Protocol I1F-JE-RHCV

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

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Ixekizumab (LY2439821)

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Protocol Electronically Signed and Approved by Lilly on date provided below.

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Table of Contents

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Appendices

1. Synopsis

Title of Study:
A Multicenter, Open-Label, Post Marketing Clinical Trial to Evaluate the Efficacy And Safety Of Ixekizumab in Patients With Generalized Pustular Psoriasis (GPP) and Erythrodermic Psoriasis (EP).

Rationale:
This study is being conducted to fulfil a regulatory commitment to the Pharmaceuticals and Medical Devices Agency (PMDA) to evaluate the efficacy and safety of ixekizumab when dosed every 2 weeks (Q2W) beyond Week 12 in patients with GPP and EP.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • To assess the efficacy of ixekizumab Q2W beyond Week 12 in patients with generalized pustular psoriasis (GPP) and erythrodermic psoriasis (EP)	• Number of patients who improve their Global Improvement Score (GIS) at least 1 point from Week12 through Week 20 and with ≤2 of GIS
Secondary • To assess the efficacy of ixekizumab Q2W beyond Week 12 in patients with GPP and EP • To assess the health outcomes of ixekizumab Q2W beyond Week 12 in patients with GPP and EP • To evaluate the potential development of anti-ixekizumab antibodies of ixekizumab Q2W beyond Week 12 in patients with GPP and EP	The following endpoints will be assessed at each scheduled visit after Week 12: • Number of patients with each GIS grade (1: Resolved, 2: Improved, 3: Unchanged, 4: Worsened) • Number of patients who achieve sPGA (0, 1) and sPGA (0) • Number of patients who achieve PASI 75, PASI 90, and PASI 100 from baseline • Change from baseline, and percent improvement from baseline in PASI • Change from baseline in PSSI in patients with scalp involvement at baseline, and percent of BSA involvement of Psoriasis • Change from baseline in DLQI total score and domains, and Itch NRS score • Number of patients who achieve DLQI (0, 1) and DLQI (0) • Number of patients who achieve Itch NRS ≥4 point reduction from baseline for patients who had baseline Itch NRS ≥4 • Number of patients who develop treatment-emergent anti-ixekizumab antibody (TE-ADA) and neutralizing anti-ixekizumab antibody (NAb) <u>GPP ONLY</u> • Change from baseline on assessment of Generalized Pustular Psoriasis Severity Index at Week 12 and Week 20/ETV.

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

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

Summary of Study Design:

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

Treatment Arms and Duration:

Study I1F-JE-RHCV consists of 3 periods: a screening period of up to 30 days, a 12-week Induction Dosing Period, and an 8-week Maintenance Dosing period. All eligible patients will be administered 160 mg ixekizumab as 2 SC injections at Week 0 (baseline; Visit 2) followed by 80 mg as 1 injection at Week 2, 4, 6, 8 and 10. Patients who are inadequate responders (Global Improvement Score [GIS] ≥2 at Week 12 and based on the investigators' discretion) will be administered 80 mg as 1 injection at Week 12, 14, 16, and 18 or until they achieve a GIS score of 1.

Number of Patients:

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

Statistical Analysis:

Primary analysis of efficacy, health outcome and safety measures will be conducted based on patients who continued ixekizumab 80 mg Q2W beyond Week 12 by disease type (ie, GPP and EP separately).

Baseline is defined as the last available value before the first dose in Period 2; in most cases, it will be the value recorded at Week 0 (Visit 2).

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

Continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, median, and number of observations. Categorical data will be summarized as frequency counts.

2. Schedule of Activities

Table RHCV.1. Schedule of Activities

Procedure	Screening Period (Period 1)	Treatment Period - Induction (Period 2)					Treatment Period - Maintenance (Period 3)				
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**ETV**
Study Week	**-**	**0**	**2**	**4**	**8**	**12**	**14**	**16**	**18**	**20**	
Visit Intervals	**-30d to -7d**	**0**	**14 ± 2d**	**28 ± 4d**	**56 ± 4d**	**84 ± 2d**	**98 ± 2d**	**112 ± 2d**	**126 ± 2d**	**140 ± 2d**	**NA**
Informed consent	X										
Complete medical history	X										
Demography[a]	X										
Full physical examination[b]	X										
Height		X									
Weight		X				X				X	X
Habits[c]		X								X	X
Chest X-ray[d]	X[d]									X[e]	X[e]
Body temperature	X	X				X				X	X
Inclusion and exclusion criteria[f]	X	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Vital sign (BP and pulse)	X	X[g]	X	X	X	X	X	X	X	X	X
Genetic information (Mutation of IL-36 RN)	X										
Adverse event (AE/SAE/AESI) review	X	X	X	X	X	X	X	X	X	X	X
Administer IP		X[gh]	X	X	X	X	X	X	X		
Dispense IP		X	X	X	X	X	X	X	X		
IP compliance		X	X	X	X	X	X	X	X	X	X
Dispense Study Drug Administration Log[i]		X	X	X	X	X	X	X	X		

Procedure	Screening Period (Period 1)	Treatment Period - Induction (Period 2)					Treatment Period - Maintenance (Period 3)				
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**ETV**
Study Week	**-**	**0**	**2**	**4**	**8**	**12**	**14**	**16**	**18**	**20**	
Visit Intervals	**-30d to -7d**	**0**	**14 ± 2d**	**28 ± 4d**	**56 ± 4d**	**84 ± 2d**	**98 ± 2d**	**112 ± 2d**	**126 ± 2d**	**140 ± 2d**	**NA**
Collect, review, & enter data from Study Drug Administration Log		X	X	X	X	X	X	X	X	X	X
Global Improvement Scores			X	X	X	X	X	X	X	X	X
PASI	X	X	X	X	X	X	X	X	X	X	X
sPGA	X	X	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X	X	X
PSSI[j]		X	X	X	X	X	X	X	X	X	X
Itch NRS		X	X	X	X	X	X	X	X	X	X
DLQI		X	X	X		X	X		X	X	X
C-SSRS Baseline	X										
C-SSRS Since Last Visit		X	X	X	X	X	X	X	X	X	X
Self-Harm Supplement Form and Self-Harm Follow-Up Form[k]	X	X	X	X	X	X	X	X	X	X	X
GPP Severity Index[l]	X	X				X				X	X
Administer PPD/QuantiFERON Gold/T-SPOT[m]	X										
12-lead ECG[n]	X										
FSH[o]	X										
HIV/HBV/HCV[p]	X										
HBV DNA[q]	X			X	X	X		X		X	X
Serum pregnancy test (Women of childbearing potential [WCBP] only)[r]	X										

Procedure	Screening Period (Period 1)	Treatment Period - Induction (Period 2)					Treatment Period - Maintenance (Period 3)				
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**ETV**
Study Week	**-**	**0**	**2**	**4**	**8**	**12**	**14**	**16**	**18**	**20**	
Visit Intervals	**-30d to -7d**	**0**	**14 ± 2d**	**28 ± 4d**	**56 ± 4d**	**84 ± 2d**	**98 ± 2d**	**112 ± 2d**	**126 ± 2d**	**140 ± 2d**	**NA**
Urine pregnancy test (WCBP only)[r]						X				X	X
Clinical chemistry	X	X				X				X	X
Hematology	X	X				X				X	X
Urinalysis	X					X				X	X
hsCRP		X				X				X	X
Beta-D-glucan[s]	X										
KL-6[t]	X										
Immunogenicity testing[u]		X				X				X	X
LY2439821 serum concentration[uv]						X				X	X
Pharmacogenetic sample (genetic sample/DNA)	X										

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BP = blood pressure; BSA = body surface area; C-SSRS = Columbia- Suicide Severity Rating Scale; d = days; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ETV = early termination visit; FSH = follicular stimulating hormone; GPP = generalized pustular psoriasis; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high sensitivity C-reactive protein; IL-36 RN = interleukin 36 receptor antagonist; IP = investigational product; KL-6 = Kerbs von Lungren 6 antigen; NA = not applicable; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PCP = pneumocystis pneumonia; PPD = purified protein derivative; Ps = psoriasis; PSSI = Psoriasis Scalp Severity Index; SAE = serious adverse event; SC = subcutaneous; sPGA = static Physician's Global Assessment; TB = tuberculosis; V = study visit.

[a] Demographics includes recording of year of birth, gender, and race.

[b] One complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at screening. All physical examinations throughout the study should include a symptom-directed physical, as well as examination of heart, lungs, abdomen, and visual examination of the skin.

[c] Habits include recording of caffeine, alcohol, and tobacco consumption.

[d] A chest X-ray will be taken at screening unless one has been obtained within the past 6 months (provided the X-ray and/or report are available for review).

[e] To be performed if more than 12 weeks have elapsed since the previous study X-ray was obtained. This X-ray may be performed within 12 weeks if medically indicated.

[f] Patients who test positive for latent TB at screening may be rescreened following appropriate treatment as described in Section 9.4.5.2. Additionally, patients who do not qualify at screening under Exclusion Criteria [10] (active or recent infection) may be rescreened as described in Section 6.2.

[g] At baseline (Week 0), BP and pulse should be measured prior to administration of the investigational product and again approximately 1 hour postadministration.

[h] All patients will receive 2 SC doses of investigational product at Week 0.

[i] Patients will record information in the Study Drug Administration Log, including the date, time, and location of administration of investigational product (for treatment compliance), and who administered.

[j] To be collected for the patient with scalp Ps at baseline.

[k] A Self-Harm Follow-Up Form is to be completed only during visits for which there is at least 1 discrete self-harm event identified on the Self-Harm Supplement Form.

[l] To be collected for patients who have confirmed pustular Ps at Screening (Visit 1) and Baseline (Visit 2).

[m] See Section 9.4.5.2 for detailed description of QuantiFERON Gold TB, T-SPOT.TB, and PPD testing. PPD test is performed at Visit 1, and patients will return approximately 48 and 72 hours after Visit 1 to have their PPD test read.

[n] ECGs should be performed prior to injection of investigational product and collection of blood sample, as applicable. ECGs are locally performed.

[o] FSH test performed for women ≥40 and <60 years of age who have had a cessation of menses for at least 12 months to confirm non-childbearing potential (≥40 mIU/mL).

[p] All patients will be tested for HBV at screening. Patients who are HBcAb+ and/or HBsAb+ at screening will have serum HBV DNA obtained by the central lab. Patients that are found to be HBV DNA positive (detectable) and/or HBsAg+ positive at screening will be excluded from the trial.

[q] If patient is HBcAb+ and/or HBsAb+, HBV DNA needs to be confirmed negative at screening and at least once every month in Periods 2 and 3. (See Section 9.4.5.4).

[r] To be performed for females of childbearing potential only. Urine pregnancy tests are locally performed.

[s] Beta-D-glucan is required at screening and if an investigator believes it is warranted at subsequent visits, a beta-D-glucan test may be included in the work-up panel at any time during the study and may be done locally. If the beta-D-glucan test is positive, PCP needs to be ruled out. If PCP is ruled out and the investigator deems the patient fit to continue, the patient may continue in the study. If a patient has a confirmed diagnosis of PCP during the study, the patient must discontinue the study.

[t] KL-6 is required at screening, and if an investigator believes it is warranted at subsequent visits, a KL-6 test may be included in the work-up panel at any time during the study and may be done locally.

[u] Additional blood samples will be collected (as specified in Appendix 5) when possible for any patients who experience a potential serious allergic/hypersensitivity reaction during the study as judged by the investigator.

[v] LY2439821 serum concentration will be analyzed to help facilitate the interpretation of immunogenicity data.

3. Introduction

3.1. Study Rationale

Psoriasis (Ps) is a common chronic skin disorder with an estimated prevalence of 1.0% in Japan (Tang et al. 2014). The pathogenesis of psoriasis has undergone many paradigm shifts during the past 3 decades. Psoriasis is no longer considered fundamentally a skin disease, but rather a chronic inflammatory process resulting from a dysfunctional immune system (Kim and Krueger 2015). For patients with psoriasis, the protective elements of the skin (corneocytes, keratinocytes, chemokines, and immunocytes, such as T cells and dendritic antigen-presenting cells [DiMeglio et al. 2011; Bergboer et al. 2012]) become disrupted, resulting in dysfunctional feedback loops and vicious cycles leading to development of life-long, thick, scaly, well-demarcated plaques (DiMeglio et al. 2014). Psoriasis includes several phenotypes often separated into the following classifications; plaque Ps, guttate Ps, pustular Ps, and erythrodermic Ps (EP). Psoriatic arthritis (PsA) may coexist in up to 30% of patients with Ps. The most common type of psoriasis is plaque Ps (psoriasis vulgaris), and clinical features include sharply demarcated, scaly erythematous plaques that are often associated with itching, pain, and cracking of the skin. These lesions most typically affect the elbows, knees, scalp, lumbar area, umbilical area, and gluteal cleft. Approximately 1/4 to 1/3 of plaque Ps patients have moderate-to-severe Ps, corresponding to involvement of over 5% of their body surface area (BSA) (Dubin et al. 2003; Menter and Griffiths 2007). Disease of this extent is physically and/or socially debilitating to a degree comparable with other chronic medical conditions (Rapp et al. 1999).

Generalized pustular Ps (GPP) and EP are relatively rare but more severe variants of Ps. Generalized pustular Ps is characterized by multiple sterile pustules all over the body and may be accompanied by systemic symptoms including fever, chills, severe itching, dehydration, rapid pulse rate, exhaustion, anemia, weight loss, and muscle weakness. Erythrodermic Ps is a particular inflammatory type of Ps that can affect the whole body. The reddening and shedding of the skin are often accompanied by severe itching and pain, heart rate increase, fluid loss, and fluctuating body temperature. Both Ps subtypes can sometimes be life-threatening without adequate treatment. Patients with these severe subtypes are known to experience frequent relapses (Rosenbach et al. 2010), and require systemic treatment. However the treatment options are further limited and there are significant unmet needs for effective treatments for patients with GPP and EP.

Study I1F-JE-RHCV (RHCV) is a multicenter, open-label, post marketing clinical trial designed to assess the efficacy and safety of ixekizumab through Week 20 when administered Q2W beyond Week 12 in patients with GPP and EP. This study is being conducted by Eli Lilly Japan to fulfil a regulatory commitment to the PMDA to evaluate the efficacy and safety of Q2W dosing in patients with GP and EPP.

3.2. Background

Ixekizumab (LY2439821, Taltz®) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (MAb) that binds with high affinity and specificity to interleukin (IL)-17A,

a proinflammatory cytokine. Ixekizumab does not bind to ligands IL-17B, IL-17C, IL-17D, IL-17E, or IL-17F.

Phase 3 clinical studies show that ixekizumab is efficacious and has an acceptable safety profile for the treatment of adult patients with moderate-to-severe Ps and for adult patients with active PsA. Ixekizumab was approved in Japan for the treatment of Ps, PsA, EP, and GPP at an initial dose of ixekizumab 160 mg followed by ixekizumab 80 mg administered Q2W from Week 2 through Week 12, and thereafter 80 mg Q4W. In August 2018, a new dosage and administration was approved in Japan to support 80mg Q2W continued dosing beyond Week 12 for patients with Ps, PsA, EP and GPP who have an inadequate response at Week 12. However, clinical studies consisting of the main data package in this new approval did not include the data from patients with EP and GPP who underwent treatment of ixekizumab 80 mg Q2W over 12 weeks. Therefore, the PMDA agreed that Eli Lilly Japan would conduct a study to evaluate the use of ixekizumab Q2W dosing beyond Week 12 in patients with EP and GPP in order to provide support for consistent dosing guidelines for the treatment of all indications (ie, Ps, PsA, EP, and GPP) with ixekizumab.

3.3. Benefit/Risk Assessment

Continued 80 mg Q2W dosing of ixekizumab was shown to be more efficacious over 52 weeks of treatment compared with continuous Q4W dosing in moderate-to-severe plaque psoriasis patients (Langley et al. 2018). Clinically meaningful benefit from continued Q2W dosing beyond Week 12 was prominent in moderate-to-severe plaque psoriasis patients who had inadequate response at Week 12. Although there are no data available for efficacy of ixekizumab Q2W dosing beyond 12 weeks in EP and GPP patients, the long term efficacy data in plaque psoriasis patients are suggestive of the incremental efficacy of ixekizumab with continued Q2W dosing in EP and GPP patients who have an inadequate response at Week 12, over the initially approved dosing regimen.

Safety profiles in plaque psoriasis patients who received ixekizumab Q2W over 52 weeks were comparable to those in Q4W treatment groups, with no unexpected safety signals observed. Meanwhile, no serious adverse events (SAEs) or adverse events (AEs) leading to treatment discontinuation were reported from EP and GPP patients who received ixekizumab via the initially approved dosing regimen. Also, overall safety profiles were comparable between EP and GPP patients and psoriasis patients.

Given the expected clinical benefit, potential risks derived from continued Q2W dosing may be acceptable in EP and GPP patients.

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of ixekizumab are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

Table RHCV.2 shows the objectives and endpoints of the study.

Table RHCV.2. Objectives and Endpoints

Objectives	Endpoints
Primary • To assess the efficacy of ixekizumab Q2W beyond Week 12 in patients with generalized pustular psoriasis (GPP) and erythrodermic psoriasis (EP)	• Number of patients who improved Global Improvement Score (GIS) at least 1 point from Week 12 through Week 20 and with ≤2 of GIS

Objectives and Endpoints

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

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

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

5. Study Design

5.1. Overall Design

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

The study consists of 3 periods:

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

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

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

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

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

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

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

Patients discontinuing from the study treatment who have received at least 1 dose of investigational product will continue to the ETV.

Ixekizumab will not be made available after conclusion of the study to patients.

Study governance considerations are described in detail in Appendix 3.

Figure RHCV.1 illustrates the study design.

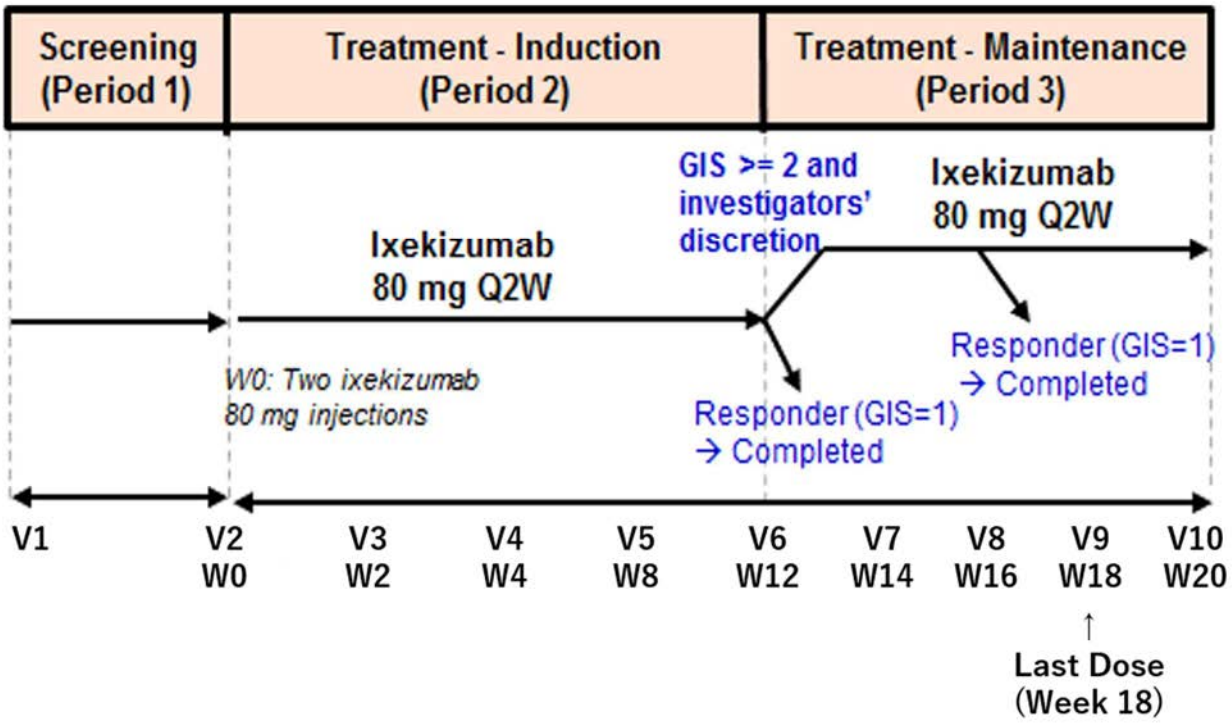

Figure RHCV.1. Illustration of study design for Clinical Protocol I1F-JE-RHCV.

5.2. Number of Participants

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

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

5.4. Scientific Rationale for Study Design

This is an open-label, single-arm study to primarily assess the efficacy of ixekizumab Q2W beyond Week 12 in patients with EP and GPP. The absence of a placebo arm is consistent with other studies evaluating efficacy and safety of investigational drugs in these severe forms of Ps. In addition, placebo-controlled studies are not ethical for patients with EP and GPP.

The Induction Dosing Period (Period 2) is based on the dosage and administration which was approved via initial regulatory review. This will be followed by the Maintenance Dosing Period (Period 3), if patients do not show a therapeutic response (GIS ≥2 at Week 12 and based on the investigators' discretion).

5.5. Justification for Dose

The dosing schedule for Study RHCV was selected based on the initially approved dosage and administration of ixekizumab, and is designed to evaluate the response of patients with EP and GPP at Week 12 following the administration of ixekizumab at a starting dose of 160 mg followed by 80 mg Q2W up to Week 12. Thereafter, according to the newly approved schedule, patients with an inadequate response will receive a dose of ixekizumab 80 mg Q2W up to and including Week 18, or until they achieve a GIS score of 1.

6. Study Population

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

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening:

Type of Patient and Disease Characteristics

[1] Present with GPP or EP based on an investigator-confirmed diagnosis and meet the associated criteria

[1a] GPP:

- Meet the criteria for GPP set by Ministry of Health, Labour and Welfare (MHLW) at screening (Visit 1) and baseline (Week 0; Visit 2) regardless of IL-36 mutation status.

[1b] EP:

- Diagnosed to have BSA ≥80% involvement (with inflammatory erythema) at screening (Visit 1) and baseline (Week 0; Visit 2).

[2] Candidates for phototherapy and/or systemic therapy

Patient Characteristics

[3] Are at least 20 years of age at the time of screening

[3a] male patients:

agree to use a reliable method of birth control* during the study

[3b] female patients:

Are women of childbearing potential who test negative for pregnancy and agree to use a reliable method of birth control* or remain abstinent during the study and for at least 12 weeks following the last dose of investigational product, whichever is longer.

-or-

Are women of non-childbearing potential, defined as:

Women who have had surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation);

-or-

Women who are ≥60 years of age;

-or-

Women ≥40 and <60 years of age who have had a cessation of menses for ≥12 months and a follicle-stimulating hormone test confirming nonchildbearing potential (≥40 mIU/mL).

* Each of the following is considered as highly effective method of birth control:

- oral contraceptives
- condom with spermicide
- intrauterine device
- vasectomized male (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients in the study, the vasectomized male partner should be the sole partner for that patient.

Informed Consent

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

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

Medical Conditions

[5] Have any other skin conditions that would affect interpretation of the results (including, but not limited to, scleroderma, eczema, drug-induced psoriasis, guttate psoriasis, parapsoriasis, or cutaneous manifestations of other autoimmune diseases such as systemic lupus erythematosus).

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

[7] Had a serious infection (for example, pneumonia, cellulitis), have been hospitalized, or have received IV antibiotics for an infection, within 12 weeks prior to baseline (Week 0; Visit 2), or had a serious bone or joint infection within 24 weeks prior to baseline, or have ever had an infection of an artificial joint, or are immunocompromised to an extent such that participation in the study would pose an unacceptable risk to the patient.

[8] Have or had an infection typical of an immunocompromised host, and/or that occurs with increased incidence in an immunocompromised host (including, but not limited to, pneumocystis pneumonia (PCP), histoplasmosis, or coccidioidomycosis); or have a known immunodeficiency. Additionally, patients with a positive beta-D-glucan test at screening and a confirmed diagnosis of PCP will be excluded.

[9] Have or had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 4 weeks of baseline (Week 0; Visit 2).

[10] 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 patients if participating in the study; these patients may be rescreened 4 or more weeks after documented resolution of symptoms.

[11] Have evidence or suspicion of active or latent tuberculosis (TB).

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

[13] Have hepatitis B or test positive for hepatitis B virus (HBV) at screening, defined as:

- Positive for hepatitis B surface antigen (HBsAg+)

OR

- Positive for hepatitis B core antibody (HBcAb+) in conjunction with positive confirmatory HBV for HBV deoxyribonucleic acid (DNA) test

OR

- Positive for hepatitis B surface antibody (HBsAb+) and positive confirmatory for HBV DNA.

Note: Patients who are HBcAb+ and/or HBsAb+ and HBV DNA negative may be enrolled in the study. Patients who meet these criteria at screening will be monitored during the study as detailed in protocol Section 9.4.5.4.

[14] Have hepatitis C or test positive for hepatitis C virus (HCV) at screening, defined as: positive result for hepatitis C antibody and positive confirmatory HCV ribonucleic acid (RNA) test (see protocol Section 9.4.5.5). Patients in sustained virologic response after HCV therapy, and patients who have spontaneously cleared HCV infection (see protocol Section 9.4.5.5) can be included in this study.

[15] 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:

[15a] Neutrophil count <1500 cells/µL

[15b] Lymphocyte count <500 cells/µL

[15c] Platelet count <100,000 cells/µL

[15d] Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN)

[15e] Total white blood cell (WBC) count <3000 cells/µL

[15f] Hemoglobin <10.0 g/dL (100.0 g/L)

[15g] Serum creatinine >2.0 mg/dL

[15h] Serum albumin <2.5 g/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.)

[16] Have received systemic nonbiologic Ps therapy or have received phototherapy at the day of baseline (however, see exception below).

- Oral corticosteroids will be permitted, if average daily doses are not greater than 10 mg/day of prednisone or its equivalent.
- All topical treatment will be permitted.
- Methotrexate or oral retinoids will be permitted before and during the study if doses are not greater than that of baseline.
- Cyclosporine and Apremilast will be permitted, if daily doses are not greater than that of baseline

[17] Presence of significant uncontrolled neuropsychiatric disorder, have recent history (within 30 days prior to screening [Visit 1] and any time between screening [Visit 1] and baseline [Visit 2]) of a suicide attempt; or have active suicidal ideation with some intent to act with or without a specific plan (yes to question 4 or 5 on the "Suicidal Ideation" portion of the Columbia-Suicide Severity Rating Scale [C-SSRS]); or are clinically judged by the investigator to be at risk for suicide.

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

[19] Have current or a history of lymphoproliferative disease, or signs or symptoms of lymphoproliferative disease within 5 years of baseline (Week 0; Visit 2); or have active or history of malignant disease within 5 years of baseline (Week 0, Visit 2), except for basal cell carcinoma, squamous cell carcinoma, skin Bowen's disease, or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks, or carcinoma in situ of the cervix, or non-invasive malignant colon polyps that have been removed.

(Note: patients with history of malignancy with no evidence of recurrence or active disease within 5 years of baseline may participate in the study).

[20] Have had fluid overload, myocardial infarction, 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 of baseline (Week 0; Visit 2).

[21] Have current or a history of inflammatory bowel disease (IBD) (ulcerative colitis and Crohn's disease), or signs or symptoms of IBD at screening (Visit 1) that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study.

Prior/Concomitant Therapy

[22] 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.

[23] Concurrent use of any biologic agent during this clinical study.

[24] Have previously received ixekizumab treatment.

[25] Have previously completed or withdrawn from this study.

[26] Had a live vaccination within 12 weeks prior to baseline (Week 0; Visit 2), 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 Japan guidelines for adult vaccination with nonlive vaccines intended to prevent infectious disease prior to therapy.

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

[27] Had a vaccination with Bacillus Calmette-Guerin (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.

Prior/Concurrent Clinical Trial Experience

[28] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[29] Have participated in any other clinical study during this clinical study.

Other Exclusions

[30] Have any other condition that precludes the patient from following and completing the protocol, in the opinion of the investigator. Investigators should read and follow especially warning, contraindications, and precautions section of most recent Japan ixekizumab package insert (Taltz Subcutaneous Injection 80 mg syringe).

[31] Have donated more than 400 ml of blood (for patients weighing ≥50 kg) or 200 ml of blood (for patients weighing <50 kg) or plasmapheresis/platelet apheresis within 30 days prior to study entry, or plan to donate blood during the study.

[32] Are women who are lactating or breastfeeding.

[33] 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.

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

6.3. Lifestyle Restrictions

Study participants should be instructed not to donate blood or blood products during the study.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) maybe rescreened. Individuals may be rescreened up to 3 times. The interval between rescreenings should be at least 1 week. Each time rescreening is performed the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. Patients who have had previous screening TB tests as per protocol within 3 months of their rescreening date of consent do not need to repeat these procedures but may do so at the discretion of the investigator.

Individuals may be rescreened as follows:

- Patients who test positive for latent TB at screening may be rescreened following appropriate treatment as described in Section 9.4.5.2.
- Patients who do not qualify at screening under Exclusion Criteria [10] (active or recent infection) may be rescreened as described in Section 6.2.

7. Treatments

7.1. Treatments Administered

The investigator (or his/her designee) is responsible for explaining the correct use of the investigational agent(s) to the patient and/or patient's caregiver, verifying that instructions are followed properly, maintaining accurate records of investigational product dispensing and collection, and returning all unused medication to Lilly or its designee at the end of the study. Further instructions regarding administration of the investigational product are provided below in this section.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

The Induction Dosing Period (Period 2) begins at Week 0 (baseline; Visit 2) when patients receive a starting dose of 160 mg ixekizumab as 2 SC injections. For the remaining doses, 80 mg is administered Q2W. All doses are administered as SC injections.

Administration of Investigational Product

Training: For training purposes, the proper procedures for administration of the investigational product and administration of the initial injection will be performed by the investigator or his/her designee at Week 0 (Visit 2) and the second injection of investigational product can be self-administered by the patient under the supervision of the investigator at Week 0 (Visit 2). Study drug must be administered under the supervision of the investigator until the investigator judges the patient sufficiently competent to perform the self-injections independently. After this time, patients will be allowed to self-inject alone.

Administration: All subsequent injections can be administered by the patient. If a patient is unable to perform the injection, the investigator or a caregiver, may inject the investigational product. In this case, the caregiver will also be trained to inject the study drug under supervision of the investigator until the investigator judges the caregiver sufficiently competent to inject.

A dose of investigational product will consist of 1 SC injection of ixekizumab (except Week 0). Possible injection sites include the abdomen, thigh, and upper arm. The injection site should not be in a psoriatic lesion and should be rotated to another area for subsequent doses.

Syringes should be at room temperature prior to injection (refer to Manual Syringe Directions for Use provided by the sponsor).

Throughout their participation in the study, enrolled patients will record information in a Study Drug Administration Log, including the date, time, injection site, and location of patient at time of administration of investigational product (for treatment compliance), who administered the investigational product, and the reason if investigational product was not fully administered in a Study Drug Administration Log. As needed, patients may use the log to record other information about the injection. At each visit, the investigator will review the log to confirm whether the self-injections were successfully performed.

Observation: Patients should remain under observation for at least 1 hour after dosing at Week 0 (Visit 2) to monitor for safety.

Table RHCV.3. Treatment Periods

Treatment Period	Weeks	Dose	Description
Induction Dosing Period (Period 2) and Maintenance Dosing Period (Period 3)	0 to 12 12 to 20	Ixekizumab 160 mg initially, followed by ixekizumab 80 mg Q2W	A starting dose of 160 mg (Week 0) given as 2 SC injections followed by 80 mg given as 1 SC injection Q2W (Weeks 2, 4, 6, 8, 10, 12, 14, 16 and 18)

Abbreviations: Q2W = every 2 weeks; SC = subcutaneous.

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

- explaining the correct use of the investigational agent(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labelling

The ixekizumab solution for injection will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practices (cGMP). Ixekizumab will be supplied as an injectable solution in 1-mL, single-dose, disposable manual prefilled syringes. Each syringe of ixekizumab is designed to deliver ixekizumab 80 mg. Syringes will be supplied in cartons, with the appropriate quantity of syringes specific to the planned dispensing schedule of the investigational product.

Clinical trial materials will be labeled according to the country's regulatory requirements. All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

Investigational products will be supplied by Lilly or its representative, in accordance with cGMP, and will be supplied with lot numbers and expiration dates.

The investigational product should be stored at 2°C to 8°C in its original carton to protect from light. Investigational product should not be frozen. Sites will be required to monitor temperature of the on-site storage conditions of the syringes.

7.2. Method of Treatment Assignment

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

7.2.1. Selection and Timing of Doses

Investigational product should be administered at approximately the same time each day, as much as possible. For injections not administered on the scheduled day of the week from Week 0 to Week 18, the missed dose should be administered within 4 days of the scheduled day. Dates of subsequent study visits should not be modified according to this delay.

The actual time of all dose administrations will be recorded in the patient's case report form (CRF).

7.3. Blinding

This is an open-label study.

7.4. Dosage Modification

Dose adjustments are not permitted in this study.

7.5. Preparation/Handling/Storage/Accountability

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

- confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 site staff.
- the investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

Detailed instructions regarding supplies and preparation and handling of investigational products will be provided by the sponsor.

Investigational products will be supplied by Lilly or its representative, in accordance with cGMP and will be supplied with lot numbers, expiry dates, and certificates of analysis, as applicable. All investigational products will be stored, inventoried, reconciled, or destroyed according to applicable regulations.

The investigational product should be stored at 2°C to 8°C in its original carton to protect from light. Investigational product should not be frozen. Sites will be required to monitor temperature of the on-site storage conditions of the syringes.

7.6. Treatment Compliance

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

Throughout their participation in the study, enrolled patients will record information in a Study Drug Administration Log, including the date, time, injection site, and location of patient at time of administration of investigational product (for treatment compliance), who administered the investigational product, and the reason if investigational product was not fully administered. As needed, patients may use the log to record other information about the injection. At each visit, the investigator will review the log to confirm whether the self-injections were successfully performed.

Patient compliance with study drug administration will be assessed at each visit. Compliance will be assessed by direct questioning, and counting returned syringes. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

7.7. Concomitant Therapy

The list of excluded medications and procedures is provided in Appendix 6.

The following medications **will not** be permitted during the course of the study (from obtaining written Informed Consent to study completion):

- Ps therapy as described in the inclusion/exclusion criteria (Sections 6.1 and 6.2) with the exceptions described below.
    - Any biologic therapy specified in Section 6.2
    - Concomitant medications as described in the inclusion/exclusion criteria (Sections 6.1 and 6.2)
    - Live vaccines
    - Phototherapy.

The following medications **will be** permitted during the course of the study:

- Vaccine: Use of nonlive seasonal vaccinations and/or emergency vaccination (such as rabies or tetanus vaccinations) is allowed.
- Methotrexate and oral retinoids will be permitted before and during the study if the patient has been using such medication before starting the study and if doses are not greater than that of baseline.
- Oral corticosteroids will be permitted before and during the study, if the patient has been using such medication before starting the study and if average daily doses are not greater than 10 mg/day of prednisone or its equivalent.

- Cyclosporine will be permitted, if the patient has been using such medication before starting the study and if daily doses are not greater than that of baseline.
- Topical steroids: topical steroids (all classes) will be permitted.
- Granulocyte-monocyte adsorption apheresis (GMA): use of GMA is allowed.
- Other Concomitant Therapies: topical treatments will be permitted.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of investigational product:

- **Patient Decision**
  - the patient requests to discontinue investigational product.
- **Discontinuation due to a hepatic event or liver test abnormality.** A patient who is discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via CRF.

  Discontinuation of the investigational product for abnormal liver tests **should be** considered by the investigator when a patient meets one of the following conditions after consultation with the Lilly designated medical monitor:

  - ALT or AST >8X ULN
  - ALT or AST >5X ULN for more than 2 weeks
  - ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or international normalized ratio (INR) >1.5
  - ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - alkaline phosphatase (ALP) >3X ULN
  - ALP >2.5X ULN and TBL >2X ULN
  - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- In addition, a patient who meets any one of the following criteria should be discontinued from the investigational product and conduct ETV, and discontinue from the study:

  - Absolute neutrophil (segmented) counts (see safety monitoring for neutropenia; Section 9.4.6.1):
    - <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 as specified in Section 9.4.6.1) - AND - an infection that is not fully resolved.
  - Total WBC count <2000 cells/µL (<2.00 x 10^3/µL).
  - Lymphocyte count <500 cells/µL (<0.50 x 10^3/µL).
  - Platelet count <50,000 cells/µL (<50 x 10^3/µL).

- The patient experiences a severe AE, an SAE, or a clinically significant change in a laboratory value occurs that, in the opinion of the investigator, merits the discontinuation of the investigational product.
- Clinically significant systemic hypersensitivity event following administration of investigational product that does not respond to symptomatic medication or results in clinical sequelae.
- The patient becomes pregnant.
- The patient develops a malignancy (Note: patients may be allowed to continue if they develop no more than 2 non-melanoma skin cancers during the study).
- The patient has a change in disease phenotype at any time.
- It is recommended that the patient be assessed by an appropriately trained professional to assist in deciding whether the patient is to be discontinued from study treatment if:
  - The patient develops active suicidal ideation with some intent to act with or without a specific plan (yes to question 4 or 5 on the "Suicidal Ideation" portion of the C-SSRS),
    -OR-
    The patient develops suicide-related behaviors as recorded on the C-SSRS, then it is recommended that the patient be assessed by a psychiatrist or appropriately trained professional to assist in deciding whether the patient is to be discontinued from the study.
  - The patient develops active TB or HIV/ acquired immunodeficiency syndrome (AIDS) during the study.
  - The patient becomes HBV (DNA) or HCV RNA positive. The patient should be referred to a specialist physician (see Sections 9.4.5.4 and 9.4.5.5).

- **Discontinuation due to Allergic Reactions or Hypersensitivity Events**
  - The investigator, after consultation with the sponsor-designated medical monitor, determines that a clinically significant hypersensitivity reaction has occurred. A clinically significant systemic hypersensitivity reaction is one that occurs after administration of the investigational intervention (for example, drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension) and requires parenteral medication, does not respond to symptomatic medication, results in clinical sequelae, or is an anaphylactic reaction.

Patients discontinuing from the investigational product prematurely for any reason should complete AE and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.2. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on

study treatment. If the investigator and the sponsor clinical research physician (CRP) agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

patient will be discontinued from the study in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- 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)
- investigator decision
    - the investigator decides that the patient should be discontinued from the study
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- patient decision
    - the patient or the patient's designee, for example, parents or legal guardian requests to be withdrawn from the study.

Patients discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessment: Global Improvement Scores

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

9.1.2. Secondary Efficacy Assessments

The following secondary and exploratory efficacy measures will be assessed in this study:

- Psoriasis Area and Severity Index (PASI)
- Static Physician Global Assessment (sPGA)
- Scalp Psoriasis Severity Index (PSSI)
- Percentage of Body Surface Area (BSA)
- GPP Severity Index

9.1.2.1. Psoriasis Area and Severity Index

The PASI combines an assessment 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 of 0 (no Ps) to 72 (the most severe disease) (Fredriksson and Pettersson 1978). The PASI has been the most frequently used endpoint and measure of Ps severity in clinical trials (EMEA 2004 [WWW]; Menter et al. 2008).

9.1.2.2. Static Physician Global Assessment

The sPGA is the physician's determination of the patient's Ps lesions overall at a given time point. The sPGA is recommended as an endpoint to use efficacy in the treatment of Ps (EMEA 2004 [WWW]). Overall lesions are categorized by descriptions for induration, erythema, and scaling. For analysis of responses, the patient's Ps is assessed as clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).

9.1.2.3. Scalp Psoriasis Severity Index

If the patient has scalp Ps at baseline, the PSSI will be used. The PSSI is a composite score derived from the sum scores for erythema, induration, and desquamation multiplied by a score for the extent of the scalp area involved (range 0 to 72).

9.1.2.4. Percentage of Body Surface Area

The investigator will evaluate the percentage involvement of Ps on each patient's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), in which 1% corresponds to the size of the patient's hand (including the palm, fingers and thumb) (National Psoriasis Foundation 2009 [WWW]).

9.1.2.5. Generalized Pustular Psoriasis Severity Index

The GPP Severity Index will be evaluated only for patients with pustular Ps at screening and at baseline. This is a composite score derived from the sum of scores for assessment of dermal symptoms, systemic symptoms, and laboratory findings (range, 0 to 17).

- **Assessment of Dermal Symptoms**
  Assessment of dermal symptoms, according to the Japanese Dermatological Association GPP revised criteria (2010) (Iwatsuki et al. 2010 [WWW]) will be evaluated only for patients with pustular Ps at screening and at baseline. Skin symptoms will be assessed by the score with the area of erythema (on a 0 to 3 scale), area of confluent pustules (on a 0 to 3 scale), and are of skin edema (on a 0 to 3 scale). The total score will be assessed (range, 0 to 9).
- **Systemic symptoms and laboratory findings**
  Systemic symptoms and laboratory findings, according to the Japanese Dermatological Association GPP revised criteria (2010) (Iwatsuki et al. 2010 [WWW]) will be evaluated only for patients with pustular Ps at screening and at baseline. It will be assessed by the score with fever (on a 0 to 2 scale), WBC (on a 0 to -2 scale), C-reactive protein (on a 0 to 2 scale) and Albumin (on a 0 to 2 scale). The total score will be assessed (range, 0 to 8).

9.1.3. Appropriateness of Assessments

All of the clinical and safety assessments in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant.

9.2. Adverse Events

investigator is responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient. The investigator will record all relevant AE/SAE information in the CRF.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator must document his\her review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via electronic data entry the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. The investigator should record his\her assessment of the potential relatedness of each AE to protocol procedure or investigational product, via electronic data entry.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via electronic data entry, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect

- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

    - when a condition related to the prefilled syringes necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

All AEs occurring after signing the ICF are recorded in the electronic data entry and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic AE should have additional data collected using the electronic data entry.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Events of Special Interest

The following AEs 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 interest for ixekizumab are:

- cytopenias (leukopenia, neutropenia, and thrombocytopenia)
- liver function test changes/enzyme elevations (ALT, AST, bilirubin, and alkaline phosphatase)
- infection
- injection-site reactions
- allergic reactions/hypersensitivities
- cerebrocardiovascular events
- malignancies
- inflammatory bowel disease
- depression
- interstitial lung disease (ILD).

If infections, injection-site reactions, or allergic/hypersensitivity reactions are reported, sites will provide details on these events as instructed on the CRF. Investigators will also educate patients and/or caregivers about the symptoms of allergic/hypersensitivity reactions and will provide instructions on dealing with these reactions. A blood sample will be collected when possible for any patient who experiences an AE of allergic/hypersensitivity reactions during the study.

Data on preferred terms associated with cerebrocardiovascular events (defined as death, cardiac ischemic events including MI and hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, coronary revascularization procedure, stroke/transient ischemic attack, peripheral revascularization procedure, and peripheral arterial event and hospitalization for hypertension) will be collected, and these events and any deaths will be adjudicated by an external Clinical Events Committee (CEC) made up of a chairman, 2 cardiologists, and a neurologist.

Data on suspected IBD, as identified by events possibly indicative of ulcerative colitis and Crohn's disease, will be collected and the events will be adjudicated by an external CEC with expertise in IBD.

The role of external CECs is to adjudicate defined clinical events in a blinded, consistent, and unbiased manner throughout the course of a study. The purpose of the CEC for adjudication of cerebrocardiovascular events and the CEC for adjudication of suspected IBD events is to ensure that all reported events are evaluated uniformly by a single group.

9.2.3. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

A patient will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product or drug delivery system so that the situation can be assessed.

9.3. Treatment of Overdose

Refer to the Taltz IB and/or Product Label.

9.4. Safety

9.4.1. Electrocardiograms

For each patient, electrocardiograms (ECGs) should be collected locally according to the Schedule of Activities (Section 2). Patients are to be resting for 5 minutes prior to the ECG. It is recommended that patients be in a supine position. The qualified physician must document his/her review of the ECG at the time of screening.

The ECG results will be stored at the site and would be made available to the sponsor as requested. The investigators are allowed to repeat the ECG collection.

9.4.2. Vital Signs

For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Section 2).

Vital signs (BP and pulse) and body temperature will be measured (sitting) after resting for a minimum of 10 minutes at times indicated in the Schedule of Activities (Section 2). At baseline (Week 0; Visit 2), 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 patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via CRF.

9.4.3. Laboratory Tests

For each patient, laboratory tests detailed in (Appendix 2) should be conducted according to the Schedule of Activities (Section 2).

Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via CRF.

9.4.4. Immunogenicity Assessments

Samples for immunogenicity testing will be collected at time points indicated in the Schedule of Activities (Section 2). Venous blood samples will be collected into tubes and used to determine antibody production against ixekizumab. The actual date of each sampling will be recorded on the laboratory requisition.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of ixekizumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of ixekizumab. Treatment-emergent immunogenicity is defined as any occurrence of a 4-fold or 2 dilution increase in titer over the pretreatment baseline titer. In the case of a negative result at baseline, treatment-emergent immunogenicity is defined as an increase in titer to ≥1:10. Immunogenicity samples will also be analyzed for ixekizumab serum concentration to facilitate the interpretation of the immunogenicity data at Week 12 (Visit 6), Week 20 (Visit 10) and ETV.

In the event of serious drug hypersensitivity reactions (such as generalized urticaria and/or anaphylaxis), additional samples will be collected as close to the onset of the event as possible and approximately 30 days following the event to evaluate antidrug antibodies (ADA), LY2439821 serum concentration, and additional exploratory biomarkers of hypersensitivity which could include tryptase, complement levels and cytokine measurements.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to ixekizumab. Any samples remaining after 15 years will be destroyed.

9.4.5. Other Safety Measures

9.4.5.1. Physical Exam

One complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at screening. This examination will determine whether the patient meets the criteria required to participate in the study and will also serve as a monitor for pre-existing conditions and as a baseline for treatment-emergent adverse event (TEAE) assessment. All physical examinations throughout the study should include a symptom-directed physical evaluation, as well as an examination of the heart, lungs, abdomen, and a visual examination of the skin.

9.4.5.2. Chest X-Ray and Tuberculosis Testing

A posterior-anterior view chest X-ray will be obtained, unless the X-ray or results from a chest X-ray obtained within 6 months prior to the study are available. The chest X-ray will be obtained locally. The chest X-ray or results will be reviewed by the investigator or designee to exclude patients with active TB infection. In the opinion of the investigator, if evaluating chest X-ray is medically necessary, the investigator may do so any time during the study.

In addition, patients will be locally tested at screening and at visits, as indicated on the Schedule of Activities (Section 2) for evidence of active or latent TB indicated by a positive purified protein derivative (PPD) skin-test response (≥5 mm induration, between approximately 48 and

72 hours after test application, regardless of BCG vaccination history). If, in the judgment of the investigator, an interferon gamma release assay (QuantiFERON-TB Gold test) is preferred as an alternative to the PPD skin test for the evaluation of TB infection, it may be used instead of the PPD test (positive tests excluded) and would be read locally. If an interferon gamma release assay (QuantiFERON-TB Gold test) is indeterminate, 1 retest is allowed. The same method should be used at the retest. If the retest is indeterminate, then the patient is excluded from the study.

Patients with documentation of a negative test result within 3 months prior to baseline (Week 0; Visit 2) do not need a TB screen at Visit 1. Documentation of this test result must include a record of the size of the induration response. A PPD test recorded as negative without documenting the size of induration will result in a retest.

However, patients with a PPD skin test ≥5 mm induration or a positive QuantiFERON-TB Gold test at screening, but no other evidence of active TB, may be rescreened 1 time and may be enrolled without repeating the PPD or QuantiFERON-TB GOLD test if the following conditions are met:

- after receiving at least 4 weeks of appropriate latent TB infection (LTBI) therapy,
- having no evidence of hepatotoxicity (ALT/AST must remain ≤2 times ULN) upon retesting of serum ALT/AST prior to administration of investigational product. Such patients must complete appropriate LTBI therapy during the course of the study in order to remain eligible, and
- meeting all other Inclusion/Exclusion criteria for participation.

Patients who have a documented history of completing an appropriate TB treatment regimen 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. These patients should not undergo TB testing at screening or at later scheduled visits in the study, as per the Schedule of Activities (Section 2).

Patients who have had household contact with a person with active TB are excluded, unless appropriate and documented prophylaxis for TB was given.

9.4.5.3. Columbia-Suicide Severity Rating Scale

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. The C-SSRS is administered by an appropriately trained healthcare professional with at least 1 year of patient care/clinical experience. The tool was developed by the National Institute of Mental Health trial group (TASA) for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. Patients will be assessed according to the Schedule of Activities (Section 2). The Self-Harm Supplement Form is a 1-question form that asks for the number of suicidal or nonsuicidal self-injurious behaviors the patient has experienced since the last assessment. For each unique event identified, a questionnaire (Self-Harm Follow-Up Form) which collects supplemental information on the self-

injurious behavior is to be completed. The Self-Harm Supplement Form will be completed according to the Schedule of Activities (Section 2).

The non-leading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered during the C-SSRS, but was not captured during the non-leading AE collection, sites should not change the AE form. If an event is serious or leads to discontinuation, this is an exception where the SAE and/or AE leading to discontinuation should be included on the AE form and the process for reporting SAEs should be followed.

9.4.5.4. Hepatitis B Screening

Patients who test HBsAg, HBcAb+ in conjunction with positive confirmatory HBV DNA test, or have positive HBV DNA test, regardless of HBsAb status, at screening will be excluded.

If an enrolled patient is positive for HBsAb and/or HBcAb, and negative for HBV DNA, the HBV DNA needs to be checked at least once every month in Periods 2 and 3 (See Section 2).

In addition to the above, any enrolled patient who is HBcAb+ and/or HBsAb+ and who experiences an elevated ALT or AST level >3x ULN must undergo HBV DNA testing. If the HBV DNA test is negative, the investigator should consult with the Lilly-designated medical monitor regarding further management of the patient.

If the result of the HBV DNA testing is positive, the patient must be discontinued from the study and should receive appropriate follow-up medical care, including consideration for antiviral therapy. A specialist physician in the care of patients with hepatitis (for example, infectious disease or hepatologist subspecialists) should be consulted and potentially start antiviral therapy prior to discontinuation of any immunosuppressant therapy (including study drug). Timing of discontinuation from the study and of any immunosuppressant therapy (including study drug) needs to be based on the recommendations of the consulting specialist physician in conjunction with the investigator and medical guidelines/standard of care.

9.4.5.5. Hepatitis C Screening

Patients who test positive for HCV antibody and have a positive confirmatory HCV RNA test at screening will be excluded.

Patients with a previous diagnosis of hepatitis C who have been treated with antiviral therapy and achieved a sustained virologic response may be eligible for inclusion in the study, provided they have no detectable RNA on the screening HCV RNA test for this protocol. A sustained virologic response is defined as an undetectable HCV RNA level, 12 weeks after completion of a full, documented course of an approved antiviral therapy for HCV.

Patients who have spontaneously cleared HCV infection, defined as (i) a positive HCV antibody test and (ii) a negative HCV RNA test, with no history of anti-HCV treatment, may be eligible for inclusion in the study, provided they have no detectable HCV RNA on screening for this study, *and* no detectable HCV RNA on the screening HCV RNA test for this protocol.

Any patient with a history of HCV infection who develops elevated ALT >3x ULN will be tested for HCV RNA.

Any patient diagnosed with hepatitis C during the study will be discontinued from the study and should receive appropriate follow-up medical care.

9.4.6. Safety Monitoring

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

9.4.6.1. Neutropenia

patient with neutrophil (segmented) counts <1500 cells/µL should be managed for neutropenia as follows:

- <500 cells/µL, see Discontinuation Criteria (Section 8.1)
- ≥500 cells/µL and <1000 cells/µL, see Discontinuation Criteria (Section 8.1)
- ≥1000 cells/µL and <1500 cells/µL, and the patient has a concurrent infection that requires systemic anti-infective therapy (for example, antibiotic, antifungal agent, antiviral agent):
    - The dose of investigational product should be withheld, the patient should receive appropriate medical care, and a repeat test for neutrophil count should be performed within 4 weeks from knowledge of the initial report. If the repeat neutrophil count has returned to ≥1500 cells/µL, and the infection has resolved or is resolving, the patient may resume dosing of investigational product and evaluation at scheduled visits. If the neutrophil count remains ≥1000 cells/µL and <1500 cells/µL, investigational product should continue to be withheld and a repeat neutrophil count should again be performed within another 4 weeks. If, after 2 repeat tests, the neutrophil count still remains ≥1000 cells/µL and <1500 cells/µL, and:
        a. the infection has not fully resolved, the patient will be discontinued from the study.
        b. the infection has resolved, the patient may resume dosing and evaluation at scheduled visits. However, if resumption of dosing is not deemed appropriate by the investigator, the patient will be discontinued from the study. Patients who discontinue the study continue to the ETV.
- ≥1000 cells/µL and <1500 cells/µL, and the patient has no concurrent infection that requires systemic anti-infective therapy (for example, antibiotic, antifungal agent, antiviral agent):
    - Dosing may continue, and a repeat neutrophil count should be performed 4 to 8 weeks from knowledge of the initial report. Testing may be at a regularly scheduled visit or at an unscheduled visit, as necessary.

Repeat testing should be performed at 4- to 8-week intervals until the neutrophil count has returned to ≥1500 cells/µL. If the patient has 3 or more post-baseline neutrophil counts of ≥1000 cells/µL and <1500 cells/µL, no value of <1000 cells/µL, and no post-baseline infection requiring systemic anti-infective therapy, the patient may continue or resume further evaluation at scheduled visits, as deemed appropriate by the investigator.

If a patient without initial concurrent infection develops an infection that requires systemic anti-infective therapy, then the patient should be managed as indicated above for patients with concurrent infection.

9.4.6.2. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

Additional safety data should be collected via the electronic case report form (CRF) if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥ 2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE

See Section 9.4.5.4 with regards to hepatitis B monitoring.

9.4.6.3. Hypertension

Patients who experience changes in BP (systolic BP at ≥160 mm Hg plus ≥20 mm Hg increase from baseline [Week 0; Visit 2]; and/or diastolic BP at ≥100 mm Hg plus ≥10 mm Hg increase from baseline) on 2 consecutive visits should receive intervention for the management of hypertension. Intervention could include the maximal intervention of withholding the dose of investigational product and/or the introduction of an anti-hypertensive agent.

9.4.6.4. Allergic Reactions and Hypersensitivity Events

All biologic agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include but are not limited to:

- Skin rash
- Pruritus (itching)
- Dyspnea
- Urticarial (hives)
- Angioedema (for example, swelling of the lips and/or tongue)
- Hypotension
- Anaphylactic reaction

Participants with clinical manifestations of systemic allergic/hypersensitivity reactions should be treated per local standard of care. Additional data describing each symptom should be provided to the sponsor in the CRF.

In case of anaphylaxis or generalized urticaria, additional blood samples should be collected as close as possible to the onset of the event (see Section 9.4.4 Immunogenicity Assessments). Follow-up samples should be obtained at the next regularly scheduled visit or 4 weeks after the event, whichever is later. The lab results are provided to the sponsor via the central laboratory.

9.5. Pharmacokinetics

Not applicable

9.6. Pharmacodynamics

Not applicable

9.7. Whole Blood Samples for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to ixekizumab and to investigate genetic variants thought to play a role in GPP and EP. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient/number. These samples and any data generated can be linked back to the patient only by the investigator site personnel. Samples will be retained at a facility selected by Eli Lilly Japan or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, and candidate gene studies. Regardless of technology utilized genotyping data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Not applicable

9.9. Health Outcomes/Quality of Life Assessment

The following health outcomes measures that will be assessed in this study:

- Itch Numeric Rating Scale (NRS)
- Dermatology Life Quality Index (DLQI)

9.9.1. Itch Numeric Rating Scale

The Itch NRS is a patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable." Overall severity of a patient's itching from Ps is indicated by circling the number that best describes the worst level of itching in the past 24 hours.

9.9.2. Dermatology Life Quality Index

The DLQI is a simple, patient-administered, 10-question, validated, quality-of-life questionnaire that covers 6 domains, including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Response categories include "not at all", "a little", "a lot", and "very much", with corresponding scores of 0, 1, 2, and 3, respectively, and unanswered ("not relevant") responses scored as "0." Totals range from 0 to 30 (the higher the score, the more quality of life is impaired) and a 5-point change from baseline is considered clinically relevant (Basra et al. 2008).

10. Statistical Considerations

10.1. Sample Size Determination

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

The sample size is based on the following:

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

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Efficacy, health outcomes and safety analyses for Period 2 will be conducted on the largest analysis set (Full Analysis Set [FAS]), defined as the set of patients with GPP and EP separately who receive at least 1 dose of study treatment in Period 2 (FAS Population).

Efficacy, health outcomes and safety analyses for Period 3 will be conducted based on patients with GPP and EP separately who receive at least 1 dose of study treatment in Period 3 (Maintenance Dosing Period Population).

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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

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.

Primary analysis of efficacy, health outcome, and safety measures will be conducted based on patients who continued ixekizumab 80 mg Q2W beyond Week 12 by disease type (ie, GPP and

EP separately) on the Maintenance Dosing Period Population. Secondary analyses of efficacy, health outcome, and safety measures will be conducted for Period 2 on the FAS Population and Period 3 on the Maintenance Dosing Period Population, respectively.

Baseline for efficacy, health outcomes, and safety analyses in Period 2 is defined as the last available value before first dose in Period 2; in most cases, it will be the value recorded at Week 0 (Visit 2). For the efficacy and health outcomes analyses in Period 3, baseline is defined as the last available value before the first dose in Period 2 and, in most cases, will be the value recorded at Week 0 (Visit 2). Unless otherwise specified, for the safety analyses during Period 3, baseline is defined as the last available value before the first dose of ixekizumab in Period 3. In most cases, this will be the measure recorded at Week 12 (Visit 6).

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

Continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, median, and number of observations. Categorical data will be summarized as frequency counts.

10.3.2. Patients

10.3.2.1. Patient Disposition

A detailed description of patient disposition will be provided at the end of the study.

10.3.2.2. Patient Characteristics

Patient characteristics and baseline clinical measures will be summarized. Baseline characteristics will include gender, age, height, weight, baseline disease severity, duration of disease, previous systemic therapy, and previous biologic therapy. Baseline clinical and health outcome measurements will include PASI, sPGA, BSA, PSSI, Itch NRS, DLQI, C-SSRS, and GPP severity index.

10.3.2.3. Concomitant Therapy

Previous and concomitant medications will be summarized and presented by World Health Organization Anatomical Therapeutic Class (WHOATC) and generic name.

10.3.2.4. Treatment Compliance

Treatment compliance with study drug will be summarized for patients who enter Periods 2 and 3 (Induction Dosing Period and Maintenance Dosing Period), respectively. Overall compliance with therapy is defined to be missing no more than 20% of the expected doses and not missing 2 consecutive doses, and does not overdose (that is, take more injections at the same time point than specified in the protocol).

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary analysis is to assess the efficacy of ixekizumab 80 mg Q2W beyond Week 12 in patients with GPP and EP separately, as measured by the number of patients who improved their

GIS from baseline by at least 1 point from Week 12 through Week 20 and with ≤2 of GIS on the Maintenance Dosing Period Population.

10.3.3.2. Secondary Analyses

Secondary analyses of the efficacy measures will be summarized for Period 2 on the FAS Population and Period 3 on the Maintenance Dosing Period Population, respectively by the following endpoints:

- Number of patients with each GIS grade (1: Resolved, 2: Improved, 3: Unchanged, 4: Worsened)
- Number of patients who achieve sPGA (0, 1) and sPGA (0)
- Number of patients who achieve PASI 75, PASI 90, and PASI 100 from baseline
- Change from baseline, and percent improvement from baseline in PASI
- Change from baseline in PSSI in patients with scalp involvement at baseline, and percent of BSA involvement of Ps.

GPP ONLY

- Change from baseline on assessment of GPP which includes assessment of dermal symptoms, whole body findings, and laboratory findings for GPP.

10.3.4. Safety Analyses

Safety will be assessed by AEs, laboratory analytes including neutrophil counts, vital signs, weight, and C-SSRS. Overall AEs will be summarized with frequencies. Other safety measures including the detailed AEs will be reviewed by listings. Summaries of overall AEs will be created for Period 2 on the FAS Population and for Period 3 on the Maintenance Dosing Period Population, respectively.

10.3.4.1. Adverse Events

Adverse events are classified based upon the Medical Dictionary for Regulatory Activities (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 onset and the date/time of the first study drug injection are considered when determining TEAEs. Treatment-emergent adverse events will be assigned to the treatment period in which they first occurred or worsened.

An overall summary of AEs will be provided for each of the treatment periods, including the number of patients who experienced TEAEs, TEAEs by maximum severity, deaths, SAEs, TEAEs related to study drug, discontinuations from the treatment due to an AE, and treatment-emergent AESIs. By-patient listings of TEAEs, SAEs including deaths, AEs that lead to treatment discontinuation, and AESIs will be provided.

Adverse events of special interest will be identified by a standardized MedDRA query (SMQ) or a Lilly defined MedDRA preferred term listing.

10.3.4.2. Clinical Laboratory Tests

By-patient listings of laboratory measurements will be provided.

10.3.4.3. Vital Signs, and Physical Findings and Other Safety Evaluations

By-patient listings of vital signs, weight, and C-SSRS will be provided.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable

10.3.6. Evaluation of Immunogenicity

The frequency of patients with preexisting ADA and with TE ADA+ to ixekizumab will be tabulated. Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). For the TE ADA+ patients the distribution of maximum titers will be described. The frequency of neutralizing antibodies will also be tabulated in TE ADA+ patients.

10.3.7. Other Analyses

10.3.7.1. Health Outcomes/Quality of Life Assessment

Health Outcomes will be evaluated in this study utilizing the Itch Numeric Rating Scale (NRS) and the DLQI. The following endpoints will be summarized using descriptive statistics described for continuous or categorical data in Section 10.3.1 for Period 2 on the FAS Population and Period 3 on the Maintenance Dosing Period Population, respectively:

- Change from baseline in DLQI total score and domains, and Itch NRS score
- Number of patients who achieve DLQI (0, 1) and DLQI (0)
- Number of patients who achieve Itch NRS ≥4 point reduction from baseline for patients who had baseline Itch NRS ≥4

10.3.7.2. Subgroup Analyses

Not applicable

10.3.8. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
Ab	antibody
ADA	anti-drug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	Bacillus Calmette-Guérin
BP	blood pressure
BSA	body surface area
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CIOMS	Council for International Organizations of Medical Sciences
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.
CRF	case report form
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.

CSR	clinical study report
C-SSRS	Columbia- Suicide Severity Rating Scale
DLQI	Dermatology Life Quality Index (Dermatology-specific quality of life)
DNA	deoxyribonucleic acid
ECG	electrocardiogram
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EP	erythrodermic psoriasis
ERB	Ethics Review Board
ETV	early termination visit
FAS	Full Analysis Set
FSH	follicle stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GIS	Global Improvement Score
GMA	granulocyte-monocyte adsorption apheresis
GPP	generalized pustular psoriasis
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
hsCRP	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
ILD	interstitial lung disease
IL	interleukin
IL-36 RN	interleukin 36 receptor antagonist
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	International Normalized Ratio
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.
IP	investigational product
IRB	Investigational Review Board
Itch NRS	Itch Numeric Rating Scale
MAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Affairs
MHLW	Ministry of Health, Labour and Welfare
NAb	neutralizing antibody
NRS	numeric rating system
PASI	Psoriasis Area and Severity Index
PASI 75	at least a 75% improvement from baseline in PASI score
PASI 90	at least a 90% improvement from baseline in PASI score
PASI 100	a 100% improvement from baseline in PASI score
PCP	pneumocystis pneumonia

PMDA	Pharmaceuticals and Medical Devices Agency
PPD	purified protein derivative
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
Ps	psoriasis
PsA	psoriatic arthritis
PSSI	Psoriasis Scalp Severity Index
Q2W	every 2 weeks
Q4W	every 4 weeks
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
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.
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SMQ	standardized MedDRA query
SOA	Schedule of Activities
sPGA	static Physician Global Assessment
SUSAR	suspected unexpected serious adverse reactions
TASA	Treatment of Adolescent Suicide Attempters
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.
TPO	third-party organization
ULN	upper limit of normal

WBC	white blood cell
WCBP	women of childbearing potential
WHOATC	World Health Organization Anatomical Therapeutic Class

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests[a]

Hematology[b]	**Clinical Chemistry[b]**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	Total bilirubin
Platelets	Direct bilirubin
Absolute Counts of:	Alanine aminotransferase (ALT/SGPT)
Neutrophils, segmented	Aspartate aminotransferase AST/SGOT)
Neutrophils, juvenile	Blood urea nitrogen (BUN)
Lymphocytes	Uric acid
Monocytes	Creatinine
Eosinophils	Calcium
Basophils	Albumin
	Gamma-glutamyl transferase (GGT)
Urinalysis (dipstick)[b]	Total protein
Color	
Specific Gravity	**Other Tests**
pH	Human immunodeficiency virus antibody (HIV)
Protein	Hepatitis B virus DNA[c]
Glucose	Hepatitis B Surface antigen (HBsAg)
Ketones	Hepatitis B Core antibody (HBcAb)
Bilirubin	Hepatitis C antibody
Urobilinogen	Hepatitis E antibody[d]
Blood	High Sensitivity C-reactive protein (CRP)
Nitrite	Purified Protein Derivative (PPD)[e]
Urine Creatinine	
Leukocyte esterase	Pregnancy test (serum and urine)[f]
	Follicle-stimulating hormone (FSH)[g]
	LY2439821 serum concentration[h]
	Immunogenicity testing (anti-ixekizumab Ab)[h]
	Beta-D-Glucan[i]
	KL-6[j]

Abbreviations: Ab = antibody; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; DNA = deoxyribonucleic acid; FSH = follicle stimulating hormone; GGT = gamma-glutamyl transferase; HbsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; HIV = human immunodeficiency virus; RBC = red blood cells; PPD = purified protein derivative; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cells.

[a] Assayed by Lilly-designated laboratory.
[b] Unscheduled or repeat blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator, as needed.
[c] If patient is HBcAb+ and/or HBsAB+, HBV DNA needs to be confirmed negative at screening and at least once every month in Periods 2 and 3.
[d] Hepatitis E antibody is not a part of routine screening for this study; however, it may be required during the study for hepatic follow-up.
[e] See section 9.4.5.2: The QuantiFERON-TB Gold/T-SPOT.TB test may be used instead of the PPD TB test, and is performed locally.
[f] To be performed for females of childbearing potential only. Urine pregnancy tests are locally performed as scheduled in the SOA (Section 2). Necessary equipment may be provided centrally if needed.
[g] FSH test performed for women ≥40 and <60 years of age who have had a cessation of menses for at least 12 months to confirm non-childbearing potential (≥40mIU/mL)
[h] Immunogenicity samples will also be analyzed for ixekizumab serum concentration to facilitate in the interpretation of the immunogenicity data at Week 12 (visit 6), Week 20 (Visit 10) and ETV. In addition, a blood sample will be collected, when possible for any patient who experiences a potential systemic allergic/hypersensitivity reaction during the study as judged by the investigator.
[i] Beta-D-glucan is required at a screening and if an investigator believes it is warranted at subsequent visits, a beta-D-glucan test may be included in the work-up panel at any time during the study and may be done locally. If the beta-D-glucan test is positive, PCP needs to be ruled out. If PCP is ruled out and the investigator deems the patient fit to continue, the patient may continue in the study. If a patient has a confirmed diagnosis PCP during the study, the patient must discontinue the study.
[j] KL-6 is required at screening, and if an investigator believes it is warranted at subsequent visits, a KL-6 test may be included in the work-up panel at any time during the study and may be done locally.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 3.1.2. Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Appendix 3.1.3. Ethical Review

The investigator or an appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study site's ERB(s) should be provided with the following:

- the protocol and related amendments and addenda, current IB and updates during the course of the study
- informed consent form
- other relevant documents (for example, curricula vitae, advertisements).

Appendix 3.1.4. Regulatory Considerations

This study will be conducted in accordance with the protocol and with the

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations.

Some of the obligations of the sponsor will be assigned to a third party.

Appendix 3.1.5. Investigator Information

Physicians with a specialty in dermatology or other relevant specialties with appropriate experience with diagnosis and treatment of patients with psoriasis will participate as investigators in this clinical trial.

Appendix 3.1.6. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 3.1.7. Final Report Signature

The investigator will sign the final clinical study report (CSR) for this study, indicating agreement with the analyses, results, and conclusions of the report.

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site

- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome (PRO) measures (for example, a rating scale), a daily dosing schedule, or an event diary.

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Eli Lilly Japan, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

The study will be discontinued if Eli Lilly Japan judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.4. Publication Policy

The publication policy for Study I1F-JE-RHCV is described in the letters of agreement between the sponsor and the investigators and institutions.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated or local laboratory.

b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 5. Tests for Allergic Reactions and Hypersensitivity Events

Selected tests may be obtained in the event of anaphylaxis or generalized urticaria.

Hypersensitivity Tests[a]

Anti-LY2439821 antibodies (immunogenicity)	Tryptase
LY243821 serum concentration	N-methylhistamine
	Drug Specific IgE[b]
	Basophil Activation Test[b]
	Complements
	Cytokine Panel

Abbreviations: IgE = Immunoglobulin E.

[a] Assayed by Lilly-designated laboratory.

[b] Basophil Activation test will be performed if a drug specific IgE assay is unavailable.

Appendix 6. List of Excluded Medications and Procedures

Excluded Medications
IV antibiotics for an infection within 12 weeks prior to baseline
Systemic nonbiologic psoriasis therapy with the exception of: • oral corticosteroids, if average daily doses are not greater than 10 mg/day of prednisone or its equivalent. • all topical treatment • methotrexate or oral retinoids administered before and during the study if doses are not greater than that of baseline. • cyclosporine and Apremilast if daily doses are not greater than that of baseline • Granulocyte-monocyte adsorption apheresis (GMA): use of GMA is allowed.
Concurrent use of any biologic agent
Previous treatment with ixekizumab
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.
Vaccination with Bacillus Calmette-Guerin (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.
Excluded Procedures
Have received phototherapy at the day of baseline (Week 0; Visit 2) and during the course of the study.
Have donated more than 400 ml of blood (for patients weighing ≥50 kg), or • 200 ml of blood (for patients weighing <50 kg), or • plasmapheresis/platelet apheresis within 30 days prior to study entry, or plan to donate blood during the study.
Excessive sun exposure or use of tanning booths for at least 4 weeks prior to baseline (Week 0; Visit 2) and during the study.

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