{365.25} \end{aligned}$$

- Mean and median total dose (in mg). For those patients randomized to 80 mg Q4W, the total dose (in mg) taken during Period 3 will be calculated as follows:

$$\begin{aligned} &Total\ Period\ 3\ dose \\ &= Total\ number\ of\ active\ injections\ (including\ loading\ doses)\ received\ in \\ &\qquad Period\ 3\ prior\ to\ relapse\ \times 80 \end{aligned}$$

Note that the total number of injections received will be calculated using the response to the question 'Was dose administered?' on the *Exposure as Collected* eCRF page and the actual dose description from IWRS study drug dispense dataset.

#### *6.12.1.2.2. Maintenance Dosing Period Relapse Population*

The duration of exposure on re-treatment will be calculated as:

$$\begin{aligned} &Duration\ of\ re\text{-}treatment\ exposure\ (days) \\ &\quad = Date\ of\ last\ visit\ (scheduled\ or\ unscheduled)\ in\ Period\ 3 \\ &\quad - Date\ of\ first\ dose\ following\ relapse + 1 \end{aligned}$$

The number and percentage of patients in each of the following categories will be summarized: >0 days, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥90 days, ≥120 days, ≥183 days, and ≥365 days.

Note that patients may be included in more than one category. The number and percentage of patients falling into the following subcategories will also be summarized: >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.

The summaries will also include the following information:

- Total exposure in patient years, calculated as:

$$Re\text{-}treatment\ exposure\ in\ patient\ years = \frac{Sum\ of\ duration\ of\ re\text{-}treament\ exposure\ for\ all\ patients\ in\ treatment\ group}{365.25}$$

- Mean and median total dose (in mg). The total dose (in mg) taken during Period 3 following relapse will be calculated as follows:

$$Total\ \text{Period 3}\ relapse\ dose = Total\ number\ of\ active\ injections\ received\ in\ Period\ 3\ following\ relapse\ \times 80$$

Note that the total number of injections received will be calculated using the response to the question 'Was dose administered?' on the *Exposure as Collected* eCRF page and the actual dose description from IWRS study drug dispense dataset.

### *6.12.2. Adverse Events*

Adverse events (AEs) will be classified based upon the latest version of the MedDRA. Any condition starting on or after the date of informed consent will be considered an AE. Any preexisting condition which worsens in severity on or after the date of informed consent will be considered and recorded as an AE on the *Adverse Event* (*AE)* eCRF page from the date of worsening onwards.

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline and on or prior to the date of the last visit within the defined treatment period. Both the date/time of the event and the date/time of the dose (that is, injection) are considered when determining TEAEs. Treatment-emergent AEs will be assigned to the study period to which it's considered treatment-emergent:

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

will be compared as far as possible to the treatment start date/time in order to determine whether the event is treatment-emergent or not. If there is any doubt, the event will be flagged as treatment-emergent.

A follow-up emergent adverse event (FEAE) is defined as an event that first occurred or worsened in severity after the date of Visit 19 (that is, Week 60) or the ETV:

- The MedDRA LLT will be used when classifying AEs as follow-up emergent.
- For AEs that are ongoing at the date of Visit 19 or ETV, the maximum severity recorded for each LLT on or prior to the date of Visit 19 or ETV will be used as the follow-up baseline severity for that LLT.

Adverse events and TEAEs will be summarized for the following time periods and analysis populations:

- Period 2 (Safety Population)
- Period 3 (Maintenance Dosing Period Primary/Secondary/Relapse Population)
- Period 4 (Follow-up Population)

An overall summary of AEs including the number and percentage of patients who experienced TEAE, TEAE by maximum severity, death, SAE, TEAE possibly related to study treatment, discontinuations from the treatment due to an AE, and TEAEs of special interest will be performed for Periods 2 (Safety Population) and 3 (Maintenance Dosing Period Primary/Secondary/Relapse Population).

The following summaries/analyses will be performed for Periods 2 (Safety Population) and 3 (Maintenance Dosing Period Primary Population), unless noted otherwise:

- TEAE by SOC and PT.
- TEAE by PT.
- TEAE by maximum severity, SOC, and PT.

Follow-up emergent AEs will be summarized for the Follow-Up Population in Period 4:

- FEAE by PT.

In general, for all AE-related summaries, the number and percentage of patients experiencing the events will be presented by treatment group. In general, events will be ordered by decreasing frequency in the total ixekizumab group, followed in the order of ixekizumab Q2W, ixekizumab Q4W, and placebo (when applicable) group, within SOC and/or PT for sorting. For events that are gender-specific (as defined by MedDRA), the denominator and computation of the percentage will include only patients from the given gender.

A by-patient listing of all AEs for safety population will be provided.

#### 6.12.2.1. Common Adverse Events

Common TEAEs are those TEAEs that occurred in ≥1% before rounding of total ixekizumab treated patients.

The following summaries will be provided for common TEAEs for Periods 2 (Safety Population) and 3 (Maintenance Dosing Period Primary Population):

- Common TEAEs by PT

### *6.12.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events*

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

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

- 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 the Period 4 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 will be provided for Periods 2 (Safety Population) and 3 (Maintenance Dosing Period Primary Population):

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

A follow-up emergent serious adverse event (FESAE) is defined as an SAE that first occurred or worsened in severity after the date of Visit 19 (that is, Week 60) or the ETV.

The following summary tables will be provided for the Follow-Up Population in Period 4:

- FESAE by PT
- FEAEs that lead to treatment discontinuation (including death) by PT.

#### 6.12.3.1. Special Safety Topics including Adverse Events of Special Interest

Safety information on special topics including AEs of special interest (AESI) will be presented by treatment group and by study period. Table RHBH. 6.8. provides the definitions/derivations and analyses methods (including analyses, summaries and by-patient listings) of special safety topics including AESIs.

Potential AESIs will be identified by a standardized MedDRA query (SMQ) or a Lilly-defined MedDRA PT listing. Preferred terms within an SMQ will be classified as broad and narrow. In the Lilly-defined MedDRA PT listings, Lilly has provided the broad and narrow classification.

The Lilly-defined broad terms are for a more sensitive search of potential events of interest and the Lilly-defined narrow terms are for a more specific search. Therefore, the summaries will include the classifications of broad term 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. For final analysis, the most current version of PSAP will be used, including PSAP released after SAP finalization but before database lock.

In general, AESI summary will not be provided for Follow-up Population during Period 4 except hepatic laboratory tests.

**Table RHBH. 6.8. Definitions and Analyses of Special Safety Topics including Adverse Events of Special Interest**

| Special Safety Topic | Definition / Derivation | Analysis / Summary / Listing |
|---|---|---|
| Hepatic | Hepatic AE analysis will include events that are potentially drug-related hepatic disorders by using the Medical Dictionary for Regulatory Activities (MedDRA) PTs contained in any of the following standardized MedDRA query (SMQ) or sub-SMQ as defined in MedDRA:<br>• Broad and narrow terms in the Liver related investigations, signs and symptoms (20000008)<br>• Broad and narrow terms in the Cholestasis and jaundice of hepatic origin (20000009)<br>• Broad and narrow terms in the Hepatitis, non-infectious (20000010)<br>• Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage (20000013)<br>• Narrow terms in the Liver-related coagulation and bleeding disturbances (20000015) | **Period 2 (Fisher's exact test), Period 3 (Fisher's exact test for Maintenance Dosing Period Primary Population):**<br>TEAE by PT within SMQ or sub-SMQ<br><br>**Listing:**<br>TEAE |
| | Elevations in hepatic laboratory tests (ALT, AST, ALP, total bilirubin) using performing lab reference ranges are defined as:<br>• Include scheduled visits, unscheduled visits, and repeat measurements.<br>• Alanine aminotransferase (ALT) or aspartate aminotransferase (AST): maximum post-baseline measurement ≥3 times (3×), 5 times (5×), 10 times (10×), and 20 times (20×) the performing lab upper limit of normal (ULN) for all patients with a post-baseline value.<br>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.<br>o The analysis of 5× ULN will be 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.<br>o The analysis of 10× ULN will contain 6 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1×ULN to <3× ULN, ≥3× ULN to <5× ULN, ≥5× ULN to <10× ULN, ≥10× ULN, or missing.<br>o The analysis of 20× ULN will contain 7 subsets: patients whose non-missing maximum baseline value is ≤1×ULN, >1×ULN to <3× ULN, ≥3× ULN to <5× ULN, ≥5× ULN to <10× ULN, ≥10× ULN to <20× ULN, ≥20× ULN, or missing.<br>• Total bilirubin: maximum post-baseline measurement ≥1.5 times (1.5×), and ≥2 times (2×) the performing lab ULN for all patients with a post-baseline value<br>o The analysis of 1.5× ULN will contain 4 subsets: patients whose non-missing | **Period 2 (Fisher's exact test), Period 3 (Fisher's exact test for Maintenance Dosing Period Primary Population), Period 4 (Summary):**<br>Elevations in hepatic laboratory tests: maximum baseline category to abnormal maximum post-baseline category |

| Special Safety Topic | Definition / Derivation | Analysis / Summary / Listing |
|---|---|---|
| | maximum baseline value is ≤1× ULN, >1× ULN to <1.5× ULN, ≥1.5× ULN, or missing.<br>o The analysis of 2× ULN will contain 5 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1× ULN to <1.5× ULN, ≥1.5× ULN to <2× ULN, ≥2× ULN, or missing.<br>• Alkaline phosphatase (ALP): maximum post-baseline measurement >1.5 times (1.5×) the performing lab ULN for all patients with a post-baseline value, and divided into 4 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1× ULN to ≤1.5× ULN, >1.5× ULN, or missing. | |
| | Shift for ALT, AST, ALP and total bilirubin from maximum baseline to maximum post-baseline will be produced with the requirements using performing lab reference ranges:<br>• Include scheduled visits, unscheduled visits, and repeat measurements.<br>• Use the maximum non-missing value in the baseline period.<br>• Use the maximum non-missing post-baseline value within each study period.<br>• Categories are:<br>o ALT: ≤1× ULN, >1 to <3× ULN, ≥3 to <5× ULN, ≥5 to <10× ULN, ≥10 to <20× ULN, and ≥20× ULN<br>o AST: ≤1× ULN, >1 to <3× ULN, ≥3 to <5× ULN, ≥5 to <10× ULN, ≥10× to <20× ULN and ≥20× ULN<br>o Total bilirubin: ≤1× ULN, >1 to <1.5× ULN, ≥1.5 to <2× ULN, ≥2× ULN<br>o ALP: ≤1× ULN, >1 to ≤1.5× ULN, >1.5× ULN<br>• With additional categories:<br>o Decreased: post-baseline category < baseline category<br>o Increased: post-baseline category > baseline category<br>o Same: post-baseline category = baseline category | **Period 2 (Summary) and Period 3 (Summary for Maintenance Dosing Period Primary Population)**:<br>Shifts from maximum baseline to maximum post-baseline category |
| | Elevated hepatic criteria: maximum ALT ≥3× ULN and maximum total bilirubin ≥2× ULN using performing lab reference ranges.<br>Listing of patients who meet any of the following criteria:<br>• Elevated hepatic criteria: defined as maximum ALT ≥3× ULN and maximum total bilirubin ≥2× ULN<br>• An ALT or AST ≥ 3× ULN<br>• An ALP ≥ 1.5× ULN<br>• A total bilirubin ≥ 2× ULN | **Period 2 (Fisher's exact test)**, **Period 3 (Fisher's exact test for Maintenance Dosing Period Primary Population), Period 4 (Summary):**<br>Elevated hepatic criteria<br><br>**Listing**:<br>Elevations in hepatic laboratory tests |

| Special Safety Topic | Definition / Derivation | Analysis / Summary / Listing |
|---|---|---|
| | 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 | |
| | Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot: use maximum ALT measurement and maximum total bilirubin measurement with patients having at least one post-baseline ALT and total bilirubin, which contributes one point to the plot. Patients will be classified into 2 groups: never on ixekizumab or ever on ixekizumab. The measurements do not need to be taken at the same blood draw. | eDISH plot |
| Cytopenias | Cytopenias are defined using the PTs from the following 2 sub-SMQs of the Haematopoietic cytopenias SMQ (20000027) as specified in MedDRA:<br>• Broad and narrow terms in the Haematopoietic leukopenia (20000030)<br>• Broad and narrow terms in the Haematopoietic thrombocytopenia (20000031) | **Period 2 (Fisher's exact test), Period 3 (Fisher's exact test for Maintenance Dosing Period Primary Population)**:<br>TEAE by PT within sub-SMQ<br><br>**Listing:**<br>TEAE |
| Infections | Infections are events including all infections (defined using all the MedDRA PTs from the Infections and infestations SOC), serious infections, potential opportunistic infections (OIs), and infections resulting in anti-infective medication administration (i.e., antibacterial, antiviral, antifungal, antiparasitic treatment). | **Period 2 (Fisher's exact test)**, **Period 3 (Fisher's exact test for Maintenance Dosing Period Primary Population):**<br>SAE by PT,<br>AE leading to treatment discontinuation by PT |
| | Anti-infective medications are defined in the LY2439821 PSAP v8 Appendix 5 (or most current version) including antibiotics, antifungals, antivirals, or antiprotozoals.<br>Listing of patients experiencing a TEAE of infections will be provided including the following additional information: anti-infective medications use (if treated) with medication start/end dates, indication for use, and route; minimum post-baseline value within treatment Period 2 for leukocytes, platelets, lymphocytes, and absolute neutrophils. | **Listing:**<br>TEAE with information collected on *Infection* eCRF page,<br>TEAE with anti-infective medications. |

| Special Safety Topic | Definition / Derivation | Analysis / Summary / Listing |
|---|---|---|
| | The list of MedDRA terms used to identify infections that are predefined as potential opportunistic infections (OI) are found in the LY2439821 PSAP v8 Appendix 10 (or most current version). This list contains PTs as contained within categories (narrow and broad) from the Infections and Infestations SOC and the Investigations SOC which can assist in identifying potential OIs. The narrow terms are considered OIs unless medical review determined 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.<br>Listing of patients experiencing a TEAE of OIs will be provided including the following additional information: source of identification (CRF or Lilly specified list), primary/secondary site of infection, primary/secondary infection type, primary/secondary identified by a laboratory diagnostic test (Yes/No), acquired in a Health care setting (Yes/No). | **Period 2 (Fisher's exact test), Period 3 (Fisher's exact test for Maintenance Dosing Period Primary Population):**<br>TEAE of OIs by PT<br><br>**Listing:**<br>TEAE of OIs. |
| | The duration of each common (≥1% of total ixekizumab) TEAE PT of Infections and narrow terms for Opportunistic infections are defined as:<br>Duration of treatment-emergent AE Infections (in weeks) = (End date of AE – Start date of AE + 1) / 7.<br>Only TEAEs of infections beginning during that treatment period will be included in the summary. If a TEAE has not ended by the date of completion of the treatment period, or date of early discontinuation, it will be censored as of that date (last visit within the treatment period, or date of early discontinuation). If a patient has multiple episodes of the same TEAE, the episode with the greatest severity will be used for the duration of event calculation. If a patient has multiple episodes of the same TEAE with the same severity, the episode with the longest duration will be used for the duration of event calculation. | **Period 2 and Period 3 (Summary)**:<br>Duration of Common TEAE – Infections |
| Allergic Reactions/Hy-persensitivities | 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.<br><br>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:<br>1) designed to specifically identify cases (following Criterion 1) based on narrow terms from the MedDRA SMQ for anaphylactic reaction (20000021). Criterion 1 for | **Period 2 (Fisher's exact test), Period 3 (Fisher's exact test for Maintenance Dosing Period Primary Population)**:<br>TEAE by maximum severity by PT within Category,<br>SAE by PT within Category,<br>AE leading to treatment discontinuation by PT within Category |

| Special Safety Topic | Definition / Derivation | Analysis / Summary / Listing |
|---|---|---|
| | anaphylaxis is defined by the presence of a TEAE based on the following MedDRA PTs from the anaphylactic reaction SMQ:<br>• Anaphylactic reaction<br>• Anaphylactic shock<br>• Anaphylactoid reaction<br>• Anaphylactoid shock<br>• Kounis Syndrome<br>• Type 1 hypersensitivity.<br>2) to identify possible cases, following Criterion 2 as defined by Sampson et al (2006). Criterion 2 for potential 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 on CRFs. All qualifying events must be within 1 day of study drug injection.<br><br>The 4 categories to be considered in Criterion 2 are:<br>• Category A: Involvement of the skin-mucosal tissue<br>• Category B: Respiratory compromise<br>• Category C: Reduced blood pressure or associated symptoms<br>• Category D: Persistent gastrointestinal symptoms<br>The specific MedDRA PTs covered by each of these Criterion 2 categories are shown in the LY2439821 PSAP v8 Appendix 6 (or most current version).<br><br>Summaries of Criterion 2 anaphylactic TEAEs will be provided by the specific combination of categories as follows:<br>• AB: events based on meeting Category A and Category B (but no other category)<br>• AC: events based on meeting Category A and Category C (but no other category)<br>• AD: events based on meeting Category A and Category D (but no other category)<br>• BC: events based on meeting Category B and Category C (but no other category)<br>• BD: events based on meeting Category B and Category D (but no other category)<br>• CD: events based on meeting Category C and Category D (but no other category)<br>• ABC: events based on meeting Category A, Category B and Category C (but no other category)<br>• ABD: events based on meeting Category A, Category B and Category D (but no other 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)<br>• BCD: events based on meeting Category B, Category C and Category D (but no other category)<br>• ABCD: events based on meeting each of the 4 Criterion 2 categories<br><br>Summaries of treatment-emergent anaphylactic AEs will be provided for patients meeting each of the 2 criteria and for patients who meet either criteria overall. Severity of treatment-emergent Criterion 2 potential anaphylactic AEs will be based on the maximum severity of the specific events met by the patient. Maximum severity of an (or overall) treatment-emergent potential anaphylactic AE will be based on the maximum severity within Criterion 1 and/or Criterion 2.<br><br>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 the LY2439821 PSAP v8 Appendix 7 (or most current version) and excluding the anaphylactic events as defined above. | |
| | A by-patient listing will be provided for all patients experiencing TEAE of allergic reactions/hypersensitivities at any time, including status/criterion of anaphylaxis or non-anaphylaxis, and the associated information collected on *Allergic / Hypersensitivity Reaction Follow-Up* eCRF page if identified by the investigator. | **Listing:**<br>TEAE including information collected on *Allergic / Hypersensitivity Reaction Follow-Up* eCRF page |
| Injection Site Reactions | Injection site reaction is defined using the PTs from the MedDRA HLT of Injection site reactions as specified by MedDRA excluding the following 10 PTs:<br>1) Embolia cutis medicamentosa<br>2) Injection site joint discomfort<br>3) Injection site joint effusion<br>4) Injection site joint redness<br>5) Injection site joint infection<br>6) Injection site joint inflammation<br>7) Injection site joint movement impairment<br>8) Injection site joint pain<br>9) Injection site joint swelling | **Period 2 (Fisher's exact test), Period 3 (Fisher's exact test for Maintenance Dosing Period Primary Population)**:<br>TEAE by maximum severity by PT<br><br>TEAE identified by the investigator PT:<br>by maximum severity,<br>by maximum redness category,<br>by maximum hardness category,<br>by maximum swelling category,<br>by maximum pain category |

| Special Safety Topic | Definition / Derivation | Analysis / Summary / Listing |
|---|---|---|
| | 10) Injection site joint warmth.<br><br>The *Injection Site Reaction* eCRF page captures the injection site reactions identified by the investigator. These TEAEs will be summarized within the MedDRA HLT by maximum severity or category. If more than one TEAE of injection site reaction occurs, the event with the worst value (within the individual categories: redness, hardness, swelling, and pain) will be used.<br>Redness (Scored 0-3)<br>• [0] No<br>• [1] Noticeable, but very mild redness<br>• [2] Clearly red<br>• [3] Bright red<br>Hardness (Scored 0-4)<br>• [0] No<br>• [1] Barely noticeable<br>• [2] Slight<br>• [3] Moderate<br>• [4] Severe<br>Swelling (Scored 0-3 after running a finger over injected area)<br>• [0] No<br>• [1] Mild edema (less than 2 mm)<br>• [2] Moderate edema (2 – 5 mm)<br>• [3] Severe edema (more than 5 mm)<br>Pain (including burning) (Scored 0-3)<br>• [0] None<br>• [1] Mild<br>• [2] Moderate<br>• [3] Severe | **Listing:**<br>TEAE including information collected on *Injection Site Reaction* eCRF page |
| Cerebro-cardiovascular Events | Cerebro-cardiovascular events will be externally adjudicated by the Clinical Events Committee (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 | **Period 2 (Fisher's exact test), Period 3 (Fisher's exact test for Maintenance Dosing Period Primary Population)**:<br>TEAE by PT within Subcategory<br><br>**Listing:** |

| Special Safety Topic | Definition / Derivation | Analysis / Summary / Listing |
|---|---|---|
| | for confirmation of an event. All events which qualify for CEC adjudication will be used for the analysis of cerebro-cardiovascular events. The categories of adjudicated events used for the analysis will include the following:<br>• Cardiovascular<br>  o Death (Cardiovascular)<br>  o Myocardial Infarction (MI)<br>  o Hospitalization for Unstable Angina<br>  o Hospitalization for Heart Failure<br>  o Serious Arrhythmia<br>  o Hospitalization for Hypertension<br>  o Resuscitated Sudden Death<br>  o Cardiogenic Shock due to Myocardial Infarction<br>  o Coronary Revascularization Procedure<br>• Neurologic<br>  o Cerebrovascular Event: Transient Ischemic Attack or Stroke (Haemorrhagic, Ischemic and Undetermined)<br>• Peripheral Vascular Events<br>  o Peripheral Arterial Event<br>  o Peripheral Revascularization Procedure<br>Events will be analyzed using MedDRA PT nested within the CEC assessment (confirmed event, no event, or insufficient documentation for event determination) and the subcategory. Subtypes of stroke (Hemorrhagic Stroke, Ischemic Stroke, and Undetermined Stroke Type) will be displayed in the analyses nested within stroke. Subcategories of Serious Arrhythmia (Atrial Arrhythmia, Ventricular Arrhythmia, Heart Block, Other, Unknown) will be displayed nested within Serious Arrhythmia. | TEAE |
| Major Adverse Cerebro-cardiovascular Events (MACE) | MACE (requiring adjudication as defined above) is defined as:<br>• Vascular Death (including cardiovascular and cerebro-vascular causes excluding hemorrhagic deaths outside of the central nervous system)<br>• Non-fatal myocardial infarction<br>• Non-fatal stroke (subtypes: hemorrhagic stroke, ischemic stroke, undetermined stroke type)<br>Where,<br>• Vascular death should be captured as an Event on *Adjudication - Death* eCRF page with | **Period 2 (Fisher's exact test), Period 3 (Fisher's exact test for Maintenance Dosing Period Primary Population)**:<br>TEAE by maximum severity by PT within Category<br><br>**Listing:**<br>TEAE |

| Special Safety Topic | Definition / Derivation | Analysis / Summary / Listing |
|---|---|---|
| | Adjudication Death Type = 'Cardiovascular'.<br>• 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.<br>• 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 specified in MedDRA (SMQ: 20000091), which includes the sub-SMQs:<br>• 20000194 [Malignant tumours], including sub-SMQs of 20000227 [Haematological malignant tumours] and 20000228 [Non-haematological malignant tumours]<br>• 20000195 [Tumours of unspecified malignancy], including sub-SMQs of 20000229 [Haematological tumours of unspecified malignancy] and 20000230 [Non-haematological tumours of unspecified malignancy]<br>Events will be summarize by the following categories:<br>• Non-Melanoma Skin Cancer (NMSC)<br>o Basal Cell Carcinoma, PTs include:<br>▪ Basal cell carcinoma<br>▪ Basosquamous carcinoma<br>▪ Basosquamous carcinoma of skin<br>o Squamous Cell Carcinoma, PTs include:<br>▪ Squamous cell carcinoma of skin<br>▪ Bowen's disease<br>▪ Lip squamous cell carcinoma<br>▪ Skin squamous cell carcinoma metastatic<br>▪ Keratoacanthoma<br>• Malignancies excluding NMSC: all PTs in the Malignant or unspecified tumors SMQ excluding the 8 defined NMSC PTs. | **Period 2 (Fisher's exact test), Period 3 (Fisher's exact test for Maintenance Dosing Period Primary Population)**:<br>TEAE by PT within Category<br><br>**Listing:**<br>TEAE |

| Special Safety Topic | Definition / Derivation | Analysis / Summary / Listing |
|---|---|---|
| Depressions | Depression is defined using the PTs from the Depression and suicide/self-injury SMQ as specified in MedDRA (SMQ: 20000035, which includes the sub-SMQs: 20000037 [Suicide/self-injury] and 20000167 [Depression (excl suicide and self injury)]). | **Period 2 (Fisher's exact test), Period 3 (Fisher's exact test for Maintenance Dosing Period Primary Population)**:<br>TEAE by PT within SMQ and sub-SMQ<br><br>**Listing:**<br>TEAE |
| Inflammatory Bowel Disease (IBD) | IBD will be identified using the following subcategory and MedDRA PTs. The narrow terms are considered IBD.<br>IBD Specific Terms (Narrow terms):<br>• Inflammatory Bowel Disease: Inflammatory bowel disease<br>• Crohn's Disease: Crohn's disease<br>• Ulcerative Colitis: Acute haemorrhagic ulcerative colitis; Colitis ulcerative; Proctitis ulcerative<br>Non-Specific Terms (Events That Can Occur with IBD (Broad Terms)): The PTs in this category are listed in the LY2439821 PSAP v8 Appendix 11 (or most current version). | **Period 2 (Fisher's exact test), Period 3 (Fisher's exact test for Maintenance Dosing Period Primary Population)**:<br>TEAE by PT within subcategory<br><br>**Listing**:<br>TEAE |
| Interstitial Lung Disease (ILD) | ILD is defined using the following terms:<br>• Narrow terms in the Interstitial lung disease SMQ (20000042)<br>• Additional 6 PTs from Eosinophilic pneumonia SMQ (20000157):<br>o Angiolymphoid hyperplasia with eosinophilia (Narrow)<br>o Eosinophilic bronchitis (Narrow)<br>o Hypereosinophilic syndrome (Narrow)<br>o Loeffler's syndrome (Narrow)<br>o Pulmonary eosinophilia (Narrow)<br>o Pulmonary vasculitis (Narrow) | **Listing**:<br>TEAE |

Abbreviations: AE = adverse event; AESI = adverse event of special interest; eCRF = electronic case report form; HLT = high-level term; PT = preferred term; SAE = serious adverse event; TEAE = treatment emergent adverse event.

### *6.12.4. Clinical Laboratory Evaluation*

Clinical laboratory assessments include hematology, serum chemistry, urinalysis, and safety-related immune markers such as neutrophil counts. All laboratory tests will be presented using the international system of unit (SI).

Continuous laboratory tests will be summarized as changes from baseline to last observation for patients who have both baseline and at least 1 postbaseline result for Periods 2 and 3:

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- For Safety Population during Period 2 and Maintenance Dosing Period Primary Population during Period 3, treatment group comparisons will be conducted using an ANCOVA model with treatment group and baseline value in the model.
- Data will be analyzed based on original scale.

Laboratory test 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 a baseline and at least one postbaseline result for Periods 2 and 3. These box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries.

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- The following summary statistics will be included as a table below the box plot: number of patients with a baseline and at least one postbaseline result, mean, standard deviation, minimum, Q1, median, Q3, and maximum.
- Data will be summarized based on original scale.
- On the box plots of the laboratory test observed values, the lines of the reference ranges/limits (by using the performing laboratory reference ranges) will be added. In cases where limits vary across age and gender, the lowest of the high limits and the highest of the low limits will be used.

The number and percentage of patients with a treatment-emergent or follow-up emergent abnormal, high, or low for laboratory tests will be summarized by treatment group for each study period. The comparisons between and among treatment groups will be conducted using Fisher's exact test for the Safety Population for Period 2 and Maintenance Dosing Period Primary Population for Period 3.

- All scheduled, unscheduled and repeated measurements will be included.
- Performing laboratory will be used to define the low and high limits reference ranges except leukocyte, neutrophil, lymphocyte and platelet counts, where Lilly defined lower limit of normal will be used for these 4 labs.
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP), neutrophils, leukocytes, platelets, and lymphocytes will not be included in the treatment-emergent abnormal, high, or low summary as a separate

analysis addressing the risk of liver injury is described in Section 6.12.3.1 and a separate analysis addressing Leukocytes (WBC) and Platelets is described in Section 6.12.4.1.

- Note that the ranges are defined by a lower limit of normal (LLN) and an upper limit of normal (ULN). A result that is greater than or equal to the LLN and less than or equal to the ULN is considered to be within the normal ranges.
- For categorical laboratory tests:
  - Treatment-emergent **abnormal** value is defined as a change from normal at all baseline visits to abnormal at any time postbaseline during the treatment period.
  - Follow-up emergent **abnormal** result is defined as a change from normal at baseline to abnormal at any time during the follow-up period.
- For continuous laboratory tests:
  - Treatment-emergent **high** value is defined as a change from a value less than or equal to the ULN at all baseline visits to a value greater than the ULN at any time postbaseline during the treatment period.
  - Treatment-emergent **low** value is defined as a change from a value greater than or equal to the LLN at all baseline visits to a value less than the LLN at any time postbaseline during the treatment period.
  - Follow-up emergent **high** value is defined as a change from a value less than or equal to the ULN at baseline to a value greater than the ULN at any time postbaseline during the follow-up period.
  - Follow-up emergent **low** value is defined as a change from a value greater than or equal to the LLN at baseline to a value less than the LLN at any time postbaseline during the follow-up period.

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.

### 6.12.4.1. Leukocytes (WBC) and Platelets

Further analyses will be conducted for total leukocytes, neutrophils, platelets, lymphocytes, monocytes, eosinophils, and basophils. Unless otherwise specified, neutrophils will be summarized as absolute neutrophils (derived by adding segmented neutrophils and band neutrophils).

Shift table will be produced showing the number and percentage of patients shifting from baseline to a minimum postbaseline result in each relevant category by treatment groups for Periods 2 and 3, respectively:

- Scheduled visits, unscheduled visits, and repeat measurements will be included.
- Baseline is defined as the minimum result during the defined baseline period or baseline.
- Use the minimum non-missing postbaseline value within each study period.
- The parameters and categories are:
  - 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).

  - Neutrophils: ≥1× LLN (Normal), < LLN to ≥1.5× 10^9/L (Grade 1), <1.5× 10^9/L to ≥1.0× 10^9/L (Grade 2), <1.0× 10^9/L to ≥0.5× 10^9/L (Grade 3), and <0.5× 10^9/L (Grade 4)
  - Platelets: ≥1 × LLN (Normal), < LLN to ≥75.0 × 10^9/L (Grade 1), <75.0 × 10^9/L to ≥50.0 × 10^9/L (Grade 2), <50.0 × 10^9/L to ≥25.0 × 10^9/L (Grade 3), and <25.0 × 10^9/L (Grade 4).
  - Lymphocytes: ≥1× LLN (Normal), < LLN to ≥0.8× 10^9/L (Grade 1), <0.8× 10^9/L to ≥0.5× 10^9/L (Grade 2), <0.5× 10^9/L to ≥0.2× 10^9/L (Grade 3), and <0.2× 10^9/L (Grade 4).
- The above LLNs are defined as:
  - Leukocytes: LLN = 4.0× 10^9/L
  - Neutrophils: LLN = 2.0× 10^9/L
  - Platelets: LLN = 150× 10^9/L
  - Lymphocytes: LLN = 1.1× 10^9/L
- With additional categories:
  - Decreased; postbaseline category < baseline category
  - Increased; postbaseline category > baseline category
  - Same; postbaseline category = baseline category.

The change from minimum baseline to minimum postbaseline result for each of these leukocytes and platelets will be summarized graphically using a box plot for Periods 2 and 3, respectively.

### 6.12.4.2. Neutrophil Follow-Up

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

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

Neutrophil clinical recovery is defined as an absolute neutrophil count ≥1500 cells/μL (SI units: ≥1.5× 10^9/L) or greater than or equal to a patient's 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 treatment groups and week interval for the Neutrophil Follow-Up Population for Period 4. The number and percentage of patients with an absolute neutrophil cell count that is at least 25%,

50%, 75%, or 100% of the patient's baseline absolute neutrophil count (that is, prior to first injection at Week 0), irrespective of absolute neutrophil minimum, will be included in the summary.

### *6.12.5. Vital Signs and Other Physical Findings*

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

Change from baseline to last observation for vital signs and physical characteristics will be summarized for patients who have both baseline and at least one post-baseline result, for Periods 2 and 3, respectively:

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- For Safety Population in Period 2 and Maintenance Dosing Period Primary Population in Period 3, treatment comparisons between and among treatment groups will be conducted using an ANCOVA with treatment group and baseline value in the model.
- Data will be analyzed based on original scale.

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 a baseline and at least one post-baseline result. These box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries.

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- The following summary statistics will be included as a table below the box plot: number of patients with a baseline and at least one post-baseline result, mean, SD, minimum, Q1, median, Q3, and maximum.
- Data will be summarized based on original scale.

To assess the effect of administration of study drug on vital signs (blood pressures and pulse rate) among patients, at Week 0 and Week 12, vital signs will be measured before the first injection and 1 hour after the injection. The box plots will be produced for pre-dose and post-dose vital signs at Week 0 (Visit 2) and Week 12 (Visit 7).

The number and percentage of patients with treatment-emergent or follow-up emergent high or low vital sign and weight at any time for Periods 2, 3 and Period 4, respectively, will be summarized.

- Table RHBH. 6.9. defines the high and low baseline values as well as the limits that are specified as treatment-emergent and follow-up emergent. Note that weight does not have an abnormal baseline; therefore, the treatment-emergent and follow-up emergent values are determined by change from baseline.

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

**Table RHBH. 6.9. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressures and Pulse Measurement, and Categorical Criteria for Weight Changes for Adults**

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

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

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

### *6.12.6. Quick Inventory of Depressive Symptomatology–Self Report 16 items (QIDS-SR16)*

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

for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity. Additional information and the QIDS-SR16 questions may be found at the University of Pittsburgh IDS/QIDS resource page (http://www.ids-qids.org/).

The 9 domains assessed by the instrument are defined as:

1) **Sleep disturbance** (initial, middle, and late insomnia or hypersomnia): the highest score recorded for the 4 sleep items: #1 (falling asleep), #2 (sleep during the night), #3 (waking up too early) and #4 (sleeping too much). Domain is missing if all items are missing.
2) **Sad mood:** Item #5 (feeling sad). Domain is missing if the item is missing.
3) **Decrease/increase in appetite/weight:** the highest score recorded for the appetite/weight items: #6 (decreased appetite), #7 (increased appetite), #8 (decreased weight within the last 2 weeks), and #9 (increased weight within the last 2 weeks). Domain is missing if all items are missing or not applicable.
4) **Concentration:** Item #10 (concentration / decision making). Domain is missing if the item is missing.
5) **Self-criticism:** Item #11 (view of myself). Domain is missing if the item is missing.
6) **Suicidal ideation:** Item #12 (thoughts of death or suicide). Domain is missing if the item is missing.
7) **Interest**: Item #13 (general interest). Domain is missing if the item is missing.
8) **Energy/fatigue:** Item #14 (energy level). Domain is missing if the item is missing.
9) **Psychomotor agitation/retardation:** the highest score recorded for the 2 psychomotor items: #15 (feeling slowed down) and #16 (feeling restless). Domain is missing if all items are missing.

The QIDS-SR16 total score is the sum of the above domain scores. The total score will be missing if any domain score is missing. The QIDS-SR16 total scores are categorized as: None (no depression) (0 – 5), Mild (6 – 10), Moderate (11 – 15), Severe (16 – 20) and Very severe (21 – 27).

For both Period 2 and 3 QIDS-SR16 analyses, baseline is defined as the last non-missing assessment recorded on or prior to the date of first injection of study treatment at Week 0 (Visit 2), as for QoL measures. In most cases, this will be the measure recorded at Week 0 (Visit 2).

Summaries will be done by treatment groups for Safety Population in Period 2 and Maintenance Dosing Period Primary Population in Period 3, respectively.

The following summaries will be produced for QIDS-SR16 total score category:

- The number and percentage of patients falling into each QIDS-SR16 total score category at each scheduled visit.
- Shift from maximum baseline to each postbaseline visit in QIDS-SR16 total score category.
- The number and percentage of patients falling into the following categories based upon the maximum postbaseline QIDS-SR16 total score:
    - Improved; maximum postbaseline category < maximum baseline category.

- Worsened; maximum postbaseline category > maximum baseline category.
- Same; maximum postbaseline category = maximum baseline category.

In addition, the number and percentage of patients falling into the following groups based upon the maximum postbaseline QIDS-SR16 item 12 (Thoughts of Death or Suicide) score will be summarized:

- Improved; maximum postbaseline item 12 score < maximum baseline item 12 score.
- Worsened; maximum postbaseline item 12 score > maximum baseline item 12 score.
- Same; maximum postbaseline item 12 score = maximum baseline item 12 score.

### *6.12.7. Columbia-Suicide Severity Rating Scale (C-SSRS)*

The 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 ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

Given that few or no suicidal ideation or behaviors are anticipated, C-SSRS will be listed by patient and visit. Only patients that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be reviewed (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

their ideation and behavior will be reviewed, even if not positive. Note, missing data should not be imputed.

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) which collects supplemental information on the self-injurious behavior is to be completed. 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.*'

## 6.13. Immunogenicity

### *6.13.1. Definitions and Terms*

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

#### 6.13.1.1. Sample Category Definitions

Samples are classified into the following categories:

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

#### 6.13.1.2. Patient Category Definitions

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

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

- **Evaluable patient:** a) Patient with an evaluable baseline sample and at least 1 evaluable postbaseline sample (that is, sample after administration of study drug); b) patient with no evaluable baseline sample whose evaluable postbaseline samples are all ADA negative.

### 6.13.1.3. Definitions for Clinical Interpretation of Assay Results

- **Baseline:** For immunogenicity analyses during Period 2, baseline is the last nonmissing observation on, or prior to, the date of the first injection of study treatment (Week 0). Unless otherwise specified, the baseline for subsequent treatment periods is defined as the last nonmissing observation on, or prior to, the date of first injection of ixekizumab. For patients originally randomized to ixekizumab during Period 2, baseline is the last non-missing observation on, or prior to, the date of the first injection of study treatment for Period 2 (Week 0). For patients who are originally randomized to placebo in Period 2, baseline is the last non-missing observation on, or prior to, the date of the first injection of ixekizumab. See Table RHBH. 6.10. for further details.

**Table RHBH. 6.10. Definition of Baseline for Immunogenicity Analysis for Maintenance Dosing Period**

| Period 2 (Induction Period) Randomized Treatment | Week 12 Responder? | Period 3 (Maintenance Dosing Period) Treatment | Relapse (sPGA ≥3)? | Baseline[1] |
|---|---|---|---|---|
| Ixekizumab | Yes/No | Ixekizumab | Yes/No | Week 0 |
| | Yes | Placebo | Yes/No | Week 0 |
| Placebo | No | Ixekizumab | Yes/No | Week 12 |
| | Yes | Placebo | Yes | Week of Relapse in Period 3 |
| | | | No | Week 0 |

Abbreviations: NA = not applicable; sPGA= static Physician Global Assessment.

[1] last nonmissing observation on, or prior to, the date of the first injection of study treatment at the defined Week

- **Baseline ADA positive (preexisting antibody) patient:** ADA detected in a sample collected at baseline.
- **TE-ADA positive patient:** a) a patient with a ≥4-fold (or 2 dilutions) increase over a positive baseline antibody titer; or b) for a negative baseline titer, a patient with an increase from the baseline to a level of ≥1:10.
- **Baseline ADA-negative patient:** ADA is not detected in a sample collected at baseline.
- **TE-ADA inconclusive patient:** A patient without a TE-ADA positive sample and with at least 1 sample for which drug levels may interfere with the ADA assay.
- **TE-ADA negative patient:** A patient who is evaluable for TE-ADA and is not either TE-ADA positive or TE-ADA inconclusive.
- **Incidence of TE-ADA:** Patients with TE-ADA as a proportion of the evaluable patient population during the treatment period. This excludes unevaluable patients.

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

- **NAb-positive patient:** A patient where a NAb positive result is detected for ≥1 TE-ADA positive samples.

- **NAb-inconclusive patient:** A patient without a NAb positive sample and with at least 1 sample for which drug levels may interfere with the NAb assay.
- **NAb-negative patient:** A patient who is evaluable for NAb and is not either NAb positive sample or NAb inconclusive.

Please see the LY2439821 PSAP v8 section 5.6.4.1.3 (or most current version) for details on the definitions for clinical interpretation of assay results.

### *6.13.2. Immunogenicity Analyses*

Immunogenicity evaluable patients will be identified as TE-ADA positive, TE-ADA negative, or TE-ADA inconclusive, according to the definitions provided in Section 6.13.1.3 and further grouped into TE-ADA status groups and time-varying TE-ADA status groups.

**TE-ADA Status Groups:**

- TE-ADA status (positive, negative, or inconclusive);
- NAb status (positive, negative, or inconclusive) for TE-ADA positive patients; and
- TE-ADA titer groups for TE-ADA positive patients:
  - Low Titer: TE-ADA titer value (LOCF) <1:160;
  - Moderate Titer: TE-ADA titer value (LOCF) ≥1:160 and <1:1280; and
  - High Titer: TE-ADA titer value (LOCF) ≥1:1280.

**Time-Varying TE-ADA Status Groups:**

Individual ADA samples will be ascribed into 3 different dichotomous variables as explained in Table RHBH. 6.11. Each variable has possible values of a "greater-TE-ADA status" or a "lesser-TE-ADA status," in the sense that the level of TE-ADA detected in the greater-TE-ADA category is higher than in the lesser-TE-ADA category.

**Table RHBH. 6.11. TE-ADA Status Dichotomous Variables for AE Analysis**

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

Abbreviations: AE = adverse event; TE-ADA = treatment-emergent anti-drug antibody.
Notes: For the purpose of this analysis, TE-ADA Inconclusive is taken to be "not TE-ADA positive."
A TE-ADA low is defined as a TE-ADA positive with a titer value <1:160; a TE-ADA moderate is defined as a TE-ADA positive with a titer value ≥1:160 and <1:1280; and a TE-ADA high is defined as a TE-ADA positive with a titer value ≥1:1280.

For each TE-ADA status dichotomous variable, a time-varying TE-ADA status will be computed. At time *t*, the TE-ADA status is taken to be the highest of the TE-ADA values bracketing time *t*. More formally, the TE-ADA status at time *t* is given by the greater of (a) the TE-ADA status at the most-recent post-baseline measurement prior to *t*, and (b) the TE-ADA

status at the first TE-ADA post-baseline measurement at or after time *t*. In this computation, "greater" is given by the greater-TE-ADA status of Table RHBH. 6.11. If there is no value satisfying criterion (a), then the value (b) is used. Similarly, if there is no value (b), then the value (a) is used.

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

#### 6.13.2.1. Analyses of Characteristics of ADA Immune Response

The analyses of ADA effects will be conducted on all evaluable patients within the defined safety population for Induction Dosing Period (Period 2), and Combined Induction and Maintenance Dosing Periods (Combined Periods 2 and 3, information prior to relapse), and for Maintenance Dosing Period Relapse Population in Maintenance Dosing Period.

Baseline definition for immunogenicity analyses for the Combined Treatment Period is the same as Table RHBH. 6.10.

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

In addition, the overall frequency and percentage (incidence) of patients will be summarized for the patients who are baseline ADA positive by TE-ADA status groups. For those patients who are TE-ADA positive, a summary of titer values and the proportion of patients who are NAb positive will also be provided.

The time to development of TE-ADAs (TE-ADA positive, Low titer, Moderate titer, High titer, and NAb positive) will be calculated as follows:

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

If a patient has not developed TE-ADA/NAb, they will be censored at the date of the last immunogenicity assessment.

A Kaplan-Meier plot of the time to development of TE-ADA/NAb will be presented by treatment group, if sufficient data is present. The log-rank test will be used to test the null hypothesis against the alternate hypothesis that the time to TE-ADA/NAb is not equal between each ixekizumab dose and placebo. Caution should be exercised in the interpretation of time-to event analyses and related statistics given the limited sampling scheme for immunogenicity testing.

For each TE-ADA status dichotomous variable (as defined in Table RHBH. 6.11.), summaries will be provided of the total post-baseline time in the greater-TE-ADA status for patients who were at some point post-baseline in the greater-TE-ADA status group. Post-baseline time in greater-TE-ADA status for each patient will be aggregated.

A by-patient listing to include treatment, visit date, visit, ADA result, TE-ADA result, NAb result, ADA titer value, ixekizumab concentration, and ADA and NAb inconclusive results will also be provided.

### 6.13.2.2. Analyses of ADA Effects on Efficacy

Efficacy analyses will be conducted on all evaluable patients within the ITT population in Period 2 and on all evaluable patients within the Maintenance Dosing Period Primary Population in Period 3.

sPGA (0), sPGA (0,1), PASI 75, PASI 90 and PASI 100 response rates at Week 12 and 60 (NRI) will be summarized by the TE-ADA status groups. A logistic regression model with treatment group, TE-ADA status group and the interaction of treatment-by-TE-ADA status group included as factors will be used to test the interaction of treatment-by-TE-ADA status group. The p-value associated with the interaction term will be used to assess if the treatment effect is consistent across the TE-ADA status group. When the interaction term is statistically significant, the association between responder status and treatment depends, in some manner, on the TE-ADA status group. The interaction will be tested at the 10% significance level. Treatment group differences will be evaluated within each subgroup using Fisher's exact test regardless of whether the interaction is statistically significant.

The relapse rate (loss of response; sPGA >=3) at Week 60 (NRI) will also be summarized by the TE-ADA status groups for the Maintenance Dosing Period Primary Population.

### 6.13.2.3. Analyses of ADA Effects on Specific Adverse Events

The analyses of ADA effects on safety will be conducted on all evaluable patients within the defined safety population for Period 2 and Combined Induction and Maintenance Dosing Periods (Combined Periods 2 and 3, information prior to relapse).

Baseline definition for immunogenicity analyses for the Combined Treatment Period is the same as Table RHBH. 6.10.

AESIs of allergic reaction/hypersensitivity (anaphylaxis and non-anaphylaxis) and of injection site reactions will be included in an assessment of AE to TE-ADA over time. Timing of an AE will be taken to be the reported AE start date.

For each TE-ADA status dichotomous variable (as defined in Table RHBH. 6.11.), patients will be categorized according to whether they were (i) always in lesser-TE-ADA status post-baseline or (ii) at some point post-baseline were in greater-TE-ADA status. For each AESI, within the time-varying TE-ADA status groups, a summary will be provided of the number of patients who had no event, events only while in lesser-TE-ADA status for group (i), or – for group (ii) – at least 1 event while in greater-TE-ADA status.

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

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

## 6.14. Subgroup Analyses

### *6.14.1. Efficacy Subgroup Analyses*

Subgroup analysis will be conducted for sPGA (0), sPGA (0,1), PASI 75, PASI 90 and PASI 100 at Week 12 (NRI) using the ITT population for Period 2 and at Week 60 (NRI) using the Maintenance Dosing Period Primary Population for Period 3.

A logistic regression model with treatment, subgroup, and the interaction of subgroup-by-dosing regimen included as factors will be used. The subgroup-by-treatment interaction will be tested at the significance level of 0.10. Treatment group differences 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. If any group within the subgroup is <10% of the total population, only summaries of the efficacy data will be provided (that is, no inferential testing).

Please see Table RHBH. 6.3. for subgroups of baseline characteristics that will be analyzed.

In addition, concomitant topical therapy subgroups will also be analyzed:

- Concomitant topical product use: yes, no
- Concomitant topical steroid product use: yes, no.

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

## 6.15. Interim Analyses and Data Monitoring

An interim database lock and the unblinding may occur at the time (that is, a cut-off date) the last patient completes Visit 19 (Week 60) or ETV per study team assessment. If performed, this interim database lock will include all data collected by the cut-off date. Because the study will still be ongoing for the Follow-Up Period at the time of this database lock, the analysis will be referred to as an interim analysis. If performed, the analyses from the Week 60 lock will be treated as a primary analysis because all primary and major secondary study objectives will be assessed at this time; therefore, there is no alpha adjustment due to this interim analysis. The analyses from the Week 60 lock will not include the Follow-Up period.

A final database lock will occur after the Post-Treatment Follow-Up Period is completed.

In addition, an independent data monitoring committee (DMC) may have access to unblinded safety data for safety monitoring during the trial. A statistical analysis Center (SAC) will prepare and provide unblinded data to the DMC. The SAC members are all external to Lilly. Information that may unblind the study for DMC analysis will not be reported to study sites or blinded study team until the study has been unblinded. The timing and frequency of the data review by the DMC and other details about the DMC are in the DMC charter.

## 6.16. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include summary of 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 preferred term.

- An adverse event is considered 'Serious' whether or not it is a treatment emergent adverse event (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 such as the CSR.

# 7. Unblinding Plan

Refer to a separate blinding and unblinding plan.

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