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.

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		

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.

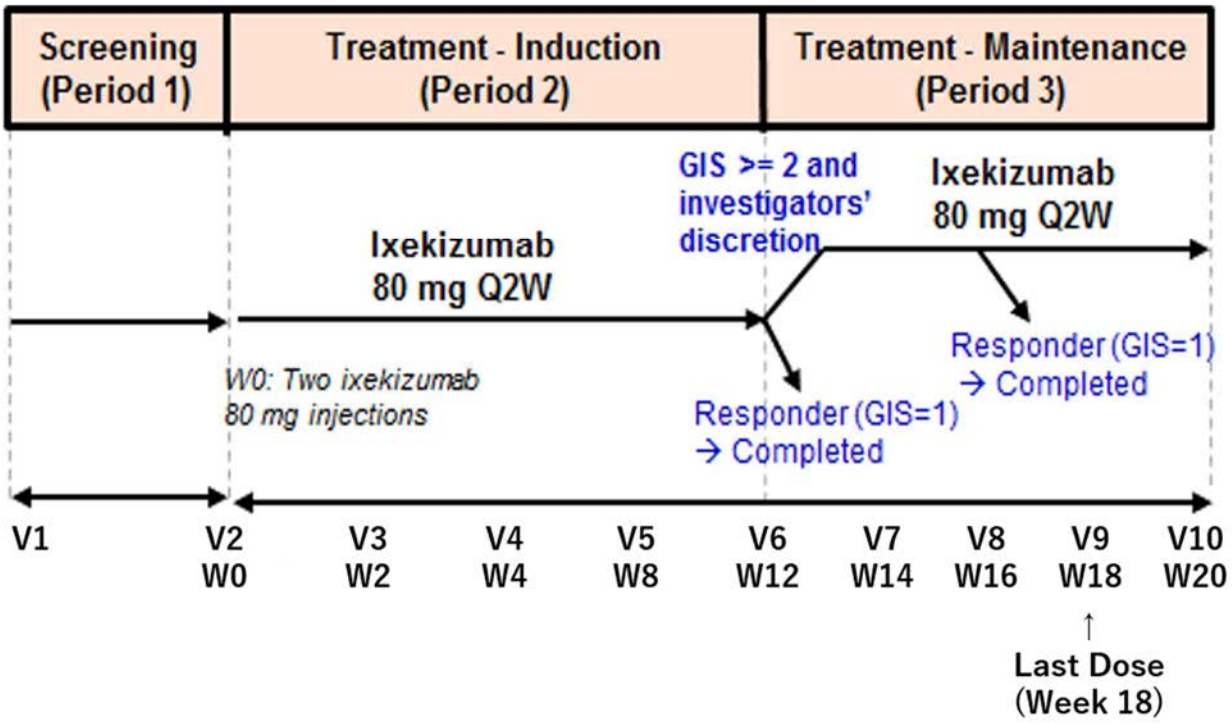

Figure RHCV.1. Illustration of study design for Clinical Protocol I1F-JE-RHCV.

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.

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.

9.2.3. 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.

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-

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).

10.3.4.2. 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.

11. References

Basra MKA, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol*. 2008;159(5):997-1035.

Bergboer JGM, Zeeuwen PLJM, Schalkwijk J. Genetics of psoriasis: evidence for epistatic interaction between skin barrier abnormalities and immune deviation. *J Invest Dermatol*. 2012;132(10):2320-2331.

Di Meglio P, Perera GK, Nestle FO. The multitasking organ: recent insights into skin immune function. *Immunity*. 2011;35(6):857-869.

Di Meglio P, Villanova F, Nestle FO. Psoriasis. *Cold Spring Harb Perspect Med*. 2014;4(8):pii:a015354.

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

[EMEA] European Medicines Agency. Committee for medicinal products for human use (CHMP). Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. Available at: https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-indicated-treatment-psoriasis_en.pdf. Accessed November 16, 2018.

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

Iwatsuki K, Terui T, Ozawa A, Komiyane M, Umezawa Y, Torii H, Nakanishi G, Hara H, Mabuchi T, Aoyama Y, Kitajima Y. Practice Guidelines 2010 for generalized pustular psoriasis (GPP): Treatment guidelines incorporating TNFα inhibitor [Japanese]. http://www.nanbyou.or.jp/pdf2/088_l.pdf. Accessed November 16, 2018.

Kim J, Krueger JG. The immunopathogenesis of psoriasis. *Dermatol Clin*. 2015;33(1):13-23.

Langley RG, Papp K, Gooderham M, Zhang L, Mallinckrodt C, Agada N, Blauvelt A, Foley P, Polzer P; of the IXORA-P Investigators. Efficacy and safety of continuous every-2-week dosing of ixekizumab over 52 weeks in patients with moderate-to-severe plaque psoriasis in a randomized phase III trial (IXORA-P). *Br J Dermatol*. 2018;178(6):1315-1323.

Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. *Nature*. 2007;445(7130):866-873.

Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, Lebwohl M, Koo JY, Elmets CA, Korman NJ, Beutner KR, Bhushan R. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2008;58(5):826-850.

Menter A, Griffiths CE. Current and future management of psoriasis. *Lancet*. 2007;370(9583):272-284.

Rapp SR, Feldman SR, Exum ML, Fleisher AB Jr., Reboussin DM. Psoriasis causes as much disability as other medical diseases. *J Am Acad Dermatol*. 1999;41(3 Pt 1):401-407.

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

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.

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										

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.

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.

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-

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.

9.4.4. 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

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.

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

Rosenbach M, Hsu S, Korman NJ, Lebwohl MG, Young M, Bebo BF Jr, Van Voorhees AS; National Psoriasis Foundation Medical Board. Treatment of erythrodermic psoriasis: from the medical board of the National Psoriasis Foundation. *J Am Acad Dermatol*. 2010;62(4):655-662.

Tang B, Annunziata K, DiBonaventura M. Burden of psoriasis in developing and developed countries [abstract]. In: International Society for Pharmacoeconomics and Outcomes Research 19th annual international meeting research abstracts. May 31-Jun 4, 2014. Montreal, Canada. Value Health. 2014;17(3): A289. Abstract PSS35.

Umezawa Y, Ozawa A, Kawasima T, Shimizu H, Terui T, Tagami H, Ikeda S, Ogawa H, Kawada A, Tezuka T, Igarashi A, Harada S. Therapeutic guidelines for the treatment of generalized pustular psoriasis (GPP) based on a proposed classification of disease severity. *Arch Dermatol Res*. 2003;295 Suppl 1:S43-S54.

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

Leo Document ID = e6d41fb9-3470-4c34-a272-74b8ebb854cf

Approver: PPD
Approval Date & Time: 01-Feb-2019 03:01:24 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 01-Feb-2019 03:32:52 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 01-Feb-2019 11:25:36 GMT
Signature meaning: Approved

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).