Statistical Analysis Plan: I1F-IN-RHCZ (v 3.0)

A 24-Week Multicenter, Open-Label, Single-Arm, Phase 4 Study to Evaluate the Safety of Ixekizumab in Patients with Moderate-to-Severe Plaque Psoriasis and/or Active Psoriatic Arthritis in India

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STATISTICAL ANALYSIS PLAN

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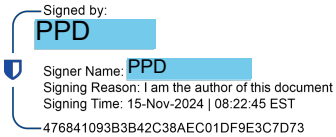

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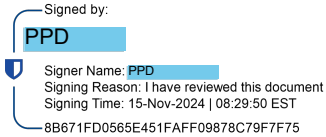

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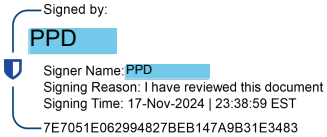

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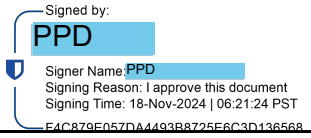

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Glossary of abbreviations

ABBREVIATION	DESCRIPTION
ACR	American college of rheumatology
AE	Adverse event
AESI	Adverse events of special interest
ACR20/50/70	20%/50%/70% Improvement in ACR criteria
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ATC	Anatomical therapeutic chemical
BSA	Body surface area
CASPAR	Classification criteria for psoriatic arthritis
CI	Confidence interval
CSR	Clinical study reports
CV	Coefficient of variation
DAS-28	Disease activity score-28
DBP	Diastolic blood pressure
DBL	Database lock
EDC	Electronic data capture system
ERB	Ethical review board
ETV	Early termination visit
eCRF	Electronic case report form
ENRL	Enrolled analysis population
FEAE	Follow-up emergent adverse event
HAQ-DI	Health assessment questionnaire – disability index
HCV	Hepatitis C virus
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HLT	High level term
IRB	Institutional review board
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International conference on harmonisation
IBD	Inflammatory bowel disease
ILD	Interstitial lung disease
ISR	Injection-site reaction
IMP	Investigational product
ITT	Intention-to-treat
LLN	Lower limit of normal

MACE	Major adverse cerebrocardiovascular events
MedDRA	Medical dictionary for regulatory activities
mITT	Modified intent-to-treat
N	Sample size
NRI	Non responder imputation
NMSC	Nonmelanoma skin cancer
ODS	Output delivery system
PASI	Psoriasis area and severity index
PASI 75/90/100	75%/90%/100% Improvement in the PASI criteria
PsA	Psoriatic arthritis
PsO	Plaque psoriasis
PT	Preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RA	Rheumatoid arthritis
SAE	Serious adverse event
SAF	Safety population
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SJC	Swollen joint count
SMQ	Standardized MedDRA query
SoA	Schedule of activities
SOC	System organ class
sPGA	Static physician global assessment of disease
TEAEs	Treatment-emergent adverse events
TESAEs	Treatment-emergent serious adverse events
TJC	Tender joint count
TLFs	Tables, data listings and figures
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO	World health organization
WHO-DD	WHO drug dictionary

1. Overview

1.1 Introduction

This document describes the rules and conventions to be used in the presentation and analysis of a 24-Week Multicenter, Open-label, Single-arm, Phase 4 study to evaluate the safety of Ixekizumab in participants with Moderate-to-Severe Plaque Psoriasis (defined as those with Psoriasis Area and Severity Index (PASI) ≥12, Static Physician Global Assessment of Disease (sPGA) ≥3, and Body surface area (BSA) ≥10%) and/or Active PsA (defined as those with the presence of at least 3 [out of 68] tender and at least 3 [out of 66] swollen joints) in India.

This Statistical Analysis Plan (SAP) is based on protocol I1F-IN-RHCZ, dated 14-Feb-2023.

2. Trial objectives

The following objectives are those stated in the Protocol Section 1.1.

2.1 Primary objectives

- To assess the type of adverse event (AE) and the proportion of Indian participants with PsO and participants with PsA reporting AEs and serious adverse events (SAEs) occurring within the duration of the study (24 weeks) after being started on Ixekizumab.

2.2 Secondary objectives

Specific to Psoriasis Group

- To evaluate percentage of participants achieving a ≥75% improvement in Psoriasis Area and Severity Index (PASI)

- To evaluate percentage of participants with a Static Physician Global Assessment (sPGA) (0,1)

Specific to Psoriatic Arthritis Group

- To evaluate percentage of participants achieving a 20% improvement in American College of Rheumatology response criteria (ACR20)

3. Endpoints

3.1 Primary endpoints

- AEs, including SAEs, treatment-emergent adverse events (TEAEs), and adverse events of special interest (AESIs) during the treatment periods (Week 0 to Week 24)

3.2 Secondary endpoints

PsO Endpoints:

- Proportion of participants who achieve the following PASI scores: PASI 75 (defined as 75% improvement from baseline in PASI) at Week 12
- Proportion of participants with an sPGA psoriasis score of 0 or 1 (0, 1) at Week 12

PsA Endpoints:

- Proportion of PsA participants achieving ACR20 at Week 24

4. Trial design

4.1 Design overview

Study RHCZ is a prospective, multicenter, open-label, single-arm, Phase 4 study with 4 study periods assessing outcomes in terms of AEs and SAEs with Ixekizumab when used in participants aged ≥18 years for PsO and PsA in an Indian population.

The study will consist of 4 periods:

4.1.1 Screening Period (Period 1; 5 to 28 days)

- The duration of the Screening Period will be 5 to 28 days before the Induction Dosing Period (Period 2) and consists of 1 screening visit (Visit 1) to assess participant eligibility.

4.1.2 Induction Dosing Period (Period 2; 12 weeks)

- The Induction Dosing Period (Period 2) will occur from Week 0 (baseline; Visit 2) to Week 12 (Visit 5).
- At Week 0, a 160-mg starting dose of Ixekizumab (two 80-mg injections) will be assigned, followed by Ixekizumab 80 mg Q2W from Weeks 2 through 12 to PsO participants with no active PsA and PsA participants who meet criteria of moderate-to-severe PsO
- At Week 0, a 160-mg starting dose of Ixekizumab (two 80-mg injections) will be assigned, followed by Ixekizumab 80 mg Q4W from Weeks 4 through 12 (i.e., at week 4, 8, 12) to PsA without PsO participants.

4.1.3 Maintenance Period (Period 3; 12 weeks)

- The Maintenance Period (Period 3) will occur from Week 12 (Visit 5) up to Week 24 (Visit 6).
- Ixekizumab 80 mg Q4W (i.e., at Weeks 16 and 20) will be assigned to all the participants. Refer to Protocol Section 6.1, Table RHCZ.6.1, and Table RHCZ.6.2 for a full description of treatment groups and dosing during Period 3.

4.1.4 Post-Treatment Follow-Up Period (Period 4)

- All participants receiving at least 1 dose of study intervention will enter the Post-Treatment Follow-Up Period (Period 4) for a minimum of 4 weeks, beginning after their last regularly scheduled visit at Week 24 (or the date of their ETV).
- Participants discontinuing from the study intervention who have received at least 1 dose of study intervention will continue to the ETV prior to entering to the Post-Treatment Follow-Up period.
- Required study visits should occur at 4 weeks (Visit 801) after the last regularly scheduled visit at Week 24 (or the date of the participant's ETV), except for participants with a concurrent infection that requires systemic anti-infective therapy (as described in protocol section 4.1.4).

4.2 Schema

a. For PsO participants with no active PsA and PsA participants who meet criteria for moderate-to-severe PsO, Ixekizumab prefilled syringes will be administered by two 80-mg SC injections at Week 0, then one 80-mg SC injection Q2W at Weeks 2, 4, 6, 8, and 10 will be administered. Starting from Week 12, 80 mg Ixekizumab will be administered by one 80-mg SC injection Q4W (i.e., at Weeks 12, 16, and 20). The last dose will be administered at Week 20.
b. For PsA participants who do not meet criteria for moderate-to-severe PsO, Ixekizumab prefilled syringes will be administered by two 80-mg SC injections at Week 0, then one 80-mg SC injection Q4W at Weeks 4, 8, 12, 16, and 20 will be administered. The last dose will be administered at Week 20.

Note: When the dosing is scheduled at home, the participants or care givers >will administer the provided Ixekizumab prefilled syringes.

4.3 Schedule of events

Refer Protocol Section 1.3 “Table RHCZ.1.1. Schedule of Activities”.

4.4 Sample size determination:

No formal sample size calculation was done for this study.

Approximately, 250 participants (PsO: 150 participants and PsA: 100 participants) was planned to be enrolled into this study, and assuming discontinuations of approximately 10%, approximately 225 participants should complete the 24-week period of treatment.

5. Changes/deviations from the planned analysis

The statistical analysis/methods as described in the protocol were adopted. There are no changes to the planned analyses. Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR).

6. Analysis populations

Agreement and authorization of participants included/excluded from each analysis population will be reached prior to final database hard lock. Sponsor will supply a list of all participants to be excluded from the relevant analysis populations, including the reason(s) for exclusion from the analysis populations. Number and percentage of patients in each analysis population will be provided along with a corresponding by-patient listing.

6.1 Enrolled Analysis Population (ENRL)

6.2 All participants who sign informed consent form. PsO with no Active PsA– Modified Intent-to-Treat (mITT) Population

Unless otherwise specified, efficacy and health outcomes analyses specific to psoriasis will be conducted on the PsO with No Active PsA- mITT population, defined as all enrolled participants with a psoriasis indication, who do not qualify for Active PsA and receives at least 1 dose of study treatment, even if the participant does not receive the correct treatment, or otherwise does not follow the protocol.

6.3 Active PsA – Modified Intent-to-Treat (mITT) Population

Unless otherwise specified, efficacy and health outcomes analyses specific to PsA will be conducted on the Active PsA mITT population, defined as all enrolled participants with an Active PsA indication who receives at least 1 dose of study treatment, even if the participant does not receive the correct treatment, or otherwise does not follow the protocol.

6.4 Safety Population (SAF)

Safety analyses will be conducted on the safety population, defined as all enrolled participants who receive at least 1 dose of study treatment. Participants will be analysed according to the treatment to which they are assigned.

7. General considerations

7.1 Visit and date conventions

- Visit day will be calculated from the reference start date which will be used to present start/stop day of assessments and events. The reference start date is defined as the date of first study treatment administration.

  The following conventions will be used for visit references:

  $$\text{Visit day} = \text{date of visit} - \text{reference start date}$$

  $$\text{Visit week} = \frac{\text{visit day}}{7}, \quad \text{rounding up to next whole number}$$

- If event date<reference start date then event day= (date of event - reference start date), Otherwise if event date is on or after reference start date then event day= (date of event - reference start date) +1

No visit windowing (i.e., remapping of visits based on visit windows) will be performed for this trial. The assigned nominal visit will be used for by-visit summaries. Unscheduled measurements will not be included in by-visit summaries. Data collected at early termination visits will be mapped to the next planned visit number for that patient.

7.2 Baseline

Baseline will be defined as the last non-missing assessment recorded on or prior to the date of first injection for efficacy and health outcomes. In most cases, this will be the measure recorded at Week 0 (Visit 2). 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.

7.3 Stratifications

Unless otherwise specified, for analysis purposes, trial participants may be sub-classified based on dosing regimen into the following stratification levels, where applicable:

- PsO dosing regimen Q2W/Q4W
  - Ixekizumab for [PsO]
  - Ixekizumab for [PsA with PsO]

- PsA dosing regimen Q4W/Q4W
  - Ixekizumab for [PsA without PsO]

7.4 Common calculations

For quantitative measurements, change from baseline will be calculated as the post-baseline visit value of interest minus the baseline value, where Baseline will be defined as the last non-missing assessment recorded on or prior to the date of first injection for efficacy and health outcomes. In most cases, this will be the measure recorded at Week 0 (Visit 2). 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. 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.

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.

7.5 Software

All analyses will be conducted using SAS® Version 9.4 or later.

8. Statistical considerations

8.1 Multicenter studies

The study will be conducted in multiple sites.

8.2 Missing data

8.2.1 Non-Responder Imputation (NRI) method

Analysis of categorical efficacy and health outcomes variables will be assessed using a non-responder imputation (NRI) method. Participants will be considered a non-responder for the NRI analysis if they:

- Do not meet the clinical response criteria (e.g., ACR20, PASI75, PASI90, PASI 100, sPGA [0,1]);
- have missing clinical response data at a timepoint of interest (e.g., Week 12, Week 24);
- discontinue study treatment at any time prior to a timepoint of interest for any reason; or
- have no postbaseline observation

The NRI may be applied at any time point specified for analysis.

8.2.2 Last Observation Carry Forward (LOCF)

The LOCF method will be used for the analysis of continuous endpoints (unless otherwise stated). The last non-missing postbaseline observation on or prior to the missed visit within the same period will be carried forward to subsequent time points for evaluation. Patients without at least 1 postbaseline observation will not be included for evaluation.

8.2.3 Modified Baseline Observation Carry Forward (mBOCF)

Missing data for continuous efficacy and health outcomes variables will be imputed using a mBOCF method. For patients discontinuing investigational product due to an AE, including death, the baseline observation will be carried forward to the corresponding primary endpoint for evaluation. That is the participant, under this method, is defined as reverting back-to-back to baseline regardless of any continuing efficacy benefits, they may still have received after the event.

8.3 As observed data

For all binary and continuous endpoints, a summary based on observed data at each postbaseline visit will be provided. For “as observed” analysis, only data from completers at the visit are relevant and therefore, the analysis does not need to deal with missing data.

8.4 Output presentation

The templates provided in the separate output templates document describe the format and content for presentation of tables, listings, and figures (TLFs).
Summary statistics will be provided for the observed value and change from baseline will be summarized.

Unless otherwise specified, continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, median, and number of observations. If the

raw data recorded in the database has N decimal places, then the summary statistics would have the following decimal places:

- Minimum, maximum: N
- Mean and median: N +1
- Standard Deviation (SD)/ Standard Error of the Mean (SEM): N + 2
- CI: N+1
- Point estimate: N+1

In general, the maximum number of decimal places reported shall be 4 for any summary statistic.

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

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.

In general outputs for Active PsA participants will be displayed as “Active PsA with PsO” to represent those mentioned in the corresponding sections as “with 3% or more BSA of PsO” and “Active PsA without PsO” for those that do not satisfy this criterion.

9. Participant disposition and withdrawal

9.1 Variables and derivations

The number of screened and screen failure participants will be provided in the summary for the participants disposition from the study.

The following parameters will be summarised for the participant's study disposition as per Electronic Case Report Form (eCRF):

- Number of participants enrolled
- Number of participants who are screen failures
- Number of participants completed study
- Number of participants in safety population
- Number of participants discontinuing study from each period
- Primary reason for discontinuation from the study

The following parameters will be summarised for the discontinuations as per eCRF participant's primary reason for discontinuation (reasons mentioned in eCRF "Study Disposition" form) :

- Screen Failure
- Adverse Event
- Protocol Deviation
- Withdrawal by subject
- Physician Decision
- Lack of Efficacy
- Pregnancy
- Study Terminated by IRB / ERB
- Study Terminated by Sponsor
- Site Terminated by Sponsor
- Death
- Lost to Follow Up
- Other

The following parameters will be summarised for the participant's study treatment disposition as per Electronic Case Report Form (eCRF):

- Number of participants completed all weekly doses within Induction and Maintenance dosing period
- Number of participants completing each period (i.e., Screening, Induction, Maintenance, Post-Treatment Follow-Up) where completion is defined as having attended the final expected visit in each period regardless of treatment status.
- Number of participants discontinuing study treatment from each period

- Permanent and Temporary discontinuation from treatment
- Primary reason for discontinuation from the study treatment during each period

9.2 Analysis

9.2.1 Treatment Disposition

Population: SAF

Stratification: Table: Total and by indication (PsO with no Active PsA) and (Active PsA)

Statistics: Participant's treatment disposition and withdrawal will be summarised using frequency and percentages for table.

9.2.2 Study Disposition

Population: ENRL

Stratification: Table: Total and by indication (PsO with no Active PsA) and (Active PsA)

Listing: By participant

Statistics: Participant's disposition and withdrawal will be summarised using frequency and percentages for table. The listing including the details of the extent of the subject participation in the study and reason for discontinuation will be provided.

10. Protocol deviations

10.1 Variables and derivations

Protocol deviations will be identified throughout the study and will be classified using different categories as included in the consolidated protocol deviation tracking document shared by IQVIA. All major protocol deviations will be considered as Important protocol deviations.

10.2 Analysis

Population:
a) PsO with no Active PsA – mITT
b) Active PsA - mITT

Stratification:
Table:
a) PsO with no active PsA
b) Active PsA with 3% or more BSA of PsO, Active PsA without PsO and Total

Listing: By participant

Statistics: The important protocol deviations will be summarized by frequency and percentage in the table. All protocol deviations will be listed by participant including dates, terms, category, and sub-category of protocol deviation.

11. Participant demographics and other baseline characteristics

11.1 Variables and derivations

The following demographic and baseline characteristics will be summarized by treatment group:

- Gender
- Age (in years)
- Age Categories (<65 years, ≥65 and < 75 Years and ≥75 Years)
- Race
- Ethnicity
- Height (in cms) at baseline (week 0)
- Weight (in kgs) at baseline (week 0)
- Body mass index (kg/m^2) at baseline (week 0)
- PASI total score at baseline only for PsO participants
- PASI Categories (<20, 20-30 and >30)
- Percentage of BSA at baseline only for PsO participants
- sPGA total score at baseline only for PsO participants
- Tender joint counts based on 68 joints for PsA participants with ≥3% BSA of PsO and <3% BSA of PsO
- Swollen joint counts based on 66 joints for PsA participants with ≥3% BSA of PsO and <3% BSA of PsO
- Patient global assessment disease activity at baseline – Psoriasis and PsA as applicable
- Patient assessment of pain VAS at baseline: PGA disease activity VAS.
- Moderate to severe psoriasis (defined as PASI ≥12, sPGA ≥3, and BSA ≥10); yes or no
- HAQ-DI administered only to PsA participants
- DAS28-CRP at baseline only for PsA participants
- DAPSA at baseline only for PsA participants

11.2 Analysis

Population:
a) PsO with no Active PsA – mITT
b) Active PsA - mITT

Stratification: Table:
a) PsO with no Active PsA
b) Active PsA with 3% or more BSA of PsO, Active PsA without PsO* and Total
*Without PsO group may include PsO <3% BSA involvement.

Listing: By participant

Statistics: Baseline and demographic variables will be summarized and listed. Overall summaries will include descriptive statistics for continuous measures (mean, standard deviation, minimum, maximum, median, and number of observations) and for categorical measures (frequency counts, and percentages and number of missing values).

12. Exposure and compliance to treatment

12.1 Variables and derivations

The date of first treatment administration will be derived as the first date of dosing from the exposure eCRF page. The date of last treatment administration will be derived as the date of last treatment administration from the exposure eCRF page.

The following parameters will be presented to summarize the exposure to treatment:

- Number of participants received first dose
- Number of participants received all doses within induction dosing period and maintenance period
- Number of participants received doses at each visit (displayed by weeks)
- Duration of exposure (days)= [Date of last injection of the treatment period - Date of first injection for the treatment period] +1
- Total exposure in patient years= (Sum of duration in days of exposures for all patients in treatment group)/ (365.25)
- Total dose (in mg) is calculated by the summation of dose for each active injection taken during the treatment period

Compliance will be assessed by the prescribed number of injections needed versus the number of injections administered to the participants.

Compliance to the treatment in percentage for Ixekizumab for PsO and Ixekizumab for PsA participants will be calculated as follows:

$$Compliance\ to\ the\ treatment\ \ (\%) = 100 \times \frac{Actual\ total\ number\ of\ injection\ administered}{Prescribed\ total\ number\ of\ injections\ to\ be\ administered}$$

For the calculation of the prescribed total number of injections to be administered refer to the Protocol section 6.2 Table RHCZ.6.2. For participants who have discontinued early from study the prescribed total number of injections are only calculated up to the visit of discontinuation. Dosing Summary for the Induction and Maintenance Periods.

A participant will be considered overall compliant for treatment if he/she is missing no more than 20% of the expected doses, does not miss 2 consecutive doses, and does not over-dose (i.e., take more injections at the same time point than specified in the protocol).

12.2 Analysis

Population: SAF

Stratification: Table: Ixekizumab dosing regimen [Q2W/Q4W] and [Q4W/Q4W] and Total

Listing: Exposure will be presented per participant and visit. Compliance will be presented per participant.

Statistics: The exposure and compliance to the treatment will be summarised.

Continuous outcomes will be summarised using descriptive statistics (mean, standard deviation, minimum, maximum, median and number of observations) and categorical outcomes will be summarised as number and percentages. By patient listing will be provided.

Additionally, the descriptive statistics will be presented for the patient days of exposure. For the patient day of exposure category refer Protocol section 6.2 Table RHCZ.6.2. Dosing Summary for the Induction and Maintenance Periods.

Number and percentages of patients falling into each below different exposure ranges will be presented.

Range for exposure (days):

- ≥ 0 to ≤14
- >14 to≤28
- >28 to ≤42
- >42 to≤56
- >56 to ≤70
- >70 to ≤84
- >84 to <112
- >= 112 to ≤140
- > 140

13. Medical and treatment history

13.1 Variables and derivations

Medical history will be coded using the MedDRA central coding dictionary, Version 26.0 or later. Partial date imputation is not done for medical history.

The following parameters will be summarised for the participant's medical history:

- Number of participants with at least one medical history
- Number of participants for each medical history by SOC and PT

Pre-existing is defined as a condition 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.

13.2 Analysis

Population:	a) PsO with no active PsA – mITT b) Active PsA - mITT
Stratification:	Table: a) PsO with no Active PsA b) Active PsA with 3% or more BSA of PsO, Active PsA without PsO* and Total *Without PsO group may include PsO <3% BSA involvement. Listing: By participant
Statistics:	Medical history and Pre-existing conditions will be summarised separately using (frequency and percentages) by SOC and PT and listing will be presented. Missing category will be presented as appropriate. Pre-existing condition will be summarized and listed separately.

14. Evaluation of disease relapse

14.1 Variables and derivations

Patients will be assessed for the presence or absence of relapse at screening as per protocol section 8.2.4. The data will be captured on eCRF page Assessment of relapse for Psoriasis participants.

14.2 Analysis

Population:
a) PsO with no active PsA – mITT
b) Active PsA - mITT

Stratification: Table:
a) PsO with no Active PsA
b) Active PsA with 3% or more BSA of PsO, Active PsA without PsO* and Total

*Without PsO group may include PsO <3% BSA involvement.

Listing: By participant

Statistics: Disease relapse for psoriasis participants and psoriatic arthritis participants at screening will be summarised (frequency and percentages) and listing will be presented.

15. Previous and concomitant medications

15.1 Variables and derivations

All medications will be coded using the WHO-DD, dated September 1, 2022, or later. Preferred ATC coding will be applied to medications.

Previous and concomitant medications will be summarized for participants who enter treatment and will be presented by the World Health Organization (WHO) Anatomic Therapeutic Class (ATC) Level 4 and WHO preferred term (PT).

Previous medications:
'Previous medications' are defined as any medication that starts and ends prior to first dose of the study treatment.

Concomitant Medications:

'Concomitant medications' are defined as any medication that starts before on, or after the first day of study treatment in the corresponding treatment period and before the last visit date in the treatment period, and continues into the treatment period, that is, either no end date (the medication is ongoing) or an end date on or after the first day of study treatment in treatment period.

In section 27 Appendix 3 the algorithm is given for calculation of partial date imputation for prior and concomitant medications, and it will be used for partially missing prior and concomitant medications, start and end date imputation.

15.2 Analysis

Population:	a) PsO with no active PsA – mITT b) Active PsA - mITT
Stratification:	Table: a) PsO with no Active PsA b) Active PsA with 3% or more BSA of PsO, Active PsA without PsO* and Total *Without PsO group may include PsO <3% BSA involvement. Listing: By participant
Statistics:	Previous and concomitant medication will be summarized separately as (frequency, percentages) and listing will be presented. The following parameters will be summarised for the participant's previous medication: • Number of participants with at least one previous medication • Number of participants for each previous medication by ATC class (level 4) and WHO Drug preferred term. The following parameters will be summarised for the participant's concomitant medication: • Number of participants with at least one concomitant medication

- Number of participants for each concomitant medication by ATC class (level 4) and WHO Drug preferred term.

16. Adverse events

16.1 Variables and derivations

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 26.0 or later.

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 treatment period. Both the date/time of the event and the date/time of the injection are considered when determining TEAEs. TEAEs will be assigned to the treatment period in which they first occurred or worsened.

The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. The maximum severity for each LLT during the baseline period will be used as baseline severity (in some cases baseline period is a single time point). Events with a missing severity during the treatment period will be considered treatment emergent. The treatment period will be included as post-baseline for the analysis. If an event is pre-existing during the baseline period but it has missing severity, and the event persists during the treatment period, then it will be considered as treatment-emergent, regardless of the post-baseline level of severity. Adverse events with a particular LLT will be classified as treatment-emergent if they first start on or after the first dose date in the treatment period (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.

A follow-up emergent adverse event (FEAE) is defined as an event that first occurred or worsened in severity after the date of Week 24 (Visit 6) or the ETV.

For events that are gender specific, the denominator and computation of the percentage will include only participants from the given gender.

In section 26 Appendix 2 the algorithm is given for calculation of partial date imputation for adverse events (AEs), and it will be used for partially missing adverse event start and end date imputation.

Safety data collected after study treatment discontinuation will be summarized separately.

The following parameters will be summarised for the overview of participants adverse events:

- Any AEs
- Any TEAEs
  - Drug-Related TEAEs
- TEAEs by maximum severity
- Action taken with study treatment (Dose not changed, Drug interrupted, Drug withdrawn, Not applicable and Unknown)

- Outcome of AEs (Recovered or resolved, Recovering or resolving, Not recovered or not resolved, Recovered or Resolved with sequelae, Fatal and Unknown)
- Most common TEAEs, defined as >=1% in either group.
- Latent and Active Tuberculosis
- Serious AEs
- Treatment-emergent AESIs (Cytopenias, Infections, Opportunistic Infections, Injection-site reactions (ISRs), Allergic reactions/hypersensitivities, Cerebrocardiovascular events, MACE, Malignancies, Depression, IBD, ILD)
- AEs leading to discontinuation from the study treatment
- AEs leading to death
- Any Follow-up emergent adverse event (FEAE)

16.2 Analysis

An overview summary will be presented for adverse events within treatment period and within study as (n=number of participants, m=number of events and %=percentage of participants) by Ixekizumab dosing regimen [Q2W/Q4W and Q4W/Q4W] and total using SAF population.

By-participant listings of Pre-treatment AEs, TEAEs, Serious AEs and AEs resulting in death and AEs leading to study/treatment discontinuation will be presented, using SAF population.

Note: If there are uncoded adverse events, then the uncoded category will be added in the AEs by SOC/PT summary tables.

When the SOC is presented, events will be ordered by decreasing frequency in the overall group and then in the Q2W/Q4W group, and then in Q4W/Q4W group within SOC.

For incidence counts, each patient will be counted only once within each PT and within each SOC. Percentages will be based on the number of patients in a particular treatment group.

For events that are gender specific, the denominator and computation of the percentage will include only patients from the given gender.

Additionally, incidence rate (IR) per 100 patient years will be added in the adverse events table. Incidence rate per 100 patient years is defined as follows:

Incidence Rate (IR) per 100 patient years= (Total number of patients with incident event)/(Total time at risk)*100. The 95% CI is calculated using below method:

The sequence of first occurrences of an event will be assumed to follow approximately a Poisson distribution with constant intensity ‘λ’, where ‘λ’ is incidence rate. For analysis, the number of subjects with events (R) will be counted. Then, the Chi-square

distribution percentile values will be identified with 0.025 percentile and 2R degree of freedom and 0.975 percentile and 2R+2 degree of freedom. 95% CI will be estimated with the following SAS syntax:

Upper limit=(cinv(0.975, 2R+2)/2)/t and lower limit= (cinv(0.025,2R)/2)/t, where t=cumulative patient time of a risk period per 100 patient year, R=Number of patients with event, cinv is the build in function for chi-square percentile calculation in SAS.

16.2.1 Incidence of AEs, TEAEs, Drug-related TEAE, Serious adverse events, AEs that lead to treatment discontinuation and AEs leading to death

Population:	SAF
Stratification:	Table: By Ixekizumab dosing regimen [Q2W/Q4W and Q4W/Q4W] and Total and by primary SOC and PT in decreasing order
Statistics:	AEs, TEAEs, Drug-related TEAE, Serious adverse events (SAEs), AEs that lead to treatment discontinuation and AEs leading to death will be summarized as (n=number of participants, m=number of events and %=percentage of participants) for table.

16.2.2 Treatment Emergent Adverse Events (TEAEs) by maximum severity

Population:	SAF
Stratification:	Table: By Ixekizumab dosing regimen [Q2W/Q4W and Q4W/Q4W] and Total, by maximum severity and by primary SOC and PT in decreasing order
Statistics:	TEAEs by severity will be summarized as (n=number of participants, m=number of events and %=percentage of participants) for table.

16.2.3 Special safety topics including adverse events of special interest

Safety information on special topics including AESI will be presented by dosing regimen using frequency and percentages. The definitions/derivations and analyses methods (including analyses, summaries, and by-patient listings) of special safety topics including AESIs will be documented in the program safety analysis plan (PSAP) which will be provided by Lilly.

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

16.2.4 Follow-up Emergent Adverse Event (FEAE)

Population: SAF

Stratification: Table: By Ixekizumab dosing regimen [Q2W/Q4W and Q4W/Q4W] and Total, by primary SOC and PT in decreasing order

Statistics: Follow-up emergent adverse event (FEAE) will be summarized as (n=number of participants, m=number of events and %=percentage of participants) for table

17. Safety laboratory tests

17.1 Variables and derivations

The laboratory tests as per Protocol Section 10.2 Appendix 2 will be analysed.

Quantitative laboratory measurements reported as "< X", i.e., below limit of quantitation, or "> X", i.e., above the upper limit of quantification, will be converted to X for quantitative summaries, but will be presented as recorded, i.e., as "< X" or "> X" in the data listings.

17.2 Analysis

Population: SAF

Stratification: Table: By Ixekizumab dosing regimen [Q2W/Q4W and Q4W/Q4W] and Total

Listing: By participant, visit and each laboratory test parameter

Statistics: Summaries of all the laboratory tests will include descriptive statistics of the following:

- Actual and change from baseline (mean, standard deviation, minimum, maximum, median, and number of observations) for quantitative measurements
- Frequency counts, and percentages and number of missing values for qualitative measurements

All the laboratory tests will be listed separately and listing of abnormal laboratory test will be presented.

Box plot will be presented for observed lab values at each visit starting at baseline and change from baseline to each visit. The outlier datapoints will be displayed in the box plot.

Laboratory assessments will be presented as incidence of treatment-emergent abnormal, high, or low laboratory values (see below).

Treatment-emergent abnormal value = a change from normal at all baseline visits to abnormal at any time post baseline. For continuous laboratory tests:

- Treatment-emergent high value = a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time postbaseline; and
- Treatment-emergent low value = a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time postbaseline.

Note: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP), neutrophils, leukocytes, platelets, and lymphocytes will not be included in this treatment-emergent abnormal, high, or low laboratory results analysis. A separate analysis to address the risk of liver injury is described in Section 16.2.3.

Shift tables will be produced showing the number and percentage of patients with a minimum post-baseline result for neutrophils, lymphocyte, platelets, and leukocytes

1. The following LLNs will be defined for the analyses:
    - Total Leukocyte count: LLN=4300 cells/c.mm
    - Absolute Neutrophils: LLN=2000 cells/c.mm
    - Absolute Lymphocytes: LLN=1000 cells/c.mm
    - Neutrophils: LLN=40%
    - Lymphocytes: LLN=20%
    - Platelets: LLN=140 × 10^3/µL
2. Shift tables will be produced using the following categories:
    - Total Leukocyte count: <4300 cells/c.mm, ≥4300 to <10300 cells/c.mm, ≥10300 cells/c.mm
    - Absolute Neutrophils: <2000 cells/c.mm, ≥2000 to <7000 cells/c.mm, ≥7000 cells/c.mm
    - Absolute Lymphocytes: <1000 cells/c.mm, ≥1000 to <3000 cells/c.mm, ≥3000 cells/c.mm
    - Neutrophils: <40%, ≥40% to <80%, ≥80%
    - Lymphocytes: < 20%, ≥20% to <40%, ≥40%
    - Platelets: < 140 × 103/µL, ≥140 × 103/µL to <440 × 103/µL, ≥ 440 × 103/µL

Change from baseline to last observation for laboratory tests will be summarized for patients who have both baseline and at least one post-baseline result for each treatment period. Baseline will be the last non-missing observation in the baseline period as defined in Section 7.2. The last non-missing observation in each treatment period will be analysed. Original-scale data will be analysed. Unscheduled visits and repeat measurements will be excluded. Analyses will be provided in both SI and conventional units (when different).

Change from the minimum value during the baseline period to the minimum value during the treatment period for laboratory tests will be summarized for subjects who have both baseline and at least one post-baseline result. Baseline will be the minimum of non-missing observations in the baseline period. The minimum value in the treatment period will be analysed. Similarly, change from the maximum value during the baseline period to the maximum value during the treatment period for laboratory tests will be summarized for subjects who have both baseline and at least one post-baseline result. Baseline will be the maximum of non-missing observations in the baseline period. The maximum value in the treatment period will be analysed. Original-scale data will be analysed. Planned and unplanned measurements will be included. Analyses will be provided in both SI and conventional units (when different).

18. Vital signs

18.1 Variables and derivations

The following vital signs will be reported for this study:

- Weight (in Kgs)
- Temperature (C)
- Pulse (bpm)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)

18.2 Analysis

Population: SAF

Stratification: Table: By Ixekizumab dosing regimen Q2W/Q4W and Q4W/Q4W and Total

Listing: By participant, visit and each vital sign parameter

Statistics: The vital signs except temperature will be summarised as actual and change from baseline (mean, standard deviation, minimum, maximum, median, and number of observations) for table. The listing will be presented for all vital sign parameters.

The frequency and percentages of patients with treatment-emergent high or low vital signs and physical characteristics results at any time will be summarized.

For treatment-emergent high and low:

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

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

Refer the below Table RHCZ 18.2.1 for the categorical criteria for abnormal blood pressure and pulse measurement and categorical criteria for weight and changes for adults post baseline:

Table RHCZ 18.2.1: Abnormal vital signs ranges

Parameter	Low	High
Systolic BP (mm Hg) [1] (supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) [1] (supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) [1] (supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Weight (kg)	(Loss) decrease from baseline ≥7%	(Gain) increase from baseline ≥7%

Abbreviations: BP = blood pressure; bpm = beats per minute.

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

The observed values at each visit (starting at baseline) and change from baseline to each scheduled visit, respectively, will be displayed in box plots for patients who have both baseline and at least 1 post-baseline result.

19. Primary endpoint analysis

19.1 AEs, including SAEs, TEAEs, and AESIs during the treatment period (Week 0 to Week 24)

19.1.1 Variables and derivations

Variables:

- TEAEs,
- TEAE by maximum severity,
- Death,
- SAEs,
- TEAE related to study treatment,
- AEs leading to treatment discontinuation and
- TEAEs of special interest (hepatic, cytopenias, infections, opportunistic infections, allergic reactions/hypersensitivities, injection-site reactions, cerebrocardiovascular events, major adverse cerebrocardiovascular events [MACE], malignancies, depression, Inflammatory Bowel Disease [IBD], interstitial lung disease [ILD])

Derivations:

- Refer Section 16.1 for details on TEAEs
- All SAEs, TEAE related to study treatment and incidence of deaths will be captured in the “Adverse event” eCRF form
- AEs leading to treatment discontinuation will be captured on in the “Treatment discontinuation” eCRF form
- For AESI’s refer to the Section 16.2.3

19.1.2 Primary analysis

Population:	SAF
Stratification:	Table: By Ixekizumab dosing regimen [Q2W/Q4W and Q4W/Q4W] and Total
Statistics:	AEs occurring within the duration of the study (24 weeks) after being started on Ixekizumab, will be summarized as (n=number of participants, m=number of events and %=percentage of participants). For events that are gender-specific (as defined by the Medical Dictionary for Regulatory Activities [MedDRA]), the denominator and computation of percentage will include only participants from the given gender.

20. Secondary efficacy assessments

20.1 Endpoint specific to Psoriasis (PsO) with no Active PsA and Psoriatic Arthritis (PsA) participants with 3% or more BSA of PsO

Endpoints:

- Proportion of participants with PASI 75 (defined as 75% improvement from baseline in PASI) at Week 12
- Proportion of participants with an sPGA psoriasis score of 0 or 1 (0, 1) at Week 12

20.1.1 Variables and derivations

20.1.1.1 PASI 75 (defined as 75% improvement from baseline in PASI) at Week 12

1. **Measure:** PASI Score
2. **Description:** The PASI will be used to assess PsO and PsA. The PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation (scaling), erythema, and plaque induration/ infiltration (thickness) in each region, yielding an overall score from 0 for no psoriasis up to 72 for the most severe disease. Refer to the protocol section 8.1.1 for more details.
3. **Variable:** PASI 75: A clinically meaningful response; at least a 75% improvement in PASI score from baseline.
4. **Derivation:** The composite PASI score is calculated by multiplying the sum of the individual-severity scores (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) for each area by the weighted area-of-involvement score for that respective area, and then summing the 4 resulting quantities as follows:

   PASI = 0.1(Rh + Th + Sh)Ah + 0.2(Ru + Tu + Su)Au + 0.3(Rt + Tt + St)At + 0.4(Rl + Tl + Sl)Al

   Where,

   Rh, Ru, Rt, Rl = redness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively.

   Th, Tu, Tt, Tl = thickness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively.

   Sh, Su, St, Sl = scaliness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively.

   Ah, Au, At, Al = 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 will be declared as missing.

20.1.1.2 sPGA psoriasis score of 0 or 1 (0, 1) at Week 12

1. **Measure:** sPGA psoriasis score
2. **Description:** The sPGA is the physician's determination of the participant's psoriatic lesions, overall, at a given time point. Overall, lesions are categorized by descriptions for induration, erythema, and scaling. For the analysis of responses, the participant's PsO/PsA is assessed as clear (0), minimal (1), mild (2), moderate (3), severe (4) or very severe (5). However, for this endpoint specific our interest is in the sPGA psoriasis score of 0 or 1 (0, 1) at Week 12.
3. **Variable:** sPGA psoriasis score of 0 or 1 (0, 1) at week 12.
4. **Derivation:** if the question in eCRF "What is the Static Physician Global Assessment Score" is answered as 0 or 1 at corresponding week 12.

20.1.2 Analyses

Population:
a) PsO with no Active PsA – mITT
b) Active PsA - mITT

Stratification: Table:
a) PsO with no Active PsA
b) Active PsA with 3% or more BSA of PsO

Statistics: The proportion of participants achieving a PASI 75 response at Week 12 and participants achieving sPGA response of 0 or 1 at Week 12 will be summarized and the associated 95% CI will be provided using normal approximation separately. Missing data will be imputed using the NRI method as defined in Section 8.2.

20.2 Endpoint specific to Psoriatic Arthritis (PsA)

Endpoint: Proportion of PsA participants achieving ACR20 at Week 24

20.2.1 Variables and derivations

1. **Measure:** ACR20
2. **Description:**

   ACR20, ACR50, and ACR70 responses are efficacy measures for which a participants must satisfy the following:

   1) ≥20%, ≥50% and ≥70% improvement from baseline in both tender joint count (TJC) and swollen joint count (SJC)

   and

   2) ≥20%, ≥50% and ≥70% improvement from baseline in at least 3 of the following 5 ACR Core Set criteria:

      a. Patient's Assessment of Pain Visual Analog Scale (VAS)

      b. Patient Global Assessment of Disease Activity VAS

      c. Physician Global Assessment of Disease Activity VAS

      d. Patient's assessment of physical function as measured by the Health Assessment Questionnaire – Disability Index (HAQ-DI)

      e. Acute-phase reactant as measured by high-sensitivity C-reactive protein (hs-CRP) assay

3. **Variable:** ACR20 at week 24
4. **Derivation:** Refer to the Appendix 4 for details of ACR20 derivation.
5. Additionally added ACR 50 score with respect to BMI categories (BMI is <25 (kg/m^2), BMI is (25 to 30) (kg/m^2), BMI > 30 (kg/m^2) with week 12 and 24.

20.2.2 Analyses

Population:	Active PsA –mITT
Stratification:	Table: a) Active PsA with 3% or more BSA of PsO b) Active PsA without PsO* *Without PsO group may include PsO <3% BSA involvement c) Total
Statistics:	The proportion of participants achieving a response of ACR20 at Week 24 (Visit 15) will be summarized and 95% CI will be provided using normal approximation. Missing data will be imputed using the NRI method as defined in Section 8.2.

21. Exploratory endpoint

21.1 Safety endpoint

21.1.1 Safety parameters including, but not limited to, infections, injection-site reactions, and laboratory evaluations (including chemistry and haematology)

21.1.1.1 Variables and derivations:

Variables:

- Infections
- Injection site reactions
- Laboratory evaluations (Chemistry and Haematology)

Derivations:

- For Infections refer to eCRF page “Infection”
- Injection site reactions refer to eCRF page “Injection Site Reaction”

21.1.1.2 Analyses

Population:	SAF
Stratification:	Table: By Ixekizumab dosing regimen [Q2W/Q4W] and [Q4W/Q4W] and Total Listing: By participant
Statistics:	Refer to Section 17 for the chemistry and haematology analysis. For the infections and injection site reactions separate listings and summary as (number of participants and percentages) will be presented. Continuous chemistry and hematology measures will be summarized as change from baseline to Week 12 as per analysis Section 17.2.

21.1.2 Permanent and temporary discontinuations of the study intervention

21.1.2.1 Variables and derivations:

The analyses will be summarised descriptively and a reference to patient characteristics Section 9.

21.1.2.2 Analyses

Population:	SAF
Stratification:	Table: By Ixekizumab dosing regimen Q2W/Q4W and Q4W/Q4W and Total Listing: By participant
Statistics:	The summary (frequency and percentage) and listing will be presented for the permanent discontinuations of the study intervention.

21.2 Efficacy endpoint

21.2.1 Other efficacy endpoint (PsO Endpoints)

Endpoint: Time course of response to treatment over week 24 as measured by

- PASI 75, 90, 100
- sPGA (0, 1), sPGA (0)
- Body surface area (BSA) change from baseline
- PASI change from baseline
- PASI 90 and 100 score by BMI categories

21.2.1.1 Variables and derivations

- **PASI 75,90 and 100:**

  1. **Measure**: PASI score
  2. **Description**: Refer Section 20.1.1.1
  3. **Variable**: PASI 75, 90, 100
  4. **Derivation**: Refer Section 20.1.1.1.

  If PASI score improved 75%, 90% and 100% from baseline to each post baseline visit then it will be considered as PASI 75, 90 and 100 respectively improvement.

- **sPGA (0, 1)], [sPGA (0)]:**

  1. **Measure**: sPGA
  2. **Description**: Refer Section 20.2
  3. **Variable**: sPGA (0, 1)], [sPGA (0)]
  4. **Derivation**: sPGA captured on the eCRF page “Static Physician Global Assessment Scale”. Refer to the Section 20.2.

- **Body surface area (BSA) change from baseline**

  Change from baseline in Body surface area (BSA**):** BSA captured on the eCRF page “Body Surface Area”.

  Change from Baseline in BSA= Post baseline BSA Value - Baseline BSA value

- **PASI total score change from baseline**

  PASI score calculated using derivation mentioned in Section 20.1.1.1.

  Change from baseline in PASI total score=Post baseline PASI total score value -Baseline PASI total score value

- **PASI 75, 90,100 and BSA**
  PASI 75, 90 and 100 score with respect to BMI categories (BMI is <25 (kg/m^2), BMI is (25 to 30) (kg/m^2), BMI > 30 (kg/m^2)

- **PASI 75, 90,100 and Age**

PASI 75, 90 and 100 score with respect to age categories (<65 years, ≥65 and <75 years ≥75 years)

- **PASI 75, 90,100 and Baseline PASI score**
  PASI 75, 90 and 100 score with respect to baseline PASI score categories (<20, 20-30, >30)

21.2.1.2 Analyses

Population:
a) PsO with no active PsA - mITT
b) Active PsA - mITT

Stratification: Table:
a) PsO with no active PsA
b) Active PsA with 3% or more BSA of PsO Active PsA without PsO* and Total
*Without PsO group may include PsO <3% BSA involvement

Statistics: The proportion of participants achieving a [PASI 75, 90, 100], [sPGA (0,1)], [sPGA (0)] response at each visit will be summarized and the associated 95% CI will be provided using normal approximation.

Actual and change from baseline through Week 24 of BSA and PASI total score will be summarised.

Time course of PASI 75, PASI 90, PASI 100, sPGA (0, 1) and sPGA (0) response rate to treatment over 24 weeks will be plotted and different lines for each measure will be presented in the same plot.

The proportion of participants achieving a PASI 75, PASI 90 and PASI 100 by BMI, Age and PASI baseline score categories will be summarized.

21.2.2 Other efficacy endpoint (PsA Endpoints)

Endpoint: Time course of response to treatment over week 24 as measured by

- ACR 20, 50, 70
- ACR components change from baseline
  I. Tender joint count (68 counts)
  II. Swollen joint count (66 counts)
  III. Patient's global assessment of arthritis pain
  IV. Patient's global assessment of disease activity
  V. Physician's global assessment of disease activity
  VI. HAQ-DI
  VII. CRP
- Disease Activity Score-28 (DAS-28) C-reactive protein (CRP) change from baseline
- PASI [75, 90, 100], PASI change from baseline
- sPGA (0, 1) and sPGA (0)
- BSA change from baseline
- DAPSA score

21.2.2.1 Variables and derivations

- **ACR 20, 50, 70:**
  1. **Measure:** ACR 20,50,70
  2. **Description:** Refer Section 20.2.1
  3. **Variable:** ACR 20,50,70 over week 24
  4. **Derivation:** Refer to the Appendix 4 for details of ACR20 derivation

- **Change from baseline in ACR components:**
  1. **Measure:** ACR components
  2. **Description:** Refer section 20.2.1
  3. **Variable:** Change from baseline in ACR components
  4. **Derivation:** Change from baseline in ACR components=Post baseline ACR value - Baseline ACR value

- **Change from baseline in Disease Activity Score28-C-reactive protein (DAS28-CRP):**
  1. **Measure:** DAS28-CRP
  2. **Description:** The DAS28-CRP is a measure of disease activity in 28 joints that consists of a composite numerical score utilizing the following variables: Tender joint count (TJC), swollen joint count (SJC), high-

sensitivity C-reactive protein (hs-CRP) (measured in mg/L), and Patient's General Assessment recorded by participants on a 0 to 100 mm visual analogue scale (VAS). For DAS28-CRP, the 28 joints to be examined and assessed as tender or not tender for TJC and as swollen or not swollen for SJC are a subset of those assessed for the TJC and SJC, and include 14 joints on each side of the participant's body: the 2 shoulders, the 2 elbows, the 2 wrists, the 10 metacarpophalangeal joints, the 2 interphalangeal joints of the thumb, the 8 proximal interphalangeal joints, and the 2 knees. The following equation will be used to calculate the DAS28:

$$DAS28\text{-}CRP = 0.56\left(\sqrt{TJC\ 28}\right) + 0.28\left(\sqrt{SJC\ 28}\right) + 0.36(\ln(CRP + 1)) + 0.014(VAS) + 0.96$$

3. **Variable:** Change from baseline in DAS28-CRP
4. **Derivation:** Change from baseline in DAS28-CRP = Post baseline DAS28-CRP value – Baseline DAS28-CRP value

- **Change from baseline in PASI [75, 90, 100]:**

  PASI score calculated using derivation mentioned in Section 20.1.1.1.

  Change from baseline in PASI total score = Post baseline PASI total score value – Baseline PASI total score value.

- **sPGA (0, 1) and sPGA (0)**: The sPGA is the physician's determination of the participant's psoriatic lesions, overall, at a given time point. sPGA captured on the eCRF page "Static Physician Global Assessment Scale". Refer to the Section 20.2.

  1. **Measure**: sPGA
  2. **Description**: Refer Section 20.2
  3. **Variable**: sPGA (0, 1)], [sPGA (0)]
  4. **Derivation**: sPGA captured on the eCRF page "Static Physician Global Assessment Scale". Refer to the Section 20.2.

- **Change from baseline in Body surface area (BSA):** BSA captured on the eCRF page "Body Surface Area".

  Change from baseline in BSA = Post baseline BSA value – Baseline BSA value

- **DAPSA outcome:**
  DAPSA=Tender Joints Count (out of 68) + Swollen Joints Count (out of 66) + CRP + Patient's assessment of disease activity + Patient's assessment of Pain
  DAPSA remission (defined as ≤ 4), DAPSA low disease activity (defined as ≤ 14) and mean change from baseline in DAPSA score by visit will be derived. The Patient's assessment of disease activity and Patient's assessment of Pain is calculated on a 10-point scale for the DAPSA score.

21.2.2.2 Analyses

Population: a) For ACR, ACR Change, DAS28, DAPSA Population: Active PsA - mITT

b) For PASI, SPGA, SPGA change, BSA
Population: Active PsA - with 3% or more BSA of PsO at baseline

Stratification: Table:

a) Active PsA with 3% or more BSA of PsO, Active PsA without PsO* and Total

*Without PsO group may include PsO <3% BSA involvement

b) Active PsA with 3% or more BSA of PsO

Statistics: The proportion of participants achieving a [ACR 20, 50, 70], [Disease Activity Score-28 (DAS-28)], [PASI 75, 90, 100], [sPGA (0, 1) and sPGA (0)] response at each visit from treatment administration will be summarized and the associated 95% CI will be provided using normal approximation.

Actual and change from baseline over time course of week 24 from baseline of ACR components, C-reactive protein (CRP), PASI and BSA will be summarised.

Time course of ACR 20, 50, 70, [PASI 75, PASI 90, PASI 100], [sPGA (0,1)], [sPGA (0)] response rate to treatment over week 24 will be plotted and different lines for each measure will be presented in the same plot.

The mean baseline and mean change from baseline at week 12 and week 24 with standard error will be presented for DAPSA.

The percentage of participants meeting DAPSA remission (defined as DAPSA <=4) and DAPSA low disease activity or remission (defined as DAPSA <=14) will also be presented.

Additionally, the analysis will be performed using LOCF and mBOCF method for missing continuous data and NRI for categorical missing data.

22. Other assessments

Physical examination and electrocardiogram data will be listed for each participant for the SAF population. The listings will include all the assessments and their findings (normal/abnormal) and the corresponding clinically significant status, if abnormal.

23. Revision history

Version	Date	Change
1.0	16-Jun-2023	Initial version
2.0	16-Aug-2024	Alignment of treatment and study disposition in section 9.2. Added demographics and other baseline characteristics parameters age categories and PASI baseline categories parameters in section 11.1 Incidence Rates and 95% Cis will be calculated for AEs per section 16. Added PASI 75, 90, and 100 summaries by age and baseline PASI score categories
3.0	15-Nov-2024	Section 8.4 : Added a sentence about the labelling of Active PsA and PsO with no Active PsA participants in outputs. Section 9.1 : Removed Completed from list of possible discontinued reasons. Added clarity on “Completed” status in each period. Section 10 : Referring to Important PDs and changed that the table will display important and the listing all PDs. Section 11.1: Amended the age category that was displayed as >=65 to >=65 and <75. Section 12.1 : Added clarity on “prescribed injections to be administered”. Section 16.1 : Added missing categories that are present in the Overall AE output. Section 18.2 : Removed the word “treatment-emergent” when discussing the table as the table only refers to the abnormal post baseline results. Section 21.2.2.1 : Added clarification that HAQ and PGAPSA is on a 10-point scale for DAPSA score calculation (not the 100 point it is captured as). Section 21.2.2.2 : Added DAPSA details. General: Active PsA without PsO has a footnote to explain what “without PsO” includes in relevant sections.

24. References

Not applicable

25. Appendix 1: Programming conventions for Tables, Data Listings and Figures (TLFs)

Programs will be developed and maintained and output will be verified in accordance with current risk-based quality control procedures. Tables, figures, and listings will be produced with validated software. The production environment for statistical analysis consists of statistical analysis software; for example, the SAS System version 9.4 or later.

The standards provided in this section are for programming reference, based on the actual data modifications can be done later.

All percentages (%) for a specific summary are calculated using the total number of participants included in the relevant analysis population as the denominator, unless otherwise specified.

Data listings will be based on all participants, unless otherwise specified.

In general, if we have no response or record for respective parameter in data (i.e. n=0) then while presenting statistics in table only n will be presented as “0” and other statistics will be left blank. In case we have only one response or record for respective parameter (i.e., n=1) in data then statistic SD in table will be left blank.

By default, for continuous measures, summary statistics will include, unless otherwise specified:

- n
- Mean
- Median
- Maximum
- Minimum
- SD
- Frequency of Missing Values.

For categorical measures, summary statistics will include, unless otherwise specified:

- Frequency of non-missing values
- Percentage, and
- Frequency of Missing Values.

25.1 Paper size, orientation and margins

The margin, page size and line size specifications as stipulated in Table 23.1 will be used for the presentation of all TLFs.

Table 25.1: Output margin, page size and line size specifications

	Landscape	Portrait
Margins (Inches):		
Top	1.25	1
Bottom	1	1
Left	1	1.25
Right	1	1
Header (Inches)	0.5	0.5
Footer (Inches)	0.5	0.5
SAS® specifications:		
PAGESIZE	46	67
LINE SIZE	134	93
Body Font Size	10	10
Heading font Size	12	12

25.2 Fonts

The font type “Times New Roman” must be used for tables, listings, and figures, with a minimum font size of 9, and it should be consistent for the whole report. The font colour must be black for tables, listings, and figures.

Colours are allowed for figures if the data series can be distinguished clearly if printed on black and white paper.

25.3 Header information

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page).
- The header should be placed at the top of the page (same place on each page).
- The Sponsor name should appear in row 1, left-aligned in header.
- The word “Interim Analysis/Final Analysis/Protocol-Specified Analysis” would be appeared in row 1, centered aligned in header.
- The protocol number should appear in row 2, left-aligned in header.
- The word “Cut-off date: DDMMMYYYY” would appear in row 2, centre aligned in header
- The word “CONFIDENTIAL” should appear in row 1, centered aligned at footer in compiled file only.
- The TLF identification number should appear in row 3, centered in header.
- The TLF title should start in row 4, centered in header.

- The TLF population should appear in row 5, centered in header. The population should be spelled out in full, e.g., Enrolled Analysis Set.
- Row 6 in header should be a continuous row of underscores ('_') (the number of underscores should equal the line size).
- Row 7 in header should be a blank line.
- Sentence case should be used for titles in header.
- Titles should not contain quotation marks or footnote references.
- The column headings should be underlined with a row of underscores ('_').
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered.
- Column headings containing numbers should be centered.
- Column headings should be in mixed case.
- In general, the analysis population count should appear in the column header in the form "(N=XX)".
- The page identification in the format Page X of Y (where Y is the total number of pages for the TLF) should appear in row 2, right aligned at Footer for compiled TLFs if required.

25.4 Table, Listing and Figure (TLF) conventions

25.4.1 General

- The first row in the body of the table or data listing should be blank.
- The left-hand column should start in Column 1.
- Rounding should be done with the SAS® function ROUND if applicable.
- Numerical values in tables should be rounded and not truncated as per Section 25.4.2 for respective statistics.
- Numerical values should be centre aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized.
- The study drug should appear first in tables with treatment group as columns.
- The width of the TLF should match the line size.

25.4.2 Univariate statistics

- Statistics should be presented in the same order across tables (i.e., n, missing values, mean, SD, SE minimum, median and maximum) as appropriate.
- If the original data has N decimal places, then the summary statistics would have the following decimal places:
  - Minimum, maximum: N.
  - Mean and median: N +1.

- SD: N + 2.
- CI: N+1
- Point estimate: N+1.

25.4.3 Frequencies and percentages [m, n (%)]

- Count values should be reported with one space between the left side of the percentage and the right side of the number of events. Percentage should be presented inside brackets or parentheses, and it should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percentage is less than 100.0. An example is given below:
  - 156, 77 (100.0)
  - 56, 50 (64.9)
  - 0 (0.0)
- Percentages of 0 or 100 may be reported to 0 decimal places. Confidence intervals (CIs)
- CIs should be presented with one additional decimal place as that of the raw data.
- CIs will be presented as [lower bound, upper bound].

25.4.4 Ratios/Estimate

- Ratios/estimates should be reported with one additional decimal place as that of the raw data.

25.4.5 Spacing

- There should be a minimum of 1 blank space between columns (preferably 2).

25.4.6 Missing values

- A “0” should be used to indicate a zero frequency.
- A blank should be used to indicate missing data in data listings.

25.5 Table, listing and figure output conventions

The compiled file will be presented in PDF format, with TOC for listings and tables/figures separately.

The tables, listings and figures will be provided in RTF and PDF files using the SAS® Output Delivery System (ODS).

All percentages (%) for a specific summary should be calculated using the total number of participants included in the relevant analysis population as the denominator, unless otherwise specified.

Data listings will be based on all participants treated, unless otherwise specified.

25.6 Dates and times

In footer of the TLFs, date and time will be presented in format ddmmyyyy and hh: mm. Depending on data available, dates and times will take the form ddmmyyyy and hh:mm.

25.7 Spelling format

The spelling format to be used is English US.

25.8 Presentation of treatment

Unless otherwise specified,

- PsO indication
  - Ixekizumab for [PsO] - Q2W/Q4W
  - Ixekizumab for [PsA with moderate to severe PsO]- Q2W/Q4W
- PsA indication
  - Ixekizumab for [PsA without moderate to severe PsO] - Q4W/Q4W

25.9 Presentation of visits

Screening Period 1

- Visit 1 Screening

Induction Dosing Period 2

- Visit 2 (Week 0)
- Visit 3 (Week 4)
- Visit 4 (Week 8)
- Visit 5 (Week 12)

Maintenance Period 3

- Visit 6 (Week 24)

Post Treatment Follow-Up (Period 4)

- Visit 801 (Last Visit +Week 4)
- Visit 802 (Last Visit +Week 12)

26. Appendix 2: Partial date conventions for adverse events.

The whole missing date will not be imputed for this study and only partial date imputation will be performed. Conventions pertaining to partial dates are presented.

Table 26.1. Algorithm for partial date imputation for Adverse events (AE)

Adverse Event	Missing	Imputation
Start Date	Day	If AE start month = First treatment start month and AE start year = First treatment start year, then AE start day= First treatment start day Otherwise AE start day=01
	Day and Month	If AE start year = First treatment start year, then AE start day and month = First treatment start day and month Otherwise AE start day = 01 and AE start month=Jan
	Day, Month and Year	No imputation will be performed
End Date	Day	If AE end month = Date of study completion/discontinuation month and AE end year = Date of completion/discontinuation year, then AE end day = date of completion/discontinuation day Otherwise AE end day = Last day of respective month, used if this does not result in a date after the participant's trial exit date (e.g., death) in which case the trial exit date will be used
	Day and Month	If AE end year = Date of study completion/discontinuation year, then AE end day and month = Date of study completion/discontinuation day and month Otherwise AE end day = Last day of respective month and AE end month = Last month of the year, used if this does not result in a date after the participant's trial exit date (e.g., death) in which case the trial exit date will be used
	Day, Month and Year	No imputation will be performed

27. Appendix 3: Partial date conventions and concomitant medication guidelines

The whole missing date will not be imputed for this study; only partial date imputation will be performed. Conventions pertaining to partial dates are presented.

Table 27.1: Algorithm for partial date imputation for Concomitant Mediation (CM)

Concomitant Medication	Missing	Imputation
Start Date	Day	If CM start Month = Treatment start month and CM start Year = Treatment start Year, then CM start Day= minimum of (Treatment Start Day or CM end Day). Otherwise, CM start day = "01".
	Day and Month	If CM start Year = Treatment start Year, then CM start Day and Month = minimum of (Treatment Start Day and Month or CM end Day and Month). Otherwise, CM start Day and Month = "01 Jan".
	Day, Month and Year	No Imputation will be performed.
End Date	Day	If CM End Month = Study conclusion Month and CM End Year= Study conclusion Year, Then CM End Day= Study Conclusion Day. Otherwise, CM End Day = last day of respective month.
	Day and Month	If CM End Year = Study Conclusion Year, then CM End Day and Month = Study Conclusion Day and Month. Otherwise, CM End Day and Month = "31 Dec".
	Day, Month and Year	No Imputation will be performed.

28. Appendix 4: Algorithm for determining ACR responses

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

ACRx response is defined as ≥x% improvement from baseline in tender joint count (68 counts) and ≥x% improvement in swollen joint count (66 counts), and ≥x% improvement in at least three of the following five items:

- Patient's global assessment of arthritis pain
- Patient's global assessment of disease activity
- Physician's global assessment of disease activity
- HAQ-DI
- CRP

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

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

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

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

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

- **Step1:** If the patient discontinued from the study prior to reaching the visit, then STOP – assign ACRx response as blank (i.e., missing). Otherwise, calculate the % improvement at the visit for all seven parameters as described above.
- **Step2:**
  - If TJC68 AND SJC66 are BOTH ≥x%, then proceed to step3.
  - If both are non-missing but one or both is <x%, then STOP – assign the patient as a non-responder for ACRx.
  - If either or both are missing, proceed as follows:

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

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

If less than three items are ≥*x*%, then STOP – assign ACR*x* response as blank.