Title: Ixekizumab in the Treatment of Pityriasis Rubra Pilaris (PRP)

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An open label pilot trial of ixekizumab in the treatment of adults with Pityriasis Rubra Pilaris (PRP)

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Sponsor:	Oregon Health & Science University
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Trial Configuration	Single center, open label, interventional, investigator-initiated trial

CLINICAL PROTOCOL SYNOPSIS

Title	An open label pilot trial of ixekizumab in the treatment of adults with pityriasis rubra pilaris (PRP)
Principal Investigator	Teri Greiling, MD, PhD
Objectives	To determine whether ixekizumab provides clinical improvement for subjects with PRP who are candidates for systemic therapy
Trial Configuration Main Trial (a) Subset Analysis (b)	(a) Single center, open label, interventional, investigator-initiated trial (b) Observational cohort
Setting	(a) The trial will recruit 15 adults with severe (defined by psoriasis severity index (PASI) score > 10) PRP through dermatologist offices, recruitment letters, and advertisement. Study visits will occur at Screening, weeks 0, 2, 4, 8, 12, 16, 24, and 36. For subjects living >30 miles from OHSU, only study visits at weeks 0 and 24 will be required in-person; the remaining visits optionally will be performed via secure video-conferencing using the OHSU Nexus (Cisco Meeting) app, between the investigator and the subject, accessed by the subjects with a one-time-use video hyperlink sent from OHSU MyChart or email, as well as a REDCap survey sent via email. (b) The observational cohort will recruit up to 15 adults to include patients with a current or historic diagnosis of PRP who are not interested in or eligible for part (a). These subjects will complete questionnaires and have the opportunity to provide specimens for banking and further research (saliva – at OHSU or through mailing services; blood and tissue – at OHSU).
Sample Size Estimate	With measurement of the mean paired difference in PASI score before and after treatment of a minimum of 10 subjects, we would have 80% power at the 0.05 level to detect a mean within-subject change of 8-points when the standard deviation is 8-points. Due to the uncertainty inherent with a pilot study, the goal number of subjects with PRP who will be recruited for the interventional study is 15. In addition, the observational cohort will recruit up to an additional 15 patients.
Number of Participants	(a) 15 subjects with severe PRP for the interventional trial, (b) Up to 15 subjects in the observational cohort.
Eligibility Criteria (a)	**Inclusion criteria** • Willingness to comply with study procedures/requirements • Capable of giving informed consent • Diagnosis of PRP by clinical assessment and biopsy. • Male age 18-99. • Female age 18-99; either of non-childbearing potential or 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 ixekizumab. • PASI score of 10 or greater at baseline (severe disease). • Are a candidate for phototherapy and/or systemic therapy. • Willingness to travel to OHSU for all study visits, or living >30 miles from OHSU and willing/able to participate in remote videoconferencing visits with access to a computer with internet and webcam capabilities. **Exclusion criteria** • Known malignancy or lymphoproliferative disease (except treated basal cell skin cancer, treated squamous cell skin cancer, or treated cervical carcinoma in situ) for at least 5 years. • Active, untreated, acute or chronic infection (such as untreated tuberculosis), or immunocompromised to an extent that such that participation in the study would pose an unacceptable risk to the subject. (Treated infections such as latent tuberculosis after completion of the appropriate therapy are not excluded.) • Positive for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus. • Previous treatment with any agent that targets interleukin 17 specifically. • Systemic treatment or phototherapy for PRP within the past 4 weeks or 5 half-lives prior to baseline, whichever is longer. For biologic therapies, the specific washout periods used will be: etanercept <28 days; infliximab, adalimumab, or alefacept <60 days; golimumab <90 days; ustekinumab <8 months; rituximab or efalizumab <12 months. • Have a known allergy or hypersensitivity to any biologic therapy that would pose an unacceptable risk to the subject if participating in this study. • Have a live vaccine within 12 weeks prior to baseline or intend to have a live vaccine during the course of study. • Had any major surgery within 8 weeks prior to baseline or will require major surgery during the study, that in the opinion of the investigator would pose an unacceptable risk to the subject. • Presence of significant uncontrolled cerebrovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic, or neuropsychiatric disorders, or abnormal laboratory screening values that, in the opinion of the investigator, pose an unacceptable risk to the subject if participating in the study or of interfering with the interpretation of the data. • Presence of inflammatory bowel disease • Have clinical laboratory test results at screening that are outside the normal reference range of the population and are considered clinically significant, or have any of the following specific abnormalities: Neutrophil count <1500 cells/μL, lymphocyte count <500 cells/μL, platelet count <100,000 cells/μL, AST or ALT > 2.5 times the upper limit of normal, hemoglobin <8.5 g/dL for male subjects and <8.0 g/dL for

	female subjects, serum creatinine >2.0 mg/dL. • Women who are lactating or breastfeeding. • Have any other condition that precludes the subject from following and completing the protocol, in the opinion of the investigator. • Are investigator site personnel directly affiliated with this study and/or their immediate families (spouse, parent, child, or sibling). • Are currently enrolled in, or discontinued from a clinical trial involving an investigational product or non-approved use of a drug or device within the last 4 weeks or a period of at least 5 half-lives of the last administration of the drug, whichever is longer, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
Eligibility Criteria (b)	**Inclusion criteria** • Willingness to comply with study procedures/requirements. • Capable of giving informed consent. • Diagnosis of PRP by clinical assessment and biopsy – may currently be in remission or on systemic therapy. • Male or Female 18-99. **Exclusion criteria** • Have any condition that precludes the subject from following and completing the protocol, in the opinion of the investigator. • Are investigator site personnel directly affiliated with this study and/or their immediate families (spouse, parent, child, or sibling). • Are currently enrolled in any type of medical research judged not to be scientifically or medically compatible with this study.
Description of Interventions	(a) Subjects with PRP will be treated with ixekizumab for 20 weeks using the FDA-approved dosing schedule for psoriasis (160 mg subcutaneous injection at week 0 followed by 80 mg subcutaneous injection at weeks 2, 4, 6, 8, 10, 12, 16, and 20). (b) No intervention
Duration of Study	(a) The duration of the study will be 36 weeks (b) Completed in a single encounter
Outcome Measures	The primary outcome will be the mean change from baseline PASI at week-24 after treatment with ixekizumab. Secondary and mechanistic outcomes include measurement of improvement in body surface area, nail involvement, quality of life, itch, pain; time to improvement by 50%; sustained remission at 36 weeks; and correlation of improvement with germline genetic mutations and cutaneous cytokine expression.
Statistical Methods	Mean improvement from baseline PASI at week-24 will be analyzed for statistical significance using a paired, two-tailed student's t-test.

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ABBREVIATIONS

AE	Adverse Event
BSA	Body Surface Area
CARD14	CAspase Recruitment Domain family, member 14
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CRF	Case Report Form
DLQI	Dermatology Life Quality Index
EDC	Electronic Data Capture
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IL17	Interleukin-17
IND	Investigational New Drug
iPRPASI	Individual PRP Area and Severity Index
NAPSI	Nail Psoriasis Severity Index
NRS	Numeric Rating Scale
OHRP	Office for Human Research Protections
OHSU	Oregon Health and Science University
PASI	Psoriasis Area and Severity Index
PGA	Physician's Global Assessment
PI	Principal Investigator
PPPGA	Palmoplantar Physician's Global Assessment
PRP	Pityriasis Rubra Pilaris
SAE	Serious Adverse Event
SC	Subcutaneous
SOAP	Subjective, Objective, Assessment, Plan
Th17	T Helper 17 cell
UP	Unanticipated Problem

1. BACKGROUND

1.1. Overview of Pityriasis Rubra Pilaris (PRP) and Ixekizumab

Pityriasis rubra pilaris (PRP) is a rare and poorly understood severe inflammatory cutaneous disease characterized by widespread (often full-body) erythematous plaques, skin flaking and ichthyosis, painful thickening and cracking of the palms and soles, hair loss, crumbling nails, and severe skin pruritus and burning. The most common type of PRP affects otherwise-healthy adults and may be explosive in onset. Although PRP does not affect internal organs and no quality-of-life impact studies have been published, the high degree of morbidity is perhaps best illustrated by the following colorful quotes from members of a PRP Facebook support group (with >800 members):

> *"All I want is normal skin... for my eyes to stop watering constantly, to take off my clothes one time and not be shrouded by a cloud of dusty skin flakes..."*
>
> *"My husband can barely walk or use his hands."*
>
> *"My scalp is like the Sahara Desert experiencing the dust storm of the century."*
>
> *"I want my life back!!! Please."*

Not surprisingly, one study showed over half of patients with PRP reporting depression (*1*).

While the pathogenesis of PRP is poorly understood, similarities with inflammatory pathways in psoriasis have been reported. For example, a recent case report showed overexpression of cytokines in the Th17 pathway in cutaneous lesions of PRP, including the primary effector cytokines IL-17A, IL-17F, and IL-22 (*2*). Additionally, familial cases of both psoriasis and PRP have been associated with germline gain-of-function mutations in the caspase recruitment domain family, member 14 (CARD14) gene (*3, 4*), and cutaneous overexpression of CARD14 was observed in cases of sporadic PRP (*5*). CARD14 overexpression *in vitro* has also been shown to activate the Th17/IL-17 inflammatory pathway (*6*).

There is no FDA-approved therapy for PRP, not a single published systematic therapeutic clinical trial, and no established guidelines for measuring disease severity. Commonly prescribed systemic medications include acitretin and methotrexate, but these have treatment failure rates of over 40% (*1*) and can be limited by side effects. Tumor necrosis factor inhibitors have been used for PRP but have even higher failure rates (*1*), despite the fact that many insurance companies require a therapeutic trial as part of "step-therapy." There are currently 3 published single-case reports of the use of IL-17 inhibitors for PRP, all of which reported rapid disease clearance after only 2-4 weeks in refractory patients who had failed many other therapies (*7-9*). Ixekizumab is a humanized IgG4 monoclonal antibody that that selectively binds with the interleukin 17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor, and is currently FDA-approved for psoriasis. For these reasons, ixekizumab is proposed as a therapeutic intervention with potential for improving the lives of PRP patients.

This will be the first clinical trial to systematically test any medication for PRP, the first to propose measurement tools for PRP, the first quality of life impact study for PRP, and the first study to correlate these measurement tools with genetic and inflammatory markers. Based on small-scale prior studies, ixekizumab is expected to be a safe and effective therapy for PRP and lead to a dramatic improvement in quality of life for these patients.

1.2. Hypothesis

Treatment of subjects who have moderate to severe PRP with ixekizumab will lead to clinically significant improvement in subjective and objective measures of disease severity.

2. OBJECTIVES

2.1. Primary Objective

Determine whether ixekizumab provides clinical improvement for subjects with PRP who are candidates for systemic therapy.

2.2. Secondary Objectives

Use systematic measurement tools to associate the severity of cutaneous involvement of PRP with quality of life measures, before and after therapy with ixekizumab.

2.3. Exploratory Objectives

Explore the mechanisms by which ixekizumab alters the cutaneous inflammatory milieu in PRP; evaluate the use of telemedicine in clinical trials for rare disease.

3. STUDY DESIGN AND ENDPOINTS

3.1. Study Design Overview

This will be an investigator-initiated, open-label pilot study of 15 subjects with moderate to severe PRP treated with ixekizumab at the FDA-approved dosing for psoriasis for 20 weeks, examining the primary efficacy endpoint of mean decrease in PASI score at week-24. Sustained remission will be assessed at week-36. Biopsies will be obtained before the first injection and at week-24. Blood tests will be performed for screening and safety at Screening, week-4 and week-24. The study schedule is outlined in Section 5.4., Table 1.

Up to 15 additional subjects with a current or historic diagnosis of PRP who do not meet eligibility criteria for the interventional study will be included in as a separate cohort. These subjects will not receive study drug but will be asked to complete quality of life and symptom severity questionnaires, and provide saliva, blood, and/or tissue samples for comparison.

3.2. Study Endpoints

3.2.1. Primary Endpoint

Mean change from baseline PASI at week-24 after treatment with ixekizumab.

The Psoriasis Severity Index (PASI) is a well-validated tool for measuring psoriasis, based on redness, thickness, scale, and body surface area assessed by the investigator, with a maximum score of 72 points. This is expected to be a useful tool for PRP, since PRP is characterized by widespread bright red erythema and scale, and is often initially misdiagnosed as severe psoriasis. The mean thickness score is expected to be lower in PRP than psoriasis but the mean body surface area (BSA) is expected to be higher than psoriasis. Like often used for psoriasis, a minimum PASI score of 10 to represent moderate to severe disease will be used as a cutoff for enrollment in the trial.

3.2.2. Secondary Endpoints Assessed by Investigator

- Time to improvement by 50% in the PASI score (PASI 50)
- Mean reduction in body surface area (BSA) at week-24. BSA is collected as part of the PASI assessment tool.
- Proportion of subjects achieving a Physician's Global Assessment (PGA) of 0 or 1 at week-24

- Proportion of subjects achieving a Palmoplantar Physician's Global Assessment (PPPGA) of 0 or 1 at week-24. Palmoplantar disease will be assessed separately from overall disease since it has high morbidity and may respond differently to therapy.
- Mean percentage improvement in nail involvement measured by Nail Psoriasis Severity Index (NAPSI) at week-24. The Nail Psoriasis Severity Index (NAPSI) (*10*) will be used for evaluating the fingernails and toenails of subjects with PRP. This is expected to be useful tool because nails in PRP have many overlapping features with psoriasis including nail plate crumbling, splinter hemorrhages, nail oil drop (yellow-brown) discoloration, and nail bed hyperkeratosis, although PRP nails are less likely to have onycholysis and red spots in the lunula (*11*).

3.2.3. Secondary Endpoints Assessed by Subject

- Proportion of subjects achieving a 4-point improvement in quality of life measured by the Dermatology Life Quality Index (DLQI) at week-24, and mean improvement in DLQI score at week-24. The DLQI (*12*) is a validated tool for inflammatory skin conditions. It is a 10-question survey, scored 0 – 30 points. For inflammatory skin conditions, a 4-point change in DLQI score is considered clinically important (*13*).
- Mean percentage in improvement of itch measured by 0 – 10-point numeric rating scale (NRS) at week-24. The Itch NRS is a subject-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable."
- Mean percentage in improvement in burning/pain measured by 0 – 10-point NRS at week-24. The burning/pain NRS is a subject-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no burning/pain" and 10 representing "worst burning/pain imaginable."
- Mean change from baseline individual PRP Area and Severity Index (iPRPASI) at week-24 after treatment with ixekizumab, and correlation of subject-assessed iPRPASI scores with investigator-assessed PASI scores. The IPRPASI is a novel subject self-assessment score of disease involvement and severity, based on a previously published similar tool validated for psoriasis (*14*).
- Sustained remission at week-36, 16 weeks after the last ixekizumab dose, as measured by the mean change in PASI from week-24 to week-36. Sporadic PRP is often a self-limited disease, resolving spontaneously after an average of 3-6 years. Other immunomodulatory medications have induced sustained remission of PRP (*15*), so there is a potential that treatment may "reset" the immune response and lead to long-term improvement in the disease, especially in subjects without genetic mutations. Subjects will be treated with ixekizumab as per the FDA-approved psoriasis treatment guidelines, and therapy will be stopped after the 20-week dose. Subjects will be monitored at 24 weeks (primary study endpoint) and then at 36 weeks to assess for sustained remission versus relapse.

3.2.4. Exploratory/Mechanistic Endpoints

- Treatment response, as measured by PASI 50, stratified by the presence or absence of germline CARD14 mutations. Genetic CARD14 gain-of-function mutations were identified in 3 families with familial PRP as well as 12.5% of individuals with sporadic PRP (*3*). Genetic CARD14 mutations will be measured in study subjects and associated with treatment response to ixekizumab. Additionally, de-identified samples will be stored indefinitely for future analysis of genes associated with PRP.
- Normalization of CARD14 epithelial expression at week-24. Despite the fact that not all patients with PRP have genetic CARD14 mutations, immunohistochemical staining of CARD14 in 6 of 6 biopsies from sporadic cases of PRP without germline genetic mutations showed increased expression of CARD14 in the keratinocyte spinous and granular layers of the epidermis (*2*). CARD14 is thought to act in a synergistic manner with IL-17, activating the transcription factor NF-kB. NF-kB activation was shown *in vitro* to stimulate IL-36gamma, which may induce an amplifying feedback loop from IL-23 to IL-17 and back again (*6*). Cutaneous biopsies will be obtained from subjects before and 24 weeks after treatment with ixekizumab. Inhibition of IL-17 by ixekizumab is expected to lead to normalization of CARD14 expression by keratinocytes.

- Normalization of cutaneous inflammatory cytokines at week-24. Upregulation of Th17 cytokines (IL-17A, IL-17F, IL-22) and pro-inflammatory innate cytokines (TNF, IL-6, IL-12, IL-23, IL-1beta) compared to normal skin were observed in lesional skin from 3 subjects with PRP (*5*). In order to better understand the inflammatory pathways involved in PRP, a lesional biopsy will be obtained from subjects at week-0 prior to the first dose of ixekizumab, and again at week-24. A non-lesional control biopsy will also be obtained at week-0 if non-lesional skin is available. Cutaneous inflammatory cytokines will be analyzed and therapeutic response to ixekizumab is expected to correlate with normalization of epidermal cytokine levels. De-identified tissue samples will be stored indefinitely for inflammatory analysis.
- Change in serum or plasma cytokine levels at weeks 0 and 24. Cytokine levels before and after treatment with ixekizumab will be analyzed. De-identified samples may be sent to outside laboratories within the United States for analysis.
- Effects of telemedicine on study size and cost. Participation in the study will be given a final questionnaire about the ease, and accessibility, cost savings of using telemedicine for research.

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Inclusion Criteria

4.1(a) Primary Trial

- Diagnosis of PRP by clinical assessment and biopsy.
- Male subject age 18-99.
- Female subject age 18-99; either of non-childbearing potential or 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 ixekizumab.
- PASI score of 10 or greater at baseline.
- Are a candidate for phototherapy and/or systemic therapy.
- Willingness to travel to OHSU for all study visits, OR living >30 miles from OHSU and willing/able to participate in remote videoconferencing visits with access to a computer with internet capabilities and webcam.
- Have given written informed consent approved by the OHSU Investigational Review Board.

4.1(b) Observational Cohort

- Diagnosis of PRP by clinical assessment and biopsy – subjects may be in remission or on current therapy.
- Male or female age 18-99.
- Have given written informed consent approved by the OHSU Investigational Review Board.

4.2. Exclusion Criteria

4.2(a) Primary Trial

- Known malignancy or lymphoproliferative disease (except treated basal cell skin cancer, treated squamous cell skin cancer, or treated cervical carcinoma in situ) for at least 5 years.
- Active, untreated, acute or chronic infection (such as untreated tuberculosis), or immunocompromised to an extent that such that participation in the study would pose an unacceptable risk to the subject. (Treated infections such as latent tuberculosis after completion of the appropriate therapy are not excluded.)
- Positive for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus.
- Previous treatment with any agent that targets interleukins 17 specifically.
- Systemic treatment or phototherapy for PRP within the past 4 weeks or 5 half-lives prior to baseline, whichever is longer. For biologic therapies, the specific washout periods used will be: etanercept <28 days; infliximab, adalimumab, or alefacept <60 days; golimumab <90

days; ustekinumab <8 months; rituximab or efalizumab <12 months.

- Have a known allergy or hypersensitivity to any biologic therapy that would pose an unacceptable risk to the subject if participating in this study.
- Have a live vaccine within 12 weeks prior to baseline or intend to have a live vaccine during the course of study.
- Had any major surgery within 8 weeks prior to baseline or will require major surgery during the study that, in the opinion of the investigator, would pose an unacceptable risk to the subject.
- Presence of significant uncontrolled cerebrovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic, or neuropsychiatric disorders, or abnormal laboratory screening values that, in the opinion of the investigator, pose an unacceptable risk to the subject if participating in the study or of interfering with the interpretation of the data.
- Presence of inflammatory bowel disease
- Have clinical laboratory test results at screening that are outside the normal reference range of the population and are considered clinically significant, or have any of the following specific abnormalities: Neutrophil count <1500 cells/μL, lymphocyte count <500 cells/μL, platelet count <100,000 cells/μL, AST or ALT > 2.5 times the upper limit of normal, hemoglobin <8.5 g/dL for male subjects and <8.0 g/dL for female subjects, serum creatinine >2.0 mg/dL.
- Women who are lactating or breastfeeding.
- Have any other condition that precludes the subject from following and completing the protocol, in the opinion of the investigator.
- Are investigator site personnel directly affiliated with this study and/or their immediate families (spouse, parent, child, or sibling).
- Are currently enrolled in, or discontinued from a clinical trial involving an investigational product or non-approved use of a drug or device within the last 4 weeks or a period of at least 5 half-lives of the last administration of the drug, whichever is longer, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

4.2(b) Observational Cohort

- Have any condition that precludes the subject from following and completing the protocol, in the opinion of the investigator.
- Are investigator site personnel directly affiliated with this study and/or their immediate families (spouse, parent, child, or sibling).
- Are currently enrolled in any type of medical research judged not to be scientifically or medically compatible with this study.

4.3. Recruitment and Identification of Participants

The main trial will recruit subjects with severe PRP, either newly diagnosed or failing other therapies due to side effects or lack of efficacy. Patients recruited for the observational cohort will be recruited through similar means but with less stringent inclusion/exclusion criteria as above. A number of recruitment strategies will be utilized for this study proven to be effective by our group in previous studies.

- OHSU and community dermatology clinics
- OHSU OCTRI Cohort Discovery tool to identify patients with PRP via Epic, and a phone call to those patients
- Publicity on the PRP Support Group Facebook page
- Publicity through the PRP Alliance patient advocacy organization, including an email to members of the PRP Alliance
- Research Match

4.4. Vulnerable Populations

Children, neonates, pregnant women, prisoners, and decisionally impaired adults will not be enrolled in the study.

5. STUDY PROCEDURES, EVALUATIONS, AND SCHEDULE

5.1 Study Visit Procedures

5.1.1 Pre-trial

During the first contact with the study team, an overview of the trial will be given. Because of the rarity of PRP, subjects may be traveling from distant locations for the study; thus the phone script is intended to be somewhat more comprehensive for a subject to determine if they are interested and able to participate. If they would like to participate, a request for information will be signed by the subject and sent to the subject's healthcare providers to review records pertinent to the diagnosis of PRP. Once the study investigator has reviewed the records and confirmed that a diagnosis of PRP has been made by a qualified healthcare provider, an appointment for a screening visit will be made. For subjects in whom the screening visit will be completed by telemedicine, the informed consent form will be emailed or mailed to the subject prior to the screening visit.

5.1.2. Screening

(a) Primary Trial

Subjects will read the informed consent form and all questions about the study will be answered by a study investigator and research staff. Screening questions will be asked and eligibility will be determined by qualified research staff. Subjects will be asked about vaccine history to ensure that recommended vaccines are up to date, and subjects will be reminded that live vaccines (such as the intranasal influenza vaccine or live varicella zoster vaccine (Zostavax)) are not permitted during the study. An investigator will perform an assessment of PASI to calculate disease severity. If all other criteria are met, a blood sample will be drawn to screen for HBV, HCV, HIV, and tuberculosis, and to check CBC and CMP. PPD skin testing may be used if blood testing for tuberculosis is unavailable. A pregnancy test will be performed for women of childbearing potential. If subjects have had HBV, HCV, HIV, and tuberculosis testing within 3 months prior to screening, records of these results will be sufficient and the tests will not be repeated.

For interested subjects who live >30 miles from OHSU, the screening visit may be performed via secure video-conferencing using the OHSU Nexus (Cisco Meeting) app, in which case the study consent will be reviewed during the telemedicine videoconference and signed via e-consent in REDCap. The blood draw will be performed at the lab of the subject's choice and results will be sent to the investigators.

Upon confirmation of normal blood tests as defined in the exclusion criteria, and receipt of the signed consent form, subjects will be scheduled for enrollment and Visit 1 as appropriate for any medication washout period required in the exclusion criteria. If blood tests are abnormal, the subject will be informed and referred to her or his primary care physician for assessment.

For Spanish-speaking subjects, the English-written consent form will be verbally translated with the help of a Spanish interpreter. All questions regarding the study will be translated to study staff and answered to patient satisfaction. Subjects will then be provided the adapted boilerplate consent, "Consent Form – Short – Spanish," to sign. A copy of both signed consents will be provided to the patient and uploaded in the patient's chart.

(b) Observational Cohort

Subjects will read the informed consent form and all questions about the study will be answered by a study investigator and research staff. Screening questions will be asked and eligibility will be determined by qualified research staff.

For interested subjects who live >30 miles from OHSU, the screening visit may be performed via secure video-conferencing using the OHSU Nexus (Cisco Meeting) app, in which case the study consent will be reviewed during the telemedicine videoconference and signed via e-consent in REDCap.

Upon confirmation receipt of the signed consent form, subjects will be scheduled for enrollment.

5.1.3. Enrollment

The inclusion/exclusion criteria will be re-reviewed and subjects may proceed with visit 1 on the same day if they continue to meet criteria.

5.1.4. Visit 1 / Week-0 (baseline)

(a) Primary Trial

Visit 1 will be performed at OHSU for all subjects.

- Study personnel will gather the following information from the subjects and record the results in REDCap:
    - Demographics (sex, gender, race, ethnicity)
    - Current medications
    - Drug allergies
    - Use of alcohol, tobacco, and other substances
    - PRP medical history
    - General medical history
    - Family medical history
    - Review of Systems
    - Height and weight
    - Blood pressure
    - Pulse
- Subjects will enter the following information about their disease and medical history via OHSU REDCap survey:
    - DLQI
    - NRS for itch and pain
    - iPRPASI
- The subject will be clinically examined by an investigator (clinician or research nurse) who will assess the following and record the results in OHSU REDCap:
    - Full body skin exam with documentation of PASI, PGA, PPPGA, and NAPSI
    - Examination of the oral mucosa
    - Heart and lung auscultation
    - Palpation of the cervical, axillary, and inguinal lymph nodes
    - Presence of peripheral edema
- Photographs will be taken of each body region to visually record extent of disease: head, face, anterior trunk, posterior trunk, arms, palms, legs, soles
- Subjects will undergo a punch biopsy (consisting of three adjacent 3 mm punch biopsies, a total surface area equivalent to the size of a 5 mm punch biopsy) from affected skin, performed by an investigator. One additional 3 mm punch biopsy will be obtained from non-lesional skin as a control if non-lesional skin is available. For consistency, skin of back will be chosen for biopsy if an affected site is available. If back skin is not available, alternate sites in order of preference will include: chest, arm, leg. Location of the biopsy will be carefully documented.
- Blood will be drawn for serum markers of disease activity (approximately 2 ml)
- A saliva sample will be collected for genetic testing
- The first dose of 160 mg of subcutaneous ixekizumab will be administered by trained study personnel while the study subject undergoes teaching for future self-administration.
- Subjects who live >30 miles from OHSU and plan to complete future visits by videoconferencing will receive a scale and sphygmomanometer for future vital sign assessments

(b) Observational Cohort

Participants in the observational cohort will be asked to fill out questionnaires regarding their medical history, disease course, and symptom severity at its worst. They will also be asked to provide one or more samples, depending on participant preference. The requested samples will include saliva, blood, and tissue, and will be collected in the same manner as outlined in 5.1.4. (a). Participants may provide only a single sample type and are NOT required to provide each.

- Questionnaires will completed through an OHSU REDCap survey and include:
    - Demographics (sex, gender, race, ethnicity)
    - Current medications
    - Drug allergies
    - Use of alcohol, tobacco, and other substances
    - PRP medical history
    - General medical history
    - Family medical history
    - DLQI
    - NRS for itch and pain
- Subjects electing to provide a saliva sample will be provided a kit for collection to complete either in office or remotely via mail
- Subjects electing to provide a blood sample with have approximately 2 mL of blood drawn for serum markers of disease activity
- Subjects electing to provide a tissue sample will undergo a punch biopsy (consisting of three adjacent 3 mm punch biopsies, a total surface area equivalent to the size of a 5 mm punch biopsy) from affected skin, performed by an investigator. One additional 3 mm punch biopsy will be obtained from non-lesional skin as a control, if non-lesional skin is available. For consistency, skin of back will be chosen for biopsy if an affected site is available. If back skin is not available, alternate sites in order of preference will include: chest, arm, leg, other. Location of the biopsy will be carefully documented.

This will be the only encounter for the observational cohort. All additional encounters listed pertain solely to the Primary Trial (a) group.

5.1.5. Visit 2 / Week-2 (14 days +/- 2 days after last visit)

Visit 2 will be performed at OHSU or optionally by secure telemedicine and REDCap survey for subjects who live >30 miles from OHSU.

- Study personnel will gather the following information from the subjects and record the results in REDCap:
    - Chance in medications since the last visit
    - Change in drug allergies since the last visit
    - Change in personal or family medical history since the last visit
    - Weight (performed by the subject for videoconferencing visits)
    - Blood pressure (performed by the subject for videoconferencing visits)
    - Pulse (performed by the subject for videoconferencing visits)
- Subjects will enter the following information about their disease and medical history via OHSU REDCap survey:
    - DLQI
    - NRS for itch and pain
    - iPRPASI
- The subject will be clinically examined by an investigator (clinician or research nurse, either in-person or via telemedicine) who will assess the following:
    - Full body skin exam with documentation of PASI, PGA, and PPPGA
- The second dose of 80 mg of subcutaneous ixekizumab will be administered by the subject with observation and teaching from study personnel.

5.1.6. Visit 3 / Week-4 (14 days +/- 2 days after last visit)

Visit 3 will be performed at OHSU or optionally by telemedicine and REDCap survey for subjects who live >30 miles from OHSU.

- Study personnel will gather the following information from the subjects and record the results in REDCap:
    - Chance in medications since the last visit
    - Change in drug allergies since the last visit
    - Change in personal or family medical history since the last visit
    - Weight (performed by the subject for videoconferencing visits)
    - Blood pressure (performed by the subject for videoconferencing visits)
    - Pulse (performed by the subject for videoconferencing visits)
- Subjects will enter the following information about their disease and medical history via OHSU REDCap survey:
    - DLQI
    - NRS for itch and pain
    - iPRPASI
- The subject will be clinically examined by an investigator (clinician or research nurse, either in-person or via telemedicine) who will assess the following:
    - Full body skin exam with documentation of PASI, PGA, and PPPGA
- Blood will be drawn for monitoring the CBC and CMP (at a local lab of the subject's choice for remote visits, within a window of +/- 2 days of the visit date)
- The third dose of 80 mg of subcutaneous ixekizumab will be administered by the subject with observation and teaching from study personnel.

5.1.7. Contact at week-6 (14 days +/- 2 days after last visit)

All subjects will be contacted by a member of the study team by telephone, e-mail, text message, or videoconference at 2 weeks ± 2 days as a reminder to complete the scheduled injection of ixekizumab and answer any questions or concerns. Injection teaching will be reviewed if needed and the subject will be asked specifically about any adverse events since the last contact.

5.1.8. Visit 4 / Week-8 (14 days +/- 2 days after last injection)

Visit 4 will be performed at OHSU or optionally by telemedicine and REDCap survey for subjects who live >30 miles from OHSU.

- Study personnel will gather the following information from the subjects and record the results in REDCap:
    - Chance in medications since the last visit
    - Change in drug allergies since the last visit
    - Change in personal or family medical history since the last visit
    - Weight (performed by the subject for videoconferencing visits)
    - Blood pressure (performed by the subject for videoconferencing visits)
    - Pulse (performed by the subject for videoconferencing visits)
- Subjects will enter the following information about their disease and medical history via OHSU REDCap survey:
    - DLQI
    - NRS for itch and pain
    - iPRPASI
- The subject will be clinically examined by an investigator (clinician or research nurse, either in-person or via telemedicine) who will assess the following:
    - Full body skin exam with documentation of PASI, PGA, and PPPGA
- The fifth dose of 80 mg of subcutaneous ixekizumab will be administered by the subject with observation and teaching from study personnel.

5.1.9. Contact at week-10 (14 days +/- 2 days after last visit)

All subjects will be contacted by a member of the study team by telephone, e-mail, text message, or videoconference at 2 weeks ± 2 days as a reminder to complete the scheduled injection of ixekizumab and answer any questions or concerns. Injection teaching will be reviewed if needed and the subject will be asked specifically about any adverse events since the last contact.

5.1.10. Visit 5 / Week-12 (14 days +/- 2 days after last injection)

Visit 5 will be performed at OHSU or optionally by telemedicine and REDCap survey for subjects who live >30 miles from OHSU.

- Study personnel will gather the following information from the subjects and record the results in REDCap:
    - Chance in medications since the last visit
    - Change in drug allergies since the last visit
    - Change in personal or family medical history since the last visit
    - Weight (performed by the subject for videoconferencing visits)
    - Blood pressure (performed by the subject for videoconferencing visits)
    - Pulse (performed by the subject for videoconferencing visits)
- Subjects will enter the following information about their disease and medical history via OHSU REDCap survey:
    - DLQI
    - NRS for itch and pain
    - iPRPASI
- The subject will be clinically examined by an investigator (clinician or research nurse, either in-person or via telemedicine) who will assess the following:
    - Full body skin exam with documentation of PASI, PGA, and PPPGA
- The seventh dose of 80 mg of subcutaneous ixekizumab will be administered by the subject with observation and teaching from study personnel.

5.1.11. Visit 6 / Week-16 (28 days +/- 4 days after last visit)

Visit 6 will be performed at OHSU or optionally by telemedicine and REDCap survey for subjects who live >30 miles from OHSU.

- Study personnel will gather the following information from the subjects and record the results in REDCap:
    - Chance in medications since the last visit
    - Change in drug allergies since the last visit
    - Change in personal or family medical history since the last visit
    - Weight (performed by the subject for videoconferencing visits)
    - Blood pressure (performed by the subject for videoconferencing visits)
    - Pulse (performed by the subject for videoconferencing visits)
- Subjects will enter the following information about their disease and medical history via OHSU REDCap survey:
    - DLQI
    - NRS for itch and pain
    - iPRPASI
- The subject will be clinically examined by an investigator (clinician or research nurse, either in-person or via telemedicine) who will assess the following:
    - Full body skin exam with documentation of PASI, PGA, and PPPGA
- The eighth dose of 80 mg of subcutaneous ixekizumab will be administered by the subject with observation and teaching from study personnel.

5.1.12. Contact at week-20 (28 days +/- 4 days after last visit)

All subjects will be contacted by a member of the study team by telephone, e-mail, text message, or videoconference at 2 weeks ± 2 days as a reminder to complete the scheduled injection of ixekizumab and answer any questions or concerns. Injection teaching will be reviewed if needed and the subject will be asked specifically about any adverse events since the last contact.

5.1.13. Visit 7 / Week-24 (primary endpoint; 28 days +/- 4 days after last injection)

Visit 7 will be performed at OHSU for all subjects.

- Study personnel will gather the following information from the subjects and record the results in REDCap:
    - Chance in medications since the last visit
    - Change in drug allergies since the last visit
    - Change in personal or family medical history since the last visit
    - Weight
    - Blood pressure
    - Pulse
- Subjects will enter the following information about their disease and medical history via OHSU REDCap survey:
    - DLQI
    - NRS for itch and pain
    - iPRPASI
- The subject will be clinically examined by an investigator (clinician or research nurse) who will assess the following:
    - Full body skin exam with documentation of PASI, PGA, PPPGA, and NAPSI
    - Examination of the oral mucosa
    - Heart and lung auscultation
    - Palpation of the cervical, axillary, and inguinal lymph nodes
    - Presence of peripheral edema
- Photographs will be taken of each body region: head, face, anterior trunk, posterior trunk, arms, palms, legs, soles
- Blood will be drawn for monitoring the CBC and CMP, as well as serum markers of disease activity
- Subjects will undergo an endpoint punch biopsy (consisting of three adjacent 3 mm punch biopsies) in the same body region as the first documented biopsy (back, chest, arm, or leg), preferably in an area affected by PRP at the first study visit and possibly cleared or improved at the endpoint visit.
- Subjects will answer questions about their experience will telemedicine and remote visits.

5.1.14. Visit 8 / Week-36 (84 days +/- 7 days after last visit)

Visit 8 will be performed at OHSU or optionally by telemedicine and REDCap survey for subjects who live >30 miles from OHSU.

- Study personnel will gather the following information from the subjects and record the results in REDCap:
    - Chance in medications since the last visit
    - Change in drug allergies since the last visit
    - Change in personal or family medical history since the last visit
    - Weight (performed by the subject for videoconferencing visits)
    - Blood pressure (performed by the subject for videoconferencing visits)
    - Pulse (performed by the subject for videoconferencing visits)
- Visit 8 Subjects will enter the following information about their disease and medical history via OHSU REDCap survey:
    - DLQI
    - NRS for itch and pain

    - iPRPASI
- The subject will be clinically examined by an investigator (clinician or research nurse, either in-person or via telemedicine) who will assess the following:
    - Full body skin exam with documentation of PASI, PGA, and PPPGA

5.2. Early Withdrawal / Unscheduled Visits

If the subject wishes to withdraw from the trial before week-24, they will be asked to attend for a final trial (early termination) visit. At this visit, if the subject is willing, the same procedures as for the primary outcome / week-24 visit will be carried out. If the subject withdraws after the week-24 visit, the final week-36 visit will be carried out early instead.

5.3. Participant Stipends and Payments

Participants enrolled in the primary trial (a) will be paid $50 for all visits that do not involve skin biopsy (Screening and visits 2, 3, 4, 5, 6, 8) and $150 for the two visits that involve skin biopsy (baseline and visit 7), for a total of $650. Other contacts are not reimbursed. For those subjects traveling >200 miles to OHSU, travel will be reimbursed at the federal Internal Revenue Service suggested rate of $0.535/mile up to 1000 miles (range $214 - $1070 for a round-trip visit to OHSU) for each of the two in-person visits (baseline and visit 7).

Participants enrolled in the observational cohort (b) will not be eligible for reimbursement.

5.4. Table 1: Study Schedule of Events (Primary Trial)

Visit	Pre-trial	Screening*	Enrollment	V1	V2	V3	-	V4	-	V5	V6	-	V7	V8
Week				**WK 0**	**WK 2***	**WK 4***	**WK 6**	**WK 8***	**WK 10**	**WK 12***	**WK 16***	**WK 20**	**WK 24**	**WK 36***
Baseline Documentation														
Informed consent		X												
Confirmation of dx	X													
Investigator assessment		X		X	X	X		X		X	X		X	X
Medical history		X		X										
Exclusion/Inclusion criteria		X	X											
Dosing														
Injection counseling/training				X										
Injection review					X	X	X	X	X	X	X	X		
Study drug dispensing				X										
Study drug injection/dose**				X	X	X	X	X	X	X	X	X		
Laboratory Studies														
Blood draw***		X		X		X							X	
Other Assessments and Procedures														
Skin biopsy				X									X	
Adverse events				X	X	X	X	X	X	X	X	X	X	X
Subject REDCap survey				X	X	X		X		X	X		X	X
Phone contact	X						X		X			X		

*Visit optionally to be performed via secure telemedicine videoconferencing for subjects >30 miles from Oregon Health & Science University.
**Ixekizumab subcutaneous dose: 160mg on W0, 80mg on all subsequent dosing time points (W2, W4, W6, W8, W10, W12, W16, and W20).
***Laboratory studies will include: HBV, HCV, HIV, tuberculosis, CBC, CMP, pregnancy testing for women who may be able to become pregnant, and markers of disease activity.

6. INVESTIGATIONAL PRODUCT AND TREATMENT PLAN

6.1. Investigational Product: Ixekizumab

Ixekizumab is a humanized monoclonal antibody that binds and blocks IL-17.

6.2. Dosing and Administration

Ixekizumab treatment will be administered at the FDA-approved dosing schedule for psoriasis as follows:

- 160 mg SC injection at week-0
- 80 mg SC injections as weeks 2, 4, 6, 8, 10, 12, 16, and 20

The 1 mL pre-filled syringe will be injected at room temperature into the subcutaneous tissue of the upper arms, thighs, or abdomen, avoiding areas affected by PRP when possible. Each injection will be administered in an anatomic location different from the previous injection, and the location will be recorded. Injections will be performed by qualified study personnel or by the subject after proper training in SC injection technique. Injections performed at home by the subject will be recorded by the subject in an injection diary and returned to the investigators.

6.3. Storage

The study drug will be stored in the Research Pharmacy and all applicable Research Pharmacy policies and procedures will be followed.

6.4. Concomitant Medications, Treatments, and Procedures

6.4.1. Concomitant Medication Recording

All concomitant medications taken during the study must be recorded. Subjects will be asked about concomitant medications at each study visit.

6.4.2. Prohibited Medications, Treatments, and Procedures

The following therapies will not be permitted for subjects enrolled in the main trial during the course of the study:

- Treatment with systemic therapy intended to treat PRP within the washout period specified in the exclusion criteria, including prednisone, methotrexate, cyclosporine, acitretin, and injectable biologic therapies. These medications could have a negative safety impact on the subjects enrolled and confound the results of the study.
- Live vaccines
- Phototherapy within the 4-week washout period

6.4.3. Permitted Medications, Treatments, and Procedures

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

- Topical therapies such as steroids or emollients
- Non-live vaccines (such as the non-live annual influenza vaccine, non-live herpes zoster vaccine (Shingrix), rabies, or tetanus) and/or emergency vaccines are allowed
- Acetaminophen, aspirin, or ibuprofen as needed
- Subjects will maintain their usual medication regimen for other concomitant diseases throughout the study unless specifically excluded in the protocol. Subjects taking concomitant medications should be on a stable dose throughout the study, unless changes need to be made for an AE or for appropriate medical management. Additional systemic drugs are to be avoided during the study, unless required to treat an AE. Other medications may be allowed, if approved by the investigator. Any changes in medications should be discussed with the investigator. Subjects

should be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements.

7. STATISTICAL CONSIDERATIONS

7.1. Sample Size Computation and Power Analysis

This is a pilot study with no published baseline data; thus a power analysis was performed with the following rough assumptions. With measurement of the mean paired difference in PASI score before and after treatment of a minimum of 10 subjects, we would have 80% power at the 0.05 level to detect a mean within-subject change of 8-points when the standard deviation is 8-points. Due to the uncertainty inherent with a pilot study, the goal number of subjects with PRP who will be recruited for the interventional study is 15.

Power (1-ß)	*Sample Size*	*α*	*ß*	*Mean Change in PASI*	*Standard Deviation*
0.9998	10	0.05	0.0002	-8	4
0.9940	10	0.05	0.0060	-8	5
0.9621	10	0.05	0.0379	-8	6
0.8942	10	0.05	0.1058	-8	7
0.8031	**10**	**0.05**	**0.1969**	**-8**	**8**
0.9873	10	0.05	0.0127	-6	4
0.9203	10	0.05	0.0797	-6	5
0.8031	10	0.05	0.1969	-6	6
0.6755	10	0.05	0.3245	-6	7
0.5620	10	0.05	0.4380	-6	8

7.2. Statistical Analysis Plan

Data analysis will be ongoing throughout the trial by the PI and is expected to be complete within 3 months after the last-subject last-visit.

7.2.1. Primary Endpoint Analysis

- Mean improvement from baseline PASI at week-24 will be analyzed for statistical significance using a paired, two-tailed student's t-test.

7.2.2. Secondary Endpoint Analyses:

- Time (weeks) to improvement by 50% in the PASI score (PASI 50) will be reported as a mean with standard deviation and also represented graphically.
- Mean improvement from baseline BSA at week-24 will be analyzed for statistical significance using a paired, two-tailed student's t-test.
- The proportion of subjects achieving a Physician's Global Assessment of 0 or 1 at week-24 will be reported as a proportion, and compared with historical estimates of treatment success with acitretin and methotrexate *(1)*.
- The proportion of subjects achieving a Palmoplantar Physician's Global Assessment of 0 or 1 at week-24 will be reported as a proportion.
- The mean improvement in nail involvement measured by NAPSI (see below) at week-24 will be analyzed for statistical significance using a paired, two-tailed student's t-test.
- The proportion of subjects achieving a 4-point improvement in quality of life measured by DLQI at week-24 will be reported as a proportion. The mean improvement in DLQI score from week-0 to week-24 will be analyzed using a paired, two-tailed student's t-test.

- The mean improvement in itch measured by 0 – 10-point subject-reported subjective numeric rating scale at week-24 will be analyzed for statistical significance using a paired, two-tailed student's t-test.
- The mean improvement in burning/pain measured by 0 – 10-point subject-reported subjective numeric rating scale at week-24 will be analyzed for statistical significance using a paired, two-tailed student's t-test.

7.2.3. Exploratory Endpoint Analyses

- Sustained remission at week-36, measured by the mean change in PASI score from week-24 to week-36, will be analyzed for statistical significance using a paired, two-tailed student's t-test.
- Treatment response, as measured by PASI 50, will be stratified by CARD14 germline mutations. The proportion of subjects with a PASI 50 response with and without CARD14 mutations will be reported and compared for statistical significance using an unpaired, two-tailed student's t-test.
- Epithelial expression of CARD14 will be assessed qualitatively by a trained dermatopathologist who is blinded to the biopsy collection time (before or after therapy).
- The concentration of 18 different cutaneous cytokines within the tissue biopsy, before and 24 weeks after treatment, will be analyzed for statistical significance using a pared, two-tailed student's t-test and also compared with normal skin using a two-tailed, two-sample student's t-test with unequal variance.

8. SAFETY

8.1. Specification of Safety Parameters

The PI is responsible for monitoring the safety of participants who have enrolled in the study. Safety assessments will be based on medical review of adverse events and the results of safety evaluations at specified time points as described in Section 5.1 Study Visit Procedures. Any clinically significant adverse events persisting at the end of treatment visit will be followed by the Investigator until resolution/stabilization or death, whichever comes first.

8.2. Definitions

8.2.1. Adverse Event (AE)

An adverse event is defined as any undesirable physical, psychological or behavioral effect experienced by a participant during their participation in an investigational study, in conjunction with the use of the investigational product, whether or not considered intervention-related. In general, this includes signs or symptoms experienced by the participant from the time of signing the informed consent to completion of the study.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the participant and/or observed by the Investigator or medical staff.
- Clinically significant laboratory abnormalities.
- A significant worsening of the participant's condition from study entry.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment that resolve but then recur after treatment.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment which increase in frequency, intensity, or a change in quality after treatment.

8.2.2. Serious Adverse Event (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- In-patient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and/or participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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 in-patient hospitalization, or
- The development of drug dependency or drug abuse.

8.2.3. Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers UPs involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

This study will use the OHRP definition of UP.

8.3. Adverse Event Assessment and Follow-Up

The occurrence of an UP, AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by the PI. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, seriousness, expectedness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until the week-36 follow-up study visit. Any SAE that occurs after treatment with alternative therapy will be reported only if the Investigator or current treating physician has assessed the SAE as related to the study treatment.

8.4. Reporting Procedures

8.4.1. OHSU IRB Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems and AEs will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site.

Events that must be reported by the Investigator to the IRB are detailed in the OHSU IRB Investigator Guidance: Prompt Reporting Requirements (HRP-801). At a minimum, events requiring reporting to the IRB include:

- Any new or increased risk related to the research, including AEs or IND safety reports that require a change to the protocol or consent,
- New FDA black box warning,
- Publications identifying new risks,
- Data Safety Monitoring Board/Committee letters recommending changes or discussing new risks
- Unauthorized disclosure of confidential participant information

8.4.2. SAE Reporting to the Study Drug Manufacturer

SAEs will also be reported to Lilly's Global Patient Safety via fax within 24 hours with a causality assessment.

8.5. Data Safety Monitoring Plan

Subject safety will be monitored in an ongoing way throughout the study. Concomitant medications will be recorded at every study visit. Vital signs including blood pressure and pulse (measured a minimum of 5 minutes after resting), and weight/BMI will be recorded at every study visit. Laboratory testing will be performed at the screening visit, visit 3 (week-4), and visit 7 (week-24) at a minimum. This will include screening for HIV, HVB, HCV, and tuberculosis as detailed in the exclusion criteria. Baseline, week-4 and week-24 laboratory testing will include complete blood counts with differential and a comprehensive metabolic panel. In the event of abnormal laboratory values, additional and/or repeat laboratory testing may be requested at the discretion of the study investigator to ensure patient safety.

Subjects will be encouraged to report any potential problems at any time to qualified research staff or PI. The occurrence of adverse events will be assessed at each study visit and details including diagnosis, severity, possibility of relationship to the study medication (ixekizumab), and action taken will be recorded on the AE log in REDCap.

Data safety monitoring will involve real-time review of adverse events (AE), dropouts, complaints or breaches of confidentiality. The review of AEs will be performed by the PI (Dr. Greiling) in real time, with

review by Dr. Ortega if Dr. Greiling is unavailable. The study will be halted if one or more unexpected AEs occur that are at least possibly related and determined to be moderate in severity or greater.

Data collected during study visits will be entered into the REDCap database by study personnel and study subjects as outlined in the description of visits above. The PI, who has no financial conflict of interest with Eli Lilly Pharmaceuticals, will review the data at least monthly.

8.6. Potential Risks

The risks associated with participation in this study include the use of ixekizumab, the collection of a skin biopsy and blood sample, genetic testing, and loss of confidentiality.

Risks of taking ixekizumab that were identified as higher than the placebo group in clinical trials of subjects with psoriasis are outlined below. The full package insert is publicly available.

- Ixekizumab is a fully humanized monoclonal antibody. Serious allergic reactions, including angioedema and urticaria occurred at a rate of 0.1% in the ixekizumab clinical trials. Anaphylaxis has been reported in post-marketing use.
- Injection site reactions including pain, erythema, bruising, and inflammation occurred in 17% of subjects who used ixekizumab (versus 3% of the placebo group).
- Ixekizumab may increase the risk of infection. In clinical trials, use of ixekizumab was associated with a higher rate of infection than the placebo group (27% versus 23%), with specifically higher rates of upper respiratory infections, oral candidiasis (thrush), conjunctivitis, and tinea infections.
- Nausea occurred in 2% of subjects using ixekizumab versus <1% of the placebo group.
- Neutropenia occurred in 11% of subjects treated with ixekizumab (versus 3% of placebo). The severity was considered grade three (<1,000 cells/mm^3) in 0.2% of subjects.
- Thrombocytopenia occurred in 3% of subjects treated with ixekizumab (versus 1% of placebo) but 98% of these were grade 1 (>75,000 cells/mm^3) and were not associated with an increased rate of bleeding.
- New cases of inflammatory bowel disease or exacerbations occurred in 0.3% of subjects treated with ixekizumab (versus zero in the placebo group).

The risk to the fetus or infant in pregnant or lactating women is unknown and this is an exclusion criterion from the study. Women who may become pregnant are asked to use a reliable form of birth control. There have been no reports to date of harm and no negative effects in laboratory animals. There may be additional drug side effects that are not yet known.

Risks of blood draw include discomfort, and a small chance of bleeding, bruising, infection, or fainting.

Risks of biopsy include allergic reaction to the local anesthetic (1 in 10,000 risk), infection, bleeding, and scar.

Risks of genetic testing include the loss of confidentiality that may affect the subject's ability to obtain life insurance, disability insurance, or long-term care insurance. Even though there are certain genetic discrimination and confidentiality protections in both Oregon law and federal law, there is still a small chance that the subject could be harmed if a release occurred.

Although medical information and medical photographs will be encoded and carefully protected, there is a small risk of loss of confidentiality and release of personal information.

8.7. Participant Removal from the Trial due to Adverse Events

Any participant who experiences an adverse event may be withdrawn from the trial at the discretion of the Investigator and/or the subject's request.

If a subject suffers any injury and/or damage from this research project through the fault of the Oregon Health & Science University, its officers or employees, they will have the right to bring legal action against the University to recover the damage done subject to the limitation and conditions of the Oregon Tort Claims Act.

9. DATA HANDLING & MANAGEMENT RESPONSIBILITIES

9.1. Participant & Data Confidentiality

The information obtained during the conduct of this clinical study is confidential, and unless otherwise noted, disclosure to third parties is prohibited. Information contained within this study will be maintained in accordance with applicable laws protecting participant privacy, including the provisions of the Health Insurance Portability and Accountability Act (HIPAA).

Participant confidentiality is strictly held in trust by the participating Investigator(s) and study team. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Biological samples may be sent to outside laboratories within the United States for analysis, samples will remain de-identified. The study protocol, documentation, data, and all other information generated will be held in strict confidence.

Representatives of the IRB or manufacturer supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Upon enrollment, participants will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files for data analysis will contain only the participant code. Codes will not contain any part of the 18 HIPAA identifiers (e.g., initials, DOB, MRN). The key associating the codes and the participants' personally identifying information will be restricted to the Investigator and study staff. The key will be kept secure on a restricted OHSU network drive in a limited access folder.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations.

9.2. Data Collection & Storage: Privacy, Confidentiality & Security

9.2.1. Data Collection

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Standard institutional practices will be followed as described in the OHSU's Information Security Directives to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures.

9.2.2. Data Confidentiality

Loss of participant confidentiality is a risk of participation. Efforts will be made to keep study participant identities confidential except as required by law. Participants' samples will be identified by code only. Specifically, each consenting participant will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will also be used to identify any participant specific samples.

9.2.3. Data Storage

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical information research system (eCRIS), hosted on OHSU secure servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Any additional printed documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

Study outcome data will be captured in electronic case report forms (eCRFs) using an electronic data capture (EDC) system (REDCap) on OHSU secure servers, which facilitates information being stored in a unified format and location. To further preserve confidentiality, PHI in the EDC system will be limited to birth date and visit dates, city of residence, and email address – for distribution of REDCap surveys. The REDCap system is password protected and encrypted with role-based security, and administered by designated informatics staff within OHSU. All users of the database are assigned a unique ID, username, and password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database.

Data from correlative studies will be entered into the EDC system by study personnel at OHSU. All other electronic data extracts will be stored only on OHSU computers and restricted drives, limited only to study investigators and staff with authorization to access the data.

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Research materials obtained specifically for the purposes of this study will include biopsies for mechanistic studies and blood tests for CBC, CMP, HIV, HBV, HCV, tuberculosis, and CARD14 genetic testing. All samples used for mechanistic testing will be coded and blinded to the investigator. Data regarding medical history and symptom questionnaires will be obtained during the course of this study. Absolute confidentiality will be maintained. Only the principal investigator and study coordinator will have access to identifiable private information to facilitate subject recruitment and subject reimbursement. All data not stored in REDCap are stored in locked compartments and are not released without consent of the participants. If data are used in scientific presentations or publications, individuals are never identified. Medical information gathered during the course of the study may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

9.2.4. Data Recording in the Electronic Medical Record (Epic)

An Epic research encounter will be created for each in-person visit. A brief S.O.A.P. note that includes study drug administration will be entered into Epic to facilitate communication with the subject's other healthcare providers. Additionally, all serious adverse events will be recorded as a brief note in Epic.

9.2.5. Photography

Photographs of the skin involvement in each subject will be captured as digital files, coded with the subject's study number and visit number, and kept on the cloud file storage solution provided by Box.com. For purposes of publication or education (i.e., viewing by anyone other than study personnel), any identifying features such as the eyes, jewelry, or a tattoo will be digitally blocked out of the photo.

9.2.6. Telemedicine Platform

The study will use a HIPAA-compliant videoconferencing platform (Nexus/Cisco Meeting). A one-time-use unique hyperlink will be sent to the study subject for each visit, via OHSU MyChart or email. No protected health information will be stored unless it is deliberately captured and downloaded by one of the participants in the videoconference session. For convenience, we will choose a platform that works natively within a browser with the use of static plugins and that allows patients to access the study "room" via a specific URL without need for preregistration. The platform will use standard audio/video capabilities and will allow access through mobile devices.

10. ETHICS/PROTECTION OF PARTICIPANTS

10.1. Ethical Standard

The Investigator will ensure that this study is conducted in adherence with the protocol and International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP).

10.2. Institutional Review Board

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

10.3. Informed Consent

Written informed consent will be obtained from all participants, or the legally authorized representative of the participant, participating in this trial, as stated in the Informed Consent section of 21 CFR Part 50. If a participant's signature cannot be obtained, and for all participants under the age of 18, the Investigator must ensure that the informed consent is signed by the participant's legally authorized representative. Documentation of the consent process and a copy of the signed consent shall be maintained in the participant's medical record.

10.4. Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families as appropriate. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks/benefits of the study, alternatives to participation, and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Consent and reconsent of Spanish-speaking subjects will be obtained through the help of an interpreter as detailed above in section 5.1.2.

10.5. Protocol Review

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU IRB prior to any participant being consented on this study.

10.6. Changes to Protocol

Any modification of this protocol must be documented in the form of a protocol revision or amendment submitted by the Investigator and approved by the IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory

approval is for a change necessary to eliminate an apparent and immediate hazard to the participant. In that event, the Investigator must notify the IRB within 5 business days after the implementation.

11. PUBLICATION AND DISSEMINATION POLICY

The study results will be published in a peer-reviewed journal. Participants will not be identified in any publications.

This protocol will be registered in the ClinicalTrials.gov website. This registration will occur after IRB approval.

12. REFERENCES

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