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

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Trial Configuration	Single center, open label, interventional, investigator-initiated trial

CLINICAL PROTOCOL SYNOPSIS

Title	An open label pilot trial of guselkumab in the treatment of adults with pityriasis rubra pilaris (PRP)
Principal Investigator	Teri Greiling, MD, PhD
Objectives	To determine whether guselkumab provides clinical improvement for subjects with PRP who are candidates for systemic therapy
Trial Configuration	Single center, open label, interventional, investigator-initiated trial
Setting	The trial will recruit 15 adults with moderate-to-severe (defined by involved body surface area (BSA) ≥ 10%) PRP through dermatologist offices, recruitment letters, and advertisement. Study visits will occur at Screening, weeks 0, 4, 8, 12, 20, 24, and 36. Study visits at weeks 0, 4, 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, as well as a REDCap survey sent via email.
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 study is 15.
Number of Participants	15 subjects with moderate-to-severe PRP
Eligibility Criteria	**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, willing to use a reliable form of birth control if sexually active with a woman who is able to become pregnant. • 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 guselkumab. • Involved BSA ≥ 10% at baseline (moderate-to-severe disease). • Are a candidate for phototherapy and/or systemic therapy. • Willingness to travel to OHSU for all study visits, or 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, or

	immunocompromised to an extent that such that participation in the study would pose an unacceptable risk to the subject. • Positive for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus. • Have latent or active untreated tuberculosis (TB), a positive QuantiFERON-TB Gold test result, signs or symptoms of active TB on medical history or physical examination, or close contact with a person with active TB who have not undergone evaluation or treatment for TB. Those who are currently undergoing treatment or who have documented completed treatment for active or latent TB without re-exposures will not be excluded. • Previous treatment with any agent that targets the interleukin 23 p19 subunit specifically. • Systemic treatment with prednisone in the last 2 weeks, or other systemic therapies 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, ixekizumab, or alefacept <60 days; golimumab <90 days; secukinumab <5 months; 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 or intend to have a live vaccine within 3 months prior to baseline or 12 months prior to baseline in the case of the BCG vaccine, or any live vaccine during the course of study or within 3 months after the last administration of study drug. • 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. • 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, white blood cell count <3500 cells/µL, platelet count <100,000 cells/µL, AST or ALT or alkaline phosphatase > 2 times the upper limit of normal, hemoglobin <10 g/dL, serum creatinine >1.5 mg/dL. A single retest of laboratory values is permitted if one or more values is out of range. • 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.
Description of Interventions	Subjects with PRP will be treated with guselkumab for 20 weeks using the FDA-approved dosing schedule for psoriasis (100 mg subcutaneous injection at weeks 0, 4, 12, and 20).
Duration of Study	The duration of the study will be 36 weeks
Outcome Measures	The primary outcome will be the mean change from baseline PASI at week-24 after treatment with guselkumab. 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 and serum 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
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IL23	Interleukin-23
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
PCQ	Product Quality Complaint
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 Guselkumab

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. The major effector cells present in psoriatic lesions are Th17 cells, and a recent case report showed similar overexpression of cytokines in the Th17 pathway in cutaneous lesions of PRP, including the primary effector cytokines IL-23, IL-22, and IL-17 (*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 induce excess IL-23 (*6*).

Guselkumab is a high affinity, humanized IgG1 lambda monoclonal antibody that selectively binds the p19 subunit of IL-23. Two phase III studies of guselkumab in the treatment of psoriasis showed excellent safety and efficacy, with "clear" or "almost clear" skin ratings in 84-85% of patients at week-16 (*7, 8*).

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*). While there are no published reports of IL-23p19 subunit-targeted therapy in PRP, there are case reports and case series of the use of IL-12/IL-23p40 subunit inhibition for PRP in over twenty patients (*2, 9-23*) with 90% of these showing marked improvement, often only 4 weeks after a single subcutaneous injection. For these reasons, guselkumab is proposed as a therapeutic intervention with potential for improving the lives of PRP patients.

1.2. Hypothesis

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

2. OBJECTIVES

2.1. Primary Objective

Determine whether guselkumab 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 guselkumab

2.3. Exploratory Objectives

Explore the mechanisms by which guselkumab alters the cutaneous and systemic inflammatory milieu in PRP

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 guselkumab 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-4 and week-24. Blood tests will be performed for screening and safety and measuring levels of inflammation at Screening, week-0, week-4, and week-24. The study schedule is outlined in Section 5.4., Table 1.

3.2. Study Endpoints

3.2.1. Primary Endpoint

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

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.

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) (*24*) 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 (*25*).

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, proportion of patients achieving a DLQI of 0 or 1 at week-24, and mean improvement in DLQI score at week-24. The DLQI (*26*) 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 (*27*).

- Mean percentage in improvement in Psoriasis Symptoms and Signs Diary (PSSD) at week-24, and proportion of patients achieving a PSSD of zero at week-24. The PSSD is an 11-question 0 – 10-point numeric rating scale (NRS) patient-reported outcome measure assessing itch, dryness, cracking, skin tightness, scaling, shedding or flaking, bleeding, burning, stinging, and pain over the last 24 hours and 7 days respectively (*28*).
- Mean change from baseline individual PRP Area and Severity Index (iPRPASI) at week-24 after treatment with guselkumab, 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 (*29*).
- Sustained remission at week-36, 16 weeks after the last guselkumab 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 (*22*), 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 guselkumab 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 guselkumab. 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 guselkumab. Inhibition of IL-17 by guselkumab is expected to lead to normalization of CARD14 expression by keratinocytes.
- Normalization of cutaneous gene expression at weeks 4 and 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, lesional and non-lesional biopsies will be obtained from subjects at week-0 prior to the first dose of guselkumab, week-4, and week-24. Cutaneous gene expression of the epidermis and dermis will be analyzed by RNA Sequencing (RNA-Seq and therapeutic response to guselkumab is expected to correlate with normalization of epidermal cytokine levels. De-identified tissue samples will be stored indefinitely for analysis.
- Change in serum cytokine levels at weeks 4 and 24. Serum levels of multiple cytokines have been shown to correlate with disease activity in patients with psoriasis (*30*) but these have not been investigated in patients with PRP. Serum cytokine levels before and after treatment with guselkumab will be analyzed by multiplexed bead-based immunoassay.

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Inclusion criteria

- Diagnosis of PRP by clinical assessment and biopsy.
- Male subject age 18-99, willing to use a reliable form of birth control if sexually active with a woman who is able to become pregnant.
- 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 guselkumab.
- Involved BSA ≥ 10% at baseline.
- Are a candidate for phototherapy and/or systemic therapy.
- Willingness to travel to OHSU for all study visits, or 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.

4.2. 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, or immunocompromised to an extent that such that participation in the study would pose an unacceptable risk to the subject.
- Positive for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus.
- Have latent or active untreated tuberculosis (TB), a positive QuantiFERON-TB Gold test result, signs or symptoms of active TB on medical history or physical examination, or close contact with a person with active TB and have not undergone evaluation or treatment for TB. Those who are currently undergoing treatment or who have documented completed treatment for active or latent TB without re-exposures will not be excluded.
- Previous treatment with any agent that targets the interleukin 23 p19 subunit specifically.
- Systemic treatment with prednisone in the last 2 weeks, or other systemic therapies 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, ixekizumab, or alefacept <60 days; golimumab <90 days; secukinumab <5 months; 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 or intend to have a live vaccine within 3 months prior to baseline or 12 months prior to baseline in the case of the BCG vaccine, or any live vaccine during the course of study or within 3 months after the last administration of study drug.
- 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.
- 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, white blood cell count <3500 cells/μL, platelet count <100,000 cells/μL, AST or ALT or alkaline phosphatase > 2 times the upper limit of normal, hemoglobin <10 g/dL, serum creatinine >1.5 mg/dL. A single retest of laboratory values is permitted if one or more values is out of range.
- 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.

4.3. Recruitment and Identification of Participants

The trial will recruit subjects with moderate-to-severe PRP, either newly diagnosed or failing other therapies due to side effects or lack of efficacy. 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 with prior approval of Facebook page manager
- Publicity through the PRP Alliance patient advocacy organization, including an email to members of the PRP Alliance, following prior approval from listserv manager
- Research Match
- Letters mailed to physicians outside of OHSU

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

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, BCG vaccine, or live varicella zoster vaccine (Zostavax)) are not permitted during the study. Contraception method will also be recorded. An investigator will perform an assessment of BSA to calculate disease severity. If all other criteria are met, a blood sample will be drawn to screen for pregnancy (in female subjects), HBV, HCV, HIV, and QuantiFERON gold for tuberculosis, and to check CBC and CMP. 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. PPD skin testing may be used if blood testing for tuberculosis is unavailable.

For interested subjects, 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. Eligible subjects willing to proceed with treatment will be asked to document consent via e-consent in REDCap, or signed written consent emailed or faxed to the investigators. Following receipt of signed consent, a screening 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 criteriasubjects 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.

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)

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 and adverse events since screening
    - 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
    - PSSD
    - 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 using a high-resolution digital camera of all body regions against a dark backdrop to visually record extent of disease. Subjects will assume standardized poses according to published recommendations (*31*), with the addition of focused photographs of the palms and nails.
- 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 measuring levels of inflammation
- A saliva sample will be collected for genetic analysis
- The first dose of 100 mg of subcutaneous guselkumab will be administered by trained study personnel while the study subject undergoes teaching for future self-administration.
- Subjects who plan to complete future visits by videoconferencing will receive a scale and sphygmomanometer for future vital sign assessments

5.1.5. Visit 2 / Week-4 (28 days +/- 4 days after last visit)

Visit 2 will be performed at OHSU for all subjects.

- Study personnel will gather the following information from the subjects and record the results in REDCap:
    - Change 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, including adverse events
    - Weight
    - Blood pressure
    - Pulse
- Subjects will enter the following information about their disease and medical history via OHSU REDCap survey:
    - DLQI
    - PSSD
    - 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, and PPPGA
- Photographs will be taken against a dark backdrop with standardized poses according to published recommendations (*31*), with the addition of focused photographs of the palms and nails.
- 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) in the same body region as the first documented biopsy (back, chest, arm, or leg)
- The second dose of 100 mg of subcutaneous guselkumab will be administered by the subject with observation and teaching from study personnel.
- Blood will be drawn for monitoring the CBC, CMP, and measuring levels of inflammation

5.1.6. Visit 3 / Week-8 (28 days +/- 4 days after last visit)

Visit 3 will be performed at OHSU or optionally by telemedicine and REDCap survey.

- Study personnel will gather the following information from the subjects and record the results in REDCap:
    - Change in medications since the last visit
    - Change in drug allergies since the last visit
    - Change in personal or family medical history, including adverse events, 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
    - PSSD
    - 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

5.1.7. Visit 4 / Week-12 (28 days +/- 4 days after last visit)

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:
    - Change in medications since the last visit
    - Change in drug allergies since the last visit
    - Change in personal or family medical history, including adverse events, 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
    - PSSD
    - 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 third dose of 100 mg of subcutaneous guselkumab will be administered by the subject with observation and teaching from study personnel.
- Blood will be drawn for CBC, CMP (for telemedicine visits this will be done at a local lab of the subject's choice within +/- 2 days of the visit)

5.1.8. Visit 5 / Week-20 (56 days +/- 7 days after last visit)

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:
    - Change in medications since the last visit
    - Change in drug allergies since the last visit
    - Change in personal or family medical history, including adverse events, 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
    - PSSD
    - 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 fourth dose of 100 mg of subcutaneous guselkumab will be administered by the subject with observation and teaching from study personnel.

5.1.9. Visit 6 / Week-24 (primary endpoint; 28 days +/- 4 days after last injection)

Visit 6 will be performed at OHSU for all subjects.

- Study personnel will gather the following information from the subjects and record the results in REDCap:
    - Change in medications since the last visit
    - Change in drug allergies since the last visit
    - Change in personal or family medical history, including adverse events, 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
    - PSSD
    - 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 against a dark backdrop with standardized poses according to published recommendations (*31*), with the addition of focused photographs of the palms and nails.
- Blood will be drawn for monitoring the CBC, CMP, and measuring levels of inflammation
- 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) 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.

5.1.10. Visit 7 / Week-36 (56 days +/- 7 days after last visit)

Visit 7 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:
    - Change in medications since the last visit
    - Change in drug allergies since the last visit
    - Change in personal or family medical history, including adverse events, 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
    - PSSD
    - 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 will be paid $50 for all visits that do not involve skin biopsy (Screening and visits 3, 4, 5, and 7) and $150 for the three visits that involve skin biopsy (baseline, visit 2, and visit 6), for a total of $700. 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 $0.545/mile up to 1000 miles (range $218 - $1090 for a round-trip visit to OHSU) for each of the three in-person visits (baseline, visit 2, and visit 6).

5.4. Table 1: Study Schedule of Events

Visit	Pre-trial	Screening*	Enrollment	V1	V2	V3	V4	V5	V6	V7
Week				**WK0**	**WK4**	**WK8***	**WK12***	**WK20***	**WK24**	**WK36***
Baseline Documentation										
Confirmation of dx	X									
Informed consent		X								
Investigator assessment		X		X	X	X	X	X	X	X
Medical history		X		X	X	X	X	X	X	X
Exclusion/Inclusion criteria		X	X							
Dosing										
Injection counseling/training				X						
Injection review					X		X	X		
Study drug dispensing				X	X					
Study drug injection/dose**				X	X		X	X		
Laboratory Studies										
Blood draw***		X		X	X		X		X	
Other Assessments and Procedures										
Skin biopsy				X	X				X	
Adverse events				X	X	X	X	X	X	X
Subject REDCap survey				X	X	X	X	X	X	X

*Visit optionally to be performed via secure telemedicine videoconferencing for subjects >30 miles from Oregon Health & Science University.
**Guselkumab subcutaneous dose: 100mg on W0, W4, W12, W20.
***Laboratory studies will include: CBC and CMP at screening, W4, W12, and W20 as well as HBV, HCV, HIV, tuberculosis, and pregnancy (for females if childbearing potential) at screening.

6. INVESTIGATIONAL PRODUCT AND TREATMENT PLAN

6.1. Investigational Product: Guselkumab

Guselkumab is a humanized monoclonal antibody that binds and blocks IL-23.

6.2. Dosing and Administration

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

- 100 mg SC injection at week-0, week-4, week-12, and week-20

The 1 mL single-dose 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 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.
- New use of topical steroids or increased potency of topical steroids after enrollment
- 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 emollients
- Topical steroids may be maintained at levels used prior to enrollment, decreased, or discontinued, but potency and weekly grams used may not be increased
- 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. If a medication is changed, the changed and reason for it will be documented. 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. All therapies (prescription, over-the-counter, vitamins, herbal supplements, vaccines) will be recorded in the eCRF as outlined in the Study Procedures.

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 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 DLQI and the proportion of subjects achieving a DLQI score of 0 or 1 at week-24 will be reported as proportions. 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 PSSD at week-24 will be analyzed for statistical significance using a paired, two-tailed Student's t-test. The proportion of subjects achieving a PSSD of zero at week-24 will be reported as a proportion.

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 gene expression level from the tissue biopsy, before, 4 weeks, 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 and psoriatic skin using a two-tailed, two-sample Student's t-test with unequal variance adjusted for multiple comparisons.
- The cytokine level from serum before, 4 weeks, 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 and psoriatic serum using a two-tailed, two-sample Student's t-test with unequal variance adjusted for multiple comparisons.

8. SAFETY

8.1. Specification of Safety Parameters

As the sponsor of the Study, OHSU and the PI shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB and any participating (co or sub) investigators, as defined in applicable laws and regulations. For the purposes of this protocol, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies. 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.

OHSU and the PI will provide safety information to Janssen Scientific Affairs on adverse events, special situations including pregnancies and product quality complaints as defined within this protocol.

This Study has been designated as an interventional study. As such, all adverse events for Janssen Study drugs regardless of causality and special situations excluding those from subjects not exposed to a Janssen Study drug and product quality complaints with or without an adverse event as described in this Protocol will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported up to week-36 (16 weeks after the last dose of study drug).

8.2. Definitions

8.2.1. Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign

(including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

8.2.2. Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Study drugs for Human Use is any untoward medical occurrence that at any dose:

- Results in death. (Note: death for any reason will be reported as a serious adverse event.)
- Is life-threatening. (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Suspected transmission of any infectious agent via a study drug
- Serious Infections
- Serious systemic hypersensitivity reactions
- Suicidality
- Cardiovascular events
- Medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

8.2.2.1. Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.

8.2.2.2. Life-Threatening Conditions

The cause of death of a subject in a study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

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. Adverse Events of Special Interest

Adverse events of special interest are events that the COMPANY is actively monitoring as a result of a previously identified signal (even if non-serious). No adverse events of special interest will be collected for this study.

8.2.4. Individual Case Safety Report (ICSR)

A valid ICSR will contain the four minimum criteria requred to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen study drug
- an adverse event, outcome, or certain special situations

The minimum information required will be:

- suspected Janssen study drug (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

8.2.5. Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination

- Suspected Counterfeit

8.2.6. 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 Tremfya package insert; 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 eCRF. 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.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, will be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

All follow-up information for serious adverse events or AEs of special interest and special situations that are not resolved at the end of the study or by the time of patient withdrawal will be reported directly by the PI, **within 24 hours becoming aware**, to Janssen Scientific Affairs using Janssen Scientific Affairs' Serious Adverse Event Report.

All available clinical information relevant to the evaluation of a related SAE, Adverse Events of Special Interest, serious ADR or special situation is required.

- The PI is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.
- Copies of any and all relevant extraordinary (not including routine initial or follow-up ICSR submission) correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the study drug, will be provided to Janssen Scientific Affairs within **24 hours of such report or correspondence being sent to applicable health authorities.**

8.4. Reporting Procedures

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to the study drug will be documented by the investigator and recorded in the eCRF and in the subject's source records. Investigators will record in the eCRF their opinion concerning the relationship of the adverse event to the study drug. All (serious and non-serious) adverse events reported for the study drug will be followed-up in accordance with clinical practice.

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. Reporting to the Study Drug Manufacturer

At a minimum, on a semi-annual basis and at the end of the Study, Janssen Scientific Affairs will provide to the PI, a listing of all SAEs reported to Janssen Scientific Affairs. The PI will review this listing and will resolve any discrepancies with the data provided byJanssen Scientific Affairs.

The following methods will be used for transmission of safety information to Janssen Scientific Affairs:

- Electronically via Janssen SECURE Email service IIS-BIO-VIRO-GCO@its.jnj.com (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
    - Facsimile (fax) at 1-866-451-0371, receipt of which is evidenced in a successful fax transmission report
    - Telephone (if fax is non-functional).

The PI will prepare a final report including a complete and full summary of all adverse events, special situations and pregnancy reports according to the timeframe outlined in the agreement.

8.4.2.1 Safety Event Reporting to the Study Drug Manufacturer

Safety events of interest for a Janssen study drug that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of the study drug
- Exposure to the study drug from breastfeeding
- Suspected abuse/misuse of the study drug
- Inadvertent or accidental exposure to the study drug
- Any failure of expected pharmacological action (i.e., lack of effect) of the study drug
- Medication error involving the study drug (with or without patient exposure to the study drug, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of the study drug
- Unexpected therapeutic or clinical benefit from use of the study drug

These safety events may not meet the definition of an adverse event; however, from a Janssen Scientific Affairs perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event section of the eCRF.

8.4.2.2 Non-Serious Adverse Event Reporting to the Study Drug Manufacturer

All non-serious adverse events will be reported to Janssen Scientific Affairs annually and at the end of the study.

8.4.2.3 Serious Adverse Event Reporting to the Study Drug Manufacturer

Any SAE, Adverse Event of Special Interest or special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs **within 24 hours of becoming aware of the event.**

8.4.2.4 PQC Reporting to the Study Drug Manufacturer

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving the study drug will be reported to Janssen Scientific Affairs by the investigators **within 24 hours after being made aware of the event.** The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen study drug under study is combined with either a serious adverse event or non-serious adverse event, the PI must report the PQC to Janssen Scientific Affairs according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs.

8.4.3. Pregnancy

All initial reports of pregnancy will be reported to Janssen Scientific Affairs by the PI within 24 hours of becoming aware of the event using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study will be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the Janssen study drug on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen study drug will be reported by the PI within 24 hours of their knowledge of the event using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be collected.

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 that will include screening for HIV, HVB, HCV, and tuberculosis as detailed in the exclusion criteria. Baseline, week-4, week-12, and week-24 laboratory testing will include complete blood counts with differential and a comprehensive metabolic panel.

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 drug, and action taken will be recorded in the eCRF.

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 a co-Investigator 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 Janssen Scientific Affairs, will review the data at least monthly.

The PI will provide all adverse events, both serious and non-serious, in report format to Janssen Scientific Affairs. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable time frame at Janssen Scientific Affairs' request.

8.6. Potential Risks

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

Risks of taking guselkumab 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.

- Guselkumab may increase the risk of infection. In clinical trials, use of guselkumab was associated with a higher rate of infection than the placebo group (23% versus 21%). Upper respiratory tract infections, gastroenteritis, tinea infections, and herpes simplex infections occurred more frequently in the guselkumab group than in the placebo group. The rate of serious infections was <1% and the same in the guselkumab and placebo groups.
- The rate of developing neutralizing antibodies against guselkumab was 6% over one year of treatment. It is uncertain whether this may lead to a loss of efficacy of the study drug over time.
- Injection site reactions including pain, erythema, bruising, and inflammation occurred in 4.5% of subjects who used guselkumab (versus 2.8% of the placebo group).
- Subjects taking guselkumab had a slightly higher rate of developing headache (4.6% vs 3.3% of placebo), arthralgias (2.7% versus 2.1% of placebo), and diarrhea (1.6% versus 0.9% of placebo).
- Elevated liver enzymes were reported more frequently in the guselkumab group (2.6%) than in the placebo group (1.9%).
- Adverse reactions that occurred in <1% of the study drug group but at a higher rate than place include migraine, candida infections, and urticaria.

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 and men who may father a child 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 Discontinuation of Study Drug or Withdrawal from the Study

8.7.1. Participant Discontinuation of Study Drug

A subject who discontinues study drug administration will not be automatically withdrawn from the study if they discontinue study drug administrations before the end of the study drug administration period. If a subject discontinues study drug before week-24, the week-24 study visit will be performed early if the subject is willing and able to participate.

A subject's study drug must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (e.g., AE) it is in the best interest of the subject to discontinue study drug
- The subject becomes pregnant or plans a pregnancy within the study period.
- The subject (or the subject's representative) withdraws consent for administration of study drug.
- The subject develops a systemic opportunistic infection.
- The subject is deemed ineligible according to the following TB screening criteria:
    - A diagnosis of active or latent TB is made.
    - A subject has symptoms suggestive of active TB based on follow-up assessment questions and physical examination, or has had recent close contact with a person with active TB, and cannot or will not continue to undergo additional evaluation.
- The subject develops an allergic reaction resulting in bronchospasm with wheezing or dyspnea that requires ventilatory support. In general, discontinuation of study drug administration must be considered for subjects who develop a severe allergic reaction.
- The subject has a reaction resulting in myalgia or arthralgia with fever or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study drug. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and headache.
- The subject has a malignancy, not including cutaneous squamous cell skin cancer < 2 cm in diameter or basal cell skin cancers that are adequately treated with no evidence of residual disease.
- The subject has any severe infection (NCI-CTCAE Grade 3 or higher) that is considered related to the study drug by the investigator.

Discontinuation of study drug will also be strongly considered if the subject develops a serious infection, including but not limited to sepsis or pneumonia, or any other serious AE at the direction of the investigator 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.

8.7.2 Subject Withdrawal from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death
- Investigator decision (e.g., participating in any other clinical study with an investigational agent)

When a subject withdraws before completing the study, the reason for withdrawal will be documented in the eCRF. Additional subjects may be enrolled to ensure the protocol-specified number of participants complete the study. If a subject withdraws after the first dose of study drug and before week-24, the week-24 study visit will be performed early if the subject is willing and able to participate. If a subject withdraws after week-24, the week-36 assessment will be performed early if the subject is willing and able to participate. If the reason for withdrawal is withdrawal of consent then no additional assessments will be performed.

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. Therefore, 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 just birth date and visit dates, email (to be used for REDCap surveys) and city of residence. 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 measuring levels of inflammation. Saliva will be collected for 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 or at the time of any SAE. 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.

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 participating in this trial, as stated in the Informed Consent section of 21 CFR Part 50. 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.

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 reviewed and approved by Janssen Scientific Affairs, then 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.

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