Protocol: I1F-IN-RHCZ (a)

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

NCT05855967

Approval Date: 14-Feb-2023

Title Page

Protocol Title: 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

Protocol Number: I1F-IN-RHCZ

Amendment Number: RHCZ(a)

Compound: Ixekizumab (LY2439821)

Brief Title: A study to investigate the safety of ixekizumab in participants aged ≥18 years with moderate-to-severe plaque psoriasis and/or active psoriatic arthritis in India

Study Phase: 4

Sponsor Name: Eli Lilly and Company (India) Pvt. Ltd.

Legal Registered Address: Eli Lilly and Company (India) Pvt. Ltd.
Plot no. 92, Sector 32, Gurugram, Haryana-122001, India

Regulatory Agency Identifier Number(s):

CDSCO Permission Reference Number: IMP/BIO/22/000012

Approval Date: Protocol Amendment (a) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-075015

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	*05 May 2022*

Overall Rationale for the Amendment:

Protocol I1F-IN-RHCZ, 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, has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The following are the overall rationale for the changes made to this protocol:

- To comply with Subject Expert Committee (SEC; Ministry of Health [MoH]) recommendations, and
- To provide more clarity regarding the assessments to be collected and analyzed for the PsA participants who have active plaque psoriasis.

Other minor corrections (spelling errors, grammar corrections, formatting, and so on) and clarifications or semantic changes not affecting content have also been made in the document.

The following table presents the overall changes and rationale for the changes made to this protocol:

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Protocol Synopsis and Section 3 Objectives and Endpoints	Added a note for Other Efficacy Endpoints (PASI 75, 90, 100, PASI change from baseline, sPGA [0, 1] and sPGA [0], and BSA change from baseline) - "For PsA participants with 3% or more body surface area (BSA) of PsO, both PsA and PsO efficacy outcomes will be collected."	To provide more clarity regarding the assessments to be collected and analyzed for the PsA participants who have active plaque psoriasis.
Section 1.1 Protocol Synopsis, Section 1.2 Schema and Section 4.1 Overall Design	Updated a statement related to study treatment.	To provide clarity that treatment regimen for PsA participants with moderate-to-severe PsO is same as that for participants with PsO.
Section 1.1 Protocol Synopsis,	Updated text regarding PsA participants with moderate-to-severe PsO is	To provide clarity that treatment regimen for PsA participants with

Section # and Name	Description of Change	Brief Rationale
Section 4.2 Scientific Rationale for Study Design, and Section 6.1 Study Intervention(s) administered	same as that for participants with PsO in synopsis and Section 6.1. Also, updated Tables RHCZ.6.1 and RHCZ.6.2 in Section 6.1.	moderate-to-severe PsO is same as that for participants with PsO.
Section 1.3 Schedule of Activities	Added a row for "Substance use (alcohol, caffeine, tobacco use)."	To collect additional participant history information.
Section 1.3 Schedule of Activities	Added "Evaluation for Disease Relapse" and footnote annotation b.	To comply with Subject Expert Committee (SEC; Ministry of Health [MoH]) recommendations, Disease Relapse Evaluation has been included at screening visit.
Section 1.3 Schedule of Activities	Added a footnote annotation "i" to update a note describing requirement of assessments for participants with psoriatic arthritis (PsA).	To provide clarity on what assessments are to be administered to which participants.
Section 1.3 Schedule of Activities	Removed baseline assessment of "Collect, review, and enter data from Study Intervention Administration Log."	Rectified original protocol typo error.
Section 1.3 Schedule of Activities	Included Week 24 evaluation of active tuberculosis (TB) in patients by QuantiFERON Tuberculosis TB Gold test and chest x-ray.	To comply with SEC (MoH) recommendations, Week 24 evaluation has been included for active tuberculosis by QuantiFERON TB Gold test and chest x-ray at Week 24 of the treatment.
Section 1.3 Schedule of Activities	Modified a general table note at the end of schedule of activities (SoA) table footnote.	To provide more clarity regarding the assessments to be collected and analyzed for the PsA participants who have active plaque psoriasis.
Section 2.1 Study Rationale	Added definition of moderate-to-severe plaque psoriasis.	To clarify original content.

Section # and Name	Description of Change	Brief Rationale
Section 4.1.4 Post-Treatment Follow-Up Period (Period 4)	Timing of follow-up visit, Visit 802 is updated to 8 weeks after Visit 801.	To clarify original content.
Section 8.1 Efficacy Assessment	Updated a statement to mention that PsO outcome will be collected among all the PsA participants with 3% or more BSA of PsO. Added Table RHCZ.8.1 to present clinician and patient assessments for different participants.	To provide clarity on what assessments are to be administered to which participants.
Section 8.1.2 American College of Rheumatology 20, 50, and 70 Responder Index	Included a statement in subsection Patient's Assessment of Pain Visual Analog Scale – "Patient's Assessment of Pain VAS will be administered only to PsA participants. The question related to pain assessment will be included in HAQ-DI assessment."	To clarify original content.
Section 8.1.3 Patient Global Assessment of Disease Activity VAS Section 8.1.4 Physician's Global Assessment of Disease Activity Visual Analog Scale	Added separate scales for PsO and PsA participants.	To clarify original content.
Section 8.2.4 Evaluation of Disease Relapse	Added details for Evaluation of Disease Relapse.	To comply with SEC (MoH) recommendations, Disease Relapse Evaluation has been included at screening visit.
Section 9.2 Analyses Populations.	Updated the definition details of analysis population,	Updated the analysis populations to include PsO with no active PsA population and active PsA population; text was defined accordingly.

Section # and Name	Description of Change	Brief Rationale
Sections 9.5.3 Secondary Endpoint(s) Analysis and 9.5.5 Safety Analyses	Updated the secondary and safety analysis details for each indication and subgroup.	To provide clarity on the analysis of the PsO and PsA endpoints based on the groups or subgroups and corresponding populations as per the data collection. Updated to provide clarity on the stratification for Safety Analyses.

Table of Contents

Table of Contents

Table **Page**

1. Protocol Summary

1.1. Synopsis

Protocol Title: 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

Brief Title: A study to investigate the safety of ixekizumab in participants aged ≥18 years with moderate-to-severe plaque psoriasis and/or active psoriatic arthritis in India

Rationale:

The rationale for this post-approval Phase 4 study is to evaluate the safety and tolerability when ixekizumab is administered to participants in India with moderate-to-severe plaque psoriasis (PsO) and/or active psoriatic arthritis (PsA). This Phase 4 safety study is being performed as per conditional marketing approval from the Central Drugs Standard Control Organization (CDSCO), India. As per permission reference, Lilly has committed to conduct a Phase 4 study with ixekizumab in India. In addition to the established safety profile for adult PsO, and PsA, the safety and tolerability data in Indian population from this study are intended to:

- further support the known safety profile for ixekizumab in adult participants with PsO and PsA, and
- establish a better understanding of the benefit-risk relationship for ixekizumab in participants with PsO and PsA.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• 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	• AEs, including SAEs, treatment-emergent adverse events (TEAEs), and adverse events of special interest (AESIs) during the treatment period (Week 0 to Week 24)
Secondary	
Specific to Psoriasis Group	
• To evaluate percentage of participants achieving a ≥75% improvement in Psoriasis Area and Severity Index (PASI)	• Proportion of participants who achieve the following PASI scores: PASI 75 (defined as 75% improvement from baseline in PASI) at Week 12
• To evaluate percentage of participants with a Static Physician Global Assessment (sPGA) (0,1)	• Proportion of participants with an sPGA psoriasis score of 0 or 1 (0, 1) at Week 12
Specific to Psoriatic Arthritis Group	
• To evaluate percentage of participants achieving a 20% improvement in American College of Rheumatology response criteria (ACR20)	• Proportion of PsA participants achieving ACR20 at Week 24
CCI [redacted]	
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

Overall Design:

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.

Brief Summary:

The study will consist of 4 periods. The study duration for the 4 study periods are:

- Screening Period (Period 1; 5 to 28 days),
- Induction Dosing Period (Period 2; 12 weeks),
- Maintenance Period (Period 3; 12 weeks), and

- Post-Treatment Follow-Up Period (Period 4; at least 4 weeks after the date of participants' early termination visit [ETV] or last regularly scheduled visit at Week 24).

The following treatment will be assessed in this study for PsO participants with no active PsA and PsA participants who meet criteria for moderate-to-severe PsO (participants with moderate-to-severe plaque psoriasis are defined as those with PASI ≥12, sPGA ≥3, and BSA ≥10%):

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

The following treatment will be assessed in this study for PsA participants who do not meet criteria of moderate-to-severe PsO:

- Ixekizumab: 80-mg SC injection
    - At Week 0, 160-mg starting dose (two 80-mg injections), followed by 80 mg Q4W (i.e., at Weeks 4, 8, 12, 16 and 20).

Statistical Analysis:

Adverse events and treatment-emergent adverse events will be summarized and analyzed for the safety population for the combined Period 2 (Induction Dosing Period) and Period 3 (Maintenance Period), including the number and percentage of participants who reported TEAEs, TEAEs by maximum severity, death, SAEs, TEAEs related to study treatment, AEs leading to treatment discontinuation, and TEAEs of special interest.

Efficacy analyses in the secondary objectives specific to PsO and PsA will be conducted on the PsO with no active PsA and active PsA participants with at least 1 dose of study intervention and will be summarized with number of responders, response rate and its corresponding 95% confidence intervals (CIs) using normal approximation.

Number of Participants:

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

Intervention Groups and Duration:

Treatment Group	Starting Dose W0	Dose W2-W10	Dose[a] W12-W20
Ixekizumab for • PsO participants with no active PsA, and • PsA participants who meet criteria for moderate-to-severe PsO.	Ixekizumab 80 mg 2 × SC (total of 160 mg)	Ixekizumab 80 mg SC Q2W at W2, 4, 6, 8, and 10	Ixekizumab 80 mg SC Q4W at W12, 16, and 20
Ixekizumab for PsA participants who do not meet criteria for moderate-to-severe PsO	Ixekizumab 80 mg 2 × SC (total of 160 mg)	Ixekizumab 80 mg SC Q4W at W4, 8, 12, 16, and 20.	

Abbreviations: PsA = psoriatic arthritis; PsO = psoriasis; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous injection; W = week.

[a] No dose is given at W24; therefore, W24 is not included in this table.

Note: When the dosing is scheduled at home (for PsO participants with no active PsA and PsA participants who meet criteria for moderate-to severe PsO: W2, W6, W10, W16, and W20; for PsA participants who do not meet criteria of moderate-to-severe PsO: W16 and W20), the participants or care givers will administer the provided ixekizumab prefilled syringes.

Data Monitoring Committee: No.

1.2. Schema

1.3. Schedule of Activities (SoA)

Table RHCZ.1.1. Schedule of Activities

	Screening (Period 1)	Induction Dosing (Period 2)				Maintenance (Period 3)		Post Treatment Follow-Up (Period 4)	
		Baseline							As Needed
CRF Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**ETV**	**V801**	**V802**
Study Week		**W0**	**W4**	**W8**	**W12**	**W24**		**LV + W4**	**LV + W8**
Study Days	**-28 to -5 d**	**0 d**	**28 ± 3 d**	**56 ± 3 d**	**84 ± 3d**	**168 ± 5 d**		**± 4 d**	**± 4 d**
Informed consent	X								
Complete medical history	X								
Demographics[a]	X								
Substance use (alcohol, caffeine, tobacco use)	X								
Electrocardiogram	X								
Evaluation for disease relapse[b]	X								
Physical examination[c]	X								
Weight	X	X			X	X	X		
Height		X							
Body mass index		X							
Inclusion/exclusion criteria[d]	X	X							
Vital signs	X	X			X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Review preexisting conditions/AEs	X	X	X	X	X	X	X	X	X
Administer study intervention[e]		X	X	X	X				
Dispense study drug		X	X	X	X				
Study drug compliance[f]		X	X	X	X				
Dispense Study Intervention Administration Log		X	X	X	X				
Collect, review, and enter data from Study Intervention Administration Log			X	X	X	X	X		

Schedule of Activities

	Screening (Period 1)	Induction Dosing (Period 2)				Maintenance (Period 3)		Post Treatment Follow-Up (Period 4)	
		Baseline							As Needed
CRF Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**ETV**	**V801**	**V802**
Study Week		**W0**	**W4**	**W8**	**W12**	**W24**		**LV + W4**	**LV + W8**
Study Days	**-28 to -5 d**	**0 d**	**28 ± 3 d**	**56 ± 3 d**	**84 ± 3d**	**168 ± 5 d**		**± 4 d**	**± 4 d**
Efficacy Measures									
Clinician-Rated or -Administered Assessments									
PAS[lg]	X	X	X	X	X	X	X		
BSA[g]	X	X	X	X	X	X	X		
sPGA[g]	X	X	X	X	X	X	X		
TJC/SJC (68/66 joints)[h]	X	X	X	X	X	X	X		
PGA Disease Activity VAS[h]		X	X	X	X	X	X		
Patient-Rated Assessments									
Patient Assessment of Pain VAS[i]		X	X	X	X	X	X		
Patient Global Assessment Disease Activity VAS		X	X	X	X	X	X		
HAQ-DI[i]		X	X	X	X	X	X		
Laboratory Tests									
Chest x-ray (local)[j]	X					X	X		
Administer Mantoux TB test/QuantiFERON®-TB Gold[k]	X					X	X		
HIV/HCV	X								
HBV[l]	X	X			X	X	X		X
Serum pregnancy test[m]	X								
Urine pregnancy test[n]		X	X	X	X	X	X		
Serum chemistry	X	X			X	X	X		

Schedule of Activities

	Screening (Period 1)	Induction Dosing (Period 2)				Maintenance (Period 3)		Post Treatment Follow-Up (Period 4)	
		Baseline							As needed
CRF Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**ETV**	**V801**	**V802**
Study Week		**W0**	**W4**	**W8**	**W12**	**W24**		**LV + W4**	**LV + W8**
Study Days	**-28 to -5 d**	**0 d**	**28 ± 3 d**	**56 ± 3 d**	**84 ± 3d**	**168 ± 5 d**		**± 4 d**	**± 4 d**
Laboratory Tests									
Hematology	X	X	X		X	X	X	X	X
hs-CRP		X	X	X	X	X	X		
Urinalysis	X	X				X	X		

Abbreviations: AE = adverse event; BSA = body surface area; CRF = case report form; d = day; ETV = early termination visit; HAQ-DI = Health Assessment Questionnaire – Disability Index; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; LV = last visit; PGA = Physician Global Assessment; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; SJC = swollen joint count; sPGA = static Physician's Global Assessment; TB = tuberculosis; TJC = tender joint count, V = visit; VAS = visual analog scale; W = week.

[a] Includes year of birth, gender, and ethnicity.

[b] Subjects will be evaluated for past and present disease relapse by the physician (Section 8.2.4).

[c] Complete physical at screening (excluding pelvic, rectal, and breast examinations). Physicals should include symptom-directed physical, as well as an examination of heart, lungs, and abdomen, and visual examination of the skin.

[d] Participants who test positive for latent TB at screening may be re-screened following appropriate treatment.

[e] See Table RHCZ.6.1. When the dosing is scheduled at home, the participants/care givers will administer the provided ixekizumab prefilled syringes. All participants should remain under observation for at least 1 hour after study intervention administration to monitor safety at Week 0.

[f] Designated site personnel will be responsible for handling and dispensing of study intervention (ixekizumab).

[g] Administered to PsA participants only at the baseline (W0) visit. For PsO participants with 3% or more BSA of PsO, administered at all study visits.

[h] Administered to PsO participants only at the baseline (W0) visit. For PsA participants, administered at all study visits.

[i] Administered only to PsA participants. The question related to pain assessment will be included in HAQ-DI assessment.

[j] To be performed if not done in the prior 6 months to rule out pulmonary TB provided the x-ray and/or report are available for review.

[k] Participants who test positive for latent TB at screening may be re-screened. QuantiFERON® may be performed by a Lilly-designated or local laboratory. See Section 8.2.7 for detailed description of QuantiFERON®-TB Gold . In case of Mantoux TB test, participants will have to come back to the site after 2 days for reading the results.

[l] All participants will be tested for HBV at screening. Participant who meet criteria for HBV monitoring (see Section 8.2.8.1) will be identified by the central laboratory at baseline and monitored according to the study schedule.

[m] To be performed for females of childbearing potential only. Additional urine pregnancy testing can be performed at the investigator's decision. Participants determined to be pregnant will be discontinued from treatment and will no longer be administered study intervention.

n To be performed for females of childbearing potential only. Participants determined to be pregnant will be discontinued from treatment and will no longer be administered study intervention.

Note: For PsO participants with no active PsA, only PsO efficacy outcomes will be collected. For PsA participants with 3% or more BSA of PsO, both PsA and PsO efficacy outcomes will be collected. For PsA participants with less than 3% BSA of PsO, only PsA efficacy outcomes will be collected. (Table RHCZ.8.1).

2. Introduction

2.1. Study Rationale

The rationale for this post-approval Phase 4 ixekizumab study is to evaluate the safety and tolerability when ixekizumab is administered to participants in India with moderate-to-severe plaque psoriasis (PsO) and/or active psoriatic arthritis (PsA). Participants with moderate-to-severe plaque psoriasis are defined as those with PASI ≥12, sPGA ≥3, and BSA ≥10%. This Phase 4 safety study is being performed as per conditional marketing approval from the Central Drugs Standard Control Organization (CDSCO), India. Per permission reference, Lilly has committed to conduct a Phase 4 study with ixekizumab in India. In addition to the established safety profile for adult PsO, and PsA, the safety and tolerability data in Indian population from this study are intended to:

- further support the known safety profile for ixekizumab in adult participants with PsO and PsA, and
- establish a better understanding of the benefit-risk relationship for ixekizumab in participants with PsO and PsA.

2.2. Background

Psoriasis is a common, lifelong and life-shortening, chronic inflammatory skin disease manifested by prototypic red, thick, and scaly plaques. PsO is the most common form and has been shown to have a significant impact on the overall health of participants. Along with an association with inflammatory arthritis in the form of PsA, PsO is associated with increased risk for multiple comorbid conditions, including myocardial infarction (MI) and stroke, metabolic syndrome, diabetes mellitus, chronic renal insufficiency, and liver abnormalities (Yeung et al. 2013). The lifespan of participants with moderate-to-severe PsO may be shortened by as many as 5 years, partly due to association with comorbidities (Gelfand et al. 2006; Ryan and Kirby 2015).

The worldwide prevalence of PsO is 2% to 3% (Christophers 2001; IFPA 2017; NPF 2018) while in India the incidence is 0.44% to 2.2%, and the prevalence is 0.8% to 2.3% (Dogra and Yadav 2010). Almost one-third of participants with PsO in the United States (US) suffer from moderate-to-severe disease (Dubin et al. 2003). Certain symptoms, such as itching, can especially impact the quality of life and is detrimental to work productivity and sleep (Zimolag et al. 2009; Gowda et al. 2010; Janowski et al. 2014; Lebwohl et al. 2014).

Early treatments for PsO obtained 50% to 75% improvement in skin clearance; however, expectations for treatment goals of efficacy are expected to be higher as new and more efficacious therapies have emerged. Recent studies of biologics which block the interleukin-17 (IL-17) or interleukin-23 (IL-23) pathways, both central to PsO pathogenesis (Leonardi et al. 2012; Langley et al. 2014; Sofen et al. 2014; Gordon et al. 2015; Griffiths et al. 2015; Krueger et al. 2015; Lebwohl et al. 2015; Papp et al. 2015), have demonstrated substantial efficacy. Complete skin clearance and improved long-term efficacy have increasingly become the desired treatment outcomes (Gniadecki et al. 2015; Bartos et al. 2016). Some studies have suggested that

increased levels of clearance resulted in greater improvement in quality of life (Takeshita et al. 2014; Feldman et al. 2016; Fairchild et al. 2017).

Ixekizumab (LY2439821) is a humanized immunoglobulin G (IgG) subclass 4 monoclonal antibody (MAb) designed and engineered to selectively inhibit IL-17A. It binds with high affinity (<3 pM) and specificity to IL-17A, a proinflammatory cytokine. Neutralization of IL-17A by ixekizumab has been shown to reduce excess keratinocyte proliferation and activation (Krueger et al. 2012). Ixekizumab does not bind the other members of the IL-17 family (IL-17B, IL-17C, IL-17D, IL-17E, or IL-17F).

Ixekizumab has demonstrated efficacy at both short- and long-term time points, with a favorable safety profile (Griffiths et al. 2015, Gordon et al. 2016, Strober et al. 2017). In all 3 pivotal Phase 3 studies (the UNCOVER studies), ixekizumab was superior to placebo with respect to all primary and major secondary endpoints. In I1F-MC-RHAJ study, the primary objective was met, as the percentage of participants who achieved Psoriasis Area and Severity Index (PASI) 75 at Week 12 (Visit 8) was superior to placebo in all ixekizumab dose groups, including statistically significant improvements ($p<0.001$) compared with placebo for the 25-mg, 75-mg, and 150-mg ixekizumab dose groups. The time course of the PASI 75 response by dose groups demonstrated increasing rapidity of onset of effect with increasing doses.

In the UNCOVER studies, 32% to 42% of participants who received treatment with ixekizumab had complete resolution (PASI 100 or static Physician Global Assessment [sPGA] score of 0; versus none in the placebo group) of their PsO at Week 12; high levels of clinical response were maintained with continued exposure to ixekizumab 80 mg every 4 weeks (Q4W) through Week 60 with at least 50% of participants maintaining or attaining PASI 100 (Gordon et al. 2016). In the UNCOVER-2 and UNCOVER-3 studies, ixekizumab had greater efficacy than etanercept, a tumor necrosis factor inhibitor (TNFi); 40.5% of participants treated with ixekizumab 80 mg every 2 weeks (Q2W), compared with 5.3% of etanercept-treated participants, achieved PASI 100 after 12 weeks (Griffiths et al. 2015, Gordon et al. 2016). In a Phase 3 head-to-head study (IXORA-S), ixekizumab demonstrated superiority over the IL-12/23 antagonist ustekinumab in participants with moderate-to-severe PsO at Week 12; this trend was maintained through Week 52. The majority (76.5%) of ixekizumab-treated participants sustained a PASI 90 response through 1 year, and more than one-half of ixekizumab-treated participants (52.2%) had completely clear skin at Week 52. The corresponding rates for the ustekinumab-treated participants were 59.0% and 35.5%, respectively.

Studies of ixekizumab suggest ability to achieve PASI 90 (as shown in the VOYAGE studies). Ixekizumab also demonstrated a high percentage of participants achieving PASI 100, and a rapid onset of skin improvement after administration of ixekizumab (UNCOVER). Long-term evaluation of ixekizumab in a study, in which safety is tested, will provide important information to clinicians trying to determine long-term safety of drug class is the best for a given participant. The purpose of this study is to evaluate efficacy and safety, as well as rapidness of efficacy, of ixekizumab.

In both UNCOVER-2 and UNCOVER-3 studies combined, the most common (≥2% of all participants given ixekizumab) were nasopharyngitis, upper respiratory tract infection, injection-site reaction, injection-site erythema, injection-site pain, pruritus, headache, and arthralgia. Most treatment-emergent adverse events (TEAEs) were mild or moderate in severity. Serious adverse events (SAEs) were reported by ≤2% of participants in each treatment group

across both studies. No deaths were recorded in either study. Rates of SAEs and discontinuations due to adverse events (AEs) were comparable across study groups in both studies.

During the extension period of Phase 3 SPIRIT-P1 study in participants with active PsA, ixekizumab Q4W or Q2W treatment demonstrated sustained efficacy in key PsA domains with a safety profile consistent with other studies investigating ixekizumab. Phase 3 SPIRIT-P1 study in participants with active PsA showed that both the 2-week and 4-week ixekizumab dosing regimens improved the signs and symptoms of participants with active PsA and who had previously inadequate response to TNFIs, with a safety profile consistent with previous studies investigating ixekizumab.

The purpose of RHCZ Phase 4 safety study is to evaluate safety and tolerability of ixekizumab in Indian participants with PsO or PsA.

More information about the known and expected benefits, risks, and reasonably anticipated AEs of ixekizumab may be found in the Copellor® package insert. Information on AEs expected to be related to the investigational product may be found in Section 6.2 (Development Core Safety Information [DCSI]) of the Investigator's Brochure (IB). Information on SAEs that are expected in the study population (independent of drug exposure) and that will be assessed by the Sponsor in aggregate, periodically during the course of the study, may be found in Section 5 (Effects in Humans) of the IB.

2.3. Benefit/Risk Assessment

Ixekizumab has been demonstrated to be safe and effective for the treatment of participants with moderate-to-severe chronic PsO and/or active PsA. The risk profile for participants within this study is anticipated to be consistent with the known safety experience for ixekizumab.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of ixekizumab are found in the IB. Information on AEs expected to be related to the study intervention may be found in Section 6.2 (DCSI) of the IB. Information on SAEs that are expected in the study population independent of drug exposure and that will be assessed by the Sponsor in aggregate periodically during the course of the study, may be found in Section 5 (Effects in Humans) of the IB.

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with ixekizumab are justified by the anticipated benefits that may be afforded to participants with PsO or PsA.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the type of adverse event (AE) and the proportion of Indian participants with plaque psoriasis (PsO) and participants with psoriatic arthritis (PsA) reporting AEs and serious adverse events (SAEs) occurring within the duration of the study (24 weeks) after being started on ixekizumab.	• AEs including SAEs, treatment-emergent adverse events (TEAEs), and adverse events of special interest (AESIs) during the treatment periods (Week 0 to Week 24)
Secondary	
Specific to Psoriasis Group	
• To evaluate percentage of participants Achieving a ≥75% Improvement in Psoriasis Area and Severity Index (PASI)	• Proportion of participants who achieve the following PASI scores: PASI 75 (defined as 75% improvement from baseline in PASI) at Week 12
• To evaluate percentage of participants with a Static Physician Global Assessment (sPGA) (0,1)	• Proportion of participants with an sPGA score of 0 or 1 (0, 1) at Week 12
Specific to Psoriatic Arthritis Group	
• To evaluate percentage of participants achieving a 20% in American College of Rheumatology improvement criteria (ACR20)	Proportion of PsA participants achieving ACR20 at Week 24
CCI [redacted]	
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

4. Study Design

4.1. Overall Design

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 Indian population (Section 1.2).

The following treatment will be assessed in this study for PsO participants with no active PsA and PsA participants who meet criteria for moderate-to-severe PsO:

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

The following treatment will be assessed in this study for PsA participants who do not meet criteria of moderate-to-severe PsO:

- Ixekizumab: 80-mg SC injection.
    - At Week 0, 160-mg starting dose (two 80-mg injections), followed by 80 mg Q4W (i.e., at Weeks 4, 8, 12, 16 and 20).

The study will consist of 4 periods:

- **Period 1 (Section 4.1.1)**: **Screening Period** (Visit 1) will assess participant eligibility and occurs approximately 5 to 28 days prior to Period 2 (baseline; Week 0 [Visit 2]).
- **Period 2 (Section 4.1.2)**: **Induction Dosing Period** occurring from Week 0 (baseline; Visit 2) to Week 12 (Visit 5).
- **Period 3 (Section 4.1.3)**: **Maintenance Period** occurring after Week 12 (Visit 5) to Week 24 (Visit 6).
- **Period 4 (Section 4.1.4)**: **Post-Treatment Follow-Up Period** (PTFU) occurring from last treatment period Week 24 (Visit 6) or early termination visit (ETV), for a minimum of 4 weeks following that visit.

All procedures to be conducted during the study, including timing and sequence (as necessary), are indicated in the Schedule of Activities (SoA; Section 1.3). Appendix 10.2 lists the specific laboratory tests that will be performed for this study.

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 PTFU period (Period 4) (see Section 7). For the management of participant safety, all participants should be monitored through Period 4 at least as frequently as indicated on the SoA (Section 1.3).

Treatment group is described in Section 6.1, Table RHCZ.6.1, and administration of the study intervention is described in Section 6.1, Table RHCZ.6.2.

Excluded and restricted therapies are detailed in Section 6.8.

Section 9.6 outlines the information regarding interim analyses, including the primary database lock at Week 12.

4.1.1. Screening Period (Period 1)

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. The participant will sign the informed consent form (ICF) before any study assessments, examinations, or procedures are performed.

All inclusion and exclusion criteria are provided in Sections 5.1 and 5.2, respectively. Screening procedures (including complete medical history, demographics, and substance use) will be performed according to the SoA (Section 1.3). At Visit 1, a QuantiFERON®-TB Gold test assay may be performed by a Lilly-designated or local laboratory (Section 8.2.7).

Participants who test positive for latent tuberculosis (TB) at screening may be re-screened once following appropriate treatment, as described in Section 8.2.7.

4.1.2. Induction Dosing Period (Period 2)

The Induction Dosing Period (Period 2) will occur from Week 0 (baseline; Visit 2) to Week 12 (Visit 5).

At Week 0 (baseline, Visit 2), routine safety assessments, laboratory tests, and clinical efficacy assessments will be performed on eligible participants, according to the SoA (Section 1.3).

At Week 4 (Visit 3) and Week 8 (Visit 4), safety and efficacy parameters in study participants will be performed according to the SoA (Section 1.3). The investigator or his/her designee is responsible for explaining the correct method for dose administration to the participant or participant's caregiver, and verifying those instructions are followed properly (Section 6.2).

During study visits, the investigator or his/her designee will administer the ixekizumab prefilled syringes to the participant and explain the correct method for dose administration to the participant or the participant's caregiver.

When the dosing is scheduled at home (Week 2, Week 6, Week 10), the participants or care givers will administer the provided ixekizumab prefilled syringes.

Please refer to Section 6.1, Table RHCZ.6.1, and Table RHCZ.6.2 for a full description of treatment groups and dosing during Period 2. Participants who discontinue from study intervention for any reason during Period 2 will continue to the ETV before entering the Post-Treatment Follow-Up Period (Period 4; Section 4.1.4).

4.1.3. Maintenance Period (Period 3)

The Maintenance Period (Period 3) will occur from Week 12 (Visit 5) up to Week 24 (Visit 6).

During Period 3, safety and efficacy parameters in participating participants will continue to be evaluated according to the SoA (Section 1.3).

At Week 12 (Visit 5), the investigator or his/her designee will administer the ixekizumab prefilled syringes to the participant and explain the correct method for dose administration to the participant or the participant's caregiver.

When the dosing is scheduled at home (Week 16 and Week 20), the participants or care givers will administer the provided ixekizumab prefilled syringes.

Please refer to Section 6.1, Table RHCZ.6.1, and Table RHCZ.6.2 for a full description of treatment groups and dosing during Period 3.

Participants who discontinue from study intervention for any reason during Period 3 will continue to the ETV before entering the Post-Treatment Follow-Up Period (Period 4; Section 4.1.4).

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).

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 (described below).

If, at Visit 801, a participant's neutrophil count is ≥1500 cells/µL or greater than or equal to the participant's baseline neutrophil count, the participant's participation in the study will be considered complete unless the investigator determines additional follow-up may be necessary. An additional study visit (Visit 802) 8 weeks after Visit 801 may be required for appropriate participant management (described below).

If, at the last scheduled visit or ETV, a participant's neutrophil count is <1500 cells/µL (<1.50 × 10^3/µL or <1.50 GI/L) and less than the participant's baseline neutrophil count, the following measures should be taken:

- Participants with concurrent infection: If there is a concurrent infection that requires systemic anti-infective therapy, the participant should receive appropriate medical care and a repeat test for neutrophil count should be performed at least Q4W (or sooner as appropriate) until resolution of infection. Upon resolution of infection, the neutrophil count should be monitored using the required study visits in the Post-Treatment Follow-Up Period (Period 4) design at Visits 801 (4 weeks after resolution of infection) and 802 (8 weeks after Visit 801); additional visits may be required depending on the degree of neutropenia.
- Participants without concurrent infection: If there is no concurrent infection that requires systemic anti-infective therapy, the neutrophil count should be monitored using the required study visits in the Post-Treatment Follow-Up Period (Period 4) design, Visits 801 (4 weeks post- ETV or last regularly scheduled visit at Week 24) and 802 (if necessary); additional visits may be required depending on the degree of neutropenia.
- For Visit 801 and subsequent visits, the following monitoring applies:
  - As long as a participant's neutrophil count is <1000 cells/µL (<1.00 × 10^3/µL or <1.00 GI/L) at any follow-up visit, the participant should return for additional visits at least Q4W (unscheduled visits may be required).
  - As long as a participant's neutrophil count is ≥1000 cells/µL and <1500 cells/µL (≥1.00 × 10^3/µL and <1.50 × 10^3/µL or ≥1.00 GI/L and <1.50 GI/L) at any follow-up visit, the participant should return for additional visit(s) at least every 4 to 8 weeks (unscheduled visits may be required).

- If at Visit 802 the participant's neutrophil count remains <1500 cells/µL (<1.50 × 10^3/µL or <1.50 GI/L) and less than the participant's baseline neutrophil count or if the investigator deems additional follow-up may be necessary, the investigator in consultation with Eli Lilly and Company (Lilly) or qualified designee will determine the appropriate management of the participant and the appropriate timing of additional contact(s) or visit(s).
- If at Visit 802 the participant's neutrophil count is ≥1500 cells/µL (≥1.50 × 10^3/µL or ≥1.50 GI/L) or greater than or equal to the participant's baseline neutrophil count (whichever is lower), the participant's participation in the study will be considered complete unless the investigator deems additional follow-up necessary.

For participants who have entered Period 4, PsO and PsA therapy is allowed, as determined appropriate by the investigator.

Note: Eli Lilly and company will provide study medication only until Week 20. Eli Lilly and company will not provide the post-trial/compassionate use for study intervention as it will be commercially available in India.

4.2. Scientific Rationale for Study Design

This study will examine the effect of ixekizumab on participants with moderate-to-severe PsO and/or PsA.

During the Induction Dosing Period (Period 2), participant's safety and efficacy will be assessed at 80 mg Q2W dose for the participants with PsO and PsA participants who meet criteria for moderate-to-severe PsO. In PsA participants who do not meet criteria of moderate-to-severe PsO, participant's safety and efficacy will be assessed at 80 mg Q4W dose. During the maintenance Period (Period 3), ixekizumab 80 mg Q4W will be studied.

Safety endpoints are in alignment with the safety endpoints for currently approved PsO and PsA therapies, as well as regulatory guidance (EMA 2004).

The Maintenance Period (Period 3) will permit collection of data for the assessment of safety and efficacy of ixekizumab.

The Post-Treatment Follow-Up Period (Period 4) is for safety monitoring following the last treatment period and last study visit.

4.3. Justification for Dose

Ixekizumab will be studied at the approved dosing regimen for treatment of adults with moderate-to-severe -PsO and PsA participants.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit or last scheduled procedure shown in the SoA (Section 1.3).

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA (Section 1.3).

5. Study Population

This study will include participants who have presence of moderate to- -severe PsO (moderate -to -severe PsO is defined as BSA ≥10, sPGA ≥3, PASI ≥12) and/or active PsA (active PsA defined as the presence of at least CCI tender and at least CCI swollen joints) for at least 6 months, treated in outpatient settings of India, who have given written informed consent approved by Lilly, or its designee, and the ethics review board (ERB) governing the site.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened only once in the following circumstances: participants who test positive for latent TB at screening may be re-screened following appropriate treatment, as described in Section 8.2.7. When re-screening is performed, the individual must sign a new ICF and will be assigned a new identification number.

Study investigator(s) will review patient records and/or patient history and screening test results/measurements to determine if the patient meets all inclusion and exclusion criteria to qualify for participation in the study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

[1] Are male or female patients 18 years or older and are of ≥50.0 kg weight.

[2] Male or nonpregnant, nonbreastfeeding female participants.

Participants of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle).

Total abstinence is defined as refraining from intercourse during the entirety of the study and for at least 12 weeks following the last dose of ixekizumab. Periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal are not acceptable methods of contraception.

Otherwise, participants and their partners of childbearing potential must agree to use 2 effective methods of contraception, where at least 1 form is highly effective for the entirety of the study and for at least 12 weeks following the last dose of ixekizumab.

The following contraception methods are considered acceptable (the participant, and their partner, should choose 2, and 1 must be highly effective [defined as <1% failure rate per year when used consistently and correctly]):

- Highly effective birth control methods:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal;
- Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or implantable;
- Intrauterine device/intrauterine hormone releasing system;
- Vasectomized partner (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

- Effective birth control methods:
  - Male or female condom with spermicide (it should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined).
  - Diaphragm with spermicide.
  - Cervical sponge.
  - Cervical cap with spermicide.

Note: When local guidelines concerning highly effective or effective methods of birth control differ from the above, the local guidelines must be followed.

Adolescent females who have started menses (even 1 cycle and any amount of spotting) are considered to be of childbearing potential.

Women of nonchildbearing potential are not required to use birth control and they are defined as:

- Women who are infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation) and congenital anomaly such as Müllerian agenesis.

[3] Have given written informed consent approved by Lilly, or its designee, and the Investigational Review Board (IRB)/ERB governing the site.

[4] Willing to self-administer study intervention.

For PsO Participants

[5] Present with chronic PsO based on a confirmed diagnosis of chronic PsO vulgaris for at least 6 months prior to baseline (Week 0; Visit 2).

[6] Have ≥10% BSA of psoriasis at screening (Visit 1) and baseline (Week 0; Visit 2).

[7] Have both an sPGA score of ≥3 and PASI score ≥12 at screening (Visit 1) and baseline (Week 0; Visit 2).

[8] Are a candidate for phototherapy and/or systemic therapy.

For PsA Participants

[9] Have a diagnosis of active PsA for at least 6 months (based on a detailed medical history provided by the patient, and a physical exam by the Study Investigator, and/or other evidence such as that provided by joint x-rays, that establishes a history consistent with a diagnosis of active PsA of at least 6 months' duration) and currently meet the Classification for PsA (CASPAR) criteria (Section 10.6).

[10] Have active PsA defined as the presence of at least 3/68 tender and at least 3/66 swollen joints, as determined by the Tender and Swollen Joint Count Assessment Form (Section 10.7) at Visit 1 (Screening) and Visit 2 (Week 0, baseline).

[11] Presence of active PsO or a documented history of psoriasis.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

[12] Have previously completed or withdrawn from this study, participated in any other study with ixekizumab, or have participated in any study investigating other IL-17 antagonists.

[13] Have a history of drug-induced PsO.

[14] Concurrent or recent use of any biologic agent within the following washout periods: etanercept <28 days; infliximab, adalimumab, or alefacept <60 days; golimumab <90 days; ustekinumab <8 months; rituximab or efalizumab <12 months; or any other biologic agent <5 half-lives prior to baseline (Week 0 Visit 2).

[15] Cannot avoid excessive sun exposure or use of tanning booths for at least 4 weeks prior to baseline (Week 0; Visit 2) and during the study.

[16] Have a known allergy or hypersensitivity to any biologic therapy that would pose an unacceptable risk to the patient if participating in this study.

[17] Have ever received natalizumab or other agents that target alpha-4-integrin.

[18] Had a live vaccination within 12 weeks prior to baseline (Week 0; Visit 2), or intend to have a live vaccination during the course of the study, or within 12 months of completing treatment in this study, or have participated in a vaccine clinical study within 12 weeks prior to baseline (investigators should review the vaccination status of their patients and follow the local guidelines for adult vaccination with non-live vaccines intended to prevent infectious disease prior to therapy).

Note: Killed/Inactive or subunit vaccines are expected to be safe; however, their efficacy with concomitant ixekizumab treatment is unknown.

[19] Had a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months prior to baseline (Week 0; Visit 2), or intend to have this vaccination with BCG during the course of the study, or within 12 months of completing treatment in this study.

[20] Had any major surgery within 8 weeks prior to baseline (Week 0; Visit 2), or will require such during the study that, in the opinion of the investigator in consultation with Lilly or its designee, would pose an unacceptable risk to the patient.

[21] Have current or a history of lymphoproliferative disease; or signs or symptoms of lymphoproliferative disease; or have active or history of malignant disease.

[22] Have diagnosis or history of malignant disease within the 5 years prior to baseline (Week 0, Visit 2).

Note: Patients with successfully treated basal-cell carcinoma (no more than 3), squamous-cell carcinoma of the skin, or cervical carcinoma in situ, with no evidence of recurrence within the 5 years prior to baseline (Week 0; Visit 2) may participate in the study.

[23] Presence of significant uncontrolled cerebrocardiovascular (e.g., MI, unstable angina, unstable arterial hypertension, moderate-to-severe [New York Heart Association (NYHA) class III/IV] heart failure, or cerebrovascular accident [CVA]), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic or neuropsychiatric disorders, or abnormal laboratory values at screening that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.

[24] Have had fluid overload, MI or new onset ischemic heart disease (e.g., unstable angina), uncompensated heart failure, or in the opinion of the investigator other serious cardiac disease within 12 weeks prior to baseline (Week 0; Visit 2).

[25] Have a current or recent acute, active infection (for at least 30 days before screening (Visit 1), participants must have no symptoms or signs of confirmed or suspected infection and must have completed any appropriate anti-infective treatment).

Note: Participants who have an upper respiratory infection, a vaginal candida infection, or an oral candida infection and who are being treated only symptomatically and not requiring systemic anti-infectives may be considered for enrollment if other study eligibility criteria are met. Enrollment of participants with other uncomplicated local infections should be discussed with the Sponsor's designated medical monitor.

[26] Have had any of the following types of infection within 3 months prior to the screening visit (Visit 1):

- Serious (requiring hospitalization, or intravenous or equivalent oral antibiotic treatment, or both).
- Opportunistic (as defined in Winthrop et al. 2015).

  Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.
- Chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer).
- Recurring (including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis).

  Note: Participants with only recurrent mild and uncomplicated orolabial herpes, or genital herpes, or both may be discussed with the Sponsor's designated medical monitor and considered for enrollment if other study eligibility criteria are met.

[27] Have active TB (refer to Section 8.2.7 for details on determining full TB exclusion criteria).

[28] Have any other active or recent infection within 4 weeks of baseline (Week 0; Visit 2) that, in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study; these patients may be rescreened (1 time) 4 or more weeks after documented resolution of symptoms.

[29] Have a body temperature ≥38°C (100.5°F) at baseline (Week 0; Visit 2); these patients may be rescreened (1 time) ≥4 weeks after documented resolution of elevated temperature.

[30] Have uncontrolled arterial hypertension characterized by a systolic blood pressure (SBP) >160 mm Hg or diastolic blood pressure (DBP) >100 mmHg.

Note: Determined by 2 consecutive elevated readings. If an initial blood pressure (BP) reading exceeds this limit, the BP may be repeated once after the patient has rested sitting for ≥10 minutes. If the repeat value is less than the criterion limits, the second value may be accepted.

[31] Are positive for human immunodeficiency virus (HIV) serology (positive for human immunodeficiency virus antibody [HIVAb]).

[32] Have evidence of or test positive for hepatitis B by any of the following criteria: 1) positive for hepatitis B surface antigen (HBsAg+); 2) positive for anti-hepatitis B core antibody (HBcAb+) and negative for anti-hepatitis B surface antibody (HBsAb–); 3) positive for anti-hepatitis B core antibody (HBcAb+) and positive for anti-hepatitis B surface antibody (HBsAb+) with a concentration of HBsAb <200 mIU/mL; or 4) HBcAb+, HBsAb+ (regardless of HBsAb level), and positive for serum hepatitis B virus (HBV) DNA.

Note: Patients who are negative for hepatitis B surface antigen (HBsAg-), HBcAb+, HBsAb+ with a concentration of HBsAb ≥200 mIU/mL, and negative for serum HBV DNA may participate in the study. Patients who meet these criteria at screening will be identified by the central laboratory and monitored during the study as detailed in Section 8.2.8.1.

[33] Have evidence of or test positive for hepatitis C virus (HCV). A positive test for HCV is defined as: 1) positive for hepatitis C antibody (anti-HCVAb), and 2) positive via a confirmatory test for HCV (e.g., HCV polymerase chain reaction [PCR]).

[34] Have clinical laboratory test results at screening that are outside the normal reference range for the population and are considered clinically significant, and/or have any of the following specific abnormalities:

[34a] Neutrophil count <1500 cells/μL

[34b] Lymphocyte count <500 cells/μL

[34c] Platelet count <100,000 cells/μL

[34d] Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN)

[34e] Total white blood cell (WBC) count <3000 cells/μL

[34f] Hemoglobin <8.5 g/dL (85.0 g/L) for male patients and <8.0 g/dL (80 g/L) for female patients

[34g] Serum creatinine >2.0 mg/dL

Note: The AST and ALT may be repeated once within a week if the initial response exceeds this limit, and the repeat value may be accepted if it meets this criterion. Other laboratory tests should not be repeated unless there is a technical error or clinical reasons to believe a result may be erroneous.

[35] Have electrocardiogram (ECG) abnormalities that are considered clinically significant and would pose an unacceptable risk to the patient if participating in the study.

[36] Have any other condition that precludes the patient from following and completing the protocol, in the opinion of the investigator.

[37] Have donated blood of >500 mL within the last 4 weeks, or intend to donate blood during the course of the study.

[38] Are women who are lactating or breastfeeding.

[39] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[40] Are Lilly employees or its designee or are employees of third-party organizations (TPOs) involved in the study.

[41] Are currently enrolled in, or discontinued from a clinical trial involving an investigational product or nonapproved use of a drug or device within the last 4 weeks or a period of at least of 5 half-lives of the last administration of the drug, whichever is longer, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

PsO Participants

[42] Have received systemic non-biologic PsO therapy (including, but not limited to, oral psoralens and ultraviolet A [PUVA] light therapy; cyclosporine; corticosteroids; methotrexate [MTX]; oral retinoids; mycophenolate mofetil; thioguanine; hydroxyurea; sirolimus; azathioprine; fumaric acid derivatives; or 1,25 dihydroxy vitamin D3 and analogues) or phototherapy (including either oral and topical PUVA light therapy, ultraviolet B [UVB] or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to baseline (Week 0; Visit 2);

or had topical PsO treatment (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, emollients and other non-prescription topical products containing urea, >3% salicylic acid, or alpha- or beta-hydroxyl acids, and medicated shampoos [e.g., those that contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues]) within the previous 2 weeks prior to baseline (Week 0; Visit 2).

Exceptions: class 6 (mild, such as desonide) or class 7 (least potent, such as hydrocortisone) topical steroids will be permitted for use limited to the face, axilla, and/or genitalia.

[43] Have pustular, erythrodermic, and/or guttate forms of PsO.

[44] Had a clinically significant flare of PsO during the 12 weeks prior to baseline (Week 0; Visit 2).

[45] Have allergy to rubber or latex.

PsA Participants

[46] Have used conventional synthetic disease-modifying antirheumatic drug (csDMARDs) other than MTX, leflunomide, sulfasalazine, or cyclosporine in the 8 weeks prior to baseline (Week 0; Visit 2).

Have discontinued MTX, sulfasalazine, or cyclosporine within 12 weeks prior to baseline (Week 0; Visit 2).

If taking MTX, leflunomide, sulfasalazine, or cyclosporine, must have been treated for at least 12 weeks prior to baseline *and* on a stable dose for at least 8 weeks prior to baseline, as follows: oral or parenteral MTX = 10 to 25 mg/week; leflunomide = 20 mg/day; sulfasalazine = up to 3 g/day; or cyclosporine up to 5 mg/kg/day. The dose of these allowed concomitant medications must remain unchanged during the study periods of the unless changes are required for safety issues. Local standard of care should be followed for concomitant administration of folic acid with MTX.

[47] Are currently receiving treatment with any biologic or small molecule therapy for PsA or PsO, including investigational therapies (such as, but not limited to, a TNFi, IL-1 receptor antagonists, IL-6 inhibitor, anti-IL-12/23p40, T cell or B cell targeted therapies, phosphodiesterase [PDE] 4 inhibitors, or Janus kinase [JAK] inhibitors), or have received denosumab.

[48] Have received treatment with IL-17 or IL12/23 targeted Mab therapy.

[49] Have used disease-modifying antirheumatic drug (DMARDs) other than MTX, leflunomide, sulfasalazine, or hydroxychloroquine (e.g., gold salts, cyclosporine, azathioprine, dapsone, 6-mercaptopurine, mycophenolate mofetil, or any other immunosuppressive agents) in the 8 weeks prior to baseline (Week 0, Visit 2).

Have discontinued MTX or sulfasalazine within the 8 weeks prior to baseline, or hydroxychloroquine within 12 weeks prior to baseline.

If taking MTX, leflunomide, sulfasalazine, or hydroxychloroquine must have been treated for at least 12 weeks prior to baseline and on a stable dose for at least 8 weeks prior to baseline, as follows: oral or parenteral MTX = 10 to 25 mg/week; leflunomide = 20 mg/day; sulfasalazine = up to 3 g/day; or hydroxychloroquine = up to 400 mg/day. The dose of these allowed concomitant medications must remain unchanged until W12 of the study, unless changes are required for safety issues. Local standard of care should be followed for concomitant administration of folic acid with MTX.

[50] Are receiving treatment with more than 1 conventional DMARD (MTX, leflunomide, sulfasalazine, or hydroxychloroquine) at study entry.
Note: Under no circumstances will simultaneous use of MTX and leflunomide be allowed at any time during the study for safety reasons.

[51] Have discontinued leflunomide within 4 weeks prior to baseline or have received leflunomide from 4 to 12 weeks prior to baseline (Week 0, Visit 2) and have not undergone a drug elimination procedure.

[52] Use of oral corticosteroids at average daily doses of >10 mg/day of prednisone or its equivalent, or use of variable doses of any oral corticosteroids, within 4 weeks prior to baseline (Week 0, Visit 2).

[53] Have received any parenteral glucocorticoid administered by intraarticular, intramuscular, or intravenous (IV) injection within 6 weeks prior to baseline (Week 0, Visit 2), or for whom a parenteral injection of glucocorticosteroids is anticipated until W12 of the study.

[54] Concomitant use of nonsteroidal anti-inflammatory drug (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors, unless the patient is on a stable dose for at least 2 weeks prior to baseline (Week 0, Visit 2).

[55] Use of any opiate analgesic at average daily doses of >30 mg/day of morphine or its equivalent or use of variable doses of any opiate analgesic within 6 weeks prior to baseline (Week 0, Visit 2).

[56] Have a diagnosis of other inflammatory arthritic syndromes such as rheumatoid arthritis (RA), ankylosing spondylitis, reactive arthritis, or enteropathic arthritis.

[57] Have active Crohn's disease or active ulcerative colitis.

[58] Have diagnosis of fibromyalgia.

[59] Have a chronic pain condition that would confound evaluation of the patient.

[60] Have evidence of active vasculitis or uveitis.

[61] Have had surgical treatment of a joint within 8 weeks prior to baseline or will require such up to Week 24.

5.3. Lifestyle Considerations

See inclusion criteria [2] in Section 5.1 for birth control requirements.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals may be re-screened only once in the following circumstances:

- Patients who test positive for latent TB at screening and have undergone documented subsequent treatment for at least 4 weeks (more details in Section 8.2.7).
- Other reasons for rescreening must be discussed, approved and documented by the Lilly Medical Team (clinical research scientist [CRS]/clinical research physician [CRP]).

5.5. Criteria for Temporarily Delaying Enrollment/Administration of Study Intervention of a Participant

Dates of subsequent study visits should not be modified according to the delay of the injection of the missed scheduled dose.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Table RHCZ.6.1. Treatment Regimens

Treatment Group	Starting Dose W0	Dose W2-W10	Dose[a] W12-W20
Ixekizumab for • PsO participants with no active PsA • PsA participants who meet criteria for moderate-to-severe PsO	Ixekizumab 80 mg × 2 SC (total of 160 mg)	Ixekizumab 80 mg SC Q2W at W2, 4, 6, 8, and 10	Ixekizumab 80 mg SC Q4W at W12, 16, and 20
Ixekizumab for PsA participants who do not meet criteria for moderate-to-severe PsO	Ixekizumab 80 mg × 2 SC (total of 160 mg)	Ixekizumab 80 mg SC Q4W at W4, 8, 12, 16, and 20	

Abbreviations: PsA = psoriatic arthritis; PsO = psoriasis; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous injection; W = week.

[a] No dose is given at W24; therefore, W24 is not included in this table.

Note: When the dosing is scheduled at home (for PsO participants with no active PsA and PsA participants who meet criteria for moderate-to-severe PsO: W2, W6, W10, W16, and W20; for PsA participants who do not meet criteria for moderate-to-severe PsO: W16 and W20), the participants or care givers will administer the provided ixekizumab prefilled syringes.

The investigator or his/her designee is responsible for the following:

- explaining the correct method of dose administration to the participant or participant's caregiver;
- explaining the correct use of the investigational agent(s) to site personnel/legal representative;
- verifying those instructions are followed properly;
- maintaining accurate records of study intervention dispensing and collection; and
- returning all unused medication to Lilly or its designee at the end of the study

During study visits, the investigator or his/her designee will administer the ixekizumab prefilled syringes to the participant. When the dosing is scheduled at home, the participants or care givers will administer the provided ixekizumab prefilled syringes.

Note: In some cases, sites may destroy clinical trial material if during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures for disposing of clinical trial materials.

Induction Dosing Period (Period 2) (Table RHCZ.6.2)

- At Week 0, a 160-mg starting dose of ixekizumab (two 80-mg injections), followed by ixekizumab 80 mg Q2W from Weeks 2 through 12 for PsO participants with no active PsA and PsA participants who meet criteria for moderate-to-severe PsO.
- At Week 0, a 160-mg starting dose of ixekizumab (two 80-mg injections), followed by ixekizumab 80 mg Q4W from Weeks 4 through 12 for PsA participants who do not meet the criteria for moderate-to-severe PsO participants.

Maintenance Period (Period 3) (Table RHCZ.6.2)

- Ixekizumab 80 mg Q4W (i.e., at Weeks 16 and 20).

Table RHCZ.6.2 presents the number of injections administered at each study week, for each dosing period.

Table RHCZ.6.2. Dosing Summary for the Induction and Maintenance Periods

		Ixekizumab Treatment Group[a]	
		Ixekizumab (80 mg)	
Dosing Period	Study Week	PsO Participants with no active PsA and PsA Participants Who Meet Criteria for Moderate-to-Severe PsO [b]	PsA Participants Who Do Not Meet Criteria for Moderate-to-Severe PsO[c]
Induction Dosing Period 2	0	2[a]	2[a]
	2	1	-
	4	1	1
	6	1	-
	8	1	1
	10	1	-
	12	1	1
Maintenance Period 3	16	1	1
	20	1	1
	24	-	-

Abbreviations: PsA = psoriatic arthritis; PsO = psoriasis; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.

[a] A starting dose of 160 mg (Week 0) of ixekizumab will be given as 2 SC injections at Week 0.

[b] For PsO participants with no active PsA and PsA participants who meet criteria for moderate-to-severe PsO, during the Induction Dosing Period, ixekizumab (80 mg) will be given as 1 SC injection Q2W (i.e., Weeks 2, 4, 6, 8, 10, and 12). During the Maintenance Period, ixekizumab (80 mg) will be given as 1 SC injection Q4W (i.e., Weeks 16 and 20).

[c] For PsA participants who do not meet criteria for moderate to severe PsO, ixekizumab (80 mg) will be given as 1 SC injection Q4W (i.e., Weeks 4, 8, 12, 16, and 20).

6.2. Preparation, Handling, Storage, and Accountability

The Pharmacy Manual provides information about the handling and storage of the study intervention, as well as the site responsibility and accountability for the administered products.

Additional information about the study intervention administration is provided in other documents.

Site responsibilities and accountability

1. The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.
3. The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

In addition, the investigator or his/her designee is responsible for the following (see also Section 6.3):

- explaining the correct use of the investigational agent to the participant or participant's caregiver; and
- verifying those instructions are followed properly.

6.3. Measures to Minimize Bias

This is an open-label study. The site will record the intervention assignment on the applicable case report form (CRF).

6.4. Study Intervention Compliance

Every attempt will be made to select participants who have the ability to understand and comply with instructions. The investigator is responsible for discussing methods with the participants and caregiver before study entry to ensure high treatment compliance.

Throughout the study, site personnel, the participant, or the caregiver will record information about injections in the Study Intervention Administration Logs, including:

- the date, time, and anatomical location of administration of ixekizumab (for treatment compliance);
- syringe number;
- who prepared (if applicable) and administered ixekizumab; and
- the reason, if ixekizumab was not fully administered or missed.

As indicated in the SoA (Section 1.3), the Study Intervention Administration Log will be dispensed to all participants or their caregivers. Either the participant or the caregiver will compete the Log with the information about injections and bring it to the site at each regular study visit.

Participants' compliance with ixekizumab will be assessed at each regular visit. Compliance will be assessed by the number of injections needed versus the number of injections administered to the participants. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

6.5. Dose Modification

Not applicable.

6.6. Continued Access to Study Intervention after the End of the Study

Ixekizumab will not be made available to participants at the conclusion of the study. Lilly will provide Ixekizumab from Week 0 to Week 20. Last study dose is scheduled at Week 20.

6.7. Treatment of Overdose

Refer to the IB for ixekizumab.

6.8. Concomitant Therapy

All concomitant medication taken during the study must be recorded on the Concomitant Medication CRF at the study visits indicated in the SoA (Section 1.3). Treatment with concomitant PsO and PsA therapies during the study will be permitted only as outlined in the inclusion and exclusion criteria (Sections 5.1 and 5.2, respectively) and as described in the paragraphs below. Participants taking permitted medications need to be documented to be in stable control. After trial enrollment, significant dose escalation of a concomitant medication should be discussed with Lilly medical before allowing participant to receive study intervention.

Table RHCZ.6.3 summarizes concomitant medications that are and are not permitted and their conditions for use during the study.

Table RHCZ.6.3. Concomitant Medications Permitted/Not Permitted in the Study and Conditions for Use

Drug Class	Permitted/Not Permitted during the Trial	Conditions for Use
Bath oils and oatmeal bath preparations	Permitted	Not to be used within 12 hours of a study visit.
NSAIDs, acetaminophen, or aspirin	Permitted	Allowed as needed.
Shampoos	Permitted	May not contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues. Not to be used within 12 hours of a study visit.
Topical moisturizers/emollients and other non-prescription topical products	Permitted	Do not contain urea, >3% salicylic acid, alpha- or beta-hydroxyl acids, corticosteroids, or vitamin D3 analogues. Not to be used within 12 hours of a study visit.
Topical steroids		
Mild (such as hydrocortisone)	Permitted	Permitted for use limited to the face, axilla, groin, and/or genitalia, as needed. These topical medications should not be used within approximately 24 hours before study visits requiring sPGA and PASI measures. More widespread use on large surfaces is not permitted.
Strong (such as mometasone), very strong (betamethasone)[a], and halogenated steroids (clobetasone)	Not permitted	
Biologic agents other than study intervention as part of this protocol	Not Permitted	Washout periods before baseline (Week 0, Visit 2); at least 5 half-lives
IL-17, IL-23p19 antagonists, other than the 2 products used as part of this protocol.	Not permitted	Must have never received ixekizumab or IL-23p19 antagonists; or participated in any study investigating IL-23p19 antagonists. Participant with previous exposure to another IL-17 antagonist(s) will be limited to approximately 15% of the total participant population.
Natalizumab or other agents targeting α 4 integrin	Not permitted	Must have never received.
Phototherapy (including either oral and topical PUVA light therapy, UVB, or self-treatment with tanning beds or therapeutic sunbathing)	Not permitted	Must not have received within 4 weeks of baseline (Week 0, Visit 2).

Concomitant Medications Permitted/Not Permitted in the Study and Conditions for Use

Drug Class	Permitted/Not Permitted	Conditions for Use
Systemic nonbiologic psoriasis therapy (e.g., oral PUVA light therapy, cyclosporine, corticosteroids, MTX, oral retinoids, mycophenolate mofetil, thioguanine, hydroxyurea, sirolimus, azathioprine, fumaric acid derivatives, apremilast, and 1,25 dihydroxy vitamin D3 and analogues)	Not permitted (for PsO participants) Permitted (for PsO participants who met PsA criteria and PsA participants) with conditions	Must not have received within 4 weeks of baseline (Week 0, Visit 2). Stable dose allowed. Stable doses with no dose adjustments, changes, and/or introduction of a new csDMARD Allowed doses: • Oral or parenteral MTX; 10 to 25 mg/week • Leflunomide: up to 20 mg/day • Sulfasalazine: up to 3 g/day • Cyclosporine: up to 5 mg/kg/day
Vaccine, Bacillus Calmette-Guérin	Not permitted	Must not have received within 12 months of baseline (Week 0, Visit 2). Should not receive within 12 months of completed treatment in this study.
Vaccines, live	Not permitted	Must not have received within 12 weeks of baseline (Week 0, Visit 2). Should not receive within 15 weeks of completed treatment in this study.
Vaccines, non-live seasonal and/or emergency	Permitted with conditions	Killed/inactive, RNA vaccine, or subunit vaccines are expected to be safe; however, their efficacy with concomitant ixekizumab treatments is unknown. Check with Lilly Medical Team (CRS/CRP) before administration.

Abbreviations: CRS/CRP = clinical research scientist/clinical research physician; csDMARD = conventional synthetic disease-modifying antirheumatic drug; IL = interleukin; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PsO = plaque psoriasis; PUVA = psoralen and ultraviolet A; RNA = ribonucleic acid; sPGA = static Physician Global Assessment; UVB = ultraviolet B.

[a] Mason et al. 2002.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. If the need for concomitant medication arises, the investigator should base decisions on the participant and clinical factors. Any additional medication (including the limited use of therapeutic agents which, if used under treatment regimens other than for treating an AE or for appropriate medical management, might be considered PsO/PsA therapies) whether prescription or over-the-counter, used at baseline (Week 0, Visit 2) and/or during the course of the study, must be documented with the start and stop dates on the Concomitant Medications CRF.

Participants will maintain their usual medication regimen for other concomitant diseases throughout the study unless those medications are specifically excluded in the protocol. Participants taking concomitant medications should be on stable doses at the time of baseline (Week 0, Visit 2) and should remain at a stable dose throughout the study, unless changes need to be made for an AE or for appropriate medical management. Other medications may be allowed if approved by the Sponsor or its designee.

Participants should be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements. Any changes in medications not addressed above should be discussed by the investigator with the Sponsor.

7. Discontinuation of Study Intervention and Participant Discontinuation/ Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1, Section 10.1.7.

7.1. Discontinuation of Study Intervention

Study intervention may be temporarily withheld or permanently discontinued during the study.

Participants who permanently discontinue study intervention early will undergo early termination procedures, which include:

- an ETV, and
- PTFU visits (V801 and V802).

The investigator will complete any AE reporting and follow-up (Section 8.3).

7.1.1. Permanent Discontinuation from Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to have ETV and PTFU visits. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Possible reasons leading to permanent discontinuation of study intervention:

- Participant decision:
    - the participant or the participant's designee, e.g., parents or legal guardian, requests to discontinue the study intervention.

Participants will be discontinued from the study intervention under the following circumstances:

- Neutrophil (segmented) counts:
    - <500 cells/µL
    - ≥500 and <1000 cells/µL (based on 2 test results; the second test performed within 1 week from knowledge of the initial result)
    - ≥1000 and <1500 cells/µL (based on 3 test results) and an infection that is not fully resolved
    - WBC count <1000 cells/µL (1.00 × 103/µL or 1.00 billion/L)
    - absolute neutrophil count (ANC) <500 cells/µL (0.50 × 103/µL or 0.50 billion/L)
    - lymphocyte count <200 cells/µL (0.20 × 103/µL or 0.20 billion/L)
    - hemoglobin <6.5 g/dL (<65.0 g/L)
    - platelet count <50,000 cells/µL.

Note: Temporary interruption rules (see Section 7.1.3) must be followed, where applicable. For laboratory values that meet permanent discontinuation thresholds, the study intervention should be discontinued. However, if in the opinion of the investigator the laboratory abnormality is due to intercurrent illness such as cholelithiasis or another identified factor, laboratory tests may be repeated. Only when the laboratory value meets resumption thresholds following the resolution of the intercurrent illness or other identified factor may the investigator restart the study intervention after consultation with the Sponsor-designated medical monitor.

In addition, participants will be discontinued from the study intervention in the following circumstances:

- The participant experiences a severe AE or SAE or has a clinically significant change in a laboratory value that, in the opinion of the investigator, merits discontinuation of the study intervention and appropriate measures being taken. This includes evidence of active viral hepatitis or active tuberculosis (TB). In such cases, the Sponsor or its designee is to be notified immediately.
- Clinically significant systemic hypersensitivity reaction following SC administration of study intervention that does not respond to symptomatic medication or results in clinical sequelae
- The participant becomes pregnant
- The participant develops a malignancy (Note: participants may be allowed to continue if they develop no more than 2 non-melanoma skin cancers during the study)
- The participant has a positive TB test using QuantiFERON®-TB Gold or T-Spot or purified protein derivative (PPD and is assessed as having latent TB infection (see Section 8.2.7), and/or develops symptoms or signs of tuberculosis.
- if the participant develops active suicidal ideation with some intent to act with or without a specific plan,

  -OR-

  if the participant develops suicide-related behaviors,

- then it is recommended that the participant be assessed by a psychiatrist or appropriately trained professional to assist in deciding whether the participant is to be discontinued from the study.

Participants discontinuing from the study intervention prematurely for any reason should complete AE and other follow-up procedures per the SoA (Section 1.3), Safety Assessments (Section 8.2), and Adverse Events and Serious Adverse Events (Section 8.3) of this protocol .

7.1.2. Liver Chemistry Stopping Criteria

The study intervention should be interrupted or discontinued if one or more of these conditions occur:

Elevation	Exception
ALT or AST >5 × ULN	
ALT or AST >3 × ULN and either TBL >2 × ULN or INR >1.5	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption/ discontinuation decisions rather than TBL>2 × ULN.
ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3 × ULN, when the source of increased ALP is the liver	
ALP >2.5 × ULN and TBL > 2 × ULN	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption/ discontinuation decisions rather than TBL>2 × ULN.
ALP >2.5 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FDA = Food and Drug Administration; INR = international normalized ratio; TBL = total bilirubin level; ULN = upper limit of normal.
Source: FDA 2009.

Resumption of the study intervention can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited non-drug etiology is identified.

7.1.3. Temporary Discontinuation

In some circumstances, participants may need to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to the study intervention. See Section 8.2.7 for details regarding managing participants who test positive for TB at any time during the study.

The abnormal laboratory values as reason for temporary discontinuation of study intervention may include HBV DNA results that are reported as positive, or as detecting HBV DNA, but HBV DNA is below the level of quantification. The Sponsor's designated medical monitor should be contacted regarding study status of the participant. HBV DNA testing is to be repeated as soon as is feasible. If HBV DNA is confirmed as positive, the participant must be permanently discontinued from study intervention (Section 7.1.1).

Participants requiring surgery at any time during the study should interrupt administration of the study intervention beginning 8 weeks before the surgery, or as early as possible, and resume administration of the study intervention only after complete wound healing.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at the participant's own request;
- at the request of the participant's designee (e.g., parents or legal guardian);
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons;
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study;
- if participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP) or
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an ETV should be conducted, as shown in the SoA (Section 1.3). See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the Sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly clinical pharmacologist and the investigator to determine if the participant may continue in the study. If both agree that it is medically appropriate to continue, the investigator must obtain documented approval from the Sponsor to allow the inadvertently enrolled participant to continue in the study with or without continued treatment with ixekizumab. Safety follow-up should be performed as outlined in the SoA (Section 1.3), Safety Assessments (Section 8.2), and Adverse Events and Serious Adverse Events (Section 8.3) of the protocol.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee are

expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were, otherwise, unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented, and the participant will not be considered lost to follow-up.

The Sponsor personnel will not be involved in any attempts to collect vital status information.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3).

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

The joint assessor (or designee) should be a rheumatologist, trained dermatologist or skilled joint assessor and will be responsible for completing the joint counts for swelling, tenderness, and limited range of motion. Additionally, the assessor will perform the following assessments: Physician's Global Assessment of Disease Activity, PASI, BSA.

To ensure consistent skin and/or joint evaluation throughout the study, individual participants should be evaluated by the same assessor for all study visits whenever possible.

Investigators or relevant clinical staff will provide age-appropriate explanations to all study participants prior to any assessment or procedure.

8.1. Efficacy Assessments

The secondary endpoints for PsO group are:

- 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 score of 0 or 1 (0, 1) at Week 12.

The secondary endpoints for PsA group are:

- Proportion of PsA participants achieving ACR20 at Week 24.

Exploratory endpoints include, but not limited to, DAS-28-CRP and ACR individual components.

For PsO participant who also meet active PsA definition, both PsA and PsO outcomes will be collected for that participant. Likewise, to fulfill the study objective, PsO outcomes will be collected among all the PsA participants with 3% or more BSA of PsO (Table RHCZ.8.1).

Table RHCZ.8.1. Efficacy Assessments

Assessments	PsO Participants with No Active PsA	PsA Participants with	
		≥3% BSA of PsO	<3% BSA of PsO
Clinician assessments	• PASI • Percentage of BSA - Psoriasis • sPGA • PGA Disease Activity VAS	• TJC/SJC (68/66 joints) • PGA of Disease Activity VAS -Psoriasis • PGA of Disease Activity VAS - PsA • PASI • Percentage of BSA - Psoriasis • sPGA • DAS28 - CRP[a] • ACR20/50/70[a]	• TJC/SJC (68/66 joints) • PGA of Disease Activity VAS - PsA • DAS28 - CRP[a] • ACR20/50/70[a]
Patient assessments	• Patient's Global Assessment of disease activity VAS - Psoriasis	• HAQ-DI • PsA Pain assessment question included in HAQ-DI • Patient's Global Assessment of Disease Activity VAS - PsA • Patient's Global Assessment of Disease Activity VAS - Psoriasis	• HAQ-DI • PsA Pain assessment question included in HAQ-DI • Patient's Global Assessment of Disease Activity VAS - PsA

Abbreviations: ACR20/50/70 = 20%/50%/70% improvement in American College of Rheumatology response criteria; BSA = body surface area; CRP = C-reactive protein; DAS28 = Disease Activity Score-28; HAQ-DI = Health Assessment Questionnaire – Disability Index; PASI = Psoriasis Area and Severity Index; hs-CRP = high-sensitivity C-reactive protein; PGA = Physician's Global Assessment; PsA = psoriatic arthritis; PsO = plaque psoriasis; SJC = swollen joint count; sPGA = static Physician's Global Assessment; TJC = tender joint count, V = visit; VAS = visual analog scale.

[a] Assessments are derived by calculations using PsA assessments and hs-CRP assay.

8.1.1. Efficacy Assessments

8.1.1.1.Psoriasis Area and Severity Index (PASI 75, PASI 90, PASI 100)

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 (Fredriksson and Pettersson 1978). The PASI has been the most frequently used endpoint and measure of psoriasis severity in clinical trials (EMA 2004; Menter et al. 2008). A clinically meaningful response is a PASI 75, which represents at least a 75% decrease (improvement) from the baseline PASI score. As minimum treatment response, the European and German guidelines mention a PASI 50 response. Higher levels of clearance (PASI 90), as well as complete resolution of psoriasis (PASI 100), have become additional endpoints because of the increasing recognition of the association of higher clearance with greater health-related quality of life (Puig 2015).

Participants achieving PASI 75, 90, or 100 are defined as having an improvement of at least 75%, 90%, or 100%, respectively, in the PASI, compared to baseline.

8.1.1.2.Static Physician Global Assessment

The sPGA is the physician's determination of the participant's psoriatic lesions, overall, at a given time point. The sPGA is recommended as an endpoint to assess efficacy in the treatment of PsO/PsA (EMA 2004). 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).

8.1.1.3.Percentage of Body Surface Area

The investigator will evaluate the percentage involvement of PsO/PsA on each participant's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), in which 1% corresponds to the size of the participant's palm of the hand, including the palm, fingers, and thumb (NPF 2018).

8.1.2. American College of Rheumatology 20, 50, and 70 Responder Index

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

1) ≥20%, ≥50%, and ≥70% improvement from baseline in tender joint count (TJC); and
2) ≥20%, ≥50%, and ≥70% improvement from baseline in swollen joint count (SJC); and
3) ≥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

ACR20, ACR50 and ACR70 responses will be assessed over Week 24 (Visit 6).

American College of Rheumatology Core Set

Tender Joint Count

For ACR measures, the number of tender and painful joints will be determined by examination of 68 joints (34 joints on each side of the participant's body). The 68 joints to be assessed and classified as tender or not tender are detailed in Section 10.7. Any joints that require intra-articular injections during the study (according to Section 6.8 should be excluded from evaluation from the time of the injection to the conclusion of the study.

Joints will be assessed for tenderness by pressure and joint manipulation on physical examination. The participant will be asked for pain sensations on these manipulations and watched for spontaneous pain reactions. Any positive response on pressure, movement, or both will then be translated into a single tender-versus-nontender dichotomy.

Joint assessments will be performed by an independent, blinded assessor to minimize bias. The same assessor should preferably perform the TJC and SJC for a given participant particularly during the Induction Dosing Period (Period 2) to minimize interobserver variation. The blinded joint assessor will not be involved in participant care and is asked not to discuss disease activity or treatment with participants or principal investigator.

Missing, replaced, ankylosed, or arthrodesed joints will be identified by the investigator at the Screening Visit and will be excluded from evaluation during the trial.

Swollen Joint Count

For ACR measures, the number of swollen joints will be determined by examination of 66 joints (33 joints on each side of the participant's body). The 66 joints to be assessed and classified as swollen or not swollen are detailed in Section 10.7. Any joints that require intra-articular injections during the study (according to Section 6.8) should be excluded from evaluation from the time of the injection to the conclusion of the study.

Joints will be classified as either swollen or not swollen. Swelling is defined as palpable fluctuating synovitis of the joint. Swelling secondary to osteoarthritis will be assessed as not swollen, unless there is unmistakable fluctuation. Dactylitis should be counted as 1 joint.

Missing, replaced, ankylosed, or arthrodesed joints will be identified by the Investigator at the Screening Visit and will be excluded from evaluation during the trial.

Joint assessments will be performed by an independent, blinded assessor to minimize bias. The same assessor should preferably perform the TJC and SJC for a given participant particularly during the Induction Dosing Period (Period 2) to minimize interobserver variation. The blinded joint assessor will not be involved in participant care and will be instructed not to discuss disease activity or treatment with participants or principal investigator.

Patient's Assessment of Pain Visual Analog Scale

Patient's Assessment of Pain VAS will be administered only to PsA participants. The question related to pain assessment will be included in HAQ-DI assessment.

The participant will be asked to assess his/her current level of joint pain by marking a vertical tick on a 100-mm horizontal VAS where the left end represents no joint pain and the right end represents worst possible joint pain. The Patient's Assessment of Pain VAS should be administered *prior to* the TJC and SJC examinations.

Results will be expressed in millimeters, measured between the left end of the scale and the crossing point of the vertical line of the tick; *this procedure is applicable for all VAS used in the trial.*

Patient's Global Assessment of Disease Activity Visual Analog Scale

The participant's overall assessment of his/her PsA activity will be recorded using the 100 mm horizontal VAS where the left end represents no disease activity, and the right end represents extreme disease activity.

Physician's Global Assessment of Disease Activity Visual Analog Scale

The Investigator will be asked to give an overall assessment of the severity of the participant's current PsA activity using a 100 mm horizontal VAS, where 0 represents no disease activity and 100 represents extremely active disease. The investigator making the assessment must be a rheumatologist or medically qualified physician. The same assessor should preferably perform the Physician's Global Assessment of Disease Activity VAS for a given participant particularly during the Induction Dosing Period (Period 2) to minimize interobserver variation.

Patient's Assessment of Physical Function as Assessed by the Health Assessment Questionnaire-Disability Index

The HAQ-DI is a patient-reported standardized questionnaire that is commonly used in PsA to measure disease-associated disability (assessment of physical function). It consists of 24 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other daily activities (Fries et al. 1980; Fries et al. 1982).

The disability section of the questionnaire scores the participant's self-perception on the degree of difficulty (0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do), covering the 8 domains. The reported use of special aids or devices and/or the need for assistance of another person to perform these activities is also assessed. The scores for each of the functional domains will be averaged to calculate the functional disability index. Details of scoring and calculations are presented in the statistical analysis plan (SAP).

C-Reactive Protein

CRP will be the ACR Core Set measure of acute phase reactant. It will be measured with a high sensitivity assay at the central laboratory to help assess the effect of ixekizumab on the participant's PsA.

Disease Activity Score based on C-Reactive Protein

The DAS28-CRP is a measure of disease activity in 28 joints that consists of a composite numerical score utilizing the following variables: TJC, SJC, hs-CRP (measured in mg/L), and Patient's General Assessment recorded by participants on a 0 to 100 mm VAS.

For DAS28-CRP, the 28 joints to be examined and assessed as tender or not tender for TJC 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 (Smolen et al. 1995). The following equation will be used to calculate the DAS28-CRP (Vander Cruyssen et al. 2005):

$$DAS28-CRP = 0.56\left(\sqrt{TJC28}\right)+0.28\left(\sqrt{SJC28}\right)+0.36(\ln(CRP+1))+0.014(VAS)+0.96$$

8.1.3. Patient Global Assessment of Disease Activity VAS

The participant's overall assessment of his/her PsO and PsA activity will be recorded using the 100 mm horizontal VAS where the left end represents no disease activity, and the right end represents extreme disease activity.

8.1.4. Physician's Global Assessment of Disease Activity Visual Analog Scale

The Investigator will be asked to give an overall assessment of the severity of the participant's current PsO and PsA activity using a 100 mm horizontal VAS, where 0 represents no disease activity and 100 represents extremely active disease. The investigator making the assessment must be a rheumatologist or medically qualified physician. The same assessor should preferably perform the Physician's Global Assessment of Disease Activity VAS for a given participant particularly during the Induction Dosing Period (Period 2) to minimize interobserver variation.

8.2. Safety Assessments

Any clinically significant findings from physical examination, vital signs measurements, or laboratory measurements that result in a diagnosis and that occur after the participant receives the first dose of the study intervention should be reported to the Sponsor or its designee as an AE via eCRF.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

The complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed according to the SoA (Section 1.3). This examination will determine whether the participant meets the criteria required to participate in the study and will also serve as a monitor for preexisting conditions and as a baseline for TEAE assessment. All physical examinations throughout the study should include an examination of the heart, lungs, and abdomen and a visual examination of the skin.

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3).

Vital signs (sitting BP and pulse) and body temperature will be measured after resting for a minimum of 10 minutes at times indicated in the study schedule. At baseline (Week 0, Visit 2),

Week 12 (Visit 5), and Week 24 (Visit 6), sitting BP and pulse should be measured prior to administration of the investigational product and again approximately 1 hour after administration.

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the participant receives the first dose of the study intervention should be reported to the Sponsor or its designee as an AE via electronic data entry. Additional measurements of vital signs may be performed at the discretion of the investigator.

8.2.3. Electrocardiograms

For each participant, a 12-lead digital ECG will be collected locally only at screening visit according to the Study Schedule (Section 1.3). Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine, but awake, during ECG collection.

Electrocardiograms will be interpreted by a qualified physician as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets entry criteria and for immediate participant management, should any clinically relevant findings be identified. The qualified physician must document his/her review of the ECG at the time of evaluation.

The ECG will be maintained at the site and made available to the Sponsor as requested.

8.2.4. Evaluation of Disease Relapse

Patients will be assessed for the presence or absence of relapse at screening based on the following definitions:

a. Assessment of relapse for psoriasis participants:

Relapse is defined as worsening of psoriasis from the previous routine medical visit by 50% PASI or 1% BSA or sPGA ≥3 (Tian and Lai 2016).

If PASI, BSA, or sPGA are not available in medical report, relapse of psoriasis is defined as any worsening of psoriatic lesions that would, if persistent, in most cases require initiation or change of systemic therapy for psoriasis.

During the study period, relapse with ixekizumab would be defined as worsening of psoriasis from the previous visit by 50% PASI or 1% BSA or sPGA ≥3.

Relapse present based on the above definition: Yes/No

Following details will be collected in addition in all PsO participants:

- Duration of the psoriasis since diagnosis:
- Duration of the psoriatic arthritis since diagnosis:
- Prior systemic medications used for psoriasis:
    - Name of the drug and dose
    - Start date
    - End date
- Prior systemic medications used for psoriatic arthritis:
    - Name of the drug and dose

- Start date
- End date

b. Assessment of relapse for psoriatic arthritis participants:

Relapse is defined as an increase in PsA disease activity from the previous routine medical records

- either DAS28 (erythrocyte sedimentation rate [ESR]) >2.6 and DAS28 (ESR) increase >0.6 or
- DAS28 (ESR) increase ≥1.2, irrespective of absolute DAS28(ESR) (Emery et al. 2020; Helliwell et al. 2021).

If DAS-28 ESR is not available in medical records, relapse of PsA is defined as any increase in disease activity that would, if persistent, in most cases require initiation or change of systemic therapy for PsA.

Relapse present based on the above definition: Yes/No

Additionally, the following details will be collected in all PsA participants:

- Duration of the psoriasis since diagnosis:
- Duration of the psoriatic arthritis since diagnosis:
- Prior systemic medications used for psoriasis:
  - Name of the drug and dose
  - Start date
  - End date
- Prior systemic medications used for psoriatic arthritis:
  - Name of the drug and dose
  - Start Date
  - End date

8.2.5. Clinical Safety Laboratory Tests

See Appendix 10.2 for the list of clinical laboratory tests to be performed by a Lilly-designated or local laboratory and the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within a time period equivalent to the maximum 5 half-lives of active interventions after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 10.2, must be conducted in accordance with the SoA (Section 1.3), standard collection requirements, and applicable study laboratory manual.

If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then report the information as an AE.

8.2.6. Pregnancy Testing

See the SoA (Section 1.3) for frequency of pregnancy testing and Appendix 10.2 for additional details about these tests.

At screening

Serum pregnancy tests will be given prior to the first dose of the study intervention for females ≥10 years of age (<10 years at investigator discretion) if menarche has been reached or if there is reason to believe the participant is sexually active. Pregnancy test results at screening must be known prior to first dose of the study intervention.

During the induction dosing and maintenance period

Female participants of childbearing potential (age 10 and older if menarche has been reached or if there is reason to believe the participant is sexually active, or younger participants per investigator assessment of sexual maturity) will undergo a urine pregnancy test at the clinic on a quarterly basis during scheduled regular visits through Week 156 or the ETV. Additional urine pregnancy testing may be performed at the investigator's discretion. Participants determined to be pregnant will be discontinued from treatment and will no longer be administered study intervention (see Section 7.1.1).

During the post-treatment follow-up period

As indicated in the SoA (Section 1.3), urine pregnancy tests will be collected during each of the post-treatment follow-up visits.

8.2.7. Chest X-Ray and Tuberculosis Testing

An anterior-posterior view chest x-ray will be obtained, unless the x-ray or results from a chest x-ray obtained within 6 months before the study are available. The chest x-ray or results will be reviewed by the investigator or designee to exclude participants with active TB infection prior to enrollment.

Tuberculosis testing will be conducted based on clinical assessment of TB risk (symptoms, signs, and known or suspected TB exposure), and as required by local regulations and/or local standard of care. Participants with a positive TB test and/or other evidence of active TB should be discontinued (Section 7.1.1).

Tuberculosis testing – QuantiFERON® TB Gold will be the preferred testing option for TB. The QuantiFERON® TB Gold test may be performed locally or centrally. If the QuantiFERON®-TB Gold test is indeterminate (not negative), 1 retest is allowed. If the retest for the QuantiFERON®-TB Gold test is indeterminate (not negative), the participant is excluded from enrollment in the study.

In countries where the QuantiFERON®-TB Gold test is not available or due to investigator's judgement (e.g., need to reduce the volume of blood collected), the T-Spot or PPD test may be used. In the case of selecting the PPD test, the participant must return within 48 to 72 hours to read the skin test.

A positive PPD skin test response for this study is defined as ≥5-mm induration between 48 and 72 hours after PPD application, regardless of BCG vaccination history.

Participants with a PPD skin test ≥5 mm induration or a positive QuantiFERON®-TB Gold or T-Spot test but no evidence of active TB, and participants who have a documented history of a positive TB test but no documented history of completion of a full, appropriate latent TB treatment course, who are assessed as having latent TB infection may be re-screened 1 time and may be enrolled without repeating a QuantiFERON®-TB Gold, T-Spot or PPD test if the following conditions are met:

- after receiving at least 4 weeks of appropriate latent TB infection therapy with no evidence of hepatotoxicity (ALT/AST must remain ≤2 × ULN) upon retesting of serum ALT/AST prior to enrolment,
- commitment by the participant and the caregiver for the participant to complete a full course of standard prophylaxis for TB, and
- meet all other inclusion/exclusion criteria for participation.

Such participants must complete appropriate latent TB infection therapy to remain eligible for continued study participation. If rescreening occurs within 6 months of the screening chest x-ray, a repeat of chest x-ray for considering enrollment is not required.

If a participant with a positive QuantiFERON®-TB Gold or T-Spot or PPD is fully assessed by the investigator and the investigator determines that the participant has no risk factors for and no symptoms or signs of *Mycobacterium tuberculosis* infection, the investigator may contact the Sponsor's medical monitor to discuss the possibility of a false-positive test result.

Participants with positive TB test results on file: Participants with a documented prior history of a positive TB test and participants who have a documented history of completion of an appropriate TB treatment regimen for latent or active TB should not have a TB test performed at Visit 1. Such participants with no history of re-exposure to TB since their treatment was completed and no evidence of active TB are eligible to participate in the study. Participants who have had household contact with a person with active TB are excluded unless an appropriate and documented course of prophylaxis for TB was completed.

Participants are to be monitored on a regular basis for any symptoms or signs of active TB and for any new risk factors for TB infection, with full medical evaluation including TB testing when medically indicated. Participants that exhibit symptoms of active TB should be referred to a specialist in the care of participants with TB.

Any clinically significant findings from TB testing that result in a diagnosis and that occur after the participant signs the ICF should be reported to the Sponsor or its designee as an AE via eCRF.

8.2.8. Safety Monitoring

The Sponsor will periodically review evolving aggregate safety data within the study by appropriate methods.

8.2.8.1. Hepatic Safety Monitoring

Close hepatic monitoring

Laboratory tests (Appendix 10.5), including ALT, AST, alkaline phosphatase (ALP), total bilirubin (TBL), direct bilirubin, gamma-glutamyltransferase (GGT), and creatine kinase (CK), should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of ...	develops the following elevations:
ALT or AST <1.5 × ULN	ALT or AST ≥3 × ULN
ALP <1.5 × ULN	ALP ≥2 × ULN
TBL <1.5 × ULN	TBL ≥2 × ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5 × ULN	ALT or AST ≥2 × baseline
ALP ≥1.5 × ULN	ALP ≥2 × baseline
TBL ≥1.5 × ULN	TBL ≥2 × baseline (except for participants with Gilbert's syndrome)

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (e.g., heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, and a history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be decreased to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5 × ULN	ALT or AST ≥3 × ULN with hepatic signs/symptoms*, or ALT or AST ≥5 × ULN
ALP <1.5 × ULN	ALP ≥3 × ULN
TBL <1.5 × ULN	TBL ≥2 × ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5 × ULN	ALT or AST ≥2 × baseline with hepatic signs/symptoms,* or ALT or AST ≥3 × baseline
ALP ≥1.5 × ULN	ALP ≥2 × baseline
TBL ≥1.5 × ULN	TBL ≥1.5 × baseline (except for participants with Gilbert's syndrome)

* Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time - international normalized ratio (PT-INR); tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (e.g., ultrasound or CT scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy.

8.2.8.1.1. Additional Hepatic Data Collection in Participants Who Have Abnormal Liver Tests During the Study

Additional hepatic safety data collection in hepatic safety eCRFs should be performed in study participants who meet 1 or more of the following 5 conditions:

- Elevation of serum ALT to ≥5 × ULN on 2 or more consecutive blood tests (if baseline ALT <1.5 × ULN):
    - In participants with baseline ALT ≥1.5 × ULN, the threshold is ALT ≥3 × baseline on 2 or more consecutive tests;
- Elevated TBL to ≥2 × ULN (if baseline TBL <1.5 × ULN) (except for cases of known Gilbert's syndrome):
    - In participants with baseline TBL ≥1.5 × ULN, the threshold should be TBL ≥2 × baseline;
- Elevation of serum ALP to ≥2 × ULN on 2 or more consecutive blood tests (if baseline ALP <1.5 × ULN):

  - In participants with baseline ALP ≥1.5 × ULN, the threshold is ALP ≥2 × baseline on 2 or more consecutive blood tests;
- Hepatic event considered to be an SAE;
- Discontinuation of study intervention due to a hepatic event.

Note: the interval between the 2 consecutive blood tests should be at least 2 days.

8.2.8.2. Hepatitis C Testing and Monitoring

Initial testing for HCV infection includes testing for antibodies to HCV:

- If anti-HCV is positive, a serum test for circulating HCV RNA is required.
- If HCV RNA test is negative, the participant is not excluded.
- If HCV RNA test is positive, the participant is excluded.

Participants who have had HCV infection and been successfully treated, defined as a sustained virologic response (HCV RNA by PCR-negative for at least 24 weeks following treatment completion) are not excluded on the basis of HCV as long as HCV RNA test is negative at screening.

If HCV RNA is detected during the study, the study intervention will be discontinued (see Section 7.1.1), and the participant should receive appropriate follow-up medical care.

8.2.8.3. Hepatitis B Testing and Monitoring

Initial testing for hepatitis B virus (HBV) infection includes hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen (anti-HBc):

- If HBsAg is positive, the participant is excluded;
- If HBsAg is negative and anti-HBc is negative, the participant is not excluded;
- If HBsAg is negative and anti-HBc is positive, further testing for HBV DNA is required:
  - If the screening HBV DNA is positive, the participant is excluded;
  - If the screening HBV DNA is negative, the participant is not excluded. Repeat testing for HBV DNA is required at least every 3 months during the study (see the SoA [Section 1.3]), with temporary withholding or permanent discontinuation of study intervention if HBV DNA is positive, as described in Section 7.1.1.

Management of enrolled participants with detectable HBV DNA during the study

If HBV DNA is detected during the study, the study intervention will be temporarily withheld or permanently discontinued, and participants should receive appropriate follow-up medical care as described in Section 7.

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Appendix 10.3:

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Product complaints (PCs)

These events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.3.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 10.3.

8.3.1. Timing and Mechanism for Collecting Events

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All AEs will be collected from the signing of the ICF until participation in the study has ended.

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event eCRF.

Although all AEs after signing the ICF and Assent Form (as applicable) are recorded by the site in the eCRF/electronic data entry, SAE reporting to the Sponsor begins after the participant has signed the ICF and has received study intervention. However, if an SAE occurs after signing the ICF, but prior to receiving ixekizumab, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.3. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available. Participants with a serious hepatic AE should have additional data collected using the electronic data entry.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive intervention.
- After learning of a pregnancy in the female partner of a study participant, the investigator will:
    - obtain a consent to release information from the pregnant female partner directly; and
    - within 24 hours after obtaining this consent, will record pregnancy information on the appropriate form and submit it to the Sponsor.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.

- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Adverse Events of Special Interest

The following adverse events of special interest (AESIs) will be used to determine the safety and tolerability of ixekizumab over the range of doses selected for this clinical study.

Adverse events of special interests for ixekizumab are the following:

- cytopenias (leukopenia, neutropenia, and thrombocytopenia),
- liver function test changes/enzyme elevations (ALT, AST, bilirubin, and ALP),
- infections,
- injection-site reactions,
- allergic reactions/hypersensitivities,
- cerebro-cardiovascular events,
- malignancies,
- inflammatory bowel disease (IBD), and
- depression.

Sites will provide details on AEs as instructed on the eCRF. Investigators will also educate participants and/or caregivers about the symptoms of systemic allergic/hypersensitivity reactions and will provide instructions on the management and reporting of these reactions. Blood samples will be collected as soon as possible for any participant who experiences an AE of a potential systemic allergic/hypersensitivity reaction during the study, as judged by the investigator. These samples may be tested for antidrug antibodies (ADAs), other laboratory tests needed to elucidate the cause of the allergic/hypersensitivity reaction, and/or ixekizumab serum concentration.

8.4. Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Health Economics or Medical Resource Utilization and Health Economics]

Health economics or medical resource utilization and health economics parameters are not evaluated in this study

9. Statistical Considerations

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical Hypotheses

No statistical hypotheses testing is planned for this study.

9.2. Analyses Populations

The following analysis populations will be used; additional analysis populations will be specified in the SAP:

Analysis Population	Description
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 receive at least 1 dose of study treatment, even if the participant does not receive the correct treatment, or otherwise does not follow the protocol.
Active PsA – 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 receive at least 1 dose of study treatment, even if the participant does not receive the correct treatment, or otherwise does not follow the protocol.
Safety Population	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 analyzed according to the treatment to which they are assigned.

9.3 Missing Data Imputation

The following methods for imputation of missing data will be used:

9.3.1 General Nonresponder Imputation for Clinical Response

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

- do not meet the clinical response criteria (e.g., ACR20, PASI75, PASI90, PASI100, 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.

9.4 Study Participant Disposition and Characteristics

9.4.1 Study Participant Disposition

All participants who prematurely discontinue from the study treatment and/or from the study will be identified, and the extent of their participation in the study will be reported.

Patient disposition will be summarized for each treatment period with reasons for discontinuation.

9.4.2 Study Participant Characteristics

Participant demographic characteristics and baseline clinical measures will be summarized overall. Baseline characteristics will include sex, age, age category, weight, body mass index, race, and other demographic characteristics as per the SoA (Section 1.3).

9.4.3 Concomitant Therapy

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).

9.4.4 Treatment Compliance

Treatment compliance with investigational product will be summarized for participants who enter the treatment. 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).

Proportions of participants compliant by visit and overall will be reported.

9.5 Statistical Analyses

9.5.1. General Considerations

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

Unless otherwise specified, continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, median, and number of observations. Categorical data will be summarized as frequency counts and percentages.

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). Change from baseline will be calculated as the visit value of interest minus the baseline value. For safety analyses using a baseline period, the baseline period is defined as the time from Visit 1 to the date/time of the first injection.

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). Additional exploratory analyses of the data will be conducted, as deemed appropriate.

Complete details of the planned analyses will be documented in the SAP.

9.5.2 Primary Endpoint Analysis

The primary analysis, the number and percentage of participants in the safety population experiencing:

- 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, allergic reactions/hypersensitivities, injection-site reactions, cerebrocardiovascular events, major adverse cerebrocardiovascular events [MACE], malignancies, depression, IBD, interstitial lung disease [ILD]).

These AEs, occurring within the duration of the study (24 weeks) after being started on Ixekizumab, will be summarized. 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.

Refer to Section 9.5.5.1 for further details.

9.5.3 Secondary Endpoint(s) Analysis

Endpoints Specific to Psoriasis (PsO) and Psoriatic Arthritis (PsA) Participants with 3% or More BSA of PsO

As a part of the secondary analyses, the following endpoints will be summarized (i) for the PsO indication and will be based on the PsO with no active PsA– mITT population, and (ii) for the active PsA indication and will be based on the active PsA – mITT population with BSA of PsO ≥3% at baseline, unless otherwise specified:

Proportion of Participants with sPGA (0 or 1)

The proportion of participants achieving sPGA response of 0 or 1 at Week 12 will be summarized and the associated 95% confidence interval (CI) will be provided using normal approximation. Missing data will be imputed using the NRI method as defined in Section 9.3.1. Further details will be provided in SAP.

Proportion of Participants with PASI 75

The proportion of participants achieving a PASI 75 response at Week 12 will be summarized and the associated 95% CI will be provided using normal approximation. Missing data will be imputed using the NRI method as defined in Section 9.3.1. Further details will be provided in SAP.

Endpoints Specific to Psoriatic Arthritis (PsA)

As a part of the secondary analyses, the following endpoint will be summarized for the PsA indication and will be based on the active PsA-mITT population:

Percentage of Participants Achieving ACR20

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. Further details will be provided in SAP.

CCI

9.5.5 Safety Analyses

Safety will be assessed by summarizing AEs, laboratory analytes and vital signs. Abnormal physical examinations and concomitant medications will be listed. The overall duration of treatment exposure will also be summarized.

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

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

All safety analyses will be based on the safety population and will be summarized overall and by dosing regimen (Q2W/Q4W and Q4W/Q4W) as specified in Table RHCZ.6.1.

Further details will be described in the SAP.

9.5.5.1.Adverse Events

Adverse events are classified based upon MedDRA. A 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. 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.

A summary of AEs will be provided overall and by dosing regimen, including the number and percentage of participants who reported TEAEs, TEAEs by maximum severity, death, SAEs, TEAEs related to study intervention, discontinuations from the treatment due to an AE, and treatment-emergent AESIs: cytopenias, infections, injection-site reactions (ISRs), allergic reactions/hypersensitivities, cerebrocardiovascular events, MACE, malignancies, depression, IBD, ILD. TEAEs (all, by maximum severity, and possibly related to study intervention by the investigator), SAEs including deaths, AEs that lead to treatment discontinuation will be summarized by MedDRA system organ class (SOC) and PT.

In addition to general safety parameters, safety information on specific topics of AESIs will also be presented. Potential AESIs will be identified by a standardized MedDRA query (SMQ) or a Lilly defined MedDRA PT listing.

FEAEs, SAEs (including deaths), and AEs that lead to study discontinuation will be summarized.

9.5.5.2.Clinical Laboratory Tests

Laboratory assessments will be presented as mean changes from baseline and as incidence of treatment-emergent abnormal, high, or low laboratory values (see below). Shift tables will be presented for selected parameters.

- For categorical laboratory tests:
  - 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.

9.5.5.3.Vital Signs

Vital signs will be presented as mean changes from baseline and as incidence of treatment-emergent high or low values (see below) and will be summarized both pre- and post dose at Week 0 (Visit 2) and postbaseline visits, as applicable.

- 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.

9.6 Interim Analysis

No interim analysis planned.

9.7 Sample Size Determination

No formal sample size calculation was done for this study.

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

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an ERB by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2 Financial Disclosure

Investigators and sub investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary.
- Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations (CFR) 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- If a participant reaches the age of legal consent during the study, an ICF must be obtained from the participant for his or her continued participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records, datasets, or tissue samples that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that the participant's personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The Sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- In addition, Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor.

An electronic data capture system (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the Sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the Sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the EDC systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Sponsor's data warehouse.

Data from complaint forms submitted to the Sponsor will be encoded and stored in the global product complaint management system.

10.1.6 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.5.

10.1.7 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the opening of the first site and will be the study start date.

Study or Site Termination

The Sponsor or Sponsor's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development;

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines;
- Inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.8 Publication Policy

In accordance with the Sponsor's publication policy the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.9 Investigator Information

Physicians with experience in the diagnosis and treatment of PsO and PsA will participate as investigators in this clinical trial.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the central laboratory or by the local laboratory as specified in the table.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Pregnancy testing is described in the SoA (Section 1.3) and in the table below.

Investigators must document their review of each laboratory safety report.

Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the Sponsor provided weight-based prioritization chart.

Hematology[a,b]
Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Mean cell volume (MCV)
Mean cell hemoglobin concentration (MCHC)
Leukocytes (WBC)
Platelets

Absolute counts of:
Neutrophils, segmented
Neutrophils, juvenile (bands)
Lymphocytes
Monocytes
Eosinophils
Basophils

Urinalysis[a,b]
Color
Specific gravity
pH
Protein
Glucose[g]
Ketones
Bilirubin
Urobilinogen
Blood
Nitrite
Urine creatinine
Leukocyte esterase
Urinalysis (microscopic):
Sediment, cells, casts

Serum Chemistry[a,b]
Sodium
Potassium
Bicarbonate
Chloride
Phosphorus
Total bilirubin
Direct bilirubin
Indirect bilirubin
Alkaline phosphatase
Alanine aminotransferase (ALT/SGPT)
Aspartate aminotransferase (AST/SGOT)
Blood urea nitrogen (BUN)
Uric acid
Creatinine
Calcium
Glucose[g]
Albumin
Cholesterol (total)
Total protein
CPK
Triglycerides
Gamma-Glutamyl Transferase (GGT)

Other Tests[a]

Human immunodeficiency virus antibody (HIV)[c,d]
Hepatitis B Surface antigen (HBsAg)[c,d]
Anti-Hepatitis B Core antibody (HBcAb)[c,d]
Anti-Hepatitis B Surface antibody (HBsAb)[d]
Anti-Hepatitis C [d]
HBV DNA[c,d]

Tuberculosis[d]

Pregnancy Test (serum and urine)[e]
Follicle stimulating hormone (FSH)[d,f]

Abbreviations: CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cells.

[a] Assayed by Sponsor-designated laboratory.
[b] Unscheduled blood chemistry, urinalysis, and hematology panels may be performed at the discretion of the investigator.
[c] See exclusion criteria (Section 5.2).
[d] Test required at Visit 1 only to determine eligibility of participant for the study (with the exception of those participants who require further HBV monitoring [Section 8.2.8.3]).
[e] Serum pregnancy test (women <60 years of age who are still of childbearing potential) and urine pregnancy test (women of childbearing potential). Participants will undergo urine pregnancy self-testing at home on a monthly basis during periods between scheduled visits until Week 24. During these intervisit periods, the site must call the participant each month to obtain her pregnancy test results. Additional urine pregnancy testing can be performed at the investigator's discretion. Participants determined to be pregnant will be discontinued from treatment and will no longer be administered study intervention (see Section 7.1.1).
[f] Women ≥40 and <60 years of age who have had a cessation of menses for ≥12 months will have an FSH test confirming nonchildbearing potential (≥40 mIU/mL). The FSH test will be performed centrally.
[g] Non-fasting glucose.

10.3 Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae. • “Lack of efficacy” or “failure of expected pharmacological action,” per se, will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life-threatening The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Definition of Product Complaints

Product Complaint

- A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he/she has a PC or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

10.3.4 Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and Product Complaint Recording

- When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and PC information is reported on the Product Complaint Form.

  Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for PCs.
- There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

10.3.5 Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable or if a pregnancy is reported, then the site will use the paper SAE or pregnancy data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor or designee by telephone.
- Contacts for SAE reporting can be found in the site training documents.

SAE Reporting via Paper Form

- In the event the electronic system is unavailable, facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the site training documents

10.3.6 Regulatory Reporting Requirements

SAE Regulatory Reporting

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

A postmenopausal female is defined as women with:

- At least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note.

OR

- With spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g., oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that induced the amenorrhea. And if age ≤50, has an FSH of ≥40 mIU/mL and estradiol of ≤ 30 pg/mL.

Contraception guidance for women of childbearing potential (WOCBP):

See Section 5.1, inclusion criterion [1b].

Contraception guidance for men:

See Section 5.1, inclusion criterion [1a].

10.4.2 Contraception Guidance

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on a male participant's female partner who becomes pregnant while the male participant is in this study.

After obtaining the necessary signed informed consent and/or assent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed up to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported, including fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed up to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, including fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor. While the investigator is not obligated to actively seek this information in former study participants, the investigator may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will permanently discontinue the study intervention (see Section 7.1.1).

10.5 Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments

See Section 8.2.8.1 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed in addition to central testing when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs – red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs – white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin A (IgA, quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin G (IgG, quantitative)
HAV total antibody	Immunoglobulin M (IgM, quantitative)
HAV IgM antibody	Phosphatidylethanol (Peth)
Hepatitis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA)[a]

Hematology	**Clinical Chemistry**
HBV DNA[d]	Anti-actin antibody[b]
Hepatitis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[d]	EBV DNA[d]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[d]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[d]	HSV (Type 1 and 2) DNA[d]
Microbiology[c]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.
[b] Not required if anti-smooth muscle antibody (ASMA) is tested.
[c] Assayed ONLY by investigator-designated local laboratory; no central testing available.
[d] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

10.6 Appendix 6: Protocol RHCZ CASPAR Criteria

CASPAR Criteria

The CASPAR criteria for psoriatic arthritis consist of inflammatory articular disease (joint, spine, or entheseal) with ≥**3 points** from the following 5 categories.

- Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis **(2 points)**
    - Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.†
    - A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a participant, family physician, dermatologist, rheumatologist, or other qualified healthcare provider.
    - A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to participant report.
- Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination **(1 point)**
- A negative test result for the presence of rheumatoid factor by any method except latex **(1 point)**
- Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist **(1 point)**
- Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot **(1 point)**

† Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

Taylor, W, Gladman, D, Helliwell, P, et al.; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum.* 2006;54(8):2665–2673.

10.7 Appendix 7: Protocol RHCZ Tender and Swollen Joint Count Assessment Form

68/66 JOINT EVALUATION												
	Patient Right						Patient Left					
	Pain/Tenderness			Swelling			Pain/Tenderness			Swelling		
JOINT* (Circle Correct Answer)	0 = Absent 1 = Present 9 = Not applicable*			0 = Absent 1 = Present 9 = Not applicable*			0 = Absent 1 = Present 9 = Not applicable*			0 = Absent 1 = Present 9 = Not applicable*		
1. Temporomandibular	0	1	9	0	1	9	0	1	9	0	1	9
2. Sternoclavicular	0	1	9	0	1	9	0	1	9	0	1	9
3. Acromioclavicular	0	1	9	0	1	9	0	1	9	0	1	9
4. Shoulder	0	1	9	0	1	9	0	1	9	0	1	9
5. Elbow	0	1	9	0	1	9	0	1	9	0	1	9
6. Wrist	0	1	9	0	1	9	0	1	9	0	1	9
7. Metacarpophalangeal I	0	1	9	0	1	9	0	1	9	0	1	9
8. Metacarpophalangeal II	0	1	9	0	1	9	0	1	9	0	1	9
9. Metacarpophalangeal III	0	1	9	0	1	9	0	1	9	0	1	9
10. Metacarpophalangeal IV	0	1	9	0	1	9	0	1	9	0	1	9
11. Metacarpophalangeal V	0	1	9	0	1	9	0	1	9	0	1	9
12. Thumb Interphalangeal	0	1	9	0	1	9	0	1	9	0	1	9
13. Proximal Interphalangeal II	0	1	9	0	1	9	0	1	9	0	1	9
14. Proximal Interphalangeal III	0	1	9	0	1	9	0	1	9	0	1	9
15. Proximal Interphalangeal IV	0	1	9	0	1	9	0	1	9	0	1	9
16. Proximal Interphalangeal V	0	1	9	0	1	9	0	1	9	0	1	9
17. Distal Interphalangeal II	0	1	9	0	1	9	0	1	9	0	1	9
18. Distal Interphalangeal III	0	1	9	0	1	9	0	1	9	0	1	9
19. Distal Interphalangeal IV	0	1	9	0	1	9	0	1	9	0	1	9
20. Distal Interphalangeal V	0	1	9	0	1	9	0	1	9	0	1	9
21. Hip	0	1	9	N/A			0	1	9	N/A		

68/66 JOINT EVALUATION												
	Patient Right						Patient Left					
	Pain/Tenderness			Swelling			Pain/Tenderness			Swelling		
JOINT* (Circle Correct Answer)	0 = Absent 1 = Present 9 = Not applicable*			0 = Absent 1 = Present 9 = Not applicable*			0 = Absent 1 = Present 9 = Not applicable*			0 = Absent 1 = Present 9 = Not applicable*		
22. Knee	0	1	9	0	1	9	0	1	9	0	1	9
23. Ankle	0	1	9	0	1	9	0	1	9	0	1	9
24. Tarsus	0	1	9	0	1	9	0	1	9	0	1	9
25. Metatarsophalangeal I	0	1	9	0	1	9	0	1	9	0	1	9
26. Metatarsophalangeal II	0	1	9	0	1	9	0	1	9	0	1	9
27. Metatarsophalangeal III	0	1	9	0	1	9	0	1	9	0	1	9
28. Metatarsophalangeal IV	0	1	9	0	1	9	0	1	9	0	1	9
29. Metatarsophalangeal V	0	1	9	0	1	9	0	1	9	0	1	9
30. Great Toe	0	1	9	0	1	9	0	1	9	0	1	9
31. Interphalangeal II	0	1	9	0	1	9	0	1	9	0	1	9
32. Interphalangeal III	0	1	9	0	1	9	0	1	9	0	1	9
33. Interphalangeal IV	0	1	9	0	1	9	0	1	9	0	1	9
34. Interphalangeal V	0	1	9	0	1	9	0	1	9	0	1	9

Abbreviation: N/A = not applicable.

* For replaced, ankylosed, or arthrodesed joints, please record as 9 (not applicable) and record details of replaced, ankylosed, arthrodesed joints.

10.8 Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [a]: 03 February 2023

Overall Rationale for the Amendment

Protocol I1F-IN-RHCZ, 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, has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The following are the overall rationale for the changes made to this protocol:

- To comply with Subject Expert Committee (SEC; Ministry of Health [MoH]) recommendations, and
- To provide more clarity regarding the assessments to be collected and analyzed for the PsA participants who have active plaque psoriasis.

Other minor corrections (spelling errors, grammar corrections, formatting, and so on) and clarifications or semantic changes not affecting content have also been made in the document.

The overall changes and rationale for the changes made to this protocol are provided in below table:

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Protocol Synopsis and Section 3 Objectives and Endpoints	Added a note for Other Efficacy Endpoints (PASI 75, 90, 100, PASI change from baseline, sPGA [0, 1] and sPGA [0], and BSA change from baseline) - "For PsA participants with 3% or more body surface area (BSA) of PsO, both PsA and PsO efficacy outcomes will be collected."	To provide more clarity regarding the assessments to be collected and analyzed for the PsA participants who have active plaque psoriasis.
Section 1.1 Protocol Synopsis, Section 1.2 Schema and Section 4.1 Overall Design	Updated a statement related to study treatment.	To provide clarity that treatment regimen for PsA participants with moderate-to-severe PsO is same as that for participants with PsO.
Section 1.1 Protocol Synopsis,	Updated text regarding PsA participants with moderate-to-severe PsO is	To provide clarity that treatment regimen for PsA participants with

Section # and Name	Description of Change	Brief Rationale
Section 4.2 Scientific Rationale for Study Design, and Section 6.1 Study Intervention(s) administered	same as that for participants with PsO in synopsis and Section 6.1. Also, updated Tables RHCZ.6.1 and RHCZ.6.2 in Section 6.1.	moderate-to-severe PsO is same as that for participants with PsO.
Section 1.3 Schedule of Activities	Added a row for "Substance use (alcohol, caffeine, tobacco use)."	To collect additional participant history information.
Section 1.3 Schedule of Activities	Added "Evaluation for Disease Relapse" and footnote annotation b.	To comply with Subject Expert Committee (SEC; Ministry of Health [MoH]) recommendations, Disease Relapse Evaluation has been included at screening visit.
Section 1.3 Schedule of Activities	Added a footnote annotation "i" to update a note describing requirement of assessments for participants with psoriatic arthritis (PsA).	To provide clarity on what assessments are to be administered to which participants.
Section 1.3 Schedule of Activities	Removed baseline assessment of "Collect, review, and enter data from Study Intervention Administration Log."	Rectified original protocol typo error.
Section 1.3 Schedule of Activities	Included Week 24 evaluation of active tuberculosis (TB) in patients by QuantiFERON Tuberculosis TB Gold test and chest x-ray.	To comply with SEC (MoH) recommendations, Week 24 evaluation has been included for active tuberculosis by QuantiFERON TB Gold test and chest x-ray at Week 24 of the treatment.
Section 1.3 Schedule of Activities	Modified a general table note at the end of schedule of activities (SoA) table footnote.	To provide more clarity regarding the assessments to be collected and analyzed for the PsA participants who have active plaque psoriasis.
Section 2.1 Study Rationale	Added definition of moderate-to-severe plaque psoriasis.	To clarify original content.

Section # and Name	Description of Change	Brief Rationale
Section 4.1.4 Post-Treatment Follow-Up Period (Period 4)	Timing of follow-up visit, Visit 802 is updated to 8 weeks after Visit 801.	To clarify original content.
Section 8.1 Efficacy Assessment	Updated a statement to mention that PsO outcome will be collected among all the PsA participants with 3% or more BSA of PsO. Added Table RHCZ.8.1 to present clinician and patient assessments for different participants.	To provide clarity on what assessments are to be administered to which participants.
Section 8.1.2 American College of Rheumatology 20, 50, and 70 Responder Index	Included a statement in subsection Patient's Assessment of Pain Visual Analog Scale – "Patient's Assessment of Pain VAS will be administered only to PsA participants. The question related to pain assessment will be included in HAQ-DI assessment."	To clarify original content.
Section 8.1.3 Patient Global Assessment of Disease Activity VAS Section 8.1.4 Physician's Global Assessment of Disease Activity Visual Analog Scale	Added separate scales for PsO and PsA participants.	To clarify original content.
Section 8.2.4 Evaluation of Disease Relapse	Added details for Evaluation of Disease Relapse.	To comply with SEC (MoH) recommendations, Disease Relapse Evaluation has been included at screening visit.
Section 9.2 Analyses Populations.	Updated the definition details of analysis population,	Updated the analysis populations to include PsO with no active PsA population and active PsA population; text was defined accordingly.

Section # and Name	Description of Change	Brief Rationale
Sections 9.5.3 Secondary Endpoint(s) Analysis and 9.5.5 Safety Analyses	Updated the secondary and safety analysis details for each indication and subgroup.	To provide clarity on the analysis of the PsO and PsA endpoints based on the groups or subgroups and corresponding populations as per the data collection. Updated to provide clarity on the stratification for Safety Analyses.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

1.1. Synopsis

Protocol Title: A 24-Week Multicenter, Open-~~l~~Label, Single-~~a~~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

Brief Title: A study to investigate the safety of ixekizumab in participants aged ≥18 years with moderate-to-severe plaque psoriasis and/or active psoriatic arthritis in India

Rationale:

The rationale for this post-approval Phase 4 study is to evaluate the safety and tolerability when ixekizumab is administered to participants in India with moderate-to-severe plaque psoriasis (PsO) and/or active psoriatic arthritis (PsA).

…

Objectives and Endpoints:

…

Objectives	Endpoints
CCI [redacted]	
[redacted]	[redacted]

Objectives	Endpoints
	[redacted]

…

Brief Summary:

The study will consist of 4 periods. The study duration for the 4 study periods are:

- Screening Period (Period 1; 5 to 28 days),
- Induction Dosing Period (Period 2; 12 weeks),
- Maintenance Period (Period 3; 12 weeks), and
- Post-Treatment Follow-Up Period (Period 4; at least 4 weeks after the date of participants' early termination visit [ETV] or last regularly scheduled visit at Week 24).

The following treatment will be assessed in this study for PsO participants with no active PsA and PsA participants who meet criteria for moderate-to-severe PsO (participants with moderate-to-severe plaque psoriasis are defined as those with PASI ≥12, sPGA ≥3, and BSA ≥10%):

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

…

Statistical Analysis:

…

Efficacy analyses in the secondary objectives specific to PsO and PsA will be conducted on the PsO with no active PsA and active PsA participants with at least 1 dose of study intervention and will be summarized with number of responders, response rate and its corresponding 95% confidence intervals (CIs) using normal approximation.

Intervention Groups and Duration:

Treatment Group	Starting Dose W0	Dose W2-W10	Dose[a] W12-W20
Ixekizumab for • PsO participants with no active PsA, and • PsA participants who meet criteria for moderate-to-severe PsO.	Ixekizumab 80 mg 2 × SC (total of 160 mg)	Ixekizumab 80 mg SC Q2W at W2, 4, 6, 8, and 10	Ixekizumab 80 mg SC Q4W at W12, ~~W~~16 and 20
Ixekizumab for PsA participants who do not meet criteria ~~of~~ for moderate-to-severe PsO	Ixekizumab 80 mg 2 × SC (total of 160 mg)	Ixekizumab 80 mg SC Q4W at W4, 8, 12, 16 and 20.	

Abbreviations: PsA = psoriatic arthritis; PsO = psoriasis; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous injection; W = week.

[a] No dose is given at W24; therefore, W24 is not included in this table.

Note: When the dosing is scheduled at home (for PsO ~~group~~ participants with no active PsA and PsA participants who meet criteria for moderate-to severe PsO: W2, W6, W10, W16, and W20; for PsA participants who do not meet criteria of moderate-to-severe PsO: W16 and W20), the participants or care givers will ~~self-~~administer the provided ixekizumab prefilled syringes.

1.2 Schema

1.3 Schedule of Activities (SoA)

Table RHCZ.1.1. Schedule of Activities

	Screening (Period 1)	Induction Dosing (Period 2)				Maintenance (Period 3)		Post Treatment Follow-Up (Period 4)	
		Baseline							As Needed
CRF Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**ETV**	**V801**	**V802**
Study Week		**W0**	**W4**	**W8**	**W12**	**W24**		**LV + W4**	**LV + W8~~12~~**
Study Days	**-28 to -5 d**	**0 d**	**28 ± 3 d**	**56 ± 3 d**	**84 ± 3d**	**168 ± 5 d**		**± 4 d**	**± 4 d**
Informed consent	X								
Complete medical history	X								
Demographics[a]	X								
Substance use (alcohol, caffeine, tobacco use)	X								
Electrocardiogram	X								
Evaluation for Disease relapse[b]	X								
Physical examination[~~c~~b]	X								
Weight	X	X			X	X	X		
Height		X							
Body mass index		X							
Inclusion/exclusion criteria[d]	X	X							
Vital signs	X	X			X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Review preexisting conditions/AEs	X	X	X	X	X	X	X	X	X
Administer study intervention[e]		X	X	X	X				
Dispense study drug		X	X	X	X				
Study drug compliance[f]		X	X	X	X				
Dispense Study Intervention Administration Log		X	X	X	X				
Collect, review, and enter data from Study Intervention Administration Log		~~X~~	X	X	X	X	X		

Schedule of Activities

	Screening (Period 1)	Induction Dosing (Period 2)				Maintenance (Period 3)		Post Treatment Follow-Up (Period 4)	
		Baseline							As Needed
CRF Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**ETV**	**V801**	**V802**
Study Week		**W0**	**W4**	**W8**	**W12**	**W24**		**LV + W4**	**LV + W8~~12~~**
Study Days	**-28 to -5 d**	**0 d**	**28 ± 3 d**	**56 ± 3 d**	**84 ± 3d**	**168 ± 5 d**		**± 4 d**	**± 4 d**
Efficacy Measures									
Clinician-Rated or -Administered Assessments									
PASI[g]	X	X	X	X	X	X	X		
BSA[g]	X	X	X	X	X	X	X		
sPGA[g]	X	X	X	X	X	X	X		
TJC/SJC (68/66 joints)[gh]	X	X	X	X	X	X	X		
PGA Disease Activity VAS[gh]		X	X	X	X	X	X		
Patient-Rated Assessments									
Patient Assessment of Pain VAS[i]		X	X	X	X	X	X		
Patient Global Assessment Disease Activity VAS		X	X	X	X	X	X		
HAQ-DI[i]		X	X	X	X	X	X		
Laboratory Tests									
Chest x-ray (local)[ej]	X					X	X		
Administer Mantoux TB test/QuantiFERON®-TB Gold[~~h~~k]	X					X	X		
HIV/HCV	X								
HBV[~~i~~l]	X	X			X	X	X		X
Serum pregnancy test[jm]	X								
Urine pregnancy test[~~k~~n]		X	X	X	X	X	X		

	Screening (Period 1)	Induction Dosing (Period 2)				Maintenance (Period 3)		Post Treatment Follow-Up (Period 4)	
		Baseline							As Needed
CRF Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**ETV**	**V801**	**V802**
Study Week		**W0**	**W4**	**W8**	**W12**	**W24**		**LV + W4**	**LV + W8~~12~~**
Study Days	**-28 to -5 d**	**0 d**	**28 ± 3 d**	**56 ± 3 d**	**84 ± 3d**	**168 ± 5 d**		**± 4 d**	**± 4 d**
Serum chemistry	X	X			X	X	X		
Hematology	X	X	X		X	X	X	X	X
hs-CRP		X	X	X	X	X	X		
Urinalysis	X	X				X	X		

Abbreviations: AE = adverse event; BSA = body surface area; CRF = case report form; d = day; ETV = early termination visit; HAQ-DI = Health Assessment Questionnaire – Disability Index; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; LV = last visit; PGA = Physician Global Assessment; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; SJC = swollen joint count; sPGA = static Physician's Global Assessment; TB = tuberculosis; TJC = tender joint count, V = visit; VAS = visual analog scale; W = week.

a Includes year of birth, gender, and ethnicity.

b Subjects will be evaluated for past and present disease relapse by the physician (Section 8.2.4).

c Complete physical at screening (excluding pelvic, rectal, and breast examinations). Physicals should include symptom-directed physical, as well as an examination of heart, lungs, and abdomen, and visual examination of the skin.

~~c. To be performed if not done in the prior 6 months to rule out pulmonary TB.~~

d Participants who test positive for latent TB at screening may be re-screened following appropriate treatment.

e See Table RHCZ.6.1. When the dosing is scheduled at home, the participants or care givers will ~~self-~~administer the provided ixekizumab prefilled syringes. All participants should remain under observation for at least 1 hour after study intervention administration to monitor safety at Week 0.

f Designated site personnel will be responsible for handling and dispensing of study intervention (ixekizumab).

g Administered to PsA participants only at the baseline (W0) visit. For PsO participants with 3% or more BSA of PsO, administered at all study visits.

~~g~~h Administered ~~only~~ to PsO participants ~~with PsO~~ only at the baseline (W0) visit. For PsA participants, administered at all study visits.

~~h~~i Administered only to PsA participants. The question related to pain assessment will be included in HAQ-DI assessment.

~~e~~j To be performed if not done in the prior 6 months to rule out pulmonary TB, provided the x-ray and/or report are available for review.

~~h~~k Participants who test positive for latent TB at screening may be re-screened. QuantiFERON® may be performed by a Lilly-designated or local laboratory. See Section 8.2.~~6~~7 for detailed description of QuantiFERON®-TB Gold . In case of Mantoux TB test, participants will have to come back to the site after 2 days for reading the results.

~~i~~l All participants will be tested for HBV at screening. Participant who meet criteria for HBV monitoring (see Section 8.2.~~7~~8.1) will be identified by the central laboratory at baseline and monitored according to the study schedule.

~~j~~m To be performed for females of childbearing potential only. Additional urine pregnancy testing can be performed at the investigator's decision. Participants determined to be pregnant will be discontinued from treatment and will no longer be administered study intervention.

~~k~~n To be performed for females of childbearing potential only. Participants determined to be pregnant will be discontinued from treatment and will no longer be administered study intervention.

Note: For PsO participants with no active PsA, only PsO efficacy outcomes ~~PASI, sPGA scores and patient related assessment~~ will be collected. For PsA participants with 3% or more BSA of PsO, both PsA and PsO efficacy outcomes will be collected. For PsA participants with less than 3% BSA of PsO, only PsA efficacy outcomes will be collected. (Table RHCZ.8.1). ~~For PsO participant who also meet active PsA definition, both PsA and PsO outcomes will be collected for that participant. For PsO only participants, PASI, sPGA scores and patient rated assessments will be collected.~~

2.1 Study Rationale

The rationale for this post-approval Phase 4 ixekizumab study is to evaluate the safety and tolerability when ixekizumab is administered to participants in India with moderate-to-severe plaque psoriasis (PsO) and/or active psoriatic arthritis (PsA). Participants with moderate-to-severe plaque psoriasis are defined as those with PASI ≥12, sPGA ≥3, and BSA ≥10%. …

2.2. Background

…

More information about the known and expected benefits, risks, and reasonably anticipated AEs of ixekizumab may be found in the Copellor® package insert. Information on AEs expected to be related to the investigational product may be found in Section 6.2~~7~~ (Development Core Safety Information [DCSI]) of the Investigator's Brochure (IB). Information on SAEs that are expected in the study population (independent of drug exposure) and that will be assessed by the Sponsor in aggregate, periodically during the course of the study, may be found in Section 5~~6~~ (Effects in Humans) of the ~~Copellor package insert~~IB.

2.3. Benefit/Risk Assessment

Ixekizumab has been demonstrated to be safe and effective for the treatment of participants with moderate-to-severe chronic PsO and/or active PsA. The risk profile for participants within this study is anticipated to be consistent with the known safety experience for ixekizumab.

3. Objectives and Endpoints

….

Objectives	Endpoints
CCI [redacted]	
[redacted]	[redacted]

Objectives	Endpoints
	[redacted]

4.1. Overall Design

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 Indian population (Section 1.2).

The following treatment will be assessed in this study for PsO participants with no active PsA and PsA participants who meet criteria for moderate-to-severe PsO:

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

…

4.1.1. Screening Period (Period 1)

…

All inclusion and exclusion criteria are provided in Sections 5.1 and 5.2, respectively. Screening procedures (including complete medical history, ~~and~~ demographics, and substance use) will be performed according to the SoA (Section 1.3). At Visit 1, a QuantiFERON®-TB Gold test assay may be performed by a Lilly-designated or local laboratory (Section 8.2.7~~8.2.6~~).
Participants who test positive for latent tuberculosis (TB) at screening may be re-screened once following appropriate treatment, as described in Section 8.2.7~~8.2.6~~.

4.1.2. Induction Dosing Period (Period 2)

…

When the dosing is scheduled at home (Week 2, Week 6, Week 10), the participants or care givers will ~~self-~~administer the provided ixekizumab prefilled syringes.

…

4.1.3. Maintenance Period (Period 3)

…

When the dosing is scheduled at home (Week 16 and Week 20), the participants or care givers will ~~self-~~administer the provided ixekizumab prefilled syringes.

…

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

…

If, at Visit 801, a participant's neutrophil count is ≥1500 cells/μL or greater than or equal to the participant's baseline neutrophil count, the participant's participation in the study will be considered complete unless the investigator determines additional follow-up may be necessary. An additional study visit (Visit 802) ~~4~~ 8 weeks after Visit 801 may be required for appropriate participant management (described below).

…

- Participants with concurrent infection: If there is a concurrent infection that requires systemic anti-infective therapy, the participant should receive appropriate medical care and a repeat test for neutrophil count should be performed at least Q4W (or sooner as appropriate) until resolution of infection. Upon resolution of infection, the neutrophil count should be monitored using the required study visits in the Post-Treatment Follow-Up Period (Period 4) design at Visits 801 (4 weeks after resolution of infection) and 802 (~~4~~ 8 weeks after Visit 801); additional visits may be required depending on the degree of neutropenia.

…

4.2. Scientific Rationale for Study Design

This study will examine the effect of ixekizumab on participants with moderate-to-severe PsO and/or PsA.

During the Induction Dosing Period (Period 2), participant's safety and efficacy will be assessed at 80 mg Q2W dose for the participants with PsO and PsA participants who meet criteria for moderate-to-severe PsO. In PsA participants who do not meet criteria of moderate-to-severe PsO, participant's safety and efficacy will be assessed at 80 mg Q4W dose. During the maintenance Period (Period 3), ixekizumab 80 mg Q4W will be studied.

…

4.3. Justification for Dose

Ixekizumab will be studied at the approved dosing regimen for treatment of adults with moderate-to-severe PsO and PsA participants ~~who do not meet criteria of moderate-to-severe PsO~~.

5. Study Population

This study will include participants who have presence of moderate-to-severe PsO (moderate-to-severe PsO is defined as BSA ≥10, sPGA ≥3, PASI ≥12) and/or active PsA (active PsA defined as the presence of at least 3 (out of 68) tender and at least 3 [out of 66] swollen joints) for at least 6 months, treated in outpatient settings of India, who have given written informed consent approved by Lilly, or its designee, and the ethics review board (ERB) governing the site.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened only once in the following circumstances: participants who test positive for latent TB at screening may be re-screened following appropriate treatment, as described in Section 8.2.7~~8.2.6~~. When re-screening is performed, the individual must sign a new ICF and will be assigned a new identification number.

…

5.2. Exclusion criteria

…

[27] Have active TB (refer to Section 8.2.7~~8.2.6~~ for details on determining full TB exclusion criteria).

…

[32] …

Note: Patients who are negative for hepatitis B surface antigen (HBsAg-), HBcAb+, HBsAb+ with a concentration of HBsAb ≥200 mIU/mL, and negative for serum HBV DNA may participate in the study. Patients who meet these criteria at screening will be identified by the central laboratory and monitored during the study as detailed in Section 8.2.8.1~~8.2.7.1~~.

5.4. Screen Failures

…

- Patients who test positive for latent TB at screening and have undergone documented subsequent treatment for at least 4 weeks (more details in Section 8.2.~~6~~7).

…

6.1. Study Intervention(s) Administered

Table RHCZ.6.1. Treatment Regimens

Treatment Group	Starting Dose W0	Dose W2-W10	Dose[a] W12-W20
Ixekizumab for • PsO participants with no active PsA ~~and~~ • PsA participants who meet criteria for moderate-to-severe PsO	Ixekizumab 80 mg × 2 SC (total of 160 mg)	Ixekizumab 80 mg SC Q2W at W2, 4, 6, 8, and 10	Ixekizumab 80 mg SC Q4W at W12, ~~W~~16 and 20
Ixekizumab for PsA participants who do not meet criteria ~~of~~ for moderate-to-severe PsO	Ixekizumab 80 mg × 2 SC (total of 160 mg)	Ixekizumab 80 mg SC Q4W at W4, 8, 12, 16 and 20.	

Abbreviations: PsA = psoriatic arthritis; PsO = psoriasis; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous injection; W = week.

[a] No dose is given at W24; therefore, W24 is not included in this table.

Note: When the dosing is scheduled at home (for PsO participants with no active PsA and PsA participants who meet criteria for moderate-to-severe PsO~~group~~: W2, W6, W10, W16, and W20; for PsA participants who do not meet criteria ~~of~~ for moderate-to-severe PsO: W16 and W20), the participants or care givers will ~~self~~ administer the provided ixekizumab prefilled syringes.

…

During study visits, the investigator or his/her designee will administer the ixekizumab prefilled syringes to the participant. When the dosing is scheduled at home, the participants or care givers will ~~self~~ administer the provided ixekizumab prefilled syringes.

…

Induction Dosing Period (Period 2) (Table RHCZ.6.2)

- At Week 0, a 160-mg starting dose of ixekizumab (two 80-mg injections), followed by ixekizumab 80 mg Q2W from Weeks 2 through 12 for PsO participants with no active PsA and PsA participants who meet criteria for moderate-to-severe PsO.
- At Week 0, a 160-mg starting dose of ixekizumab (two 80-mg injections), followed by ixekizumab 80 mg Q4W from Weeks 4 through 12 for PsA participants who do not meet the criteria for moderate-to-severe ~~without~~ PsO participants.

…

Table RHCZ.6.2. Dosing Summary for the Induction and Maintenance Periods

		Ixekizumab Treatment Group[a]	
		Ixekizumab (80 mg)	
Dosing Period	Study Week	PsO Participants with no active PsA and PsA Participants Who Meet Criteria for Moderate-to-Severe PsO ~~with or without PsA Participants~~[b]	PsA Participants Who Do Not Meet Criteria for Moderate-to-Severe PsO ~~PsA without PsO Participants~~[c]
Induction Dosing Period 2	0	2[a]	2[a]
	2	1	-
	4	1	1
	6	1	-
	8	1	1
	10	1	-
	12	1	1
Maintenance Period 3	16	1	1
	20	1	1
	24	-	-

Abbreviations: PsA = psoriatic arthritis; PsO = psoriasis; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.

[a] A starting dose of 160 mg (Week 0) of ixekizumab will be given as 2 SC injections at Week 0.

[b] For PsO participants with no active PsA and PsA participants who meet criteria for moderate-to-severe PsO, during the Induction Dosing Period, ixekizumab (80 mg) will be given as 1 SC injection Q2W (i.e., Weeks 2, 4, 6, 8, 10, and 12). During the Maintenance Period, ixekizumab (80 mg) will be given as 1 SC injection Q4W (i.e., Weeks 16 and 20).

[c] For PsA participants who do not meet criteria ~~of~~ for moderate to severe PsO, ixekizumab (80 mg) will be given as 1 SC injection Q4W (i.e., Weeks 4, 8, 12, 16, and 20).

6.8. Concomitant Therapy

All concomitant medication taken during the study must be recorded on the Concomitant Medication CRF at the study visits indicated in the SoA (Section 1.3). Treatment with concomitant PsO and PsA therapies during the study will be permitted only as outlined in the inclusion and exclusion criteria (Sections 5.1 and 5.2, respectively) and as described in the paragraphs below. Participants taking permitted medications need to be documented to be in stable control. After trial enrollment, significant dose escalation of a concomitant medication should be discussed with Lilly medical before allowing participant to receive study intervention.

…

7.1.1. Permanent Discontinuation from Study Intervention

…

- The participant has a positive TB test using QuantiFERON®-TB Gold or T-Spot or purified protein derivative (PPD and is assessed as having latent TB infection (see Section 8.2.7~~8.2.6~~), and/or develops symptoms or signs of tuberculosis.

...

7.1.3. Temporary Discontinuation

In some circumstances, participants may need to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to the study intervention. See Section 8.2.7~~8.2.6~~ for details regarding managing participants who test positive for TB at any time during the study.

…

8.1. Efficacy Assessments

…

For PsO participant who also meet active PsA definition, both PsA and PsO outcomes will be collected for that participant. Likewise, to fulfill the study objective, PsO outcomes will be collected among all the PsA participants with 3% or more BSA of PsO (Table RHCZ.8.1).

Table RHCZ.8.1. Efficacy Assessments

Assessments	PsO ~~p~~Participants with No Active PsA	PsA Participants ~~W~~with	
		≥3% BSA of PsO	<3% BSA of PsO
Clinician assessments	• PASI • Percentage of BSA-- Psoriasis • sPGA • PGA Disease Activity VAS	• TJC/SJC (68/66 joints) • PGA of Disease Activity VAS - Psoriasis and PsA • PASI • Percentage of BSA • sPGA • DAS28 - CRP[a] • ACR20/50/70[a]	• TJC/SJC (68/66 joints) • PGA of Disease Activity VAS - PsA • DAS28 - CRP[a] • ACR20/50/70[a]
Patient assessments	• Patient's Global Assessment of Disease Activity VAS - Psoriasis	• HAQ-DI • PsA Pain assessment question included in HAQ-DI • Patient's Global Assessment of Disease Activity VAS - PsA • Patient's Global Assessment of Disease Activity VAS - Psoriasis	• HAQ-DI. • PsA Pain assessment question included in HAQ-DI • Patient's Global Assessment of Disease Activity VAS – PsA

Abbreviations: ACR20/50/70 = 20%/50%/70% improvement in American College of Rheumatology response criteria; BSA = body surface area; CRP = C-reactive protein; DAS28 = Disease Activity Score-28; HAQ-DI = Health Assessment Questionnaire – Disability Index; PASI = Psoriasis Area and Severity Index; hs-CRP = high-sensitivity C-reactive protein; PGA = Physician's Global Assessment; PsA = psoriatic arthritis; PsO = plaque psoriasis; SJC = swollen joint count; sPGA = static Physician's Global Assessment; TJC = tender joint count, V = visit; VAS = visual analog scale.

[a] Assessments are derived by calculations using PsA assessments and hs-CRP assay.

8.1.1. Efficacy Assessments ~~for Plaque Psoriasis and Psoriatic Arthritis Participants with 3% of more BSA of PsO~~

…

~~8.1.2. Efficacy Assessments Specific to Psoriatic Arthritis Participants~~

8.1.2.~~1.~~ American College of Rheumatology 20, 50, and 70 Responder Index

…

Patient's Assessment of Pain Visual Analog Scale

Patient's Assessment of Pain VAS will be administered only to PsA participants. The question related to pain assessment will be included in HAQ-DI assessment.

…

Patient's Global Assessment of Disease Activity Visual Analog Scale

The participant's overall assessment of his/her PsO and PsA activity will be recorded using the 100mm horizontal VAS where the left end represents no disease activity, and the right end represents extreme disease activity.

Physician's Global Assessment of Disease Activity Visual Analog Scale

The Investigator will be asked to give an overall assessment of the severity of the participant's current PsO and PsA activity using a 100mm horizontal VAS, where 0 represents no disease activity and 100 represents extremely active disease. The investigator making the assessment must be a rheumatologist or medically qualified physician. The same assessor should preferably perform the Physician's Global Assessment of Disease Activity VAS for a given participant particularly during the Induction Dosing Period (Period 2) to minimize interobserver variation.

…

Disease Activity Score based on C-Reactive Protein

The DAS28-CRP is a measure of disease activity in 28 joints that consists of a composite numerical score utilizing the following variables: TJC, SJC, hs-CRP (measured in mg/L), and Patient's General Assessment recorded by participants on a 0 to 100 mm VAS.

For DAS28-CRP, the 28 joints to be examined and assessed as tender or not tender for TJC 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 (Smolen et al. 1995). The following equation will be used to calculate the DAS28-CRP (Vander Cruyssen et al. 2005):

$$DAS28-CRP = 0.56\left(\sqrt{TJC28}\right)+0.28\left(\sqrt{SJC28}\right)+0.36\left(\ln\left(CRP+1\right)\right)+0.014\left(VAS\right)+0.96$$

8.1.3. Patient Global Assessment of Disease Activity VAS

The participant's overall assessment of his/her PsO and PsA activity will be recorded using the 100 mm horizontal VAS where the left end represents no disease activity, and the right end represents extreme disease activity.

8.1.4. Physician's Global Assessment of Disease Activity Visual Analog Scale

The Investigator will be asked to give an overall assessment of the severity of the participant's current PsO and PsA activity using a 100 mm horizontal VAS, where 0 represents no disease activity and 100 represents extremely active disease. The investigator making the assessment must be a rheumatologist or medically qualified physician. The same assessor should preferably perform the Physician's Global Assessment of Disease Activity VAS for a given participant particularly during the Induction Dosing Period (Period 2) to minimize interobserver variation.

8.2.4. Evaluation of Disease Relapse

Patients will be assessed for the presence or absence of relapse at screening based on the following definitions:

a. Assessment of relapse for psoriasis participants:

Relapse is defined as worsening of psoriasis from the previous routine medical visit by 50% PASI or 1% BSA (in each case if sPGA ≥3) (Tian and Lai 2016).

If PASI, BSA, or sPGA are not available in medical charts, relapse of psoriasis is defined as any worsening of psoriatic lesions that would, if persistent, in most cases require initiation or change of systemic therapy for psoriasis.

During the study period, relapse with ixekizumab would be defined as worsening of psoriasis from the previous visit by 50% PASI or 1% BSA or sPGA ≥3.

Relapse present based on the above definition: Yes/No

Following details will be collected in addition in all PsO participants:

- Duration of the psoriasis since diagnosis:
- Duration of the psoriatic arthritis since diagnosis:
- Prior systemic medications used for psoriasis:
  - Name of the drug and dose
  - Start date
  - End date
- Prior systemic medications used for psoriatic arthritis:
  - Name of the drug and dose
  - Start date
  - End date

b. Assessment of relapse for psoriatic arthritis participants:

Relapse is defined as an increase in PsA disease activity from the previous routine medical either DAS28(ESR) >2.6 and DAS28(ESR) increase >0.6 or DAS28(ESR) increase ≥1.2, irrespective of absolute DAS28(ESR) (Emery et al. 2020; Helliwell et al. 2021).

If DAS-28 CRP is not available in medical charts, relapse of PsA is defined as any increase in disease activity that would, if persistent, in most cases require initiation or change of systemic therapy for PsA.

Relapse present based on the above definition: Yes/No

Additionally, the following details will be collected in all PsA participants:

- Duration of the psoriasis since diagnosis:
- Duration of the psoriatic arthritis since diagnosis:
- Prior systemic medications used for psoriasis:
  - Name of the drug and dose
  - Start date
  - End date
- Prior systemic medications used for psoriatic arthritis:
  - Name of the drug and dose
  - Start date
  - End date

8.2.4.5. Clinical Safety Laboratory Tests

…

8.2.5.6. Pregnancy Testing

…

8.2.6.7. Chest X-Ray and Tuberculosis Testing

…

8.2.7.8. Safety Monitoring

…

8.2.7.1.8.1. Hepatic Safety Monitoring

…

8.2.7.1.8.1.1 Additional Hepatic Data Collection in Participants Who Have Abnormal Liver Tests During the Study

…

8.2.7.2.8.2Hepatitis C Testing and Monitoring

…

8.2.7.3.8.3Hepatitis B Testing and Monitoring

…

9.2. Analyses Populations

The following analysis populations will be used; additional analysis populations will be specified in the SAP:

Analysis Population	Description
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- ~~PsO~~ mITT population, defined as all enrolled participants with a psoriasis indication, who do not qualify for Active PsA and ~~who~~ receive~~s~~ at least 1 dose of study treatment, even if the participant does not receive the correct treatment, or otherwise does not follow the protocol.
Active PsA – 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 receive~~s~~ at least 1 dose of study treatment, even if the participant does not receive the correct treatment, or otherwise does not follow the protocol.
Safety Population	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 analyzed according to the treatment to which they are assigned.

9.5.2 Primary Endpoint Analysis

…

Refer to Section 9.5.5.1~~8.2~~ for further details.

9.5.3 Secondary Endpoint(s) Analysis

Endpoints Specific to Psoriasis ~~Group~~ (PsO) and Psoriatic Arthritis (PsA) Participants with 3% or More BSA of PsO

As a part of the secondary analyses, the following endpoints will be summarized (i) for the PsO indication and will be based on the PsO with no active PsA – mITT population, and (ii) for the Active PsA indication and will be based on the active PsA – mITT population with BSA of PsO ≥ 3% at baseline, unless otherwise specified:

…

Endpoints Specific to Psoriatic Arthritis ~~Group~~ (PsA)

As a part of the secondary analyses, the following endpoint will be summarized for the PsA indication and will be based on the active PsA-mITT population:

…

9.5.5 Safety Analyses

…

All safety analyses will be based on the safety population and will be summarized overall and by dosing regimen (Q2W/Q4W and Q4W/Q4W) as specified in Table RHCZ.6.1~~indications (PsO and PsA)~~.

Further details will be described in the SAP.

9.5.5.1. Adverse Events

…

A summary of AEs will be provided overall and by dosing regimen~~, indications~~, including the number and percentage of participants who reported TEAEs, TEAEs by maximum severity, death, SAEs, TEAEs related to study intervention, discontinuations from the treatment due to an AE, and treatment-emergent AESIs: cytopenias, infections, injection-site reactions (ISRs), allergic reactions/hypersensitivities, cerebrocardiovascular events, MACE, malignancies, depression, IBD, ILD. TEAEs (all, by maximum severity, and possibly related to study intervention by the investigator), SAEs including deaths, AEs that lead to treatment discontinuation will be summarized by MedDRA system organ class (SOC) and PT.

…

10.2 Appendix 2: Clinical Laboratory Tests

…

[d] Test required at Visit 1 only to determine eligibility of participant for the study (with the exception of those participants who require further HBV monitoring [Section 8.2.8.3~~8.2.7.3~~]).

…

10.5 Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments

See Section 8.2.8.1~~8.2.7.1~~ for guidance on appropriate test selection.

…

11 References

…

Emery P, Burmester GR, Naredo E, et al. Adalimumab dose tapering in patients with rheumatoid arthritis who are in long-standing clinical remission: results of the phase IV PREDICTRA study. *Ann. Rheum. Dis*. 2020;79(8):1023-30.

…

Helliwell PS, Tillett W, Waxman R, et al. Evaluation and validation of a patient-completed psoriatic arthritis flare questionnaire. *J. Rheumatol*. 2021;48(8):1268-71.

…

Tian D, Lai Y. The relapse of psoriasis: mechanisms and mysteries. *JID Innovations*. 2022;2(3):100116.

…

10.9 Appendix 9: Abbreviations and Definitions

Term	Definition
ACR	American College of Rheumatology
ACR20/50/70	20%/50%/70% Improvement in ACR criteria
ADA	antidrug antibodies
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Class
BCG	Bacillus Calmette-Guérin
BP	blood pressure
BSA	body surface area
CASPAR	**C**l**AS**sification criteria for **P**soriatic **AR**thritis
CDISC	Clinical Data Interchange Standards Consortium
CDSCO	Central Drugs Standard Control Organization
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CMV	cytomegalovirus
companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.

Term	Definition
CONSORT	Consolidated Standards of Reporting Trials
COX-2	Cyclooxygenase-2
CRF	Case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Sponsor for each trial participant.
CRP	Clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRS	clinical research scientist
csDMARDs	Conventional synthetic disease-modifying antirheumatic drug
CSR	clinical study report
CTA	clinical trial agreement
CVA	cerebrovascular accident
DAS-28	Disease Activity Score-28
DBP	Diastolic blood pressure
device deficiencies	equivalent to product complaint
DMARD	disease-modifying antirheumatic drug
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture system
EMA	European Medicines Agency
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethical review board: a board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
ERCP	endoscopic retrograde cholangiopancreatography

Term	Definition
ESR	erythrocyte sedimentation rate
ETV	early termination visit
FEAE	follow-up emergent adverse event
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBcAb	hepatitis B core antibodies
HBsAb	hepatitis B surface antibodies
HBsAg	hepatitis B surface antigens
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibodies
HDV	hepatitis D virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HIVAb	human immunodeficiency virus antibodies
hs-CRP	high-sensitivity C-reactive protein
IB	investigator's brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IL-17	interleukin-17
IL-23	interleukin-23
ILD	interstitial lung disease

Term	Definition
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional review board: a board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
ISR	injection-site reaction
ITT	Intention-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (i.e., the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
JAK	Janus kinase
LV	last visit
MAb	monoclonal antibodies
MACE	major adverse cerebrocardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified intent-to-treat
MoH	Ministry of Health
MRCP	magnetic resonance cholangiopancreatography
MTX	methotrexate
NRI	nonresponder imputation

Term	Definition
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PASI	Psoriasis Area and Severity Index
PASI 75/90/100	75%/90%/100% Improvement in the PASI criteria
PC	product complaint
PCR	polymerase chain reaction
PDE4	phosphodiesterase 4
PsA	psoriatic arthritis
PsO	plaque psoriasis
PT	preferred term
PTFU	post-treatment follow-up
PT-INR	prothrombin time - international normalized ratio
PUVA	psoralens and ultraviolet a light therapy
Q2W	every 2 weeks
Q4W	every 4 weeks
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SEC	Subject Expert Committee
SERM	selective estrogen receptor modulators
SJC	swollen joint count

Term	Definition
SMQ	Standardized MedDRA Query
SoA	Schedule of Activities
SOC	system organ class
sPGA	Static Physician Global Assessment of Disease
TB	tuberculosis
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TJC	tender joint count
TNFi	tumor necrosis factor inhibitor
TPO	third-party organization
ULN	upper limit of normal
UVB	Ultraviolet B light
VAS	visual analogue scale
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of childbearing potential

11 References

Bartos S, Hill D, Feldman SR. Review of maintenance of response to psoriasis treatments. *J Dermatolog Treat*. 2016;27(4):293-297. doi: 10.1080/09546634.2016.1177158.

Christophers E. Psoriasis—epidemiology and clinical spectrum. *Clin Exp Dermatol.* 2001;26(4):314-320. doi: 10.1046/j.1365-2230.2001.00832.x.

Dogra S, Yadav S. Psoriasis in India: prevalence and pattern. *Indian J Dermatol Venereol Leprol.* 2010;76(6):595-601. doi: 10.4103/0378-6323.72443. PMID: 21079301.

Dubin DB, Tanner W, Ellis R. Biologics for psoriasis. *Nat Rev Drug Discov.* 2003;2(11):855-856. doi: 10.1038/nrd1231.

Emery P, Burmester GR, Naredo E, et al. Adalimumab dose tapering in patients with rheumatoid arthritis who are in long-standing clinical remission: results of the phase IV PREDICTRA study. *Ann. Rheum. Dis*. 2020;79(8):1023-30.

[EMA] European Medicines Agency. Committee for medicinal products for human use (CHMP). Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. November 2004. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003329.pdf. Accessed June 5, 2018.

Fairchild AO, Reed SD, Johnson FR, et al. What is clearance worth? Patients' stated risk tolerance for psoriasis treatments. *J Dermatolog Treat*. 2017;28(8):709-715. doi: 10.1080/09546634.2017.1329499.

Feldman SR, Bushnell DM, Klekotka PA, et al. Differences in psoriasis signs and symptom severity between patients with clear and almost clear skin in clinical practice. *J Dermatolog Treat*. 2016;27(3):224-227. doi: 10.3109/09546634.2015.1093589. Epub 2015 Oct 7.

Fredriksson T, Pettersson U. Severe psoriasis—oral therapy with a new retinoid. *Dermatologica*. 1978;157(4):238-244. doi: 10.1159/000250839.

Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum*. 1980;23(2):137-145. doi: 10.1002/art.1780230202.

Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol*. 1982;9(5):789-793.

Gelfand JM, Neimann AL, Shin DB, et al. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296(14):1735-1741. doi: 10.1001/jama.296.14.1735.

Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med.* 2016;375(4):345-356. doi: 10.1056/NEJMoa1512711.

Gordon KB, Duffin KC, Bissonnette R, et al. A Phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. *N Engl J Med*. 2015;373(2):136-144. doi: 10.1056/NEJMoa1501646.

Gowda S, Goldblum OM, McCall WV, Feldman SR. Factors affecting sleep quality in patients with psoriasis. *J Am Acad Dermatol*. 2010;63(1):114-123. doi: 10.1016/j.jaad.2009.07.003.

Gniadecki R, Bang B, Bryld LE, et al. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. *Br J Dermatol*. 2015;172:244-252. doi: 10.1111/bjd.13343.

Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two Phase 3 randomised trials. *Lancet.* 2015; 386:541-551. doi: 10.1016/S0140-6736(15)60125-8. Epub 2015 Jun 10.

Helliwell PS, Tillett W, Waxman R, et al. Evaluation and validation of a patient-completed psoriatic arthritis flare questionnaire. *J. Rheumatol*. 2021 Aug 1;48(8):1268-71.

[IFPA] International Federation of Psoriasis Associations. Profile of psoriasis page. International Federation of Psoriasis Associations web site. Available at: https://ifpa-pso.com/our-cause/. Accessed June 5, 2018.

Janowski K, Steuden S, Bogaczewicz J. Clinical and psychological characteristics of patients with psoriasis reporting various frequencies of pruritus. *Int J Dermatol*. 2014;53(7):820-829. doi: 10.1111/ijd.12074. Epub 2013 Nov 21.

Krueger JG, Ferris LK, Menter A, Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol.* 2015;136(1):116-124.e7. doi: 10.1016/j.jaci.2015.01.018. Epub 2015 Mar 11.

Krueger JG, Fretzin S, Suárez-Fariñas M, et al. IL-17A is essential for cell activation and inflammatory gene circuits in subjects with psoriasis. *J Allergy Clin Immunol*. 2012;130(1):145-154. doi: 10.1016/j.jaci.2012.04.024. Epub 2012 Jun 5.

Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis – results of two Phase 3 trials. *N Engl J Med*. 2014;371(4):326-338. doi: 10.1056/NEJMoa1314258. Epub 2014 Jul 9.

Lebwohl MG, Bachelez H, Barker J, et al. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Study. *J Am Acad Dermatol.* 2014;70(5):871-881. doi: 10.1016/j.jaad.2013.12.018. Epub 2014 Feb 24.

Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med*. 2015;373(14):1318-1328. doi: 10.1056/NEJMoa1503824.

Leonardi C, Matheson R, Zachariae C, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med.* 2012;366(13):1190-1199. doi: 10.1056/NEJMoa1109997.

Mason J, Mason A, Cork MJ. Topical preparations for the treatment of psoriasis in primary care: a systematic review. York (UK): Centre for Health Economics. 2002. Available at: https://www.york.ac.uk/che/pdf/op41.pdf. Accessed April 17, 2015.

Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled Phase III trial. *J Am Acad Dermatol.* 2008;58(1):106-115. doi: 10.1016/j.jaad.2007.09.010. Epub 2007 Oct 23.

[NPF] National Psoriasis Foundation. Psoriasis severity resource page. National Psoriasis Foundation. Available at: https://www.psoriasis.org/about-psoriasis/causes. Accessed June 5, 2018.

Papp K, Thaçi D, Reich K, et al. Tildrakizumab (MK-3222), an antiinterleukin- 23p19 monoclonal antibody, improves psoriasis in a Phase IIb randomized placebo-controlled trial. *Br J Dermatol.* 2015;173(4):930-939. doi: 10.1111/bjd.13932. Epub 2015 Oct 15.

Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. *J Eur Acad Dermatol Venereol*. 2015;29(4):645-648. doi: 10.1111/jdv.12817. Epub 2014 Nov 4.

Ryan C, Kirby B. Psoriasis is a systemic disease with multiple cardiovascular and metabolic comorbidities. *Dermatol Clin*. 2015;33(1):41-55. doi: 10.1016/j.det.2014.09.004.

Smolen JS, Breedveld FC, Eberl G, et al. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. *Arthritis Rheum*. 1995;38(1):38-43. doi: 10.1002/art.1780380106.

Sofen H, Smith S, Matheson RT, et al. Guselkumab (an IL-23-specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. *J Allergy Clin Immunol.* 2014;133(4):1032-1040. doi: 10.1016/j.jaci.2014.01.025.

Strober B, Leonardi C, Papp KA, et al. Short- and long-term safety outcomes with ixekizumab from 7 clinical trials in psoriasis: etanercept comparisons and integrated data. *J Am Acad Dermatol*. 2017;76(3):432-440.e417. doi: 10.1016/j.jaad.2016.09.026. Epub 2016 Nov 23.

Takeshita J, Duffin KC, Shin DB, et al. Patient-reported outcomes for psoriasis patients with clear versus almost clear skin in the clinical setting. *J Am Acad Dermatol.* 2014;71(4):633-641. doi: 10.1016/j.jaad.2014.05.001. Epub 2014 Jun 11.

Tian D, Lai Y. The relapse of psoriasis: mechanisms and mysteries. *JID Innovations*. 2022;2(3):100116.

Vander Cruyssen B, Van Looy S, Wyns B, et al. DAS28 best reflects the physician's clinical judgment of response to infliximab therapy in rheumatoid arthritis patients: validation of the DAS28 score in patients under infliximab treatment. *Arthritis Res Ther.* 2005;7(5):R1063-R1071. doi: 10.1186/ar1787. Epub 2005 Jul 8.

Winthrop KL, Novosad SA, Baddley JW, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. *Ann Rheum Dis.* 2015;74(12):2107–2116. doi: 10.1136/annrheumdis-2015-207841. Epub 2015 Sep 22.

Yeung H, Takeshita J, Mehta NN, et al. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. *JAMA Dermatol*. 2013;149(10):1173-1179. doi: 10.1001/jamadermatol.2013.5015.

Zimolag I, Reich A, Szepietowski J. Influence of psoriasis on the ability to work [abstract]. 13th Congress of the European Society for Dermatology and Psychiatry; Sep 17-22, 2009; Venice, Italy. *Acta Derm Venereol*. 2009;89:575-576. Abstract OP76.

Signature Page for VV-CLIN-075015 v1.0

Approval	PPD 14-Feb-2023 13:55:48 GMT+0000

Approval	PPD rector 14-Feb-2023 16:34:13 GMT+0000

Signature Page for VV-CLIN-075015 v1.0