I1F-MC-RHCR Statistical Analysis Plan Version 1

I1F-MC-RHCR A 24-Week Multicenter, Randomized, Double-Blind, Parallel-Group Study Comparing the Efficacy and Safety of Ixekizumab to Guselkumab in Patients with Moderate-to-Severe Plaque Psoriasis

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1. Statistical Analysis Plan: I1F-MC-RHCR A 24-Week Multicenter, Randomized, Double-Blind, Parallel-Group Study Comparing the Efficacy and Safety of Ixekizumab to Guselkumab in Patients with Moderate-to-Severe Plaque Psoriasis

Ixekizumab (LY2439821) Psoriasis

Study I1F-MC-RHCR is a Phase 3b/4, multicenter, randomized, double-blind, parallel-group study comparing the effect on PASI 100 measured at 12 weeks of 80 mg ixekizumab (every 2 weeks; with a starting dose of 160 mg at week 0) versus 100 mg guselkumab (every 8 weeks; with a starting dose of 100 mg at week 0 and 4) in patients with moderate-to-severe plaque psoriasis. Efficacy and safety of ixekizumab versus guselkumab will be evaluated for up to 24 weeks.

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Indianapolis, Indiana USA 46285

Protocol I1F-MC-RHCR
Phase 3b/4

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly:

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3. Revision History

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

4. Study Objectives

Study objectives are listed in Table RHCR.4.1.

Estimands (International Conference on Harmonisation [ICH] E9 R1) of the study are defined based on the following 4 attributes:

- Population of interest is patients with moderate-to-severe plaque psoriasis per the protocol inclusion/exclusion criteria. Analysis populations are defined in Section 6.1.1. The analysis population corresponding to each of the efficacy and health outcome endpoints is specified in Table RHCR 6.5 and Table RHCR.6.7.
- Primary, major secondary, and exploratory endpoints/variables are listed in Table RHCR.4.1. A full list of efficacy and health outcome endpoints/variables are given in Table RHCR 6.4 and Table RHCR.6.6.
- Population Level Summary: binary variables will be summarized by proportion and continuous variables will be summarized by average. Details are given in Table RHCR 6.5 and Table RHCR.6.7.
- Intercurrent Event(s) Strategy: intercurrent events will be handled by the composite strategy, the hypothetical strategy, or a combination of the composite and while-on-treatment strategies. Specific statistical methods to be used for handling intercurrent events under different strategies are described in Section 6.3. Statistical methods corresponding to each of efficacy and health outcome variables are summarized in Table RHCR 6.5 and Table RHCR.6.7.

Table RHCR.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary To assess whether ixekizumab is superior to guselkumab at Week 12 in the treatment of patients with moderate-to-severe plaque psoriasis, as measured by PASI 100	• Proportion of patients achieving PASI 100 at Week 12
Major Secondary To assess whether ixekizumab is superior to guselkumab in the treatment of patients with moderate-to-severe plaque psoriasis at different time points, as measured by: • PASI 75 • PASI 90 • PASI 100 • sPGA (0) • PASI 50	• Proportion of patients achieving PASI 75 at Week 2 • Proportion of patients achieving PASI 90 at Weeks 4 and 8 • Proportion of patients achieving PASI 100 at Weeks 4, 8, 24 • Proportion of patients achieving sPGA (0) at Week 12 • Proportion of patients achieving PASI 50 at Week 1
Exploratory To assess whether ixekizumab is superior to guselkumab in the treatment of patients with moderate-to-severe plaque psoriasis at different time points, as measured by: • sPGA (0, 1) • Itch NRS • Skin Pain VAS • DLQI (0,1) To assess whether ixekizumab is non-inferior	• The proportion of patients with a static sPGA (0,1) at Weeks 4, 8, 12, 24 • The proportion of patients achieving the Itch NRS Responder definition at Weeks 4, 8, 12, and 24 (restricted to those patients with Itch NRS score ≥4 at baseline) • Change from baseline in Itch NRS score at Weeks 4, 8, 12, and 24 • The proportion of patients achieving Itch NRS (0) at Weeks 4, 8, 12, and 24 (restricted to those patients with Itch NRS score >0 at baseline). • The proportion of patients achieving Skin Pain VAS (0) at Weeks 4, 8, 12, and 24 (restricted to those patients with Skin Pain VAS >0 at baseline) • Change from baseline in Skin Pain VAS score at Weeks 4, 8, 12, and 24 • The proportion of patients achieving DLQI (0,1) at Weeks 2, 4, 8, 12, and 24

Objectives	Endpoints
to guselkumab in the treatment of patients with moderate-to-severe plaque psoriasis at Week 24, as measured by: • PASI 100	• Proportion of patients achieving PASI 100 at Week 24

Abbreviations: DLQI = Dermatology Life Quality Index; NRS = Numeric Rating Scale; PASI = Psoriasis Area and Severity Index score; sPGA = static Physician Global Assessment; VAS = visual analog scale.

5. Study Design

5.1. Summary of Study Design

Study I1F-MC-RHCR (RHCR) is a Phase 3b/4, multicenter, randomized, double-blind, parallel-group study evaluating the efficacy and safety of ixekizumab versus guselkumab in patients with moderate-to-severe plaque psoriasis during a 24-week treatment period.

The following treatment groups will be assessed in this study:

- Ixekizumab: 80-mg subcutaneous (SC) injection. At Week 0, a 160-mg starting dose (two 80-mg injections), followed by 80 mg every 2 weeks (Q2W) from Weeks 2 through 12, and then followed by 80 mg every 4 weeks (Q4W), thereafter (i.e., at Weeks 16 and 20).
- Guselkumab: 100-mg SC injection. At Weeks 0 and 4, a 100 mg injection, followed by 100 mg every 8 weeks (Q8W), thereafter (i.e., at Weeks 12 and 20).

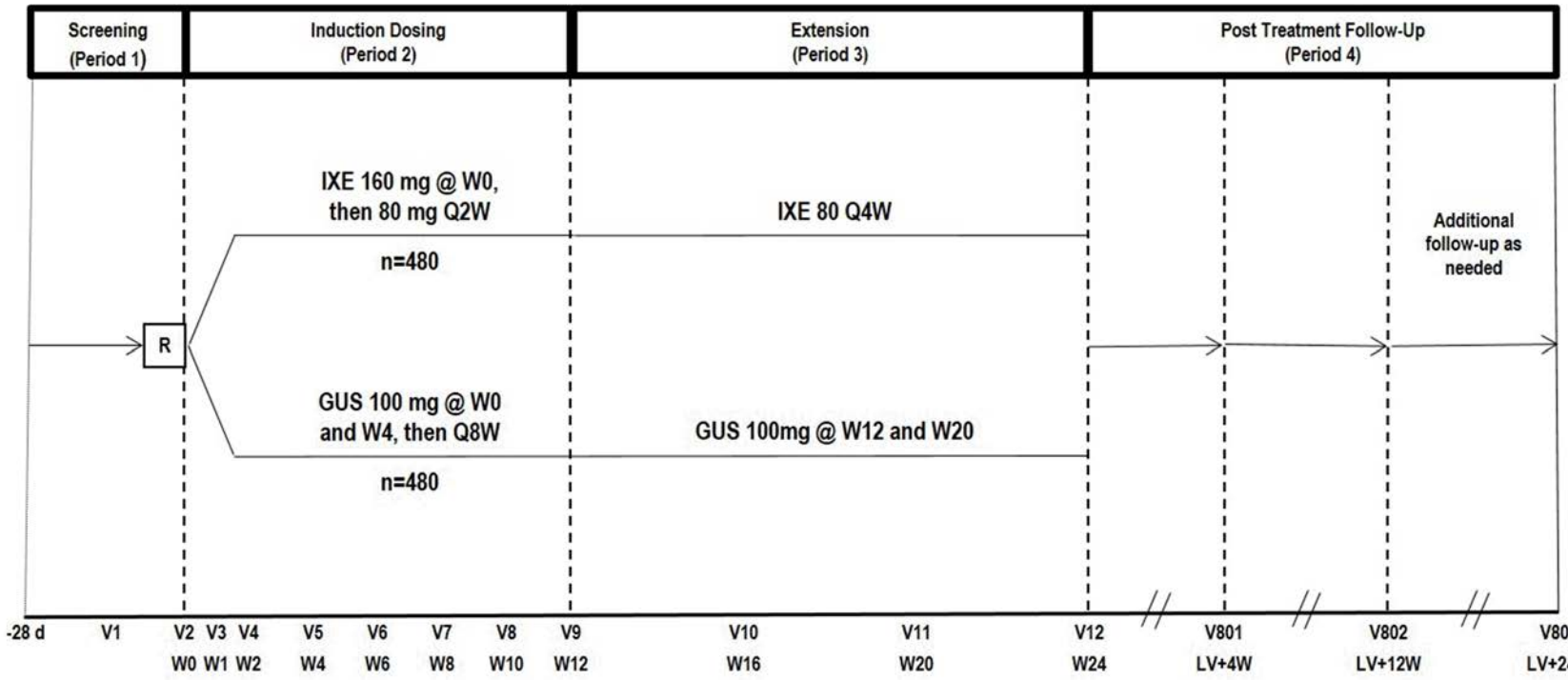
The study will consist of 4 periods:

- **Period 1: Screening Period** (Visits 1) will assess patient eligibility, occurring approximately 5 to 28 days prior to Period 2 (baseline; Week 0 [Visit 2]).
- **Period 2**: **Induction Dosing Period** will occur from Week 0 (baseline; Visit 2) to Week 12 (Visit 9), inclusive.
- **Period 3**: **Extension Period** will occur from Week 12 (Visit 9) up to Week 24 (Visit 12), inclusive.
- **Period 4**: **Post-Treatment Follow-Up Period** occurring from last treatment period visit (Week 24) or Early Termination Visit (ETV), for a minimum of 12 weeks following that visit.

In the remainder of this statistical analysis plan (SAP), if Period 2 (Induction Dosing Period) and Period 3 (Extension Period) are combined for analysis, they will be referred to as **Blinded Treatment Periods**.

Figure RHCR.5.1 illustrates the study design.

In addition to procedures specified in the protocol, a subset of patients will participate in a Photograph and/or Skin Biopsy addendum/addenda. Sites will be selected by the Sponsor, and some patients at those sites will participate in the addendum/addenda; separate informed consent(s) will be obtained.



Abbreviations: d = day(s); GUS = guselkumab; IXE = ixekizumab; LV = last visit; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; R = randomization; V = study visit; W = study week.

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

5.2. Method of Assignment to Treatment

At Week 0 (Visit 2), patients who meet all criteria for enrollment at Visits 1 and 2 will be randomized at a 1:1 ratio to double-blind treatment groups (i.e., ixekizumab or guselkumab) as determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign double-blind investigational product to each patient. The Unblinded Site Personnel at the site will confirm that they have located the correct assigned study drug package by entering a confirmation number found on the package into the IWRS.

Randomization will be stratified by site for this study.

5.3. Determination of Sample Size

Approximately 960 patients will be randomized at a 1:1 ratio to ixekizumab and guselkumab. With 480 patients per treatment group, this study will have 98% power to test the superiority of ixekizumab to guselkumab for a 100% reduction in the Psoriasis Area and Severity Index (PASI 100) at Week 12. The following assumptions were used for the power calculation response rate at Week 12: 35.3% and 23.0% for the ixekizumab and guselkumab groups, respectively. A 2-sided Fisher's exact test at a significance level of 0.05 is assumed. This study is also powered at 95% to test the superiority of ixekizumab for PASI 100 at Week 24, assuming the response rate of ixekizumab and guselkumab at 56% and 44%, respectively. These assumptions are based on the ixekizumab and guselkumab clinical studies in psoriasis (Griffiths et al. 2015; Gordon et al. 2016; Blauvelt et al. 2017; Reich et al. 2017).

For the non-inferior test of PASI 100 at Week 24, a non-inferiority margin of -11.4% is considered sufficiently small to be clinically unimportant difference in outcome between guselkumab and ixekizumab. This non-inferior margin is based on a 70% retention rate approach assuming a placebo response rate of 6.0% at Week 24 observed in a phase 2 study (Deodhar et al. 2018). The sample size of 480 patient per treatment group provides >99% power to test the non-inferiority.

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.

Not all displays described in this SAP will necessarily be included in the clinical study report (CSR). Any display described in this SAP and not provided in the CSR would be available upon request. Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of or in addition to a static display. Any display created interactively will be included in the CSR if deemed relevant to the discussion.

6.1.1. Analysis Populations

Unless otherwise specified, efficacy and health outcome analyses will be conducted on the intent-to-treat (ITT) population. Safety analyses for the Blinded Treatment Periods will be conducted on the safety population. Safety analyses for the Post-Treatment Follow-Up Period will be conducted on the post-treatment follow-up population. Analyses populations are defined in Table RHCR.6.1.

Table RHCR.6.1. Definition of Analyses Populations

Population	Description
Intent-to-treat (ITT)	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 group to which they were assigned in Period 2.
Safety	All randomized patients who take at least 1 dose of study drug. Participants will be included in the treatment group to which they were randomized. Patients will be analyzed according to the treatment group to which they were assigned in Period 2.
Post-treatment follow-up	All randomized patients who take at least 1 dose of study treatment and have entered the Post-Treatment Follow-Up Period. Patients will be analyzed according to the treatment group to which they were assigned in Period 2.

Table RHCR.6.2 describes treatment groups and the comparisons for each study period and the analysis population.

Table RHCR.6.2. Treatment Groups and Comparisons for Each Study Period and Analysis Population

Study Period	Analysis Population	Treatment	Abbreviation	Comparison
Blinded Treatment Periods	Intent-to-Treat Population; Safety Population	Ixekizumab; Guselkumab	IXE GUS	IXE vs. GUS
Post-Treatment Follow-Up Period[a]	Post-treatment Follow-Up Population	Ixekizumab; Guselkumab	IXE GUS	No comparison

Abbreviations: GUS = guselkumab; IXE = ixekizumab; vs. = versus.

[a] Treatment group refers to the treatment that the patients were assigned in Period 2.

6.1.2. Baseline Definition

For the Blinded Treatment Periods, the baseline value will be defined as the last available value before the first treatment injection for both 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 will be calculated as the postbaseline value minus the baseline value. Percent change from baseline is defined as: 100 times the change from baseline divided by baseline). Percent improvement from baseline is calculated as: the positive percent change from baseline if a higher value postbaseline means improvement from baseline; and as the negative percent change from baseline if a lower value postbaseline means improvement from baseline. If the baseline value is missing for a particular variable, then the change from baseline and the percent improvement from baseline will not be calculated.

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.

For the Post-Treatment Follow-Up Period, the baseline is defined as the last nonmissing assessment on or prior to entering Period 4, that is, on or prior to Week 24 (Visit 12), or at the early termination visit (ETV).

6.1.3. Analysis Methods

The randomization to treatment groups is stratified by site, as described in Section 5.2. For statistical purposes, study sites with fewer than 5 randomized patients per treatment group will be pooled from smallest to largest (in terms of total number of patients per site and site identification number), until the pooled site had 5 or more patients per treatment group. If there are still sites with fewer than 5 patients per treatment group remaining after the pooling, those sites will be included in a pooled site with the smallest number of patients in total. Each pooled site will be considered as a single site for all efficacy and health outcome analyses.

The primary analysis method for treatment comparisons of categorical efficacy and health outcomes variables will be made using a Cochran-Mantel-Haenszel (CMH) test stratified by pooled site. Missing data will be imputed using the nonresponder imputation (NRI) method. The treatment response rates and their corresponding 95% confidence intervals (CIs), using normal approximation, as well as the treatment differences, will be reported. Secondary analysis will be conducted using a Fisher's exact test.

The primary analyses for the continuous efficacy and health outcome variables will be performed using mixed effects model for repeated measures (MMRM) analysis. The model will include treatment, pooled site, baseline value, visit, treatment-by-visit interaction, and baseline value-by-visit as fixed factors. A secondary analysis for continuous efficacy and health outcomes variables at specific time point will be made using analysis of covariance (ANCOVA) adjusting for pooled site and baseline value.

When the MMRM model is used, the covariance structure to model the within-patient errors will be unstructured. The restricted maximum likelihood (REML) will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. The Newton-Raphson with ridging optimization technique will be used to aid with convergence. 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 symmetric structure will be used. The first structure to yield convergence will be used for inference. Type III tests for the least squares (LS) means will be used for the statistical comparisons; the corresponding 95% CIs will also be reported.

When the ANCOVA model is used, missing data will be imputed using the modified baseline observation carried forward (mBOCF). Type III sums of squares for the LS means will be used for the statistical comparisons; the 95% CI will be reported.

The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to-event variables. Treatment comparisons will be performed using the log-rank test. Patients completing the Blinded Treatment Periods without event will be censored at the date of completion (that is, the date of the last visit in the Blinded Treatment Periods). Patients without a date of completion or discontinuation for the Blinded Treatment Periods will be censored at the latest non-missing date out of the following dates: date of last dose and date of last attended visit in the Blinded Treatment Periods.

Fisher's exact test will be used for all adverse event (AE), categorical baseline characteristics, discontinuation, and other categorical safety data. The continuous baseline characteristics will be analyzed using an analysis of variance (ANOVA) model with treatment as a factor. Continuous vital sign data and laboratory values will be analyzed by an ANCOVA with treatment and baseline value in the model. For condition/event that is gender-specific (as defined by the Medical Dictionary for Regulatory Activities [MedDRA]), the denominator and computation of the percentage will include only patients from the given gender.

Data collected at ETVs will be mapped to the next planned visit number for that patient. For by-visit summaries, only visits in which a measure was scheduled to be collected will be

summarized. Unplanned/Unscheduled measurements will be excluded from the MMRM analysis. However, the data will still be used in other analyses; such analyses include, but are not limited to, shift analyses and mBOCF endpoint analyses.

All CIs and statistical tests will be 2-sided with an alpha-level of 0.05, unless specified otherwise.

6.2. Adjustments for Covariates

Randomization at the beginning of Period 2 is stratified by site. Unless otherwise specified, all efficacy and health outcome analyses during the Blinded Treatment Periods will include pooled site in the model.

In general, when an MMRM is used for analyses, treatment, pooled site, baseline value, visit, treatment-by-visit interaction, and baseline value-by-visit are included as covariates; when an ANCOVA is used for analyses, treatment, pooled site and baseline value will be included as covariates.

6.3. Handling of Dropouts or Missing Data

Intercurrent events (ICH E9 R1) are events which occur after the treatment initiation and make it impossible to measure a variable or influence how it would be interpreted. Potential intercurrent events include: missing scheduled visits, treatment discontinuation due to death or AEs, lost to follow-up, etc. The methods for handling 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).

6.3.1. Nonresponder Imputation (NRI)

An NRI imputation method can be justified based on the composite strategy (ICH E9 R1) for handling intercurrent events. In this strategy a patient is defined as a responder only if: (i) they meet the clinical requirements for response at the predefined time; and (ii) they remain on the assigned study treatment. Failing either criteria by definition makes them a nonresponder.

Binary efficacy and health outcome variables will be assessed using NRI. Patients will be considered nonresponders 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 postbaseline observation will also be defined as nonresponders for the NRI analysis.

6.3.2. Mixed-effects Model for Repeated Measures (MMRM)

An MMRM method can be justified based on the hypothetical strategy (ICH E9 R1) for handling intercurrent events. In this strategy, the effect of study treatment is assessed in a hypothetical trial where all patients have complete data and continue to take study treatment without dropping out of the study. The MMRM method assumes that missing data can bias results but the bias can be attenuated by modeling random effects using the within-subject error correlation structure. These correlations between the repeated measurements provide the platform used to account for the bias from subject dropout.

All continuous efficacy and health outcomes variables will be assessed using MMRM as a primary analysis. The MMRM model details are provided in Section 6.1.3.

6.3.3. Modified Baseline Observation Carried Forward (mBOCF)

An mBOCF imputation method can be justified based on the composite and while-on-treatment strategies (ICH E9 R1) for handling intercurrent events. The composite strategy handles an intercurrent event of a patient with treatment discontinuation due to AE by defining the patient as not receiving any benefit from study drug after the event. For the rest of intercurrent events, the effect of study treatment is assessed using the while-on-treatment strategy, based on the last observed value at or before the visit of interest, while the patient was still on study drug.

All continuous efficacy and health outcomes variables will be assessed using mBOCF as a secondary analysis. For a patient discontinuing study drug due to an AE, the baseline observation for the endpoint will be carried forward to the corresponding visit for all missing observations after the patient discontinued. For a patient discontinuing study drug for any other reasons, the last nonmissing postbaseline observation before discontinuation will be carried forward to the corresponding visit for all missing observations after the patient discontinued. For all sporadically missing observations prior to discontinuation, the last nonmissing observation before the sporadically missing observation will be carried forward to the corresponding visit. Randomized patients without at least 1 postbaseline observation will not be included for evaluation with the exception of patients discontinuing study drug due to an AE.

6.4. Multiple Comparisons/Multiplicity

A multiple testing strategy for the primary and major secondary objectives will be implemented to control the family-wise type I error rate at a 2-sided alpha level of 0.05. The primary and major secondary endpoints will be sequentially tested in the following order to compare ixekizumab (IXE) versus guselkumab (GUS), using the primary analysis method.

1) Proportion of patients achieving PASI 100 at Week 12 (NRI) – IXE versus GUS
2) Proportion of patients achieving PASI 75 at Week 2 (NRI) – IXE versus GUS
3) Proportion of patients achieving PASI 90 at Week 4 (NRI) – IXE versus GUS
4) Proportion of patients achieving PASI 100 at Week 4 (NRI) – IXE versus GUS
5) Proportion of patients achieving PASI 90 at Week 8 (NRI) – IXE versus GUS
6) Proportion of patients achieving sPGA (0) at Week 12 (NRI) – IXE versus GUS
7) Proportion of patients achieving PASI 50 at Week 1 (NRI) – IXE versus GUS
8) Proportion of patients achieving PASI 100 at Week 8 (NRI) – IXE versus GUS
9) Proportion of patients achieving PASI 100 at Week 24 (NRI) – IXE versus GUS

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

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

6.5. Patient Disposition

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

Patient disposition from study will be listed and summarized with reasons for disposition for the ITT population and the post-treatment follow-up population, respectively.

Patient disposition from study treatment will be listed and summarized for the ITT population for the Blinded Treatment Periods with reasons for disposition, which will be compared between treatment groups using Fisher's exact test.

Time to study treatment discontinuation due to any reason (in weeks) will be summarized by treatment group and graphically presented using Kaplan-Meier Product-Limit method. The log-rank test will be used to compare time to study treatment discontinuation between treatment groups. Time to study treatment discontinuation will be calculated as:

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

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 visit in the Blinded Treatment Periods). Patients without a date of completion for the Blinded Treatment Periods will be censored at the latest non-missing date out of the following dates: date of last dose and date of last attended visit in the Blinded Treatment Periods.

6.6. Protocol Deviations

Protocol deviations will be identified throughout the study by monitors and through programmed criteria. 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.

The categories and subcategories of important protocol deviations, the source of identification for the deviation, and the statistical programming guidance for the clinical study report (CSR) are included in RHCR Trial Issue Management Plan document.

A by-patient listing of important protocol deviations will be provided. The number and percentage of patients having important protocol deviation(s) will be summarized within category and subcategory of deviations by treatment group for ITT population for the Blinded Treatment Periods.

6.7. Patient Characteristics

6.7.1. Demographics and Baseline Characteristics

Patient demographic variables and baseline characteristics are listed in Table RHCR.6.3 will be summarized for ITT population with the baseline values defined for the Blinded Treatment Periods.

The comparisons between treatment groups will be conducted using an ANOVA model with treatment group as a factor for continuous data, and using Fisher's exact test for categorical data. In the case where Fisher's exact test is too computational intensive, Monte Carlo estimate will be used instead.

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

Table RHCR.6.3. Patient Characteristics and Variables for Subgroup Analysis

Variable[a]	Quantitative Summary	Categorical Summary	Subgroup Analysis[b]
Demographic Characteristics			
Age[c]	Yes	<65 years, ≥65 years to <75 years, ≥75 years	X
		<40 years, ≥40 years	X
Sex	No	Male, Female	X
Age within sex	No	Male <40 years, Male ≥40 years, Female <40 years, Female ≥40 years	
Ethnicity	No	Hispanic/Latino, Non-Hispanic/Non-Latino, Not Applicable	X
Race	No	American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian or other Pacific Islander, White, or Multiple	X
Country	No	United States (including Puerto Rico), Canada	
Height (cm)	Yes	None	
Weight (kg)	Yes	<60 kg, ≥60 kg	
		<80 kg, ≥80 to <100kg, ≥100 kg	
		<90 kg, ≥90 kg	
		<100 kg, ≥100 kg	X
BMI[d]	Yes	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)	X
Prior Psoriasis Therapy			
Prior systemic therapy[e,f]	No	Never used, Non-biologic only, Biologic only, Biologic and non-biologic	X
Prior non-biologic systemic therapy[f]	No	Never used, Ever used	X
		0, 1, 2, ≥3	X
Prior non-biologic systemic therapy: inadequate response, loss of response, intolerance or contraindication	No	<3, ≥3	X
Prior biologic therapy[e]	No	Never used, Ever used	X
		0, 1, 2, ≥3	X
Prior biologic therapy class[e]	No	IL-12/23 only, IL-17 only, TNF only, Other only, Multiple	X
Prior anti-TNF alpha[g]	No	Never used, Ever used	X
Prior IL-17 (except ixekizumab) therapy[h]	No	Never used, Ever used	X
Previous topical therapy	No	Never used, Topical prescription therapy only, Topical non-prescription therapy only, Topical prescription and non-prescription therapy	
Previous phototherapy (UVB or PUVA)	No	Never used, PUVA only, UVB only, PUVA and UVB	X
Prior biologic failure[i] within prior biologic exposures	No	Not exposed, Exposed but not failed, Exposed and failed	X
Prior systemic failure[i]	No	Failed, Not failed	X

Patient Characteristics and Variables for Subgroup Analysis

Variable[a]	Quantitative Summary	Categorical Summary	Subgroup Analysis[b]
Psoriasis Duration and Age at Diagnosis			
Duration of psoriasis diagnosis (years)[j]	Yes	<5 years, 5 to <10 years, 10 to <20 years, ≥20 years	
Age at psoriasis diagnosis (years)[k]	Yes	<25, ≥25	
		<40, ≥40	
Baseline Disease Severity			
Baseline PASI	Yes	<20, ≥20	X
		<15, ≥15	
Baseline sPGA	No	3, 4, 5	X
Baseline BSA (%)	Yes	<20%, ≥20%	X
Baseline PGA-F	No	0, 1, 2, 3, 4	
		< 3, ≥3	X
Baseline Itch NRS	Yes	<4, ≥4	
		=0, >0	
Baseline DLQI	Yes	<5, ≥5	
		<11, ≥11	
Baseline Skin Pain VAS	Yes	=0, >0	
Baseline PatGA	No	0, 1, 2, 3, 4, 5	
Psoriatic arthritis at baseline	No	Yes, No	X
Baseline patient's global assessment of disease activity VAS for patients with baseline psoriatic arthritis	Yes	None	
Baseline patient's assessment of pain VAS for patients with baseline psoriatic arthritis	Yes	None	
Baseline physician's global assessment of disease activity VAS for patients with baseline psoriatic arthritis	Yes	None	

Abbreviations: BMI = body mass index; BSA = body surface area; DLQI = Dermatology Life Quality Index; eCRF = electronic case report form; IL-17 = interleukin-17; NRS = Numeric Rating Scale; PASI = Psoriasis Area and Severity Index; PGA-F = Physician's Global Assessment of Fingernail Psoriasis; PUVA = psoralen ultraviolet A; sPGA = static Physician Global Assessment; TNF = tumor necrosis factor; UVB = ultraviolet B; VAS = visual analog scale.

[a] Refer to Sections 6.10 and 6.11 for variable abbreviation.

[b] Subgroup analysis will be used for efficacy endpoints only. See Section 6.16.1 for more details.

[c] Age (in years) will be calculated as length of the time interval from the imputed date of birth (July 1st in the year of birth collected in the eCRF) to the date that the patient was randomized.

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

[e] Biologic therapies (biologic therapy class) include: efalizumab (other), ustekinumab (IL-12/23), infliximab (TNF), etanercept (TNF), alefacept (other), adalimumab (TNF), golimumab (TNF), certolizumab pegol (TNF), secukinumab (IL-17), brodalumab (IL-17), and other biologic agent (other).

[f] Non-biologics systemic therapies include: cyclosporine, methotrexate, corticosteroids, acitretin, fumaric acid derivatives, apremilast, and other systemic agent.

[g] Anti-TNF alpha biologics include: infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol.

[h] Anti-IL-17 (except ixekizumab) biologics include: secukinumab, brodalumab.

[i] Reasons for discontinuation are: loss of response; or inadequate response.

[j] Time since psoriasis diagnosis (years) = *(date of first injection – date of psoriasis diagnosis + 1) / 365.25.* If the date of first dose is missing, the date of randomization will be used. Patients who have a completely missing date of diagnosis will have a missing value for the time since diagnosis, otherwise, "January" and "01" will be imputed for the missing month and day, respectively, in cases where these 2 date components are missing.

[k] Age at diagnosis in years will be calculated as the time interval from the imputed date of birth (July 1st in the year of birth collected in the eCRF) to the date of psoriasis diagnosis.

6.8. Historical Illnesses and Preexisting Conditions

Historical illnesses and preexisting conditions will be classified using the latest version of MedDRA.

Historical illness/condition is defined as the condition/event recorded on the *Preexisting Conditions and Medical History* electronic case report form (eCRF) page or on the *Prespecified Medical History* eCRF page with an end date prior to the date of informed consent.

Preexisting condition is defined as the condition/event recorded on the *Preexisting 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 AEs occurring prior to first dose will be reported. Notice if a preexisting condition worsens in severity on or after the date of informed consent, it will be recorded as an AE on *Adverse Events* eCRF page from the date of worsening onwards.

The following summaries will be provided for the ITT population:

- The number and percentage of patients with historical illnesses by treatment and overall, by System Organ Class (SOC) and preferred term.
- The number and percentage of patients with preexisting conditions by treatment and overall, by SOC and preferred term.
- 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; stroke; dyslipidemia; psoriatic arthritis; Crohn's disease; ulcerative colitis), by treatment and overall.

6.9. 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.

6.9.1. Previous Therapy

Previous therapy is defined as the therapy that starts and ends prior to the date of first dose of study treatment in the Induction Dosing Period. 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 the Induction Dosing Period. If there is clear evidence to suggest that the therapy stopped

prior to the first dose of study treatment in the Induction Dosing Period, the therapy will be assumed to be previous only.

The following summaries will be provided for the ITT 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 tumor necrosis factor alpha (TNF-α) inhibitor (includes infliximab, etanercept, adalimumab, golimumab, certolizumab pegol), interleukin- (IL-) 12/23 inhibitor (includes ustekinumab), IL-17 inhibitor (includes secukinumab and brodalumab), 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.

6.9.2. Concomitant Therapy

Concomitant therapy for the Blinded Treatment Periods is defined as a therapy that starts before, on, or after the day of first injection in the Induction Dosing Period and before the last visit date in the Extension Period and continues into the Blinded Treatment Periods, that is, either no end date (the therapy is ongoing) or an end date on or after the day of first injection in the Induction Dosing Period. Note that concomitant therapy will belong to the Blinded Treatment Periods if it starts and ends on the exact same day as the day of first injection in the Induction Dosing Period.

Concomitant therapy for the Post-Treatment Follow-Up Period is defined as therapy that starts before, on, after the last visit date of the Extension Period and continues into the Post-Treatment Follow-Up Period, that is, either no end date (the therapy is ongoing) or an end date after the last visit date of the Post-Treatment Follow-Up Period.

The following summaries will be provided:

- Concomitant therapy by WHO ATC Level 4 and WHO preferred term for the ITT population during the Blinded Treatment Periods, and for the post-treatment follow-up population during the Post-Treatment Follow-Up Period, respectively.
- 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 for the ITT population during the Blinded Treatment Periods. The definition of concomitant topical therapy can be found in the compound level safety standard.

Concomitant medications between treatment groups will be compared for the ITT population using Fisher's exact test.

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

- For the start date:
  - If year, month, and day are missing, then use the earlier of the patient's first visit date or the consent date.
  - If either month or month and day are missing, then use 01 January.
  - If only day is missing, impute the first day of the month.
- For the start time:
  - Impute as 23:59
- For the end date:
  - If year, month, and day are missing, then use the patient's last visit date.
  - If either month or month and day are missing, then use 31 December.
  - If only day is missing, then use the last day of the month.
  - The imputed date will not be beyond the patient's last visit date.
- For the end time:
  - Impute as 23:59.
- If there is any doubt, the medication will be flagged as concomitant.

6.10. Treatment Compliance

Throughout the Blinded Treatment Periods, trained unblinded site personnel will record information in a Study Drug Administration Log (captured in the *Exposure* eCRF page), including the date, time, and anatomical location of administration of study drug, syringe number, and the reason if the study drug was not fully administered.

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

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

- Number of injections prescribed (that is, expected) during the Blinded Treatment Periods is 10 for patients completing the Blinded Treatment Periods.
- For patients who discontinue during the Blinded Treatment Periods, the number of injections prescribed can be derived from the IWRS study drug dispense dataset.
- The total number of injections administered will be derived using the response to the question, "Was dose administered?" on the *Exposure* eCRF page.

A patient will be considered overall compliant with study treatment 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).

Patient treatment compliance during the Blinded Treatment Periods will be summarized for the safety population. The comparisons between treatment groups will be conducted using Fisher's exact test.

6.11. Efficacy Analyses

Table RHCR 6.4 includes the description and derivation of primary and major secondary efficacy outcomes. Table RHCR 6.5 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment group comparisons for primary and major secondary efficacy analyses.

Table RHCR 6.4. Description and Derivation of Efficacy Outcomes

Measure	Description	Variable	Derivation/Comment	Processing of Missing Components
PASI	PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head/neck, trunk, arms, and legs) and the severity of scaling (S), redness (R), and plaque induration/infiltration (thickness [T]) in each region, yielding an overall score of 0 for no psoriasis to 72 for the most severe disease (Fredriksson and Pettersson 1978). Severity is rated for each index (R, S, T) on a 0-4 scale (0 for no involvement up to 4 for severe involvement): 0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe The body is divided into 4 anatomical regions comprising the head (h), upper limb (u), trunk (t), and lower limb (l). In each of these areas, the fraction of total body surface area affected is graded on a 0-6 scale (0 for no involvement; up to 6 for 90% - 100% involvement): 0 = 0% (clear) 1 = >0% to <10% 2 = 10% to <30% 3 = 30% to <50% 4 = 50% to <70% 5 = 70% to <90%	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: $PASI = 0.1(R_h + T_h + S_h)A_h + 0.2(R_u + T_u + S_u)A_u + 0.3(R_t + T_t + S_t)A_t + 0.4(R_l + T_l + S_l)A_l$, where: R_h, R_u, R_t, R_l = redness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4, respectively; T_h, T_u, T_t, T_l = thickness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4, respectively; S_h, S_u, S_t, S_l = scaliness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4, respectively; A_h, A_u, A_t, A_l = numerical value translation of % area of psoriatic involvement score for the head, upper limb, trunk, and lower limb, respectively. PASI scores are treated as a continuous score, with 0.1 increments within these values.	If any individual score is missing, the PASI score will not be calculated, hence, missing.
		PASI change from baseline	Calculated as: observed PASI – baseline PASI.	Missing if baseline or observed value is missing
		PASI percent improvement from baseline	Calculated as: $Percent\ improvement\ from\ baseline = 100 \times \frac{Baseline\ PASI - Observed\ PASI}{Baseline\ PASI}$ If a patient has experienced an improvement,	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation/Comment	Processing of Missing Components
	6 = 90% to 100% The various body regions are weighted to reflect their respective proportion of body surface area.		this measure will be positive. If a patient has experienced a worsening in the condition, this measure will be negative.	
		PASI 50	A clinically meaningful response; at least a 50% improvement in PASI score from baseline.	Missing if baseline or observed value is missing.
		PASI 75	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 *(Primary)*	Complete resolution of plaque psoriasis; a 100% improvement in PASI score from baseline.	Missing if baseline or observed value is missing.
		PASI ≤1	A PASI ≤1.	Missing if PASI is missing.
		PASI ≤3	A PASI ≤3.	Missing if PASI is missing.
		PASI ≤5	A PASI ≤5.	Missing if PASI is missing.
		Time to first PASI 50; Time to first PASI 75; Time to first PASI 90; Time to first PASI 100	Calculated as: (Date of first PASI 50 response in defined treatment period – Date of first dose + 1) / 7. If the date of first dose is missing, the date of randomization is used. Similarly for PASI 75, PASI 90, and PASI 100.	
sPGA	sPGA is the physician's global assessment of the patient's psoriasis lesions at a given time point (EMA 2004 [WWW]). Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is	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)	An sPGA assessed as either 0 or 1, which represents a clinically meaningful response of minimal plaque severity or complete	Missing if sPGA is missing.

Measure	Description	Variable	Derivation/Comment	Processing of Missing Components
	given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).		resolution of plaque psoriasis.	
		sPGA (0)	An sPGA assessed as 0, which represents a clinically important endpoint indicating complete resolution of plaque psoriasis.	Missing if sPGA is missing.
Percentage of BSA	The investigator will evaluate the percentage involvement of psoriasis on each patient's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), in which 1% corresponds to the size of the patient's hand (including the palm, fingers, and thumb) (NPF 2009).	BSA	Collected as a single scale as part of PASI 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.
		BSA ≤1	A BSA ≤1, which represents treat to target concept by NPF.	Missing if BSA is missing.
Physician's Global Assessment of Disease Activity VAS	Overall assessment of the severity of the patient's current psoriatic arthritis activity using a 100-mm horizontal VAS. The investigator making the assessment must be a rheumatologist or medically qualified physician.	Physician's global assessment VAS score	Range from 0 to 100 mm: 0 represents no disease activity, 100 represents extremely active disease activity.	Single item, missing if missing.
		Physician's global assessment VAS change from baseline	Calculated as: observed physician's global assessment VAS – baseline physician's global assessment VAS.	Missing if baseline or observed value is missing.
		Physician's global assessment VAS percent improvement from baseline	Calculated as: $Percent\ improvement\ from\ baseline\ = 100 \times \frac{Baseline - Observed}{Baseline}$ 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.	
PGA-F	Assessment of the severity of fingernail abnormalities in patients with nail psoriasis. The scale assesses the nail bed and nail matrix signs of disease on a 0 to 4 scale: clear (0), minimal (1), mild (2), moderate (3), or severe (4) (Hudgens et al. 2016)	PGA-F	PGA-F score is the maximum of observed nail bed and nail matrix scores. Range from 0 to 4: clear (0), minimal (1), mild (2), moderate (3), or severe (4).	If any nail bed or nail matrix score is missing, the PGA-F score will not be derived, hence, missing.

Measure	Description	Variable	Derivation/Comment	Processing of Missing Components
		PGA-F (0, 1)	A PGA-F assessed as either 0 or 1, which represents a clinically meaningful response of clear or minimal nail psoriasis.	Missing if PGA-F is missing.
		PGA-F (0)	A PGA-F assessed as 0, which represents a clinically meaningful response of clear nail psoriasis.	Missing if PGA-F is missing.

Abbreviations: BSA = body surface area; eCRF = electronic case report form; EMA = European Medicines Agency; NPF = National Psoriasis Foundation; PASI = Psoriasis Area and Severity Index; PGA-F = Physician's Global Assessment of Fingernail Psoriasis; sPGA = Static Physician Global Assessment; VAS = visual analog scale.

Table RHCR 6.5. Description of Efficacy Outcomes Analyses

Measure	Variable	Analysis Method (Sections 6.1.3 and 6.3)	Analysis Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
PASI	PASI 50	CMH test with NRI; Fisher's Exact test with NRI	ITT Population; ITT population with PASI ≥ 12	IXE vs. GUS at Week 1 and all other postbaseline visits	Major secondary analysis is CMH test with NRI for ITT population comparing IXE vs. GUS at Week 1 (Section 6.11.2). Other analyses and comparisons are exploratory (Section 6.11.3).
	PASI 75	CMH test with NRI; Fisher's Exact test with NRI	ITT Population; ITT population with PASI ≥ 12	IXE vs. GUS at Week 2 and all other postbaseline visits	Major secondary analysis CMH test with NRI for ITT population comparing IXE vs. GUS at Week 2 (Section 6.11.2). Other analyses and comparisons are exploratory (Section 6.11.3).
	PASI 90	CMH test with NRI; Fisher's Exact test with NRI	ITT Population; ITT population with PASI ≥ 12	IXE vs. GUS at Weeks 4 and 8, and all other postbaseline visits	Major secondary analysis CMH test with NRI for ITT population comparing IXE vs. GUS at Weeks 4 and 8 (Section 6.11.2). Other analyses and comparisons are exploratory (Section 6.11.3).
	PASI 100	CMH test with NRI; Fisher's Exact test with NRI	ITT Population; ITT population with PASI ≥ 12	IXE vs. GUS at Week 12, Weeks 4, 8, 24, and all other postbaseline visits	Primary analysis is CMH test with NRI for ITT population comparing IXE vs. GUS at Week 12 (Section 6.11.1). Major secondary analysis CMH test with NRI for ITT population comparing IXE vs. GUS at Weeks 4, 8, and 24 (Section 6.11.2). Other analyses and comparisons are exploratory (Section 6.11.3).

Measure	Variable	Analysis Method (Sections 6.1.3 and 6.3)	Analysis Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
	PASI score; PASI change from baseline; PASI percent improvement from baseline	MMRM; ANCOVA with mBOCF for the Blinded Treatment Periods	ITT Population	IXE vs. GUS at all postbaseline visits	Exploratory analysis (Section 6.11.3).
	PASI≤1	CMH test with NRI; Fisher's Exact test with NRI	ITT Population	IXE vs. GUS at all postbaseline visits	Exploratory analysis (Section 6.11.3).
	PASI≤3	CMH test with NRI; Fisher's Exact test with NRI	ITT Population	IXE vs. GUS at all postbaseline visits	Exploratory analysis (Section 6.11.3).
	PASI≤5	CMH test with NRI; Fisher's Exact test with NRI	ITT Population	IXE vs. GUS at all postbaseline visits	Exploratory analysis (Section 6.11.3).
	Time to first PASI 50; Time to first PASI 75; Time to first PASI 90; Time to first PASI 100	Log-rank test Kaplan-Meier product limit method; Kaplan-Meier plot (survival curve)	ITT Population	IXE vs. GUS during the Blinded Treatment Periods	Exploratory analysis (Section 6.11.3).
sPGA	sPGA (0, 1)	CMH test with NRI; Fisher's Exact test with NRI	ITT Population; ITT population with sPGA ≥ 3	IXE vs. GUS at all postbaseline visits	Exploratory analysis (Section 6.11.3).
	sPGA (0)	CMH test with NRI; Fisher's Exact test with NRI	ITT Population; ITT population with sPGA ≥ 3	IXE vs. GUS at Week 12 and all other postbaseline visits	Major secondary analysis CMH test with NRI for ITT population comparing IXE vs. GUS at Week 12 (Section 6.11.2). Other analyses and comparisons are exploratory (Section 6.11.3).

Measure	Variable	Analysis Method (Sections 6.1.3 and 6.3)	Analysis Population (Section 6.1.1)	Comparison/Time Point	Analysis Type
BSA	BSA change from baseline	MMRM; ANCOVA with mBOCF for the Blinded Treatment Periods	ITT Population	IXE vs. GUS at all postbaseline visits	Exploratory analysis (Section 6.11.3).
	BSA≤1	CMH test with NRI; Fisher's Exact test with NRI	ITT Population	IXE vs. GUS at all postbaseline visits	Exploratory analysis (Section 6.11.3).
Physician's Global Assessment of Disease Activity VAS	Physician's global assessment VAS score; Physician's global assessment VAS change from baseline; percent improvement	ANCOVA with mBOCF; MMRM for the Blinded Treatment Periods	ITT Population – patients with baseline psoriatic arthritis	IXE vs. GUS at all postbaseline visits	Exploratory analysis (Section 6.11.3).
PGA-F	PGA-F (0, 1) with at least a 2-point improvement from baseline; PGA-F (0) with at least a 2-point improvement from baseline	CMH test with NRI; Fisher's Exact test with NRI	ITT Population – Patients with baseline PGA-F ≥3	IXE vs. GUS at all postbaseline visits	Exploratory analysis (Section 6.11.3).

Abbreviations: ANCOVA = Analysis of Covariance; BSA = Percentage of Body Surface Area; CMH = Cochran-Mantel-Haenszel; GUS = guselkumab 100 mg; ITT = Intent-to-Treat; IXE = ixekizumab 80 mg; mBOCF = modified baseline observation carried forward; MMRM = Mixed-effects Model of Repeated Measures; NRI = Nonresponder Imputation; PASI = Psoriasis Area and Severity Index; PASI 50/75/90/100 = at least a 50%/75%/90%/100% improvement from baseline in PASI score; PGA-F = Physician's Global Assessment of Fingernail Psoriasis; sPGA=static Physician Global Assessment; VAS = Visual Analogue Scale; vs. = versus.

6.11.1. Primary Outcome and Primary Analysis Methodology

The primary efficacy outcome is

- proportion of patients achieving PASI 100 at Week 12.

The primary analysis for comparison of ixekizumab with guselkumab using PASI 100 at Week 12 will be the CMH test stratified by pooled site as described in Section 6.1.3, based on the ITT population in the Blinded Treatment Periods. Missing data will be imputed using the NRI method (Section 6.3.1).

6.11.2. Major Secondary Efficacy Analyses

All major secondary analyses will be based on the ITT population. Treatment comparisons between ixekizumab and guselkumab will be made using the CMH test stratified by pooled site. Missing data will be imputed using the NRI method (Section 6.3.1). These major secondary comparisons will be tested based on the multiple testing procedure detailed in Section 6.4.

6.11.3. Exploratory Efficacy Analyses

The exploratory efficacy analyses will be based on the ITT population except:

- Physician's global assessment of disease activity visual analog scale (VAS): based on the ITT population – patients with baseline psoriatic arthritis
- PGA-F: based on the ITT population – patients with baseline PGA-F ≥ 3

These analyses will be conducted on the Blinded Treatment Periods. There will be no adjustment for multiple comparisons. The exploratory efficacy analyses are detailed in Table RHCR 6.4 and Table RHCR 6.5.

The following additional summaries will be provided for each treatment group:

- Among PASI 50 responders at Week 1, proportion of patients achieving PASI 75, PASI 90, and PASI 100 at Week 12, respectively.
- Based on the ITT population with PASI ≥ 12 at baseline, proportion of patients achieving PASI 50, PASI 75, PASI 90, and PASI 100 at each post-baseline visit, respectively.
- Based on the ITT population with sPGA ≥ 3 at baseline, proportion of patients achieving sPGA (0) and sPGA (0, 1) at each post-baseline visit, respectively.

For assessing the non-inferiority of ixekizumab to guselkumab in PASI100 at Week 24, missing PASI data at Week 24 will be imputed using NRI method outlined in Section 6.3.1. Non-inferiority analysis will be performed on the ITT population using a pre-specified fixed margin approach, with the non-inferiority margin of -11.4%. The non-inferiority will be established if the lower bound of the 2-sided 95% CI for the difference in proportion of responders on the ixekizumab minus guselkumab is greater than the pre-specified margin. The CI for the difference in proportion will be calculated using the simple asymptotic method without continuity correction.

Area under the curve (AUC) for PASI 75, PASI 90, PASI 100, sPGA (0,1), itch NRS≥4 point improvement for patients with baseline itch NRS≥4, itch NRS (0), and DLQI (0,1) at weeks 12, 16, and 24 will be analyzed and compared between ixekizumab and guselkumab . AUC for each individual patient data (IPD AUC) based on the exact date of each visit and the responder status or improvement value for that patient will be calculated; total IPD AUC will be determined as the sum of the AUC over all visits during the study period. Treatment differences in terms of AUC will be compared using an analysis of covariance (ANCOVA) model after adjusting for baseline PASI values.

The AUC analyses will be conducted after the final database lock.

6.12. Health Outcomes and Quality of Life Analyses

The health outcomes and quality of life (QoL) measures are Itch NRS, DLQI, Skin Pain VAS, Patient's Global Assessment of Disease Severity (PatGA), Patient's Assessment of Pain VAS, and Patient's Global Assessment of Disease Activity VAS.

The health outcomes and QoL analyses will be conducted on the Blinded Treatment Periods. There will be no adjustment for multiple comparisons.

Table RHCR.6.6 include the description and derivation of the health outcomes and QoL measures. Table RHCR.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 RHCR.6.6. Description and Derivation of Health Outcomes and Quality-of-Life Measures

Measure	Description	Variable	Derivation / Comment	Handling of Missing Components
Itch NRS	Itch Numeric Rating Scale (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 score 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
DLQI	Dermatology Life Quality Index (DLQI): is a validated, dermatology-specific, patient-reported measure that evaluates patient's health-related quality of life. This questionnaire has 10 items that are grouped in 6 domains, including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall	DLQI symptoms and feelings domain	Sum of responses of questions #1 and #2: #1. How itchy, sore, painful or stinging has your skin been? #2. How embarrassed or self-conscious have you been because of your skin?	If one question in a domain is missing, that domain is missing.
		DLQI daily activities domain	Sum of responses of questions #3 and #4: #3. How much has your skin interfered with you going shopping or looking after your home or garden? #4. How much has your skin influenced the clothes you wear?	If one question in a domain is missing, that domain is missing.
		DLQI leisure domain	Sum of responses of questions #5 and #6: #5. How much has your skin affected any social or leisure activities? #6. How much has your skin make it difficult for you to do any sport?	If one question in a domain is missing, that domain is missing.
		DLQI work and school	Sum of responses of questions question #7A and #7B:	If the answer to question

Measure	Description	Variable	Derivation / Comment	Handling of Missing Components
	period of this scale is over the "last week". Response categories and corresponding scores are: Very much = 3 A lot = 2 A little = 1 Not at all = 0 Not relevant = 0	domain	#7A. Has your skin prevented you from working or studying? #7B. If No: how much has your skin been a problem at work or studying?	#7A is missing, this domain is missing. If #7A is No, and #7B is missing, this domain is missing.
		DLQI personal relationships domain	Sum of responses of questions #8 and #9: #8. How much has your skin created problems with your partner or any of your close friends or relatives? #9. How much has your skin caused any sexual difficulties?	If one question in a domain is missing, that domain is missing.
		DLQI treatment	Response of question #10: #10. How much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	If one question in a domain is missing, that domain is missing.
		DLQI total score	A DLQI total score is calculated by summing all 10 question responses, and has a range of 0 to 30 (less to more impairment) (Finlay and Khan 1994; Basra et al. 2008).	If two or more questions are missing, the total score is missing. Note: #7B could be a valid missing while #7A is not "No." That is, #7 should be considered as one question.
		DLQI (0,1)	A DLQI (0,1) response is defined as a post-baseline DLQI total score of 0 or 1. A DLQI total score of 0 to 1 is considered as having no effect on a patient's HRQoL (Khilji et al. 2002; Hongbo et al. 2005).	Missing if DLQI total score is missing
		DLQI (0)	A DLQI (0) response is defined as a post-baseline DLQI total score of 0.	Missing if DLQI total score is missing
		DLQI total score ≥ 5 improvement from baseline	Reduction/decrease of ≥5 points from baseline. A 5-point change from baseline is considered as the minimal clinically important difference threshold.	Missing if baseline or observed value is missing
		DLQI total score and domain scores change from baseline	Calculated as: observed DLQI (total score or domain scores) – baseline DLQI (total score or domain scores)	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation / Comment	Handling of Missing Components
Skin pain VAS	Skin Pain Visual Analog Scale (VAS): is a patient-administered scale designed to measure skin pain from psoriasis using a 100-mm horizontal VAS. Overall severity of a patient's skin pain from psoriasis at the present time is indicated by placing a single mark on the horizontal scale (0 = no skin pain; 100 = severe skin pain).	Skin Pain VAS	Range from 0 (no skin pain) to 100 (severe skin pain). Note: higher value indicates greater severity of illness.	Single item, missing if missing
		Skin Pain VAS change from baseline	Calculated as: observed skin pain VAS – baseline skin pain VAS	Missing if baseline or observed value is missing
		Skin Pain VAS = 0	Defined as a post-baseline Skin Pain VAS score of 0	Missing if observed value is missing
Patient's Global Assess-ment of Disease Severity (PatGA)	Patient's Global Assessment of Disease Severity (PatGA) is a patient-administered, single-item scale assessing a number on a 0 to 5 on a NRS.	PatGA score	Severity of the patient's psoriasis "today" from 0 (clear; no psoriasis) to 5 (severe)	Single item, missing if missing
		PatGA(0,1)	Defined as a post-baseline PatGA score of 0 or 1	Missing if observed value is missing
		PatGA (0)	Defined as a post-baseline PatGA score of 0	Missing if observed value is missing
Patient's Assess-ment of Pain VAS	Patient's Assessment of Pain Visual Analog Scale (VAS): is a patient-administered scale designed to measure joint pain using a 100-mm horizontal VAS. Overall severity of a patient's joint pain at the present time is indicated by placing a single mark on the horizontal scale (0 = no	Patient's assessment of pain VAS	Range from 0 (no joint pain) to 100 (severe joint pain). Note: higher value indicates greater severity of illness.	Single item, missing if missing
		Patient's assessment of pain VAS change from baseline	Calculated as: observed Patients Assessment of Pain VAS – baseline Patients Assessment of Pain VAS	Missing if baseline or observed value is missing
		Patient's assessment of pain VAS percent improvement from baseline	Calculated as: $Percent\ improvement\ from\ baseline\ = 100 \times \frac{Baseline - Observed}{Baseline}$ 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

Measure	Description	Variable	Derivation / Comment	Handling of Missing Components
	joint pain; 100 = severe joint pain).			
Patient Global Assessment of Disease Activity VAS	Patient's Global Assessment of Disease Activity Visual Analog Scale (VAS): is a patient-administered scale designed to measure overall disease activity of psoriatic arthritis using a 100-mm horizontal VAS. Overall severity of a patient's joint pain at the present time is indicated by placing a single mark on the horizontal scale (0 = no arthritis activity; 100 = extremely active arthritis).	Patient global assessment of disease activity VAS	Range from 0 (no disease activity) to 100 (severe disease activity). Note: higher value indicates greater severity of illness.	Single item, missing if missing
		Patient global assessment of disease activity VAS change from baseline	Calculated as: observed Patient Global Assessment of Disease Activity VAS – baseline Patient Global Assessment of Disease Activity VAS	Missing if baseline or observed value is missing
		Patient global assessment of disease activity VAS percent improvement from baseline	Calculated as: $Percent\ improvement\ from\ baseline\ = 100 \times \frac{Baseline - Observed}{Baseline}$ 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

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

Measure	Variable	Analysis Method (Sections 6.1.3 and 6.3)	Analysis Population (Section 6.1.1)	Comparison / Time Point	Analysis Type
Itch NRS	Itch NRS change from baseline	MMRM; ANCOVA with mBOCF for the Blinded Treatment Periods	ITT Population	IXE vs. GUS at all post-baseline visits	Exploratory analysis (Section 6.11.3).
	Itch NRS ≥ 4 improvement from baseline	CMH test with NRI; Fisher's Exact test with NRI	ITT Population - with baseline Itch NRS Score ≥ 4	IXE vs. GUS at all post-baseline visits	Exploratory analysis (Section 6.11.3).
	Itch NRS = 0	CMH test with NRI; Fisher's Exact test with NRI	ITT Population - with Baseline Itch NRS Score > 0	IXE vs. GUS at all post-baseline visits	Exploratory analysis (Section 6.11.3).
DLQI	DLQI total score and domain scores change from baseline	MMRM; ANCOVA with mBOCF for the Blinded Treatment Periods	ITT Population	IXE vs. GUS at all post-baseline visits	Exploratory analysis (Section 6.11.3).
	DLQI ≥ 5 improvement from baseline	CMH test with NRI; Fisher's Exact test with NRI	ITT Population with Baseline DLQI ≥ 5	IXE vs. GUS at all post-baseline visits	Exploratory analysis (Section 6.11.3).
	DLQI (0, 1)	CMH test with NRI; Fisher's Exact test with NRI	ITT Population	IXE vs. GUS at all post-baseline visits	Exploratory analysis (Section 6.11.3).
Skin Pain VAS	Skin Pain VAS change from baseline	MMRM; ANCOVA with mBOCF for the Blinded Treatment Periods	ITT Population	IXE vs. GUS at all post-baseline visits	Exploratory analysis (Section 6.11.3).
	Skin Pain VAS = 0	CMH test with NRI; Fisher's Exact test with NRI	ITT Population – with baseline Skin Pain VAS > 0	IXE vs. GUS at all post-baseline visits	Exploratory analysis (Section 6.11.3).
Patient's Global Assessment of Disease Severity (PatGA)	PatGA (0)	CMH test with NRI; Fisher's Exact test with NRI	ITT Population	IXE vs. GUS at all post-baseline visits	Exploratory analysis (Section 6.11.3).
	PatGA (0, 1)	CMH test with NRI; Fisher's Exact test with NRI	ITT Population	IXE vs. GUS at all post-baseline visits	Exploratory analysis (Section 6.11.3).
	PatGA ≥2 improvement from baseline	CMH test with NRI; Fisher's Exact test with NRI	ITT Population with Baseline PatGA ≥ 2	IXE vs. GUS at all post-baseline visits	Exploratory analysis (Section 6.11.3).

Measure	Variable	Analysis Method (Sections 6.1.3 and 6.3)	Analysis Population (Section 6.1.1)	Comparison / Time Point	Analysis Type
Patient's Assessment of Pain VAS	Patient's Pain VAS change from baseline; percent improvement	ANCOVA with mBOCF; MMRM for the Blinded Treatment Periods	ITT Population – with psoriatic arthritis at baseline	IXE vs. GUS at all post-baseline visits	Exploratory analysis (Section 6.11.3).
Patient Global Assessment of Disease Activity VAS	Patient's global assessment VAS change from baseline; percent improvement	ANCOVA with mBOCF; MMRM for the Blinded Treatment Periods	ITT Population – with psoriatic arthritis at baseline	IXE vs. GUS at all post-baseline visits	Exploratory analysis (Section 6.11.3).

Abbreviations: ANCOVA = Analysis of Covariance; CMH = Cochran-Mantel-Haenszel; DLQI = Dermatology Life Quality Index; GUS = Guselkumab 100 mg; ITT = Intent-to-Treat; IXE = Ixekizumab 80 mg; mBOCF = modified baseline observation carried forward; MMRM = Mixed-effects Model of Repeated Measures; NRI = Nonresponder Imputation; NRS = Numeric Rating Scale; PatGA = Patient Global Assessment of Disease Severity ;VAS = Visual Analogue Scale.

6.12.1. Exploratory Health Outcome and Quality of Life Analyses – Optimal Psoriasis Assessment Tool (OPAT) Validation

Exploratory Health Outcome and Quality of Life Analyses – Optimal Psoriasis Assessment Tool (OPAT) Validation PASI, as a complex index to measure psoriasis severity, is time-consuming to complete, and it is known that this is not regularly collected by physicians for their psoriasis patients. Development of a real-world useful tool (e.g., Optimal Psoriasis Assessment Tool [OPAT]) could serve as a substitute for PASI and would have much interest for physicians in the treatment of psoriasis patients. Preliminary work in regression modeling has shown that a two-factor model utilizing the clinical measure of BSA, as well as one health outcome measure (Itch NRS, Skin Pain VAS, or PatGA), predicts PASI very well and predicts DLQI moderately well. As Itch NRS is a regularly collected measure in medical practice, Itch NRS combined with BSA would provide a convenient tool for physicians to use for the assessment of psoriasis severity.

All possible regression model selection will be performed using ordinary least square models for PASI in the following three populations at week 12: (1) ITT population (pooled treatment groups); (2) ITT population treated with ixekizumab; (3) ITT population with guselkumab. For each population, 29 models adjusting for different independent variables will be fitted. Independent variables in each model will include individual or combinations of BSA, one of the patient reported assessment variables (Itch NRS, Skin Pain VAS, PatGA), interaction between BSA and patient reported outcome variables, as well as the higher order polynomials/interactions of BSA and patient reported outcome variables (Itch NRS, Skin Pain VAS, PatGA). 20 repeated 10-fold cross-validation (CV) will be used to assess the performance of each model. For each 10-fold CV, 9 out of 10 subsets will be used for model development (training data) and the remaining one subset will be used for validation (test data). Measures including R-squared, adjusted R-squared, Akaike information criterion (AIC), Bayesian information criterion (BIC), mean error (ME), mean absolute error (MAE), mean squared error (MSE), predicted residual error sum of squares (PRESS) will be reported for the 29 models and the testing data based on repeated 10-fold CV in order to select the best performing model. Estimated values from model(s) with high prediction power for PASI based on R-squared will be compiled. Assessments will be done to evaluate the gain in R-squared from adding in factors into the models.

Using the information from the modeling described above, while keeping with the main objective of a simpler alternative for PASI, two-factor regression models for PASI and for DLQI will be assessed using the same predictors, i.e., BSA and each of the patient outcome measures (Itch NRS, Skin Pain VAS, or PatGA) with the primary focus on Itch NRS, in order to see if the results show good prediction of PASI. The primary timepoint will be week 12 although baseline, Week 4, and Week 8 will also be considered. The models will be assessed with pooled data of both ixekizumab and guselkumab treatment groups, as well as data from each treatment group individually. Graphs will be provided for residuals and for the predicted vs actual PASI values for the Week 12 models. In addition, for each of the models at Week 12, the concordance of the 50/75/90/100 percentage improvement in predicted PASI with observed PASI50/75/90/100 will

be summarized. For Week 12, Youden's Index will be calculated for each of the models, and the sensitivity/specificity /NPV/PPV will be provided as well as the McNemar's Test and Gamma Statistic for the predicted PASI improvement versus the observed PASI50/75/90/100.

The information from both the all possible regression modeling and the delve into the simpler, two-predictor models will be evaluated in order to determine the subsequent results to be incorporated into an interactive tool. Physician will then be able to utilize this simple tool in the office setting while evaluating their psoriasis patients.

The above analyses will be conducted based on the combined treatment group at the interim database lock to keep the integrity of Blinded Treatment Periods. The analyses based on both combined and by treatment group analyses will be conducted after the final database lock.

6.13. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Blood sample collection for pharmacokinetic analysis is not planned for this study. However, blood samples collected for immunogenicity assessment may be analyzed for ixekizumab serum concentrations to facilitate the interpretation of the immunogenicity data, if needed.

If applicable, a by-patient listing of the ixekizumab serum concentrations will be provided.

6.14. Safety Analyses

Safety will be assessed by summarizing and analyzing AEs, laboratory analyses, vital signs, and Columbia-Suicide Severity Rating (C-SSRS). The duration of treatment exposure will also be summarized.

The primary safety analyses will focus on the comparison of ixekizumab to guselkumab for the Blinded Treatment Periods. For the Post-Treatment Follow-Up Period, safety data will be summarized according to the treatment which patients had received in the Blinded Treatment Periods.

All safety analyses will be conducted on the Safety Population.

Comparisons between treatment groups will be conducted using Fisher's exact test

6.14.1. Extent of Exposure

Duration of exposure to study drug will be summarized by treatment for safety population during the Blinded Treatment Periods using descriptive statistics.

The duration of exposure to treatment during the Blinded Treatment Periods will be calculated as:

Duration of exposure (days) =

> *Date of last visit (scheduled or unscheduled) in the Blinded Treatment Periods – Date of first injection + 1*

For patients who discontinued treatment due to lost to follow-up, duration of exposure will be calculated with date of second to the last visit (scheduled or unscheduled) in treatment period will be used in replacement of date of last visit (scheduled or unscheduled) in treatment period.

The number and percentage of patients in each of the following categories will be included in the summaries:

- >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥90 days, ≥120 days, and ≥168 days. Note that patients may be included in more than 1 category.
- >0 to <7 days, ≥7 to <14 days, ≥14 to <30 days, ≥30 to <60 days, ≥60 days to <90 days, ≥90 to <120 days, ≥120 to <168 days, and ≥168.

The summaries will also include the following information:

- Total exposure in patient years, calculated as:

Total exposure in patient years =

Sum of duration of exposures with the defined treatment period (for all patients in treatment group) / 365.25

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

Total Dose = Sum of dose for each active injection taken during the defined treatment period

6.14.2. Adverse Events

Adverse events will be classified based upon the latest version of the MedDRA. AEs will be recorded at every study visit. Condition starting on or after the date of informed consent will be considered an AE. A preexisting condition which worsens in severity on or after the date of informed consent will be considered and recorded as an AE on the *AE* eCRF page from the date of worsening onwards.

A 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. A TEAE will be assigned to the study period to which it is 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 Induction Dosing 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 pre-existing conditions with that LLT), or if the severity is greater than the pre-treatment severity for that LLT. 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 12 (that is, Week 24) 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 12 or ETV, the maximum severity recorded for each LLT on or prior to the date of Visit 12 or ETV will be used as the follow-up baseline severity for that LLT.
- If a partial AE start date is present, the date will be compared as far as possible to the date of Visit 12 or ETV in order to determine whether the event is follow-up emergent or not. If there is any doubt, the event will be flagged as follow-up emergent, unless the same event was already counted as treatment-emergent during the Blinded Treatment Periods.

AEs and TEAEs will be summarized and analyzed for the safety population for the Blinded Treatment Periods.

- An overall summary of AEs including the number and percentage of patients who experienced TEAE, TEAE by maximum severity, death, serious adverse events (SAE), TEAE related to study treatment, discontinuations from the treatment due to an AE, and TEAEs of special interest.
- TEAE by system organ class (SOC) and preferred term (PT).
- TEAE by PT.
- TEAE by maximum severity, SOC and PT.

FEAEs will be summarized for the post-treatment follow-up population for the Post-Treatment Follow-Up Period:

- FEAE by PT.

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

- For the start date:
    - If year, month, and day are missing, then use the earlier of the patient's first visit date or the consent date.
    - If either month or month and day are missing, then use January 1.
    - If only day is missing, impute the first day of the month.
- For the start time:
    - Impute as 23:59
- For the end date:
    - If year, month, and day are missing, then use the patient's last visit date in the follow-up period.
    - If either month or month and day are missing, then use December 31.
    - If only day is missing, then use the last day of the month.
    - The imputed date will not be beyond the patient's last visit date in the follow-up period.
- For the end time:
    - Impute as 23:59.
- If there is any doubt, the event will be flagged as treatment-emergent or follow-up emergent according the corresponding study period. If a follow-up emergent event was already counted as treatment-emergent during the prior treatment period, it will not be counted as a follow-up emergent event.

In general, for all AE related summaries, the number and percentage of patients experiencing the events will be presented by treatment. The events will be ordered by decreasing frequency in the overall group, followed in the order of ixekizumab and then in the order of guselkumab treatment, within SOC and/or PT for sorting.

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

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

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

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

- 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.

The following summary tables (including treatment comparison) will be provided for the safety population for the Blinded Treatment Periods:

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

Follow-up emergent serious adverse event (FESAE) is defined as an SAE that first occurred or worsened in severity after the date of Visit 12 (that is, Week 24) or the ETV. The following summary tables will be provided for the follow-up population for the Post-Treatment Follow-Up Period:

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

6.14.3.1. 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. Table RHCR.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 (same as pooling narrow and broad terms together) and narrow term.

In the event that the listing of terms or analysis changes for a special safety topic, it will be documented in the compound level safety standard (Program Safety Analysis Plan 2018) which will supersede this document; it will not warrant an amendment to the individual study SAP.

Fisher's exact tests will be used to compare the treatment groups for the safety population during the Blinded Treatment Periods.

Table RHCR.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: • Broad and narrow terms in the Liver related investigations, signs and symptoms (20000008) • Broad and narrow terms in the Cholestasis and jaundice of hepatic origin (20000009) • Broad and narrow terms in the Hepatitis, non-infectious (20000010) • Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage (20000013) • Narrow terms in the Liver-related coagulation and bleeding disturbances (20000015)	**Blinded Treatment Periods (Fisher's exact test)**: TEAEs by PT within SMQ or sub-SMQ
	Elevations in hepatic laboratory tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin) using Performing Laboratory Reference Ranges are defined as: • Include scheduled visits, unscheduled visits, and repeat measurements. • ALT or AST: maximum post-baseline measurement ≥3 times (3×), 5 times (5×), 10 times (10×), and 20 times (20×) the Performing lab upper limit of normal (ULN) for all patients with a post-baseline value. • 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. • The analysis of 5× ULN will contain 5 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1× ULN to <3× ULN, ≥3× ULN to <5× ULN, ≥5× ULN, or missing. • The analysis of 10× ULN will contain 6 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1×ULN to <3× ULN, ≥3× ULN to <5× ULN, ≥5× ULN to <10× ULN, ≥10× ULN, or missing. • The analysis of 20× ULN will contain 7 subsets: patients whose non-missing maximum baseline value is ≤1×ULN, >1×ULN to <3× ULN, ≥3× ULN to <5× ULN, ≥5× ULN to <10× ULN, ≥10× ULN to <20× ULN, ≥20× ULN, or missing. • Total bilirubin: 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 o The analysis of 1.5× ULN will contain 4 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1× ULN to <1.5× ULN, ≥1.5× ULN, or missing. o The analysis of 2× ULN will contain5 subsets: patients whose non-missing maximum baseline value is ≤1× ULN, >1× ULN to <1.5× ULN, ≥1.5 × ULN to <2 × ULN, ≥2 ×	**Blinded Treatment Periods (Fisher's exact test)**: Elevations in hepatic laboratory tests: maximum baseline category to abnormal maximum post-baseline category **Post-Treatment Follow-Up Period (Summary)**: Elevations in hepatic laboratory tests: maximum baseline category to abnormal maximum post-baseline category

	ULN, or missing. • 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. • The number and percentages of patients meeting the following elevated hepatic criteria: maximum ALT ≥ 3× ULN and maximum Total Bilirubin ≥2× ULN during the treatment period will be summarized.	
	Shift for ALT, AST, and total bilirubin from maximum baseline to maximum post-baseline will be produced with the requirements using Performing Laboratory Reference Ranges: • Include scheduled visits, unscheduled visits, and repeat measurements. • Use the maximum non-missing value in the baseline period. • Use the maximum non-missing post-baseline value within each study period. • Categories are: o ALT: ≤1× ULN, >1 to <3× ULN, ≥3 to <5× ULN, ≥5 to <10× ULN, ≥10 to <20× ULN, and ≥20× ULN o AST: ≤1× ULN, >1 to <3× ULN, ≥3 to <5× ULN, ≥5 to <10× ULN, ≥10× to <20× ULN and ≥20× ULN o Total bilirubin: ≤1× ULN, >1 to <1.5× ULN, ≥1.5 to <2× ULN, ≥2× ULN o ALP; ≤1× ULN, >1 to ≤1.5× ULN, >1.5× ULN • With additional categories: o Decreased: post-baseline category < baseline category o Increased: post-baseline category > baseline category o Same: post-baseline category = baseline category	**Blinded Treatment Periods (Summary)**: Shifts from maximum baseline to maximum post-baseline category **Post-Treatment Follow-Up Period (Summary)**: Shifts from maximum baseline to maximum post-baseline category
	Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot: Each patient with at least one post-baseline ALT and total bilirubin contributes one point to the plot. The maximum ALT measurement and the maximum total bilirubin measurement after the first injection will be included. 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. There will only be 1 eDISH plot for each indication regardless of treatment periods.	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: • Broad and narrow terms in the Haematopoietic leukopenia (20000030) • Broad and narrow terms in the Haematopoietic thrombocytopenia (20000031)	**Blinded Treatment Periods (Fisher's exact test)**: TEAEs by PT within sub-SMQ

Infections	Infections are events including all infections (defined using all the MedDRA PTs from the Infections and infestations SOC), serious infections, potential opportunistic infections (OIs), and infections resulting in anti-infective medication administration (i.e., antibacterial, antiviral, antifungal, antiparasitic treatment).	**Blinded Treatment Periods (Fisher's exact test)**: SAEs by PT, AEs leading to treatment discontinuation (including death) by PT, TEAEs by PT, TEAEs by maximum severity by PT
	Anti-infective medications are defined in the compound level safety standard, including antibiotics, antifungals, antivirals, or antiprotozoals.	**Listing:** TEAE with anti-infective medications
	The list of MedDRA terms used to identify infections that are pre-defined as potential OIs are found in the compound level safety standards. This list contains PTs as contained within Categories (narrow or broad) from the Infections and infestations SOC and from the Investigations SOC which can assist in identifying potential OIs. The narrow terms are considered opportunistic infections unless medical review determines that the reported term is not consistent with the patient's clinical history/presentation/course. Medical review of broad terms is needed for final determination of patients meeting the program definition of OIs. The number and percentage of patients with TEAEs that represent potential OIs and as potential OIs will be summarized by treatment group using MedDRA PT nested within categories. Events will be ordered by decreasing frequency in the ixekizumab group nested within categories.	**Blinded Treatment Periods (Fisher's exact test)**: TEAE of OIs by PT within Category **Listing:** TEAE of OIs
	The duration of each common (≥1% of total ixekizumab) TEAE PT of Infections and narrow terms for OIs is defined as: *Duration of treatment-emergent AE Infections (in weeks) =* *(End date of AE – Start date of AE + 1) / 7.* Patients who do not have the PT will not be included in the analysis. If the TEAE has not been reported as ended by the date of completion from the study, or date of early discontinuation, it will be censored as of that date. If a patient has multiple episodes of the same TEAE, the episode with the greatest severity will be used for the duration of event calculation. If a patient has multiple episodes of the same TEAE with the same severity, the episode with the longest duration will be used for the duration of event calculation.	**Blinded Treatment Periods (Summary)**: Duration of common TEAEs-infections and narrow terms for opportunistic infections
Allergic Reactions/Hypersensitivities	Allergic reactions/hypersensitivity events will be categorized as either anaphylaxis or non-anaphylaxis events (these will refer to events that are not localized to the site of injection) and summarized separately. Medical reviews are needed for final determination of patients with allergic-reactions/hypersensitivities.	**Blinded Treatment Periods (Fisher's exact test)**: TEAE by PT within Category, TEAE by maximum severity by

	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: • designed to specifically identify cases (following Criterion 1) based on narrow terms from the MedDRA SMQ for anaphylactic reaction (20000021). Criterion 1 for anaphylaxis is defined by the presence of a TEAE based on the following MedDRA PTs from the anaphylactic reaction SMQ: o Anaphylactic reaction o Anaphylactic shock o Anaphylactoid reaction o Anaphylactoid shock o Kounis Syndrome o Type I hypersensitivity • to identify possible cases, following Criterion 2 as defined by Sampson et al (2006). Criterion 2 for anaphylaxis requires having TEAEs from two or more of four categories of AEs as described by Sampson et al (2006). Occurrence of these events should be nearly coincident; based on recording of events on eCRFs. All qualifying events must be within 1 day of study drug injection. The 4 categories to be considered in Criterion 2 are: o Category A: Involvement of the skin-mucosal tissue o Category B: Respiratory compromise o Category C: Reduced blood pressure or associated symptoms o Category D: Persistent gastrointestinal symptoms	PT within Category, SAE by PT within Category, AE leading to treatment discontinuation (including death) by PT within Category,

	Summaries of Criterion 2 anaphylactic TEAEs will be provided by the specific combination of categories as follows: • AB: events based on meeting Category A and Category B (but no other category) • AC: events based on meeting Category A and Category C (but no other category) • AD: events based on meeting Category A and Category D (but no other category) • BC: events based on meeting Category B and Category C (but no other category) • BD: events based on meeting Category B and Category D (but no other category) • CD: events based on meeting Category C and Category D (but no other category) • ABC: events based on meeting Category A, Category B and Category C (but no other category) • ABD: events based on meeting Category A, Category B and Category D (but no other category) • ACD: events based on meeting Category A, Category C and Category D (but no other category) • BCD: events based on meeting Category B, Category C and Category D (but no other category) • ABCD: events based on meeting each of the 4 Criterion 2 categories Summaries of treatment-emergent anaphylactic AEs will be provided for patients meeting each of the 2 criteria and for patients who meet either criteria overall. Severity of treatment-emergent Criterion 2 anaphylactic AEs will be based on the maximum severity of the specific events met by the patient. Maximum severity of an (or overall) treatment-emergent anaphylactic AE will be based on the maximum severity within Criterion 1 and/or Criterion 2. <u>Allergic Reactions/Hypersensitivity Events, Non-Anaphylaxis</u>: 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 compound level safety standards and excluding the anaphylactic events as defined above.	
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: 1) Embolia cutis medicamentosa 2) Injection site joint discomfort 3) Injection site joint effusion 4) Injection site joint redness 5) Injection site joint infection 6) Injection site joint inflammation 7) Injection site joint movement impairment 8) Injection site joint pain 9) Injection site joint swelling 10) Injection site joint warmth.	**Blinded Treatment Periods (Fisher's exact test)**: TEAEs by PT within HLT, TEAEs by maximum severity by PT within HLT,TEAEs identified by the investigator by PT within HLT: by maximum severity, by maximum redness category, by maximum swelling category, by maximum pain category Duration of treatment-emergent

	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, swelling and pain) will be used. Redness (Scored 0-4) o [0] Subject's normal skin color, no increased redness o [1] Noticeable, but very mild redness o [2] Clearly red o [3] Bright red o [4] Dark with some scar formation Swelling (Scored 0-4 after running a finger over injected area) o [0] No bump o [1] Barely noticeable o [2] Clear bump but very thin o [3] Clear bump 1 mm thick o [4] Clear bump 2 mm thick or more Pain (including burning) (Scored 0-3) o [0] None o [1] Mild o [2] Moderate o [3] Severe The duration of TEAE PT for Injection Site Reactions is defined as: *Duration of TEAE PT for ISRs (in weeks) = (End date of AE – Start date of AE + 1) / 7.* Patients who do not have the PT will not be included in the analysis. If the TEAE has not been reported as ended by the date of completion from the study, or date of early discontinuation, it will be censored as of that date. If a patient has multiple episodes of the same TEAE, the episode with the greatest severity will be used for the duration of event calculation. If a patient has multiple episodes of the same TEAE with the same severity, the episode with the longest duration will be used for the duration of event calculation. The number of TEAE PT for ISRs per 100 active injections is defined as: *Number of TEAE PT for ISRs per 100 active injections =* *100 ×total number of AEs / total active injections.*	ISRs by PT within HLT, Number of treatment-emergent ISRs per 100 active injections by PT within HLT Time to onset of initial treatment-emergent ISRs by PT within HLT

	Time to onset of initial TEAE PT for ISRs is defined as: *Time to onset of initial TEAE PT for ISRs (in days) =* *Start date of first AE – first injection date + 1.*	

Cerebro-cardiovascular Events	Cerebro-cardiovascular events will be externally adjudicated by the Central 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 for confirmation of an event. All events selected by investigator 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:
	
	• Cardiovascular
	  o Death (Cardiovascular)
	  o Myocardial Infarction (MI)
	  o Hospitalization for Unstable Angina
	  o Hospitalization for Heart Failure
	  o Serious Arrhythmia
	  o Hospitalization for Hypertension
	  o Resuscitated Sudden Death
	  o Cardiogenic Shock due to Myocardial Infarction
	  o Coronary Revascularization
	• Neurologic
	  o Cerebrovascular Event: Transient Ischemic Attack or Stroke (Hemorrhagic, Ischemic, and Undetermined)
	
	• Peripheral Vascular Events
	  o Peripheral Arterial Event
	  o Peripheral Revascularization
	
	Events will be analyzed using MedDRA PT nested within the CEC assessment (confirmed event, no event, or insufficient documentation for event determination) and the subcategory. Subtypes of stroke (Hemorrhagic Stroke , Ischemic Stroke, and Undetermined Stroke Type) will be displayed in the analyses nested within Cerebrovascular Event. Subtypes of Serious Arrhythmia (Atrial Arrhythmia, Ventricular Arrhythmia, Heart Block, Other, Unknown) will be displayed nested within Serious Arrhythmia.
		Blinded Treatment Periods (Fisher's exact test):
		TEAE by PT within Subcategory

Major Adverse Cerebro-cardiovascular Events (MACE)	MACE (requiring adjudication as defined above) is defined as: • Vascular death (including cardiovascular and cerebro-vascular causes excluding hemorrhagic deaths outside of the central nervous system) • Non-fatal myocardial infarction • Non-fatal stroke (subcategories: ischemic, hemorrhagic, unknown stroke type) Where, • Vascular death should be captured as an Event on *Adjudication - Death* eCRF page with Adjudication Death Type = "Cardiovascular." • Non-fatal myocardial infarction should be captured as an Event on *Adjudication - Cardiac Ischemic Event* eCRF page with Type of Ischemic Event = "Myocardial Infarction" and the Event is NOT on *Adjudication - Death* eCRF page. • Non-fatal strokes (ischemic, hemorrhagic) should be captured as an Event on *Adjudication - Cerebrovascular Event* eCRF page with Stroke Cerebrovascular Event Subtype in one of the following categories: hemorrhagic stroke, ischemic stroke, undetermined stroke type, and the Event is NOT on *Adjudication - Death* eCRF page. Subcategories of non-fatal stroke (Hemorrhagic Stroke, Ischemic Stroke, and Undetermined Stroke Type) will be displayed nested within non-fatal stroke category.	**Blinded Treatment Periods (Fisher's exact test)**: TEAE by maximum severity by PT within Category
Malignancies	Malignancy is defined using PTs from the Malignant or unspecified tumors SMQ as defined in MedDRA (SMQ: 20000091, which includes the sub-SMQs: (1) 20000194 [Malignant tumours], including sub-SMQs of 20000227 [Haematological malignant tumours] and 20000228 [Non-haematological malignant tumours]; (2) 20000195 [Tumours of unspecified malignancy], including sub-SMQs of 20000229 [Haematological tumours of unspecified malignancy] and 20000230 [Non-haematological tumours of unspecified malignancy]. Events will be summarized by the following categories: • Non-Melanoma Skin Cancer (NMSC) o Basal Cell Carcinoma, PTs include: ▪ Basal cell carcinoma ▪ Basosquamous carcinoma ▪ Basosquamous carcinoma of skin o Squamous Cell Carcinoma, PTs include: ▪ Squamous cell carcinoma of skin ▪ Bowen's disease ▪ Lip squamous cell carcinoma ▪ Skin squamous cell carcinoma metastatic ▪ Keratoacanthoma • Malignancies excluding NMSC: all PTs in the Malignant or unspecified tumors SMQ excluding the 8 defined NMSC PTs.	**Blinded Treatment Periods (Fisher's exact test)**: TEAE by PT within Category

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)]).	**Blinded Treatment Periods (Fisher's exact test)**: TEAE by PT within SMQ or sub-SMQ
Interstitial Lung Disease (ILD)	ILD is defined using the PTs: • Narrow terms in the Interstitial Lung Disease SMQ (20000042) • Additional 6 PTs from Eosinophilic Pneumonia SMQ (20000157): o Angiolymphoid hyperplasia with eosinophilia (Narrow) o Eosinophilic bronchitis (Narrow) o Hypereosinophilic syndrome (Narrow) o Löeffler's syndrome (Narrow) o Pulmonary eosinophilia (Narrow) o Pulmonary vasculitis (Narrow)	
Inflammatory Bowel Disease (IBD)	IBD will be identified based on adjudication results. IBD will be also presented according to the following subcategory and MedDRA PTs. IBD Specific Terms (Narrow terms): • Inflammatory Bowel Disease: Inflammatory bowel disease • Crohn's Disease: Crohn's disease • Ulcerative Colitis: Acute haemorrhagic ulcerative colitis; Colitis ulcerative; Proctitis ulcerative IBD Non-Specific Terms: The PTs in this category are listed in the compound level safety standard.	**Blinded Treatment Periods (Fisher's exact test)**: TEAE by PT within Subcategory

Abbreviations: AE = adverse event; eCRF = electronic case report form; FEAE = follow-up emergent adverse event; HLT = high-level term; PT = preferred term; SAE = serious adverse event; SOC = System Organ Class; TB = tuberculosis; TEAE = treatment emergent adverse event.

6.14.4. Columbia-Suicide Severity Rating Scale (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 displayed (i.e., 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 his/her ideation and behavior will be displayed, even if not positive.

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 *Self Harm Questionnaire Supplement* eCRF.

6.14.5. Clinical Laboratory Evaluation

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

Continuous laboratory tests will be summarized as changes from baseline to last observation for patients who have both baseline and at least one post-baseline result for the Blinded Treatment Periods, respectively:

- The scheduled visits/measurements will be included. The unscheduled visits and the repeat measurements will be excluded.
- Both international system of units (SI) and conventional units will be summarized when different.
- For the safety population the comparisons between and among treatment groups will be conducted using an ANCOVA with treatment 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 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 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 the Blinded Treatment Periods.

- All scheduled, unscheduled and repeated measurements will be included.

- Performing laboratory will be used to define the low and high limits reference range except for 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 6.14.5.1.
- 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 post-baseline during the treatment period.
    - Follow-up emergent abnormal result is defined as a change from normal at baseline to abnormal at any time during the follow-up period.
- For continuous laboratory tests:
    - Treatment-emergent high value is defined as a change from a value less than or equal to the ULN at all baseline visits to a value greater than the ULN at any time post-baseline during the treatment period.
    - Treatment-emergent low value is defined as a change from a value greater than or equal to the LLN at all baseline visits to a value less than the LLN at any time post-baseline during the treatment period.
    - Follow-up emergent high value is defined as a change from a value less than or equal to the ULN at baseline to a value greater than the ULN at any time post-baseline during the follow-up period.
    - Follow-up emergent low value is defined as a change from a value greater than or equal to the LLN at baseline to a value less than the LLN at any time post-baseline during the follow-up period.

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.

6.14.5.1. Leukocytes (WBC) and Platelets

Further analyses will be conducted for total leukocytes, neutrophils, platelets, lymphocytes, monocytes, eosinophils, and basophils. Neutrophils is defined as absolute neutrophils (derived by adding segmented neutrophils and band neutrophil).

Shift table will be produced showing the number and percentage of patients shifting from baseline to a minimum post-baseline result in each relevant category by treatment group for the Blinded Treatment Periods:

- 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 post-baseline value within each study period.
- The parameters and categories are:
  - Leukocytes; $\geq 1 \times$ LLN, < LLN to $\geq 3.0 \times 10^9$/L, $<3.0 \times 10^9$/L to $\geq 2.0 \times 10^9$/L, $<2.0 \times 10^9$/L to $\geq 1.0 \times 10^9$/L, and $<1.0 \times 10^9$/L
  - Neutrophils: (absolute neutrophils); $\geq 1 \times$ LLN, < LLN to $\geq 1.5 \times 10^9$/L, $<1.5 \times 10^9$/L to $\geq 1.0 \times 10^9$/L, $<1.0 \times 10^9$/L to $\geq 0.5 \times 10^9$/L, and $<0.5 \times 10^9$/L
  - Platelets; $\geq 1 \times$ LLN, < LLN to $\geq 75.0 \times 10^9$/L, $<75.0 \times 10^9$/L to $\geq 50.0 \times 10^9$/L, $<50.0 \times 10^9$/L to $\geq 25.0 \times 10^9$/L, and $<25.0 \times 10^9$/L
  - Lymphocytes; $\geq 1 \times$ LLN, < LLN to $\geq 0.8 \times 10^9$/L, $<0.8 \times 10^9$/L to $\geq 0.5 \times 10^9$/L, $<0.5 \times 10^9$/L to $\geq 0.2 \times 10^9$/L, and $<0.2 \times 10^9$/L
- 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; post-baseline category < baseline category
  - Increased; post-baseline category > baseline category
  - Same; post-baseline category = baseline category.

The change from minimum baseline to minimum post-baseline result for each of these leukocytes and platelets will be summarized graphically using a box plot for the Blinded Treatment Periods:

- All scheduled, unscheduled and repeated measurements will be included.

6.14.5.2. Neutrophil Follow-Up

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

The neutrophil follow-up analysis will be conducted on the neutrophil follow-up population defined as patients who have an absolute neutrophil count <1500 cells/µL (SI units: $<1.5 \times$

10^9/L) at the last scheduled visit or early termination visit prior to entering the Post-Treatment Follow-Up Period and less than the patient's baseline absolute neutrophil count (that is, prior to first injection at Week 0). These patients are monitored during the Period 4 until neutrophil recovery.

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

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

The number and percentage of patients achieving neutrophil clinical recovery will be presented by treatment group and week interval for neutrophil follow-up population for Post-Treatment Follow-Up Period. 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.

6.14.6. Vital Signs - Weight

Weight and its change from baseline will be summarized by treatment for safety population at scheduled visits during the Blinded Treatment Periods using descriptive statistics.

6.15. Biomarker Analyses

Refer to a separate SAP addendum for biomarker analyses plan.

6.16. Immunogenicity

6.16.1. Definitions and Terms

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

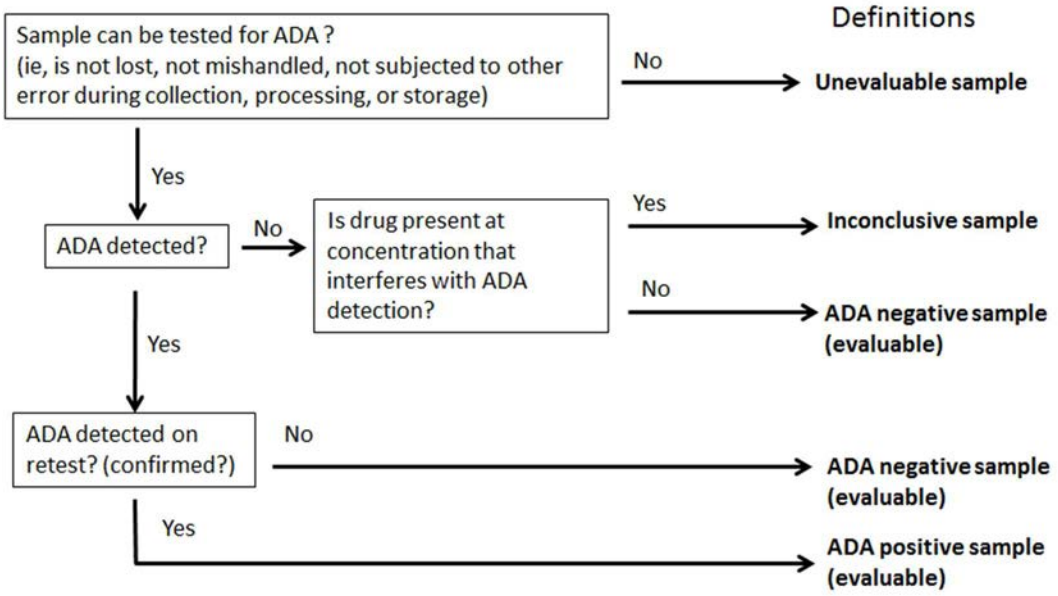
6.16.1.1. Sample Category Definitions

Samples are classified into the following categories:

- **Unevaluable sample:** Sample could not be tested for anti-drug antibody (ADA) due to sample loss, mishandling, or errors in collection, processing, storage, etc.
- **Antidrug antibody (ADA) Positive sample:** The presences of ADA is detected and confirmed. The samples are reported as positive. If the sample is positive, a titer value is reported.

- **Neutralizing anti-drug antibody (NAb) Positive sample:** NAb are reported as detected.
- **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.

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 (i.e., above the limit of drug tolerance of the ADA/NAb assay). The upper limit of drug tolerance in the ADA assay is 480.5 µg/mL and the upper limit of drug tolerance in the NAb assay is 1.1 µg/mL. A negative ADA/NAb result cannot be confirmed if drug concentrations present in the testing sample is above the limit of drug tolerance of the assay, and the sample should be considered inconclusive. Figure RHCR.6.1 illustrates the relationship of some of the above terms.



Abbreviation: ADA = anti-drug antibody.

Figure RHCR.6.1. Sample definitions.

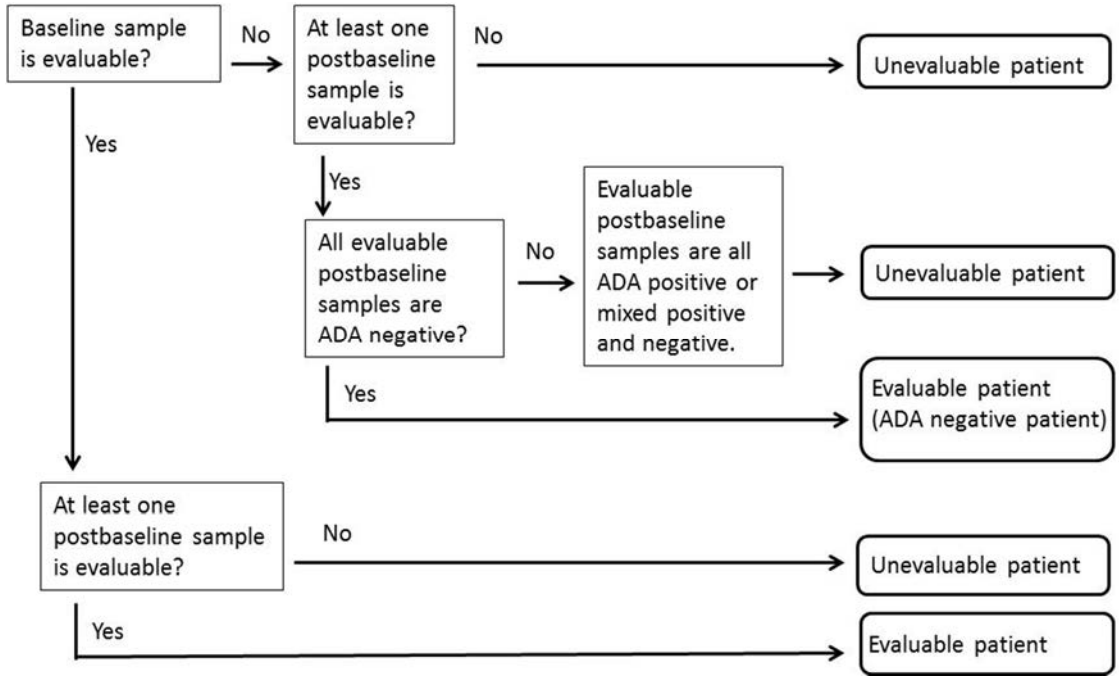
6.16.1.2. Patient Category Definitions

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

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

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



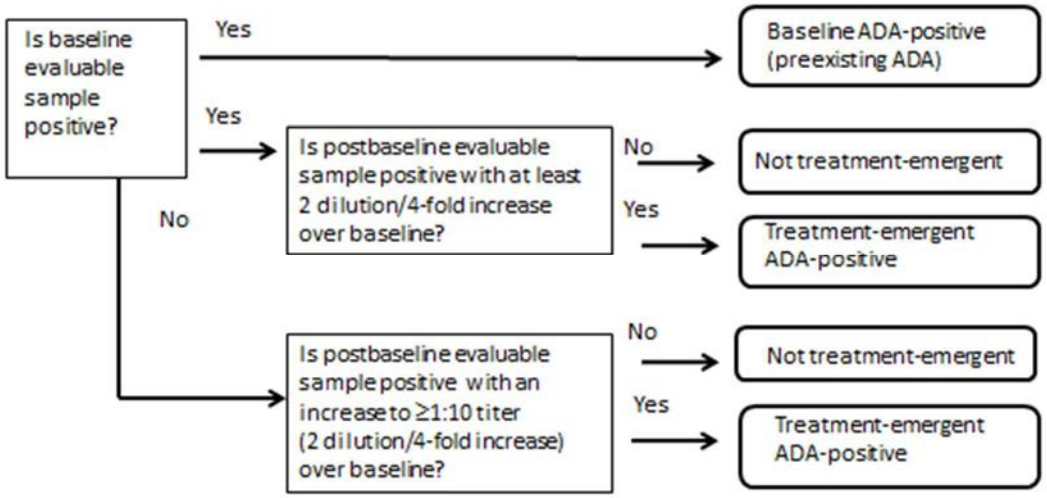
Abbreviation: ADA = anti-drug antibody.

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

6.16.1.3. Definitions for Clinical Interpretation of Assay Results

- **Baseline:** For immunogenicity analyses, baseline is the last nonmissing observation on, or prior to, the date of the first injection of study treatment of ixekizumab (Week 0).
- **Baseline ADA positive (preexisting antibody):** ADA detected in a sample collected at baseline.
- **TE-ADA positive:** 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:** 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.

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



Abbreviation: ADA = anti-drug antibody.

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

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

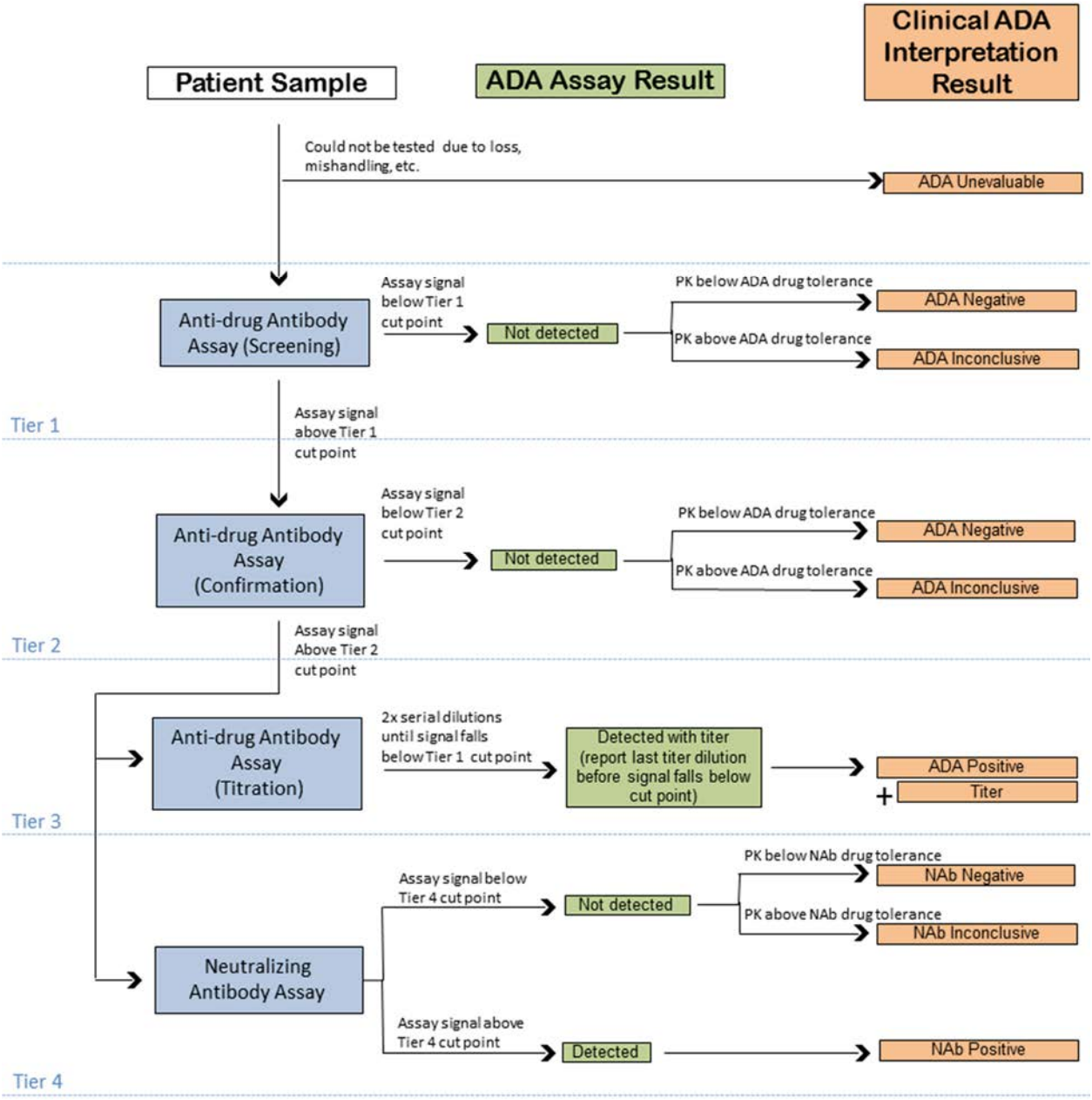
All ADA positive samples will be evaluated for NAb. NAb patient status will be defined as follows:

- **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.

ADA and TE-ADA titer values will be categorized as follows:

- Low Titer if titer value (LOCF) <1:160;
- Moderate Titer if titer value (LOCF) ≥1:160 and <1:1280; and
- High Titer if titer value (LOCF) ≥1:1280.

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



Abbreviation: ADA = anti-drug antibody.

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

6.17. Subgroup Analyses

6.17.1. Efficacy Subgroup Analyses

Subgroup analysis will be conducted on the following efficacy assessments:

- PASI 75, 90, 100 at Week 12 on ITT Population
- sPGA (0, 1) and sPGA (0) at Week 12 on ITT Population

A logistic regression model with treatment, subgroup, and the interaction of subgroup-by-treatment 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. The treatment differences with 95% CIs by each subgroup category will be reported. If any group within the subgroup is <10% of the total ITT population, only summaries of the efficacy data will be provided (that is, no inferential testing).

The subgroups to be analyzed are listed in Table RHCR.6.3. Additional subgroup analyses on efficacy may be performed as deemed appropriate and necessary.

6.17.2. Safety Subgroup Analyses

Subgroup analyses on safety may be performed as deemed appropriate and necessary.

6.18. Interim Analyses

The study will have one interim database lock once all patients complete Visit 9 (Week 12) or discontinue in the Induction Dosing Period. The interim analysis will include all data collected by the cutoff date, including the data from the Extension Period and the Post Treatment Follow-Up Period. The interim database lock at Week 12 will be considered the primary database lock because all primary and major secondary objectives, except for PASI 100 at Week 24, will be assessed at this time.

Prior to the Week 12 database lock, all members of the study team will be blinded to the treatment allocations. At the time of the Week 12 database lock, study team members that have direct access to study sites and data collection will remain blinded to the treatment allocations until all patients have completed the study (or discontinued on or prior to Week 24) and final database lock has occurred. Site staff, clinical monitors, and patients will remain blinded to the patient treatment allocation until the final Clinical Study Report (CSR) has been approved.

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

6.19. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include 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 dosing regimen, 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.

8. References

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