Statistical Analysis Plan: I1F-JE-RHCV

A Multicenter, Open-Label, Post Marketing Clinical Trial to Evaluate the Efficacy And Safety Of Ixekizumab in Patients With Generalized Pustular Psoriasis and Erythrodermic Psoriasis

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1. Statistical Analysis Plan: I1F-JE-RHCV: A Multicenter, Open-Label, Post Marketing Clinical Trial to Evaluate the Efficacy And Safety Of Ixekizumab in Patients With Generalized Pustular Psoriasis and Erythrodermic Psoriasis

Ixekizumab (LY2439821) Generalized Pustular Psoriasis and Erythrodermic Psoriasis

Study I1F-JE-RHCV is a multicenter, open-label, post marketing clinical trial to evaluate the efficacy and safety of ixekizumab Q2W beyond Week 12 until Week 20 in patients with Generalized Pustular Psoriasis and Erythrodermic Psoriasis.

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Protocol I1F-JE-RHCV
Phase 4

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

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3. Revision History

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

SAP Version 2 was approved prior to the final analysis. The overall changes incorporated in Version 2 are as follows:

1) Section of protocol deviation was updated to refer to the latest version of Trial Issue Management Plan (TIMP).
2) Race and race subcategory were added to the section of demographics and baseline characteristics.
3) Section of historical illnesses and preexisting conditions was added.
4) Summary of treatment compliance as continuous variable was added to the section of treatment compliance.
5) Wording was slightly updated to clarify the definition of primary analysis of the primary endpoint in the section of primary outcome and methodology.
6) Minor grammatical or formatting changes were made.

4. Study Objectives

Objectives	Endpoints
Primary • To assess the efficacy of ixekizumab Q2W beyond Week 12 in patients with generalized pustular psoriasis (GPP) and erythrodermic psoriasis (EP)	• Number of patients who improved Global Improvement Score (GIS) at least 1 point from Week 12 through Week 20 and with ≤2 of GIS
Secondary • To assess the efficacy of ixekizumab Q2W beyond Week 12 in patients with GPP and EP • To assess the health outcomes of ixekizumab Q2W beyond Week 12 in patients with GPP and EP • To evaluate the potential development of anti-ixekizumab antibodies of ixekizumab Q2W beyond Week 12 in patients with GPP and EP	The following endpoints will be assessed at each scheduled visit after Week 12: • Number of patients with each GIS grade (1: Resolved, 2: Improved, 3: Unchanged, 4: Worsened) • Number of patients who achieved sPGA (0, 1) and sPGA (0) • Number of patients who achieved PASI 75, PASI 90, and PASI 100 from baseline • Change from baseline, and percent improvement from baseline in PASI • Change from baseline in PSSI in patients with scalp involvement at baseline, and percent of BSA involvement of Psoriasis • Change from baseline in DLQI total score and domains, and Itch NRS score • Number of patients who achieved DLQI (0, 1) and DLQI (0) • Number of patients who achieved Itch NRS ≥4 point reduction from baseline for patients who had baseline Itch NRS ≥4 • Number of patients who developed treatment-emergent anti-ixekizumab antibody (TE-ADA) and neutralizing anti-ixekizumab antibody (NAb) <u>GPP ONLY</u> • Change from baseline on assessment of Generalized Pustular Psoriasis Severity Index at Week 12 and Week 20/ETV.

Note: Global improvement scores will be assessed in the four grades by comparing the psoriatic findings: (1) resolved, (2) improved, (3) unchanged, and (4) worsened. The global improvement score is assessed based on the comparison of the psoriatic findings, sPGA, PASI score, and other evaluations with those at the baseline.

Abbreviations: BSA = body surface area; DLQI = Dermatology Life Quality Index; EP = erythrodermic psoriasis; GIS = Global Improvement Score; GPP = generalized pustular psoriasis; NAb = neutralizing anti-ixekizumab antibody; NRS = Numeric Rating Scale; PASI = Psoriasis Area and Severity Index; PASI 75 = at least a 75% improvement from baseline in PASI score; PASI 90 = at least a 90% improvement from baseline in PASI score ; PASI 100 = a 100% improvement from baseline in PASI score; PSSI = Psoriasis Scalp Severity Index; Q2W = every 2 weeks; sPGA = static Physician Global Assessment; TE-ADA = treatment-emergent anti-drug antibody.

5. Study Design

5.1. Summary of Study Design

Study I1F-JE-RHCV is a multicenter, open-label, post marketing clinical trial to evaluate the efficacy and safety of ixekizumab Q2W beyond Week 12 until Week 20 in patients with GPP and EP.

The study consists of 3 periods:

- **Period 1**: Screening Period (Visit 1) lasting from 7 to 30 days prior to Period 2 (baseline; Week 0; Visit 2)

  Study investigator(s) will review patient history and screening test results to determine if the patient meets all inclusion and none of the exclusion criteria to qualify for participation in the study.

- **Period 2**: Induction Dosing Period from Week 0 (Visit 2) to Week 12 (Visit 6)

  All eligible patients will be administered 160 mg ixekizumab as 2 SC injections at Week 0 (baseline; Visit 2) followed by 80 mg as 1 injection at Week 2, 4, 6, 8 and 10.

- **Period 3**: Maintenance Dosing Period from Week 12 to Week 20

  Responders (GIS = 1 at Week 12) will complete the study.

  Inadequate responders (GIS ≥2 at Week 12 and based on investigators' discretion) will continue to use ixekizumab 80 mg Q2W during Period 3. If patients show a therapeutic response (GIS = 1) with 80 mg Q2W after Week 12, the patient will complete the study. Patients who complete the study before Week 20 will have an early termination visit (ETV) instead of the original scheduled visit.

Figure RHCV.5.1 illustrates the study design.

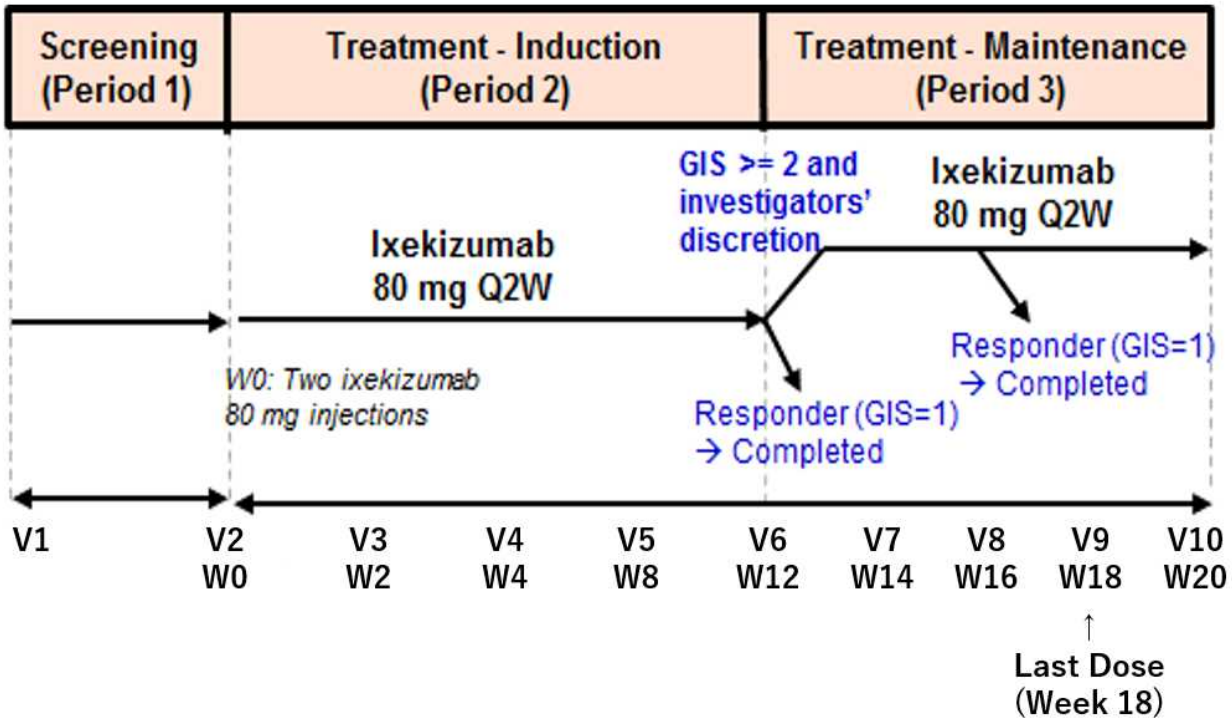


Figure RHCV.5.1. Illustration of study design for Clinical Protocol I1F-JE-RHCV.

5.2. Determination of Sample Size

A total of 12 patients will be enrolled so that at least 5 patients with EP and 5 patients with GPP who are inadequate responders (GIS ≥2 at Week 12 and based on investigators' discretion) will continue to use ixekizumab beyond Week 12. Additional enrollment may occur and the sample size may be increased, if no GPP or EP patients enter into Period 3 (Maintenance Dosing Period) of the study.

The sample size is based on the following:

- In the I1F-JE-RHAT (RHAT) study, 5 GPP and 8 EP patients were enrolled. One GPP patient achieved GIS = 1 (resolved) at Week 12 and the other 4 GPP patients achieved GIS = 2 (improved). One EP patient achieved GIS = 1 at Week 12 and 7 EP patients achieved GIS = 2. Although the sample size is very small, based on the result of RHAT study, it is assumed that approximately 5 patients at maximum may not achieve GIS = 1 at Week 12 and may continue ixekizumab Q2W beyond Week 12 based on the investigators' discretion.
- The sample size is determined based on the feasibility in Japan. The prevalence rate of these patients is very low in Japan and it is also difficult to conduct a placebo-controlled study for these severe conditions (Umezawa et al. 2003, Rosenbach et al. 2010).

5.3. Method of Assignment to Treatment

Patients are assigned to treatment and will receive their assigned treatment as outlined in the protocol Section 7.1.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly Japan.

Efficacy, health outcomes and safety analyses for Period 2 will be conducted on the largest analysis set (Full Analysis Set [FAS]), defined as the set of patients with GPP and EP separately who receive at least 1 dose of study treatment in Period 2 (FAS Population). Efficacy, health outcomes and safety analyses for Combined Periods 2 and 3 will be conducted based on patients with GPP and EP separately who receive at least 1 dose of study treatment in Period 3 (Maintenance Dosing Period Population) although the protocol stated that these analyses wll be conducted only for Period 3 on the Maintenance Dosing Period Population.

Baseline for efficacy, health outcomes, and safety analyses in Period 2 and Combined Periods 2 and 3 is defined as the last available value before the first dose in Period 2; in most cases, it will be the value recorded at Week 0 (Visit 2).

Change from baseline will be calculated as the value at the visit of interest minus the baseline value. If all baseline values are missing for a particular variable, then the change from baseline and the percent improvement from baseline will not be calculated.

In the analysis of adverse events for Period 2 and Combined Periods 2 and 3, all pre-existing conditions recorded at Visit 1 and any on-study adverse events recorded prior to the first dose in Period 2 will be used as baseline events.

As this is a single arm study with very small sample size, no statistical inference will be performed.

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

The statistical analyses will be performed using SAS® Version 9.4 or higher.

6.2. Adjustments for Covariates

No statistical adjustments for covariates will be made as statistical inference will not be performed in this single arm study with very small sample size.

6.3. Handling of Dropouts or Missing Data

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

6.3.1. Nonresponder Imputation (NRI)

Categorical binary efficacy and health outcomes variables will be summarized using a nonresponder imputation (NRI) method. Patients will be considered a nonresponder if they do not meet the clinical response criteria or have missing clinical response data at the scheduled time point. All patients who discontinue study treatment at any time prior to the scheduled visit for any reason will be defined as nonresponders regardless of study continuation without study treatment at the visit. Enrolled patients without at least 1 post-baseline observation will also be defined as nonresponders.

6.3.2. Last Observation Carried Forward (LOCF)

Continuous efficacy and health outcomes variables will be summarized using a last observation carried forward (LOCF) method. For patients discontinuing study treatment for any reason, the last non-missing post-baseline observation before the missing data will be carried forward to the corresponding time point for evaluation. Enrolled patients without at least 1 post-baseline observation will not be included for evaluation.

6.4. Multicenter Studies

This study will be conducted in multiple investigators at multiple sites. However, since all sites will have small numbers of subjects, center differences will not be explored.

6.5. Multiple Comparisons/Multiplicity

No statistical multiple comparisons will be made in this single arm study with very small sample size.

6.6. Use of an "Efficacy Subset" of Patients

An efficacy subset will not be used in this study because of very small sample size.

6.7. Patient Disposition

The following patient disposition summaries will be provided for patients with GPP and EP separately and total:

- Number of patients:
    - failed in screening, by primary reason for screen failure
    - enrolled (defined as patients who have been assigned to a treatment) at Week 0 (Visit 2)
    - completing Period 2 (Week 12, Visit 6)
    - discontinuing the study in Period 2, by primary reason for study discontinuation
    - completing Period 3 including patients who complete the study because of GIS = 1 prior to Week 20 (Visit 10)
    - discontinuing the study in Period 3, by primary reason for study discontinuation

  (Analysis population: All Entered Patients)
- Number of patients:
    - completing the study treatment in Period 2
    - discontinuing the study treatment in Period 2, by primary reason for treatment discontinuation

(Analysis population: FAS Population)

- Number of patients:
  - completing the study treatment in Period 3
  - discontinuing the study treatment in Period 3, by primary reason for treatment discontinuation

(Analysis population: Maintenance Dosing Period Population)

A by-patient listing will be provided to include the following information (Analysis population: All Entered Patients):

- Patient disposition during treatment periods, including the date of enrollment at Visit 2, the date of first and last dose, the date of study completion or study discontinuation, the primary reason for study discontinuation if applicable, and the number of days in treatment periods. The number of days in treatment periods will be calculated as: date of treatment discontinuation (or treatment completion) - date of first dose in Period 2 + 1. For patients who discontinue due to lost to follow-up, the date of discontinuation captured in the *Disposition Event: Lost to Follow Up* electronic case report form (eCRF) page will be used for this calculation.

6.8. Patient Characteristics

6.8.1. Demographics and Baseline Characteristics

The following demographic variables and baseline characteristics will be summarized descriptively for patients with GPP and EP separately and total (Analysis population: FAS Population):

- Age at the time of informed consent (in years): It will be calculated using an imputed date of birth of July 1st in the year of birth collected in the *Demographics* eCRF page as follows:

$$Age\ (years) = \frac{Date\ of\ informed\ consent - Imputed\ date\ of\ birth}{365.25}$$

- Age group: <65 years, ≥65 years to <75 years, ≥75 years
- Gender
- Race
- Race subcategory: Japanese, other (if "No" is selected for the "Race Asian" collected in the *Demographics* eCRF page)
- Height (cm)
- Weight (kg)
- Weight category: <80 kg, ≥80 kg and <100 kg, ≥100 kg
- Body mass index (BMI) (kg/m^2): It will be calculated as follows:

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

- Alcohol use: never, current, former
- Caffeine use: never, current, former
- Tobacco use: never, current, former
- Previous systemic therapy: never used, non-biologic only, biologic only, biologic and non-biologic.
  - Non-biologics are defined as: methotrexate, cyclosporine, retinoids, corticosteroids, fumaric acid derivatives, apremilast, other non-biologics, and psoralen and ultraviolet A (PUVA)
  - Biologics are defined as: efalizumab, ustekinumab, infliximab, etanercept, alefacept, adalimumab, golimumab, certolizumab pegol, secukinumab, brodalumab, or other biologics
- Previous non-biologic systemic therapy: never used, ever used
- Previous biologic therapy: never used, ever used
- Previous phototherapy (ultraviolet B [UVB] or PUVA): never used, ever used
- Previous IL-17 therapy (secukinumab or brodalumab): never used, ever used
- Age at GPP or EP diagnosis (in years)
- Duration since GPP or EP diagnosis (in years): It will be calculated using the date of GPP or EP diagnosis as follows:

$$Duration\ since\ GPP\ or\ EP\ diagnosis\ (years) = \frac{Date\ of\ informed\ consent - Date\ of\ GPP\ or\ EP\ diagnosis}{365.25}$$

  In case of partial date of GPP or EP diagnosis, the following imputation rules will be utilized:

  - If both month and day are missing, impute July 1.
  - If month is missing and day is not missing, impute July 1.
  - If only day is missing, impute 15.
- Psoriasis vulgaris: yes, no
- Psoriatic arthritis: yes, no
- Baseline sPGA as continuous variable
- Baseline sPGA category: 0, 1, 2, 3, 4, 5
- Baseline PASI score
- Scalp psoriasis: yes, no
- Baseline PSSI score
- Baseline BSA (%)

- Baseline Itch NRS score
- Baseline DLQI total score
- Diagnosis of GPP (GPP only): acute GPP, other
- Type of GPP (GPP only): GPP with preceding psoriasis vulgaris, other: If start date of psoriasis vulgaris is prior to diagnosis date of GPP, it will be classified into GPP with preceding psoriasis vulgaris. Otherwise, it will be classified into other. If start date of psoriasis vulgaris and/or diagnosis date of GPP are missing or partial, these dates will be compared as far as possible. If there is clear evidence to suggest that the psoriasis vulgaris started prior to the diagnosis of GPP, the patient will be assumed to be GPP with preceding psoriasis vulgaris.
- Mutation of IL-36 RN (GPP only): compound heterozygous, heterozygous, homozygous, no mutation, other, unknown
- Baseline assessment of dermal symptoms total score (GPP only): It will be assessed by the score with the area of erythema (on a 0 to 3 scale), area of confluent pustules (on a 0 to 3 scale), and are of skin edema (on a 0 to 3 scale) (see table below). The total score will be calculated (range, 0 to 9).

Assessment of dermal symptoms (0 - 9 points)				
	Severe	Moderate	Mild	None
Area of erythema*	3	2	1	0
Area of erythema with pustules**	3	2	1	0
Area of edema**	3	2	1	0

*% against body surface area (Severe: ≥75%, Moderate: <75% ≥25%, Mild: <25%)

**% against body surface area (Severe: ≥50%, Moderate: <50% ≥10%, Mild: <10%)

- Baseline systemic symptoms and laboratory findings total score (GPP only): It will be assessed by the score with body temperature (on a 0 to 2 scale), leucocytes (on a 0 to -2 scale), C-reactive protein (on a 0 to 2 scale) and serum albumin (on a 0 to 2 scale) (see table below). The total score will be calculated (range, 0 to 8).

Systemic symptoms and laboratory findings (0 - 8 points)			
Score	2	1	0
Body temperature (℃)	≥ 38.5	37 ≤, < 38.5	< 37
Leucocytes (/ μ L)	≥ 15,000	10,000 ≤, < 15,000	< 10,000
C-reactive protein (mg/dl)	≥ 7.0	0.3 ≤, < 7.0	< 0.3
Serum albumin (g/dl)	< 3.0	3.0 ≤, < 3.8	≥ 3.8

- Baseline GPP severity index total score (GPP only): It will be calculated by the sum of assessment of dermal symptoms total score and systemic symptoms and laboratory findings total score (range, 0 to 17).

- Baseline GPP severity: mild, moderate, severe (GPP only): It will be defined as mild (0 – 6 points), moderate (7 – 10 points), and severe (11 – 17 points) from GPP severity index total score.
- Baseline Columbia-Suicide Severity Rating Scale (C-SSRS) in lifetime: Category 1 – Wish to be Dead, Category 2 – Non-specific Active Suicidal Thoughts, Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act, Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan, Category 5 – Active Suicidal Ideation with Specific Plan and Intent, Category 6 – Preparatory Acts or Behavior, Category 7 – Aborted Attempt, Category 8 – Interrupted Attempt, Category 9 – Actual Attempt (non-fatal), and Self-injurious behavior without suicidal intent.

A by-patient listing of demographic and baseline characteristics will be provided (Analysis population: FAS Population).

6.8.2. Historical Illness and Preexisting Conditions

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

Historical illness/condition is defined as the condition/event recorded on the Pre-Existing Conditions and Medical History eCRF page or on the Prespecified Medical History eCRF page with an end date prior to the date of informed consent.

Preexisting condition is defined as the condition/event recorded on the Pre-Existing Conditions and Medical History eCRF page or on the Prespecified Medical History eCRF page with 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. 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.

By-patient listings of historical illnesses and preexisting conditions will be provided, respectively (Analysis population: FAS Population).

6.9. Treatment Compliance

Throughout treatment periods, enrolled patients will record information in a Study Drug Administration Log (captured in the *Exposure as Collected* eCRF page), including the date, time, and anatomical location of administration of investigational product, package number, who administered the investigational product, and the reason if the investigational product was not fully administered.

Treatment compliance for each patient will be calculated as:

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

- For patients who complete Period 2, the number of injections prescribed (that is, expected) during Period 2 will be equal to 7 (2 injections at Week 0 and 1 injection every 2 weeks from Week 2 to Week 10).
- For patients who discontinue during Period 2, the number of injections prescribed during Period 2 can be derived from the IWRS study drug dispense dataset.
- For patients who complete Period 3, the number of injections prescribed (that is, expected) during Period 3 will be equal to 4 (1 injection every 2 weeks from Week 12 to Week 18).
- For patients who discontinue during Period 3 or who complete study treatment because of GIS = 1 (i.e., Responder) before Week 18 , the number of injections prescribed during Period 3 can be derived from the IWRS study drug dispense dataset.
- The total number of injections administered will be derived using the response to the question "Was dose administered?" on the *Exposure as Collected* eCRF page.

A patient will be considered overall compliant with study treatment if he/she misses no more than 20% of the expected doses, does not miss 2 consecutive doses (all injections at an injection week are counted as 1 dose), and does not over-dose (that is, take more injections at the same time point than specified in the protocol).

The treatment compliance (continuous variable) and the number of patients that are compliant and non-compliant (categorical variable) will be summarized for patients with GPP and EP separately and total for Period 2 and for Combined Periods 2 and 3, respectively (Analysis population: FAS Population for Period 2, Maintenance Dosing Period Population for Combined Periods 2 and 3).

By-patient listings of study drug dispensed (including lot number and package number) and study treatment administration and compliance will be provided (Analysis population: FAS Population).

6.10. 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.

A by-patient listing of previous and concomitant therapy, and a by-patient listing of previous psoriasis therapy will be provided (Analysis population: FAS Population).

6.10.1. Previous Therapy

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

The number of patients with the followings will be presented for patients with GPP and EP separately and total (Analysis population: FAS Population):

- Previous therapy (captured in the *Prior Therapy: Indication* eCRF page and *Concomitant Therapy* eCRF page) by WHO ATC Level 4 and WHO drug generic name
- Previous psoriasis therapy (captured in the *Prior Therapy: Indication* eCRF page) by type (topical prescription therapy, topical non-prescription therapy, non-biologic systemic agent, biologic agent, non-biologic non-systemic agent, phototherapy) and therapy. The previous biologic agent will be further classified as TNF-α inhibitor (including infliximab, etanercept, adalimumab, golimumab, certolizumab pegol), interleukin (IL) 12/23 inhibitor (including ustekinumab), IL-17 inhibitor (including secukinumab and brodalumab), and other (including efalizumab, alefacept, or other biological agent).
- Reason for discontinuation of previous psoriasis therapy (captured in the *Prior Therapy: Indication* eCRF page) by type and therapy.

6.10.2. Concomitant Therapy

Concomitant therapy for Period 2 is defined as the therapy that starts before, on, or after the first day of study treatment of Period 2 and before the last visit date of Period 2, and continues into Period 2, that is, either no end date (the therapy is ongoing) or an end date on or after the first day of study treatment of Period 2. Concomitant therapy will belong to Period 2 if the therapy starts and ends on the exact same day as the first day of study treatment of Period 2.

Concomitant therapy for Period 3 is defined as the therapy that starts before, on, or after the last visit date of Period 2 and continues into Period 3, that is, either no end date (the therapy is ongoing) or an end date after the last visit date of Period 2. Concomitant therapy will belong to Period 3 if the therapy starts and ends on the exact same day as the last visit date of Period 2.

If a partial medication start date is present, the following imputation rules will be utilized in the analysis:

- 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.
- If there is any doubt, the medication will be flagged as concomitant.

The number of patients with the following will be presented for patients with GPP and EP separately and total for Period 2 and for Period 3, respectively (Analysis population: FAS Population for Period 2, Maintenance Dosing Period Population for Period 3):

- Concomitant therapy (captured in the *Concomitant Therapy* eCRF page) by WHO ATC Level 4 and WHO drug generic name.

6.11. Efficacy Analyses

Table RHCV.6.1 includes the description and derivation of the primary and secondary efficacy measures.

Summaries of efficacy measures will be provided in patients with GPP and EP separately for Period 2 and for Combined Periods 2 and 3, respectively (Analysis population: FAS Population for Period 2, Maintenance Dosing Period Population for Combined Periods 2 and 3).

By-patient listings of each efficacy measure will be provided (Analysis population: FAS Population).

Table RHCV.6.1. Description and Derivation of Primary and Secondary Efficacy Measures

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
GIS	Global Improvement Score (GIS): will be assessed in the 4 grades by comparing the psoriatic findings: (1) resolved, (2) improved, (3) unchanged, or (4) worsened. The GIS is assessed based on the comparison of the psoriatic findings, sPGA, PASI score, and other evaluations with those at the baseline.	GIS	Range from 1 to 4: resolved (1), improved (2), unchanged (3), or worsened (4)	Single item, missing if missing
sPGA	Static Physician Global Assessment (sPGA): the physician's global assessment of the patient's psoriasis lesions at a given time point (European Medicines Agency [EMA] 2004 [WWW]). Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).	sPGA score	Range from 0 to 5: clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).	Single item, missing if missing
		sPGA (0,1)	An sPGA assessed as either 0 or 1, which represents a clinically meaningful response of minimal plaque severity or complete resolution of psoriasis.	Missing if sPGA is missing
		sPGA (0)	An sPGA assessed as 0, which represents a clinically important endpoint indicating complete resolution of psoriasis.	Missing if sPGA is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
PASI	Psoriasis Area and Severity Index (PASI): combines assessments of the extent of body-surface involvement in 4 anatomical regions (head and neck, trunk, arms, and legs) and the severity of scaling (S), redness (R), and plaque induration/infiltration (thickness, T) in each region, yielding an overall score of 0 for no psoriasis to 72 for the most severe disease (Fredriksson and Pettersson 1978). Severity is rated for each index (R, S, T) on a 0-4 scale (0 for no involvement up to 4 for very severe involvement): 0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe The body is divided into four anatomical regions comprising the head (h), upper extremity (u), trunk (t), and lower extremity (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% 6 = 90% to 100%	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 extremity, trunk, and lower extremity, scored 0-4 respectively; T_h, T_u, T_t, T_l = thickness score of plaques on the head, upper extremity, trunk, and lower extremity, scored 0-4 respectively; S_h, S_u, S_t, S_l = scaliness score of plaques on the head, upper extremity, trunk, and lower extremity, 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 extremity, trunk, and lower extremity, 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, 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	Imputation Approach if with Missing Components
	The various body regions are weighted to reflect their respective proportion of body surface area.	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	Complete resolution of Ps; a 100% improvement in PASI score from baseline	Missing if baseline or observed value is missing
BSA	Percentage of Body Surface Area (BSA): The investigator will evaluate the percentage involvement of psoriasis on each patient's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), in which 1% corresponds to the size of the patient's hand (including the palm, fingers, and thumb) (National Psoriasis Foundation [NPF] 2009).	BSA	Collected as a single scale as part of *Psoriasis Area and Severity Index* 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
PSSI	Psoriasis Scalp Severity Index (PSSI): will be used if the patient has scalp psoriasis at baseline. The scalp will be assessed for erythema (redness), induration (hardness), and desquamation (shedding of skin) and percentage of area affected as follows: Erythema, Induration and Desquamation: 0 = Absent 1 = Slight 2 = Moderate 3 = Severe 4 = Severest Possible Percent of Scalp Involved: 0 = none 1 = <10% 2 = 10 – 29% 3 = 30 – 49%	PSSI score	The PSSI score is a composite score derived from the sum of the scores for erythema, induration and desquamation multiplied by the score for the extent of scalp area involved (percent of scalp involved). The range is 0 to 72.	If any individual score is missing, the PSSI score will not be calculated, hence missing.
		PSSI score change from baseline	Calculated as: observed PSSI – baseline PSSI	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	4 = 50 – 69% 5 = 70 – 89% 6 = 90 – 100%			
GPP Severity Index	Generalized Pustular Psoriasis (GPP) Severity Index: will be evaluated only for patients with pustular Ps at screening and at baseline according to the Japanese Dermatological Association GPP revised criteria (2010) (Iwatsuki et al. 2010 [WWW]). This is a composite score derived from the sum of scores for assessment of dermal symptoms, systemic symptoms, and laboratory findings (range, 0 to 17).	Assessment of dermal symptoms total score	Assessment of dermal symptoms will be assessed by the score with the area of erythema (on a 0 to 3 scale), area of confluent pustules (on a 0 to 3 scale), and are of skin edema (on a 0 to 3 scale). The total score will be calculated (range, 0 to 9).	If any individual score is missing, the total score will not be calculated, hence missing.
		Systemic symptoms and laboratory findings total score	Systemic symptoms and laboratory findings will be assessed by the score with fever (on a 0 to 2 scale), WBC (on a 0 to 2 scale), C-reactive protein (on a 0 to 2 scale) and Albumin (on a 0 to 2 scale). The total score will be calculated (range, 0 to 8).	If any individual score is missing, the total score will not be calculated, hence missing.
		GPP severity index total score	GPP severity index total score will be calculated by the sum of assessment of dermal symptoms total score and systemic symptoms and laboratory findings total score (range, 0 to 17).	Missing if assessment of dermal symptoms total score or systemic symptoms and laboratory findings total score is missing
		Assessment of dermal symptoms total score change from baseline	Calculated as: observed total score – baseline total score	Missing if baseline or observed value is missing
		Systemic symptoms and laboratory findings total	Calculated as: observed total score – baseline total score	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
		score change from baseline		
		GPP severity index total score change from baseline	Calculated as: observed total score – baseline total score	Missing if baseline or observed value is missing

6.11.1. Primary Outcome and Methodology

The primary analysis is to assess the efficacy of ixekizumab 80 mg Q2W beyond Week 12 in patients with GPP and EP separately, by presenting the number of patients who decreased their GIS by at least 1 point from Week 12 through Week 20 and with ≤2 of GIS at any visit of Week 14 (Visit 7), Week 16 (Visit 8), Week 18 (Visit 9), Week 20 (Visit 10), or ETV. (Analysis population: Maintenance Dosing Period Population).

6.11.2. Additional Analyses of the Primary Outcome

As an additional analysis of the primary efficacy measure (i.e., GIS), the following endpoint will be summarized descriptively at each scheduled visit for Period 2 and for Combined Periods 2 and 3, respectively (Analysis population: FAS Population for Period 2, Maintenance Dosing Period Population for Combined Periods 2 and 3):

- Number of patients with each GIS grade (1: Resolved, 2: Improved, 3: Unchanged, 4: Worsened).

6.11.3. Other Secondary Efficacy Analyses

For other efficacy measures, the following endpoints will be summarized descriptively at each scheduled visit for Period 2 and for Combined Periods 2 and 3, respectively (Analysis population: FAS Population for Period 2, Maintenance Dosing Period Population for Combined Periods 2 and 3):

- Number of patients who achieve sPGA (0, 1) and sPGA (0)
- Number of patients who achieve PASI 75, PASI 90, and PASI 100 from baseline
- Change from baseline, and percent improvement from baseline in PASI
- Change from baseline in PSSI in patients with scalp involvement at baseline
- Change from baseline in percent of BSA involvement of psoriasis.

GPP ONLY

- Change from baseline in assessment of dermal symptoms total score
- Change from baseline in systemic symptoms and laboratory findings total score
- Change from baseline in GPP severity index total score.

6.12. Health Outcomes/Quality-of-Life Analyses

Table RHCV.6.2 includes the description and derivation of the health outcomes measures.

Summaries of health outcomes measures will be provided in patients with GPP and EP separately for Period 2 and for Combined Periods 2 and 3, respectively (Analysis population: FAS Population for Period 2, Maintenance Dosing Period Population for Combined Periods 2 and 3).

By-patient listings of each health outcome measure will be provided (Analysis population: FAS Population).

Table RHCV.6.2. Description and Derivation of Health Outcomes Measures

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with 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." (Kimball et al. 2016)	Itch NRS score	Range from 0 to 10.	Single item, missing if missing
		Itch NRS change from baseline	Calculated as: observed Itch NRS – baseline Itch NRS	Missing if baseline or observed value is missing
		Itch NRS ≥4 point reduction from baseline	Reduced/decreased of ≥4 point from baseline	Missing if baseline or observed value is missing
DLQI	Dermatology Life Quality Index (DLQI): is a validated, dermatology-specific, patient-reported measure that evaluates patient's health-related QoL. This questionnaire has 10 items that are grouped in 6 domains, including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the "last week". Response categories and corresponding scores are: Very much = 3 A lot = 2 A little = 1 Not at all = 0 Not relevant = 0 (Finlay and Khan 1994; Basra et al. 2008)	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 yard? #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 made it difficult for you to do any sport?	If one question in a domain is missing, that domain is missing.
		DLQI work and school domain	Sum of responses of questions question #7A and #7B: #7A. Has your skin prevented you from working or studying? #7B. If No: how much has your skin been a problem at work or studying?	If the answer to question #7A is missing, this domain is missing. If #7A is No, and #7B is missing, this domain is missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
		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 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

For health outcomes measures, the following endpoints will be summarized descriptively at each scheduled visit for Period 2 and for Combined Periods 2 and 3, respectively (Analysis population: FAS Population for Period 2, Maintenance Dosing Period Population for Combined Periods 2 and 3):

- Change from baseline in Itch NRS score
- Number of patients who achieve Itch NRS ≥4 point reduction from baseline for patients who had baseline Itch NRS ≥4
- Change from baseline in DLQI total score and domains (i.e., symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment)
- Number of patients who achieve DLQI (0, 1) and DLQI (0).

6.13. Safety Analyses

Safety will be assessed by AEs, laboratory analytes including neutrophil counts, vital signs, weight, and C-SSRS.

Overall AEs and treatment-emergent adverse events (TEAEs) will be summarized with frequencies. The duration of dosing exposure will also be summarized. Other safety measures will be reviewed by listings.

Summaries of overall AEs and TEAEs will be provided in patients with GPP and EP separately and total for Period 2 and for Combined Periods 2 and 3, respectively (Analysis population: FAS Population for Period 2, Maintenance Dosing Period Population for Combined Periods 2 and 3).

6.13.1. Extent of Exposure

Exposure to study drug will be summarized descriptively for Period 2 and for Combined Periods 2 and 3, respectively (Analysis population: FAS Population for Period 2, Maintenance Dosing Period Population for Combined Periods 2 and 3).

A by-patient listing of exposure duration with number of active injections and total dose will be provided (Analysis population: FAS Population).

The duration of exposure will be calculated as:

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

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

- >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, and ≥84 days (Period 2). 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 to <84 days, ≥84 days (Period 2)
- >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥90 days, ≥120 days, and ≥140 days (Combined Periods 2 and 3). 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 to <90 days, ≥90 to <120 days, ≥120 to <140 days, and ≥140 days (Combined Periods 2 and 3).

Total dose (in mg) is calculated by the number of active injections taken during the treatment period multiplied by a dose of 80 mg.
Total number of injections received will be derived using the response to the question "Was dose administered?" on the *Exposure as Collected* eCRF page and the actual dose description from IWRS study drug dispense dataset.

6.13.2. Adverse Events

Adverse events will be classified based upon the latest version of the MedDRA. Adverse events will be recorded at every study visit. Any condition starting on or after the date of informed consent will be considered an AE. Any preexisting condition which worsens in severity on or after the date of informed consent will be considered and recorded as an AE on the *Adverse Events* (*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. The TEAEs will be assigned to the study period to which it's considered treatment-emergent:

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

Overall AEs and TEAEs will be summarized for the following study periods and analysis populations:

- Period 2 (Analysis population: FAS Population)
- Combined Periods 2 and 3 (Analysis population: Maintenance Dosing Period Population).

The following summaries will be provided for Period 2 and for Combined Periods 2 and 3 (Analysis population: FAS Population for Period 2, Maintenance Dosing Period Population for Combined Periods 2 and 3):

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

In general, events will be ordered by decreasing frequency in the total patient group (i.e., combined GPP and EP) within SOC and PT for sorting.

A by-patient listing of all AEs will be provided (Analysis population: FAS Population).

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

By-patient listings of deaths, SAEs, and AEs leading to treatment discontinuation will be provided (Analysis population: FAS Population).

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.

An SAE is any AE that results in one of the following outcomes: death, life-threatening, initial or prolonged hospitalization, disability or permanent damage, congenital anomaly or birth defect, or any other serious/important medical events.

6.13.3.1. Special Safety Topics including Adverse Events of Special Interest

Safety information on special topics including AESIs will be provided.

Table RHCV.6.3 provides the definitions and derivations 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.

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

By-patient listings of each special safety topic will be provided (Analysis population: FAS Population).

Table RHCV.6.3. Definitions and Derivations of Special Safety Topics including Adverse Events of Special Interest

Special Safety Topic	Definition / Derivation	Summary / Listing
Hepatic	Hepatic AE will include events that are potentially drug-related hepatic disorders by using the MedDRA PTs contained in any of the following SMQ or sub-SMQ as defined in MedDRA: • Broad and narrow terms in the Liver related investigations, signs and symptoms (20000008) • Broad and narrow terms in the Cholestasis and jaundice of hepatic origin (20000009) • Broad and narrow terms in the Hepatitis, non-infectious (20000010) • Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage (20000013) • Narrow terms in the Liver-related coagulation and bleeding disturbances (20000015).	**Overall summary:** ● Period 2 ● Combined Periods 2 and 3 **Listing:** TEAE (included in the same listing with cytopenia, depression and interstitial lung disease AESIs)
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).	**Overall summary:** ● Period 2 ● Combined Periods 2 and 3 **Listing:** TEAE (included in the same listing with hepatic, depression and interstitial lung disease AESIs)
Infections	Infections are events including all infections (defined using all the MedDRA PTs from the Infections and infestations SOC), serious infections, potential opportunistic infections, and infections resulting in anti-infective medication administration (i.e. antibacterial, antivirals, antifungals, antiparasitic treatments). Listing of patients experiencing a TEAE of infections will include the following additional information: types of infection, potential opportunistic infections (OIs) (Yes/No), anti-infective medications use (if treated) with medication start/end dates, indication for use, and route; minimum postbaseline value within each treatment period for leukocytes, platelets, lymphocytes, and absolute neutrophils. Anti-infective medications are defined in Appendix 5 of the PSAP Version 8. The list of MedDRA terms used to identify infections that are predefined as potential OIs are found in Appendix 10 of the PSAP Version 8.	**Overall summary:** ● Period 2 ● Combined Periods 2 and 3 **Listing:** TEAE (including information collected on *Infection* eCRF page)
Allergic Reactions/Hy-persensitivities	Allergic reactions/hypersensitivity events will be categorized as either anaphylaxis or non-anaphylaxis events (these will refer to events that are not localized to the site of injection) and summarized separately. 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).	**Overall summary:** ● Period 2 ● Combined Periods 2 and 3

Special Safety Topic	Definition / Derivation	Summary / Listing
	Identification of cases of potential anaphylaxis from the clinical trial data involves two criteria: 1) designed to specifically identify cases (following Criterion 1) based on narrow terms from the MedDRA SMQ for anaphylactic reaction (20000021). Criterion 1 for anaphylaxis is defined by the presence of a TEAE based on the following MedDRA PTs from the anaphylactic reaction SMQ: • Anaphylactic reaction • Anaphylactic shock • Anaphylactoid reaction • Anaphylactoid shock • Kounis Syndrome • Type 1 hypersensitivity. 2) to identify possible cases, following Criterion 2 as defined by Sampson et al. (2006). Criterion 2 for anaphylaxis requires having TEAEs from two or more of four categories of AEs as described by Sampson et al. (2006). Occurrence of these events should be nearly coincident based on recording of events on the eCRF. All qualifying event must be within 1 day of study drug injection. The 4 categories to be considered in Criterion 2 are: • Category A: Involvement of the skin-mucosal tissue • Category B: Respiratory compromise • Category C: Reduced blood pressure or associated symptoms • Category D: Persistent gastrointestinal symptoms. The specific MedDRA PTs covered by each of these Criterion 2 categories are shown in Appendix 6 of the PSAP Version 8. Criterion 2 anaphylactic TEAEs will be defined 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	

Special Safety Topic	Definition / Derivation	Summary / Listing
	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. Overall summaries of treatment-emergent anaphylactic AEs will be provided for patients who meet either criteria. Allergic Reactions/Hypersensitivity Events, Non-Anaphylaxis: TEAEs of allergic reaction/hypersensitivity categorized as non-anaphylaxis events are defined by the narrow terms within Hypersensitivity SMQ (20000214) excluding the PTs noted in Appendix 7 of the PSAP Version 8 and excluding the anaphylactic events as defined above.	
	A by-patient listing will be provided for all patients experiencing TEAE of allergic reactions/hypersensitivities at any time, including status/criterion of anaphylaxis or non-anaphylaxis, and the associated information collected on *Hypersensitivity, Anaphylactic, and Infusion Related Reactions* eCRF page.	**Listing:** TEAE (including information collected on *Hypersensitivity, Anaphylactic, and Infusion Related Reactions* eCRF page)
Injection Site Reactions	Injection site reaction is defined using the PTs from the MedDRA HLT of Injection site reactions as specified by MedDRA excluding the following 10 PTs: 1) Embolia cutis medicamentosa 2) Injection site joint discomfort 3) Injection site joint effusion 4) Injection site joint erythema 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.	**Overall summary:** ● Period 2 ● Combined Periods 2 and 3 **Listing:** TEAE (including information collected on *Injection Site Reaction* eCRF page)
Cerebro-cardiovascular Events	Cerebro-cardiovascular events will be externally adjudicated by the Clinical Events Committee (CEC) made up of a chairman, 2 cardiologists, and a neurologist. 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. Confirmed cerebro-cardiovascular events by CEC will be	**Overall summary:** ● Period 2 ● Combined Periods 2 and 3 **Listing:** TEAE

Special Safety Topic	Definition / Derivation	Summary / Listing
	summarized overall. All events which qualify for CEC adjudication will be listed. The categories and subcategories of adjudicated events used for the listing will include the following: • Cardiovascular o Death (Cardiovascular) o Cardiac Ischemic Event: Myocardial Infarction and Hospitalization for Unstable Angina o Serious Arrhythmia o Hospitalization for Heart Failure o Hospitalization for Hypertension o Resuscitated Sudden Death o Cardiogenic Shock o Coronary Revascularization. • Neurologic o Cerebrovascular Event: Transient Ischemic Attack or Stroke (Hemorrhagic, Ischemic and Undetermined). • Peripheral Vascular Events o Peripheral Arterial Event o Peripheral Revascularization. Listing of patients experiencing a cerebro-cardiovascular TEAE will include the following additional information: CEC assessment (confirmed event, no event, or insufficient documentation for event determination), categories/subcategories of adjudicated events, subtypes of stroke (Hemorrhagic Stroke, Ischemic Stroke, and Undetermined Stroke Type), major adverse cerebro-cardiovascular events (MACE defined below; Yes/No), and subcategories of MACE (Vascular Death, Non-fatal myocardial infarction, and Non-fatal stroke).	
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 (subtypes: hemorrhagic stroke, ischemic stroke, undetermined stroke type). Where, • Vascular death should be captured as an Event on *Adjudication - Death* eCRF page with Adjudication Death Type = 'Cardiovascular'. • Non-fatal myocardial infarction should be captured as an Event on *Adjudication - Cardiac Ischemic Event* eCRF page with Type of Ischemic Event = "Myocardial Infarction" and the Event	**Listing:** TEAE (included in the same listing with cerebro-cardiovascular events)

Special Safety Topic	Definition / Derivation	Summary / Listing
	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.	
Malignancies	Malignancy is defined using PTs from the Malignant or unspecified tumors SMQ as specified in MedDRA (SMQ: 20000091, which includes the sub-SMQs: • 20000194 [Malignant tumours], including sub-SMQs of 20000227 [Haematological malignant tumours] and 20000228 [Non-haematological malignant tumours] • 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 categorized as follows: • Nonmelanoma Skin Cancer (NMSC) o Basal Cell Carcinoma, PTs include: ▪ Basal cell carcinoma ▪ Basosquamous carcinoma ▪ Basosquamous carcinoma of skin. o Squamous Cell Carcinoma, PTs include: ▪ Squamous cell carcinoma of skin ▪ Bowen's disease ▪ Lip squamous cell carcinoma ▪ Skin squamous cell carcinoma metastatic ▪ Keratoacanthoma. • Malignancies excluding NMSC: all PTs in the Malignant or unspecified tumors SMQ excluding the 8 defined NMSC PTs.	**Overall summary:** ● Period 2 ● Combined Periods 2 and 3 **Listing:** TEAE
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)]).	**Overall summary:** ● Period 2 ● Combined Periods 2 and 3 **Listing:** TEAE (included in the same listing with hepatic, cytopenia and

Special Safety Topic	Definition / Derivation	Summary / Listing
		interstitial lung disease AESIs)
Inflammatory Bowel Disease (IBD)	IBD will be identified using the following subcategory and MedDRA PTs. The narrow terms are considered IBD and summarized overall. IBD events will also be externally adjudicated by the CEC with expertise in IBD. IBD (Narrow terms) • Inflammatory Bowel Disease: Inflammatory bowel disease • Crohn's Disease: Crohn's disease • Ulcerative Colitis: Acute haemorrhagic ulcerative colitis; Colitis ulcerative; Proctitis ulcerative. Non-Specific Terms (Events That Can Occur with IBD (Broad Terms)): The PTs in this category are listed in Appendix 11 of the PSAP Version 8.	**Overall summary:** ● Period 2 ● Combined Periods 2 and 3 **Listing:** TEAE (including adjudicated results)
Interstitial Lung Disease (ILD)	ILD is defined using the following terms: • Broad and narrow terms in the Interstitial lung disease SMQ (20000042) • Additional 6 PTs from Eosinophilic pneumonia SMQ (20000157): o Angiolymphoid hyperplasia with eosinophilia (Narrow) o Eosinophilic bronchitis (Narrow) o Hypereosinophilic syndrome (Narrow) o Loeffler's syndrome (Narrow) o Pulmonary eosinophilia (Narrow) o Pulmonary vasculitis (Narrow).	**Overall summary:** ● Period 2 ● Combined Periods 2 and 3 **Listing**: TEAE (included in the same listing with hepatic, cytopenia and depression AESIs)

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

6.13.4. Clinical Laboratory Evaluation

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

By-patient listings of all laboratory test values, and abnormal laboratory test results (criteria defined below) for parameters of special interest (hepatic, leukocytes and platelets) will be provided (Analysis population: FAS Population). Both international system of unit (SI) and conventional unit will be listed when the SI and the conventional units are different.

6.13.4.1. Hepatic Tests

Categories in abnormal hepatic laboratory test results (including scheduled visits, unscheduled visits, and repeat measurements) using Performing Lab Reference Ranges are defined as:

- Abnormal alanine aminotransferase (ALT) or aspartate aminotransferase (AST): >1×upper limit of normal (ULN) to <3× ULN, ≥3× ULN to <5× ULN, ≥5× ULN to <10× ULN, ≥10× ULN to <20× ULN, and ≥20× ULN
- Total bilirubin: >1× ULN to <1.5× ULN, ≥1.5× ULN to <2× ULN, and ≥2× ULN.
- Alkaline phosphatase (ALP): >1× ULN to <1.5× ULN, and ≥1.5× ULN.

In addition, a by-patient listing of patients who meet any of the following criteria will be provided (Analysis population: FAS Population):

- Elevated hepatic criteria: defined as maximum ALT ≥3× ULN and maximum total bilirubin ≥2× ULN within the same study period
- An ALT or AST ≥3× ULN
- A total bilirubin ≥2× ULN
- An ALP ≥1.5× ULN

The listing will include the following information: patient demographics, concomitant medications, ALT/AST/total bilirubin/ALP/ GGT by visit, treatment start and stop dates, and reason for treatment discontinuation.

6.13.4.2. Leukocytes (WBC) and Platelets

Categories in abnormal leukocytes (total leukocytes, neutrophils, and lymphocytes) and platelets laboratory test results (including scheduled visits, unscheduled visits, and repeat measurements) are defined as:

- Leukocytes (total leukocytes): < lower limit of normal (LLN) to ≥3.0× 10^9/L (Grade 1), <3.0× 10^9/L to ≥2.0× 10^9/L (Grade 2), <2.0× 10^9/L to ≥1.0× 10^9/L (Grade 3), and <1.0× 10^9/L (Grade 4).
- Neutrophils (absolute neutrophils): < LLN to ≥1.5× 10^9/L (Grade 1), <1.5× 10^9/L to ≥1.0× 10^9/L (Grade 2), <1.0× 10^9/L to ≥0.5× 10^9/L (Grade 3), and <0.5× 10^9/L (Grade

4). Absolute neutrophils will be derived by adding segmented neutrophils and band neutrophils.

- Lymphocytes: < LLN to ≥0.8× 10^9/L (Grade 1), <0.8× 10^9/L to ≥0.5× 10^9/L (Grade 2), <0.5× 10^9/L to ≥0.2× 10^9/L (Grade 3), and <0.2× 10^9/L (Grade 4)
- Platelets: < LLN to ≥75.0 × 10^9/L (Grade 1), <75.0 × 10^9/L to ≥50.0 × 10^9/L (Grade 2), <50.0 × 10^9/L to ≥25.0 × 10^9/L (Grade 3), and <25.0 × 10^9/L (Grade 4).

The above LLNs are defined as:

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

6.13.5. Vital Signs and Other Physical Findings

Vital signs and physical characteristics include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse (bpm), weight (kg), BMI (kg/m^2), and body temperature (°C).

A by-patient listing of vital signs and physical characteristics (including scheduled visits, unscheduled visits, and repeat measurements) will be provided (Analysis population: FAS Population).

6.13.6. Electrocardiograms

As a 12-lead electrocardiogram (ECG) will be locally performed only at screening visit (Visit 1), no ECG data analysis is planned in this study.

6.13.7. Columbia-Suicide Severity Rating Scale (C-SSRS)

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

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

Category 1 – Wish to be Dead
Category 2 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5 – Active Suicidal Ideation with Specific Plan and Intent
Category 6 – Preparatory Acts or Behavior
Category 7 – Aborted Attempt
Category 8 – Interrupted Attempt

Category 9 – Actual Attempt (non-fatal)
Category 10 – Completed Suicide.

Self-injurious behavior without suicidal intent is also a C-SSRS outcome (although not suicide-related) and has a binary response (yes/no).

Composite endpoints based on the above categories are defined below.

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

By-patient listings of C-SSRS and Self-Harm supplement and follow-up data will be provided (Analysis population: FAS Population). Given that few or no suicidal ideation or behaviors are anticipated, C-SSRS will be listed by patient and visit. Only patients that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be displayed (that is, if a patient's answers are all 'no' for the C-SSRS, then that patient will not be displayed). However, if a patient reported any suicidal ideation/ behavior or self-injurious behavior without suicidal intent at any time point then all their ideation and behavior will be displayed, even if not positive. Note, missing data should not been imputed.

The *Self-Harm Supplement Form* in the eCRF is a one-question form that is completed, at any visit, including baseline visit, that asks for the number of suicidal behaviors, possible suicidal behaviors or nonsuicidal self-injurious behaviors the patient has experienced since the last assessment. For each unique event identified, a questionnaire (*Self-Harm Follow-Up Form* in the eCRF) which collects supplemental information on the self-injurious behavior is to be completed. The Self-Harm data will be listed by patient and visit if number of events on Self-Harm Supplement Form is not zero.

6.14. Immunogenicity

6.14.1. Definitions and Terms

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

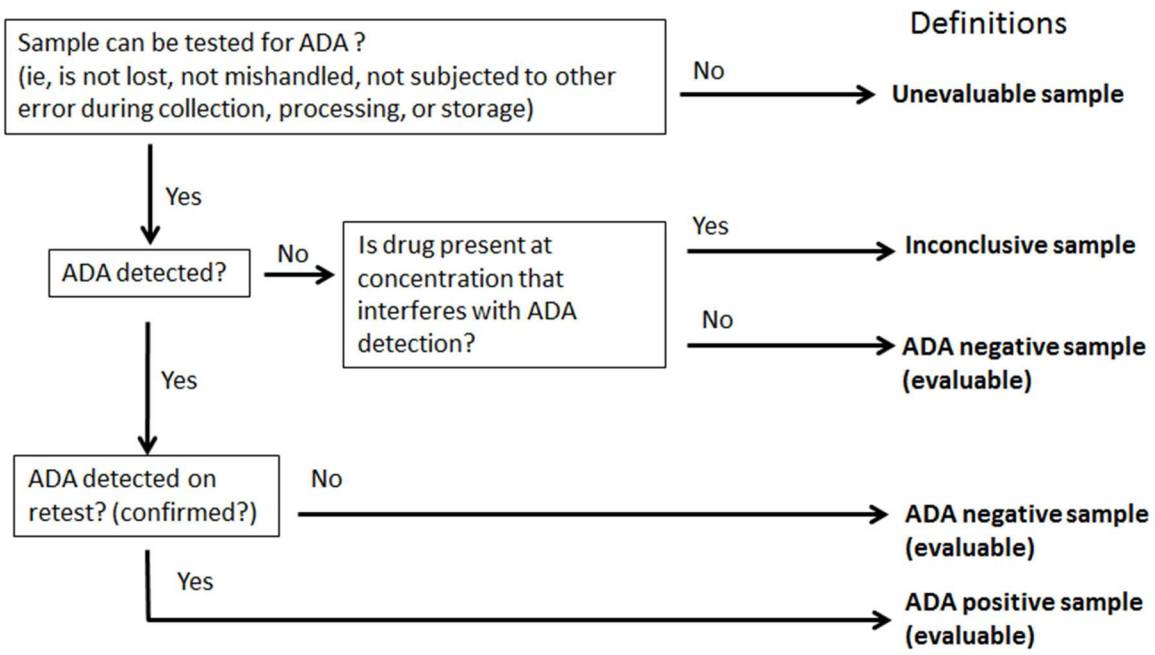
6.14.1.1. Sample Category Definitions

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, then the negative ADA/NAb result cannot be confirmed and the sample should be considered inconclusive.
    - Using the psoriasis disease-specific cut point, 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 1100 ng/mL. Confirmation of a negative ADA result is based on measured ixekizumab levels. Ixekizumab concentration below the determined drug tolerance of the ADA/NAb assays allow for confirmation of negative ADA/NAb results.

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



Abbreviation: ADA = anti-drug antibody.

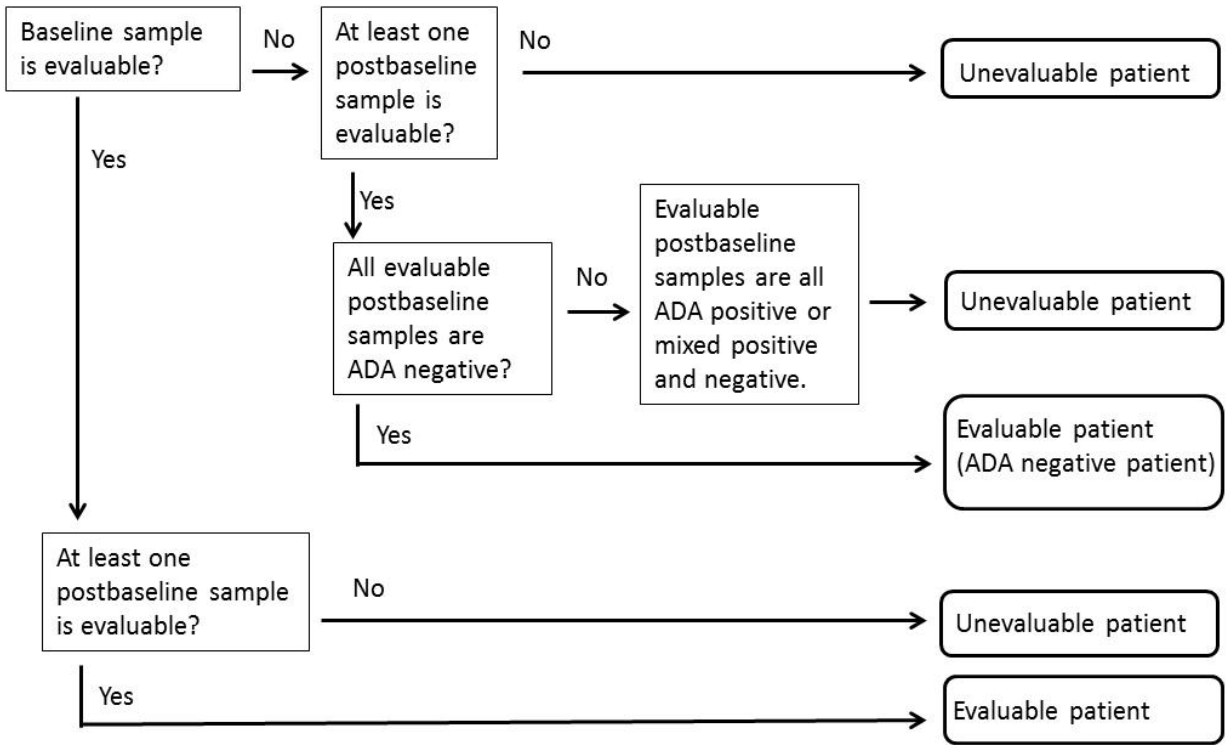
Figure RHCV.6.1. Sample definitions.

6.14.1.2. 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 RHCV.6.2 illustrates the relationship of the above terms.



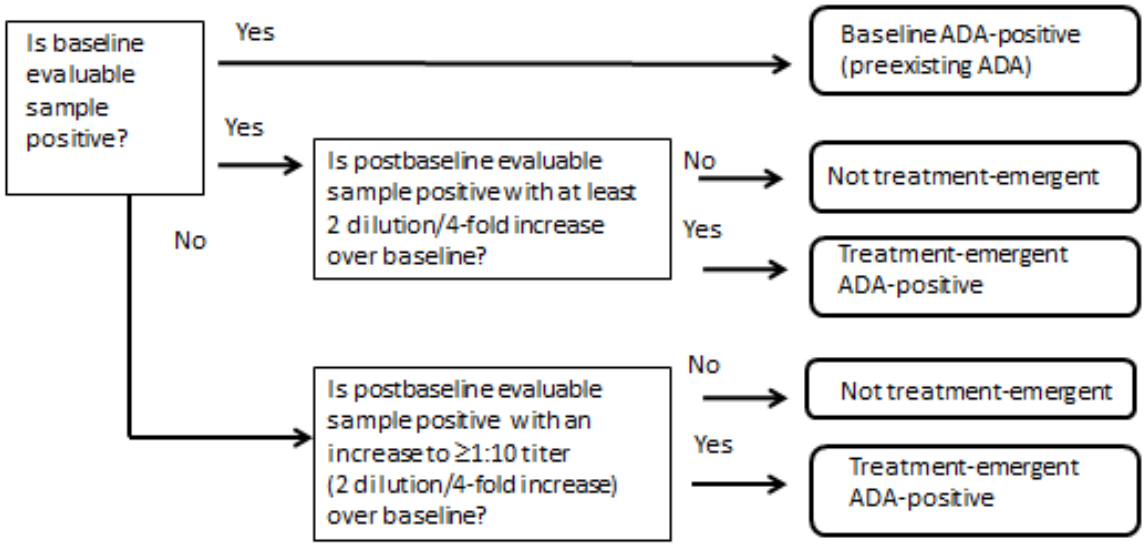
Abbreviation: ADA = anti-drug antibody.

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

6.14.1.3. Definitions for Clinical Interpretation of Assay Results

- **Baseline:** For immunogenicity summaries, 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 RHCV.6.3 illustrates the relationship of some of these terms.



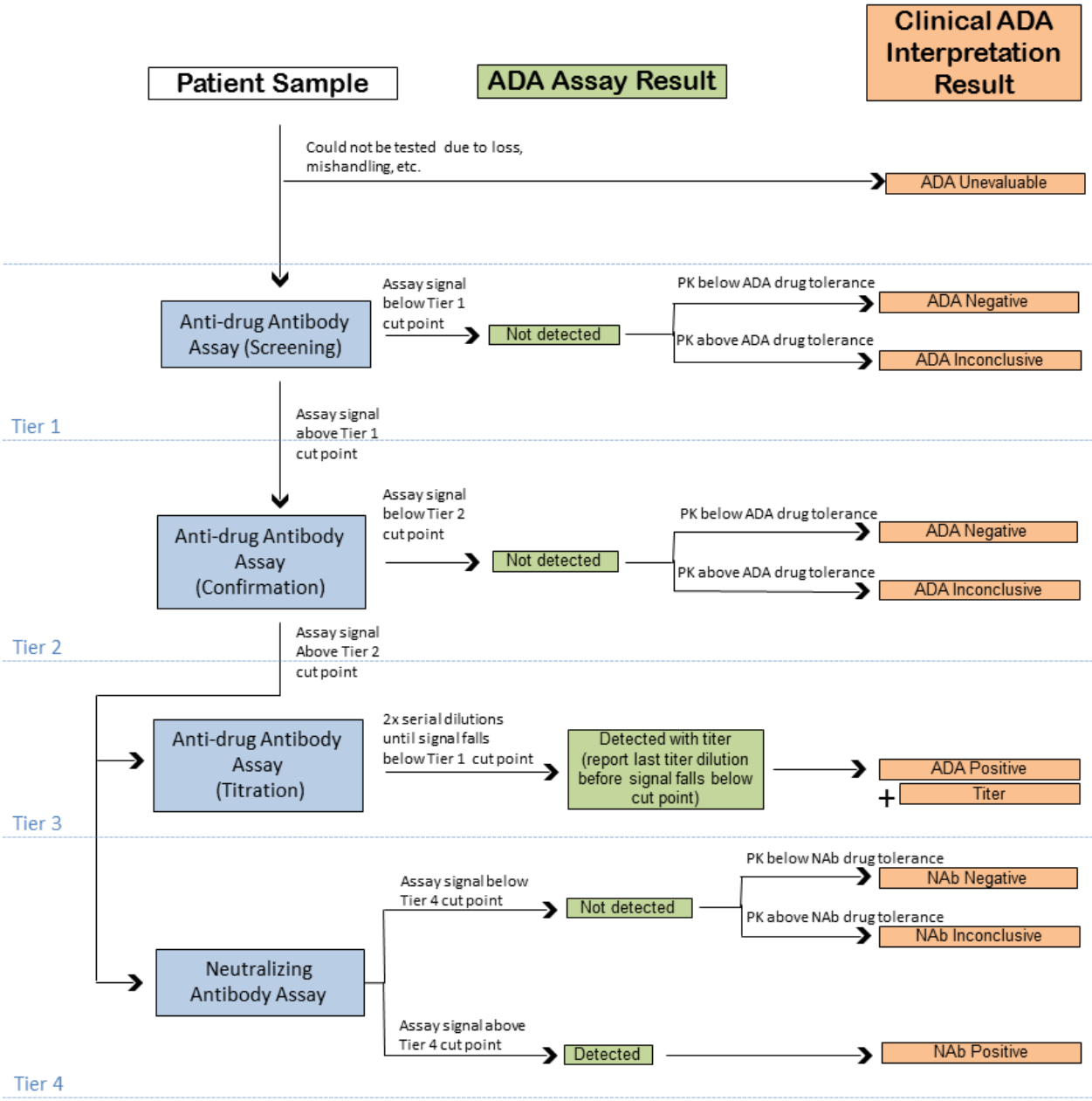
Abbreviation: ADA = anti-drug antibody.

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

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

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

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



Abbreviation: ADA = anti-drug antibody.

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

6.14.2. Immunogenicity Analyses

Immunogenicity evaluable patients will be grouped into TE-ADA status groups as follows:

TE-ADA Status Groups:

- TE-ADA status (positive, negative, or inconclusive);
- NAb status (positive, negative, or inconclusive) for TE-ADA positive patients; and
- TE-ADA titer groups for TE-ADA positive patients:

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

6.14.2.1. Analyses of Characteristics of ADA Immune Response

Overall ADA effects will be summarized on all evaluable patients within the following study periods and analysis populations:

- Period 2 (Analysis population: FAS Population)
- Combined Periods 2 and 3 (Analysis population: Maintenance Dosing Period Population).

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

A by-patient listing to include visit, sample date, injection date, ADA result, ADA titer value, TE-ADA result, NAb result, ixekizumab concentration, and GIS result will be provided (Analysis population: FAS Population).

6.15. Subgroup Analyses

No subgroup analyses are planned for this study because of very small sample size.

6.16. Protocol Deviations

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

Important protocol deviations are identified in the TIMP. Rerfer to the latest version of TIMP.

The number of patients having important protocol deviations will be summarized within category and subcategory of deviations for Combined Periods 2 and 3 in patients with GPP and EP separately and total (Analysis population: FAS Population).

A by-patient listing of important protocol deviations will be provided (Analysis population: FAS Population).

6.17. Interim Analyses and Data Monitoring

No interim analyses are planned for this study.

6.18. Annual Report Analyses

Summary table of treatment-emergent adverse events related to study treatment will be presented for Periodic Safety Report (PSR). A by-patient listing will also be provided for re-examination.

6.19. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by 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, 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 in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

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