**Clinical Research Protocol**

# IMMUNOGENETIC PROFILING OF GUSELKUMAB FOR THE TREATMENT OF PLAQUE AND GUTTATE PSORIASIS

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| Protocol Number: | 20-32273 |
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| Investigational Product: | Guselkumab |
| IND Number: | ***** |
| Development Phase: | Phase IV |
| Sponsor: | Wilson Liao, MD<br>UCSF Psoriasis and Skin Treatment Center<br>515 Spruce Street<br>San Francisco, CA 94118-2616 |
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**Approval**:

PI or Sponsor Signature (Name and Title) Date

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**PROTOCOL AGREEMENT**

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Janssen with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 20-32273

Protocol Title: Immunogenetic profiling of guselkumab for the treatment of plaque and guttate psoriasis

Protocol Date: September 6, 2022

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Investigator Signature Date

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Print Name and Title

Site # _____

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**List of Abbreviations**

| | |
|---|---|
| **AE** | adverse event |
| **ALT** | alanine aminotransferase |
| **AST** | aspartate aminotransferase |
| **BUN** | blood urea nitrogen |
| **CFR** | Code of Federal Regulations |
| **CRF** | case report form |
| **CRP** | C-reactive protein |
| **DMC** | Data Monitoring Committee |
| **DSMB** | Data Safety Monitoring Board |
| **ESR** | erythrocyte sedimentation rate |
| **FDA** | Food and Drug Administration |
| **FEF25%-75%** | forced expiratory flow |
| **FEV1** | forced expiratory volume over one second |
| **FVC** | forced vital capacity |
| **GCP** | Good Clinical Practice |
| **GGT** | gamma-glutamyl transferase |
| **HIPAA** | Health Insurance Portability and Accountability Act of 1996 |
| **ICF** | informed consent form |
| **ICH** | International Conference on Harmonisation |
| **IEC** | Independent Ethics Committee |
| **IL-8** | Interleukin-8 |
| **IRB** | Institutional Review Board |
| **IV** | intravenous |
| **LDH** | lactate dehydrogenase |
| **mEq** | milliequivalent |
| **PI** | Principal Investigator |
| **PK** | pharmacokinetic |
| **SAE** | serious adverse experience |
| **SGOT** | serum glutamic oxaloacetic transaminase |
| **SGPT** | serum glutamate pyruvate transaminase |

**PROTOCOL SYNOPSIS**

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|---|---|
| **TITLE** | Immunogenetic profiling of guselkumab for the treatment of plaque and guttate psoriasis |
| **SPONSOR** | Wilson Liao, MD |
| **FUNDING ORGANIZATION** | Janssen |
| **NUMBER OF SITES** | One |
| **RATIONALE** | Guselkumab (Tremfya®), an IL-23 inhibitor approved for the treatment of moderate-to-severe plaque psoriasis, is an extremely efficacious option with rapid onset of action. Given the potential role of IL-23 in the pathogenesis of guttate psoriasis, guselkumab may be an effective option to treat guttate psoriasis. |
| **STUDY DESIGN** | This is a two-arm open-label study to evaluate the clinical and immunogenetic responses of patients with plaque and guttate psoriasis to treatment with guselkumab. |
| **PRIMARY OBJECTIVES** | The primary objective of this study is to assess how treatment with guselkumab changes the immune milieu of the skin in patients with plaque and guttate psoriasis. |
| **SECONDARY OBJECTIVES** | The secondary objectives of this study are to assess how treatment with guselkumab affects the quality of life and extent of skin disease in patients with plaque and guttate psoriasis. |
| **NUMBER OF SUBJECTS** | 25 |
| **SUBJECT SELECTION CRITERIA** | **Inclusion Criteria:**<br>For subjects with guttate psoriasis:<br>1. Ability to provide written informed consent and comply with the protocol.<br>2. At least 18 years of age.<br>3. Diagnosis of guttate psoriasis.<br>4. Body surface area (BSA) involvement greater than or equal to 5%.<br>5. PASI greater than or equal to 4.<br>6. Subject is considered a candidate for phototherapy or systemic therapy.<br>7. Subject is unlikely to conceive due to male, post-menopausal, or using adequate contraceptive (barrier, hormonal, implant, or permanent sterilization methods). Women of childbearing potential will be allowed to enroll provided they practice adequate forms of birth control.<br>8. Physical exam with no evidence of active skin infection and/or other findings that indicate chronic disease or concomitant inflammatory/immune-mediated skin disease other than psoriasis.<br><br>For subjects with chronic plaque psoriasis (control): |

1. Ability to provide written informed consent and comply with the protocol.
2. At least 18 years of age.
3. Diagnosis of plaque psoriasis.
4. Duration of plaque psoriasis >5 years.
5. Body surface area (BSA) involvement greater than or equal to 5%.
6. Subject is considered a candidate for phototherapy or systemic therapy.
7. Subject is unlikely to conceive due to male, post-menopausal, or using adequate contraceptive (barrier, hormonal, implant, or permanent sterilization methods). Women of childbearing potential will be allowed to enroll provided they practice adequate forms of birth control.
8. Physical exam with no evidence of active skin infection and/or other findings that indicate chronic disease or concomitant inflammatory/immune-mediated skin disease other than psoriasis.

**Exclusion Criteria:**

For subjects with guttate psoriasis:

1. Subject is unable to provide written informed consent or comply with the protocol.
2. Subject is younger than 18 years of age or older than 70 years.
3. Have a history of active, chronic or recurrent infectious disease including HIV, hepatitis B, or hepatitis C.
4. Have active tuberculosis or latent tuberculosis without at least 4 weeks of treatment with isoniazid or equivalent therapy.
5. Have current signs or symptoms of severe, progressive, or uncontrolled medical disease.
6. Known allergies, hypersensitivity, or intolerance to guselkumab (Tremfya®) excipients.
7. Have a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
8. Have any known malignancy or have a history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to screening)
9. Are pregnant, nursing, or planning a pregnancy while enrolled in the study or for 12 weeks after the last study agent injection for women or are planning to father a child while enrolled in the study or for 12 weeks after the last study agent injection.
10. Are participating in another study using an investigational agent or procedure during participation in this study.

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| | 11. Have any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements.<br>12. Subjects possess other diagnoses that, in the investigator's opinion, interfere with the evaluation of the subject's guttate psoriasis.<br>13. Pre-existing psoriasis type other than guttate psoriasis for longer than 6 months. (i.e. plaque, pustular, erythrodermic)<br><br><u>For subjects with chronic plaque psoriasis:</u><br>1. Subject is unable to provide written informed consent or comply with the protocol.<br>2. Subject is younger than 18 years of age or older than 70 years.<br>3. Have a history of active, chronic or recurrent infectious disease, including HIV, hepatitis B, or hepatitis C.<br>4. Have active tuberculosis or latent tuberculosis without at least 4 weeks of treatment with isoniazid.<br>5. Have current signs or symptoms of severe, progressive, or uncontrolled medical disease.<br>6. Known allergies, hypersensitivity, or intolerance to guselkumab (Tremfya®) excipients.<br>7. Have a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.<br>8. Have any known malignancy or have a history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to screening)<br>9. Are pregnant, nursing, or planning a pregnancy while enrolled in the study or for 12 weeks after the study agent injection for women or are planning to father a child while enrolled in the study or for 12 weeks after the last study agent injection.<br>10. Are participating in another study using an investigational agent or procedure during participation in this study.<br>11. Have any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements.<br>12. Subjects possess other diagnoses that, in the investigator's opinion, interfere with the evaluation of the subject's plaque psoriasis.<br>13. Prior history of guttate psoriasis. |
| **TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION** | Guselkumab 100 mg injected subcutaneously at week 0, week 4, and then every 8 weeks thereafter until week 44. Subjects who achieve PASI 75 or greater at week 44 (responders) will have their guselkumab discontinued, with subsequent reintroduction in those responders who lose 50% or more of their week-44 PASI response |

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| | prior to week 96. Guselkumab will be reintroduced at 100 mg every 8 weeks. The loading dose will not be repeated. Patients who achieve between PASI 50 and PASI 75 at week 44 (partial responders) will continue on drug throughout the remainder of the study. Subjects who achieve less than PASI 50 at week 44 (nonresponders) will be removed from the study. |
| **DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY** | Subjects will be on study for up to 96 weeks<br>• **Screening**: up to 7 days<br>• **Treatment**: Between 44 and 96 weeks depending on clinical response<br>• **Follow-up:** Between 4 and 52 weeks depending on clinical response<br>The total duration of the study is expected to be 116 weeks: 20 weeks for subject recruitment and 96 weeks for final subject follow-up. |
| **CONCOMMITANT MEDICATIONS** | **Allowed:** Bland emollients and other non-medicated interventions<br><br>**Prohibited:**<br>• Systemic anti-psoriatic treatments including methotrexate, cyclosporine, corticosteroids, and cyclophosphamide: 4 weeks<br>• Biological immunomodulating agents including infliximab, etanercept, and adalimumab: 12 weeks<br>• Any therapeutic agent directly targeted to IL-12, IL-17, or IL-23 (ustekinumab, tildrakizumab, Risankizumab, secukinumab, ixekizumab, or brodalumab): 3 months<br>• Other systemic psoriasis treatments including retinoids: 4 weeks<br>• Photochemotherapy: 4 weeks<br>• Phototherapy (UVA/UVB): 2 weeks<br>• Topical treatment that is likely to impact signs and symptoms of psoriasis such as corticosteroids, vitamin D analogues, pimecrolimus, retinoids, salicylic acid, lactic acid, tacrolimus, tar, urea, alpha-hydroxy or fruit acids: 2 weeks<br>• Live vaccinations: 6 weeks<br>• Any investigational treatment or participation in any interventional trial: 4 weeks or 5 half-lives, whichever is longer |
| **EFFICACY EVALUATIONS** | Treatment efficacy will be evaluated using the Psoriasis Area and Severity Index (PASI) scored from 0 to 72 with higher scores indicating worse disease and the Investigator's Global Assessment Scale (IGA) scored from 0 to 5 with high scores indicating worse disease. |
| **PRIMARY ENDPOINT** | • Mean change from baseline in percent of lesional CD4+ and CD8+ T effector cells producing IL-17 at weeks 20 and 44. |
| **SECONDARY ENDPOINTS** | • Patients with DLQI 0/1 at weeks 20, 44, 68, and 96<br>• Change from baseline in DLQI and PHQ-9 score at week 44, 68, and 96<br>• DLQI and PHQ-9 at all on-study time points<br>• PSSD symptom score at all on-study time points |

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| | • Proportion of patients achieving PSSD symptom score of 0 at week 44, 68, and 96<br>• SF-36 at all on-study time points<br>• Proportion of patients with PASI 75, PASI 90, PASI 100, IGA 0, or IGA 0/1 at week 20 and 44 in patients with guttate or plaque psoriasis treated with guselkumab.<br><br><u>Exploratory Endpoints:</u><br>• RNA-seq analysis of pathways impacted by guselkumab treatment at week 12 compared to baseline<br>• PASI 50, 75, 90, and 100, IGA of 0, or IGA 0/1 at all other on-study time points<br>• Proportion of patients with plaque and guttate psoriasis who achieve PASI 75, PASI 90, PASI 100 at week 44 who, after treatment withdrawal, maintain PASI 75 PASI 90, or PASI 100 at weeks 68 and 96<br>• Time to loss of PASI 75 or 90 response after week 44 |
| **OTHER EVALUATIONS** | Quality of life and patient-reported outcomes will be assessed at various points throughout the study using Dermatology Life Quality Index (DLQI), Patient Health Questionnaire Version 9 (PHQ-9), Short Form-36 (SF-36), and Psoriasis Symptom and Sign Diary (PSSD).<br><br>Changes in cutaneous cell populations and cytokine profiles will be evaluated using various laboratory techniques including single cell RNA sequencing.<br>Analysis of molecular pathways impacted by guselkumab treatment will be evaluated via RNA sequencing. |
| **SAFETY EVALUATIONS** | Safety and tolerability will be assessed by incidence of adverse events, vital signs, physical examinations (including skin examinations and injection-site evaluations), and concomitant medication review. Laboratory assessments will be performed at screening. |
| **PLANNED INTERIM ANALYSIS** | Interim statistical analysis will be completed after 12 months. Efficacy and safety data from the first 12 weeks of the study as well as biomarker data from week 12 vs baseline will be analyzed. |
| **STATISTICS PRIMARY ANALYSIS PLAN** | Single cell compositional analysis: Compare change in IL17A/F+ cells in post vs pretreatment lesional skin samples. |
| **RATIONALE FOR NUMBER OF SUBJECTS** | Empiric data from prior studies also informed the sample size. In ten psoriasis patients receiving anti-IL17 therapy, the percentage of IL-17 expressing CD4+ T-effector cells in lesional skin decreased from an average of 11.6% at week zero to 5.8% at week twelve, $p<0.05$. |

# 1 BACKGROUND

Psoriasis is an inflammatory skin disorder that affects 7.5 million Americans [1]. A substantial fraction of these patients, up to 30%, have guttate psoriasis, a subtype of psoriasis characterized by small, inflammatory, scaly erythematous plaques that may either self-resolve or evolve into chronic guttate or plaque psoriasis [2-6]. Guselkumab is an interleukin-23 blocker approved for treatment of chronic plaque psoriasis. The goal of this study is to determine whether intervention with guselkumab in guttate psoriasis can lead to rapid clearance of the guttate lesions and long-term psoriasis remission. Chronic plaque psoriasis will be used as a comparator group.

Guttate psoriasis affects a younger cohort of patients, most commonly children and young adults, compared to plaque psoriasis in which the onset is most commonly in adulthood [7-8]. Guttate psoriasis is often preceded by streptococcal infection with most studies showing that positive skin swabs or positive serum anti-streptolysin O (ASO) titer is observed in more than 50% of patients [7, 9]. In most cases, the infection precedes the skin manifestations by 1-2 weeks.

The pathophysiology of guttate psoriasis is not well understood. Given the clinical association with streptococcal infection, the role of superantigens is speculated; streptococcal antigens bind to major histocompatibility complex (MHC) molecules of antigen-presenting cells, which stimulates T-cells to release various cytokines that are important in the pathophysiology of psoriasis [11]. Studies have shown that T-cells isolated from psoriatic plaques show strong reactivity to the M-peptide on streptococcal antigens. The M-peptide shares amino acid sequences with keratin and may cause specific T cells to cross-react with human keratin [12]. We hypothesize that early intervention with guselkumab may halt the development of cross-reactive T cells in patients with acute-onset (< 6 months) guttate psoriasis, leading to symptom improvement and possible remission. We also hypothesize that management of chronic guttate psoriasis (onset > 6 months) with guselkumab could improve guttate psoriasis lesions and potentially lead to remission.

Only a few studies to date have attempted to characterize the immunologic environment of guttate psoriasis. Overall, the immunopathogenesis of guttate psoriasis has been assumed to be generally similar to that of plaque psoriasis in which cytokines such as interleukin (IL)-23, IL-17, tumor necrosis factor-alpha (TNF-α), IL-22, and interferon-gamma (IFN-γ) contribute to the inflammatory cascade [13]. Higher levels of inflammatory markers, including IL-17A, IL-22, and IL-23, are found in both guttate and plaque psoriasis when compared to healthy controls. Two studies to date have shown that the levels of IL-17 within guttate plaques and in serum are variable and may be lower in some patients with guttate psoriasis as compared to plaque and pustular psoriasis [14, 15]. Another study has shown that the numbers of Foxp3+ Tregs in lesional skin and peripheral blood were higher in plaque psoriasis than in guttate psoriasis, whereas the percentage of IL-17 CD4+ cells was higher in guttate psoriasis than in plaque psoriasis [16]. Two other studies reported higher levels of IL-12 and IL-23 in plaque psoriasis as compared to guttate [32, 33]. From the limited available data, guttate psoriasis and plaque psoriasis appear to have different etiologies.

In addition to immunologic factors, guttate psoriasis also has a strong genetic component and has been shown to be more strongly associated with HLA-Cw6*0602 than plaque psoriasis [17-19]. Family history of psoriasis and recent stress has also been found to be associated with new onset guttate psoriasis [20]. Furthermore, patients who had incomplete remission or progression to plaque psoriasis were more likely to have a family history of psoriasis [20].

The disease course of guttate psoriasis varies. Studies have shown that approximately 2/3 of patients with guttate psoriasis will experience complete remission, while approximately 1/3 will experience progression to chronic psoriasis [7, 10]. Of patients who achieve full remission, clearance of lesions typically occurs in 3-6 months [7]. The exact time course of guttate psoriasis progressing to chronic plaque psoriasis has not been studied.

The management of guttate psoriasis typically involves topical therapies and phototherapy. Although biologic therapies such as the TNF-α inhibitors (adalimumab,

etanercept, infliximab), the IL 12/23 inhibitor (ustekinumab), the IL-23 inhibitors (guselkumab, tildrakizumab, and risankizumab) the IL-17A inhibitors (secukinumab, ixekizumab), and the IL

17 receptor inhibitor (brodalumab) exist for the treatment of moderate-to-severe plaque psoriasis, none of these options are currently FDA-approved for guttate psoriasis. There have been several reports of TNF-α therapy causing paradoxical psoriasiform reactions in which patients with no previous history of psoriasis developed new onset psoriasis following anti-TNFα therapy for the treatment of other conditions such as inflammatory bowel disease, rheumatoid arthritis, and ankylosing spondylitis [21, 22]. Furthermore, rare patients with existing plaque psoriasis have experienced morphologic change to guttate psoriasis following anti-TNFα therapy [22]. It is speculated that TNF-α blockade may cause cytokine imbalance toward IFNs, chemokines and IL-17 [23]. In addition, it has been reported that the development of such psoriasiform lesions could be modulated by the cytokine IL-23 [24]. There have been no similar reports of paradoxical psoriasiform reactions with IL-23 or IL-17 inhibitors.

Biologics are not currently part of the standard of care for guttate psoriasis, since it is more likely to have a self-limited course than plaque psoriasis, for which biologics are indicated for long-term control of moderate-to-severe disease. However, the use of a biologic for the treatment of severe, recalcitrant guttate psoriasis unresponsive to conventional treatment modalities has been reported [28-29]. There are nine reported cases of patients with recalcitrant guttate psoriasis successfully treated with ustekinumab, an anti-IL 12/23 inhibitor. However, there are only a few published reports or studies to date for the use of any biologic for treatment of guttate psoriasis.

Although treatment options for guttate psoriasis are currently limited, treatment of initial manifestation of guttate psoriasis may be important in affecting the disease course. One retrospective study of 36 patients showed that 14 out of 36 patients progressed to have chronic psoriasis. Out of these 14 patients, 2 patients progressed to plaque psoriasis while the other 12 remained with guttate psoriasis. The 2 patients who progressed to plaque psoriasis did not receive initial treatment for guttate psoriasis [7]. This implies that early treatment of guttate psoriasis may have an impact on clinical course. Interestingly, treatment of streptococcal infection with antibiotics does not appear to affect the disease course [25-26].

To date, no prospective trials have been conducted to identify how treatment of the initial manifestation of guttate psoriasis affects disease course. If the initial manifestation is treated promptly and effectively, it is possible that patients may have an increased chance of achieving long-term remission. Guselkumab (Tremfya®), an IL-23 inhibitor approved for the treatment of moderate-to-severe plaque psoriasis, is an extremely efficacious option with rapid onset of action with 73.3% of patients achieving PASI -90 (90% improvement or better in Psoriasis Area and Severity Index) at week 16 [27]. Given the potential role of IL-23 in the pathogenesis of guttate psoriasis, guselkumab may be an effective option to treat guttate psoriasis, in addition to inducing remission.

Platform Technologies at UCSF

At UCSF, we have developed innovative technologies to characterize individual skin cell populations at the protein level. Using an optimized cytometry protocol, we are able to separately analyze distinct cell populations in human skin such as CD4+ T effector cells, CD8+ T cells, T regulatory cells, and innate lymphoid type 3 cells for production of TNF, IL-17, IFN-gamma, and IL-22. Moreover, we have recently upgraded this technology to single cell RNA-seq, which provides transcriptome information on most cell types within a skin lesion.

We have expertise in performing and analyzing RNA-sequencing data. Our group was the first to show RNA-seq can also identify the expression of noncoding transcripts in inflammatory skin disease that are important for the regulation of coding transcripts and may play an important role in the pathogenesis of inflammatory skin disease. We also have expertise in state-of-the-art gene network analysis, which can identify modules of significantly correlated genes and define key driver genes.

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## 2 STUDY RATIONALE

The University of California at San Francisco Psoriasis Center has expertise in the clinical, immunologic, and genetic analyses of patients with psoriasis. Therefore, this unique proposal will examine the clinical and immunogenetic effects of treatment with guselkumab in patients with plaque and guttate psoriasis.

# 3 RISK / BENEFIT ASSESSMENT

Details of the risks and benefits of guselkumab are outlined in the prescribing information. Side effects that occurred in more than 1% of patients treated with guselkumab for 16 weeks include upper respiratory infections (14.3%), headache (4.6%), injection site reactions (4.5%), arthralgia (2.7%), diarrhea (1.6%), gastroenteritis (1.3%), tinea infections (1.1%), and herpes simplex infections (1.1%). The risks to the subjects in this trial will be minimized by compliance with the inclusion/exclusion criteria, proper study design, and close clinical monitoring.

In regards to skin biopsy procedures, as in any surgical procedure, there are certain inherent risks including bleeding, post-operative pain, infection, scarring, and reactions to sutures, anesthetics, or topical antibiotics. All reasonable efforts will be made to minimize the possibility of these potential complications.

The benefit to subjects is that they will be receiving an approved therapy for moderate to severe psoriasis. Although outcomes cannot be guaranteed, guselkumab has been shown to be safe and effective in moderate to severe psoriasis. An additional benefit to patients is that they are contributing to society by helping the enhancement of our scientific knowledge.

# 4 STUDY OBJECTIVES

## 4.1 Primary Objective

The primary objective of this study is to assess how treatment with guselkumab changes the immune milieu of the skin in patients with plaque and guttate psoriasis.

## 4.2 Secondary Objectives

The secondary objectives of this study are to assess how treatment with guselkumab affects the quality of life and extent of skin disease in patients with plaque and guttate psoriasis.

# 5 STUDY DESIGN

## 5.1 Study Overview

This is a single center, open-label study. Twenty-five subjects are planned (15 with guttate psoriasis and 10 with chronic plaque psoriasis). Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study. All subjects will initially be treated with guselkumab 100 mg SQ at weeks 0, 4, and then every 8 weeks thereafter until week 44. At week 44, patients whohave not achieved PASI 50 (nonresponders) will be removed from the trial. Patients who achievebetween PASI 50 and PASI 75 (partial responders) will continue on drug throughout the remainder of the study. Patients who achieve PASI 75 or greater at week 44 (responders) will have their guselkumab therapy withdrawn. Responders who maintain at least 50% of their week 44 PASI improvement will continue without treatment until week 96. If at any time during the study a responder experiences loss of 50% or more of week 44 PASI response, they will restart guselkumab 100 mg SQ every 8 weeks until week 96. Patients will be evaluated at screening and weeks 0, 4, 12, 20, 28, 36, 44, 52*, 68*, 84*, and 96* and, depending on study arm, may have skin biopsies done at weeks 0, 12, 44, 68*, 96*, and at loss of PASI visit for molecular profiling Two biopsies will be done from lesional skin. The total duration of the study is expected to be 116 weeks, with 20 weeks of recruitment and 96 weeks of treatment and follow-up.

* Responders who maintain their week 44 response without losing at least 50% of their improvement from baseline will continue to follow the visit and biopsy schedule outlined in the above paragraph. Responders who believe they have lost 50% of their week 44 response will contact the study team and present for an evaluation. If they indeed have lost 50% of their week 44 response, they will be restarted on guselkumab and will be biopsied at that time point. They will then follow-up every 16 weeks and will undergo final skin biopsies at the close out visit at week 96.

# 6 CRITERIA FOR EVALUATION

## 6.1 Primary Analysis Endpoint

- Mean change from baseline in percent of lesional CD4+ and CD8+ T effector cells producing IL-17 at weeks 20 and 44

## 6.2 Secondary Analysis Endpoints

- Patients with DLQI 0/1 at weeks 20, 44, 68, and 96
- Change from baseline in DLQI and PHQ-9 score at week 44, 68, and 96
- DLQI and PHQ-9 at all on-study time points
- PSSD symptom score at all on-study time points
- Proportion of patient achieving PSSD symptom score of 0 at week 44, 68, and 96
- SF-36 at all on-study time points
- Proportion of patients with PASI 75, PASI 90, PASI 100, IGA 0, or IGA 0/1 at week 20 and 44 in patients with guttate or plaque psoriasis treated with guselkumab.

## 6.3 Exploratory Endpoints

- RNA-seq analysis of pathways impacted by guselkumab treatment at week 12 compared to baseline
- PASI 50, 75, 90, and 100, IGA 0, or IGA 0/1 at all other on-study time points
- Proportion of patients with plaque and guttate psoriasis who achieve PASI 75, PASI 90, or PASI 100 at week 44 who, after treatment withdrawal, maintain PASI 75, PASI 90, or PASI 100 at weeks 68 and 96
- Time to loss of PASI 75 or 90 response after week 44

## 6.4 Safety Evaluations

Safety and tolerability will be assessed by incidence of adverse events, vital signs, physical examinations (including skin examinations and injection-site evaluations), and concomitant medication review. Laboratory assessments will be performed at screening.

# 7 SUBJECT SELECTION

## 7.1 Study Population

Subjects with a diagnosis of guttate psoriasis and plaque psoriasis who meet the inclusion and exclusion criteria will be eligible for participation in this study.

### 7.1.1 Inclusion Criteria

For subjects with guttate psoriasis:

1. Ability to provide written informed consent and comply with the protocol.
2. At least 18 years of age.
3. Diagnosis of guttate psoriasis.
4. Body surface area (BSA) involvement greater than or equal to 5%.
5. PASI greater than or equal to 4.
6. Subject is considered a candidate for phototherapy or systemic therapy.
7. Subject is unlikely to conceive due to male, post-menopausal, or using adequate contraceptive (barrier, hormonal, implant, or permanent sterilization methods). Women of childbearing potential will be allowed to enroll provided they practice adequate forms of birth control.

8. Physical exam with no evidence of active skin infection and/or other findings that indicate chronic disease or concomitant inflammatory/immune-mediated skin disease other than psoriasis.

For subjects with chronic plaque psoriasis (control):

1. Ability to provide written informed consent and comply with the protocol.
2. At least 18 years of age.
3. Diagnosis of plaque psoriasis.
4. Duration of plaque psoriasis >5 years.
5. Body surface area (BSA) involvement greater than or equal to 5%.
6. Subject is considered a candidate for phototherapy or systemic therapy.
7. Subject is unlikely to conceive due to male, post-menopausal, or using adequate contraceptive (barrier, hormonal, implant, or permanent sterilization methods). Women of childbearing potential will be allowed to enroll provided they practice adequate forms of birth control.
8. Physical exam with no evidence of active skin infection and/or other findings that indicate chronic disease or concomitant inflammatory/immune-mediated skin disease other than psoriasis.

#### 7.1.2 Exclusion Criteria

For subjects with guttate psoriasis:

1. Subject is unable to provide written informed consent or comply with the protocol.
2. Subject is younger than 18 years of age or older than 70 years.
3. Have a history of active, chronic or recurrent infectious disease including HIV, hepatitis B, or hepatitis C.
4. Have active tuberculosis or latent tuberculosis without at least 4 weeks of treatment with isoniazid.
5. Have current signs or symptoms of severe, progressive, or uncontrolled medical disease.
6. Known allergies, hypersensitivity, or intolerance to guselkumab (Tremfya™) excipients.
7. Have a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
8. Have any known malignancy or have a history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to screening)
9. Are pregnant, nursing, or planning a pregnancy while enrolled in the study or for 12 weeks after the study agent injection for women or are planning to father a child while enrolled in the study or for 12 weeks after the last study agent injection.
10. Are participating in another study using an investigational agent or procedure during participation in this study.
11. Have any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements.
12. Subjects possess other diagnoses that, in the investigator's opinion interfere with the evaluation of the subject's guttate psoriasis.
13. Pre-existing psoriasis type other than guttate psoriasis for longer than 6 months. (i.e. plaque, pustular, erythrodermic)

For subjects with chronic plaque psoriasis:

1. Subject is unable to provide written informed consent or comply with the protocol.
2. Subject is younger than 18 years of age or older than 70 years.
3. Have a history of active, chronic or recurrent infectious disease, including HIV, hepatitis B, or hepatitis C.
4. Have active tuberculosis or latent tuberculosis without at least 4 weeks of treatment with isoniazid.
5. Have current signs or symptoms of severe, progressive, or uncontrolled medical disease.
6. Known allergies, hypersensitivity, or intolerance to guselkumab (Tremfya™) excipients.
7. Have a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
8. Have any known malignancy or have a history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to screening)
9. Are pregnant, nursing, or planning a pregnancy while enrolled in the study or for 12 weeks after the study agent injection for women or are planning to father a child while enrolled in the study or for 12 weeks after the last study agent injection.
10. Are participating in another study using an investigational agent or procedure during participation in this study.
11. Have any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements.
12. Subjects possess other diagnoses that, in the investigator's opinion, interfere with the evaluation of the subject's plaque psoriasis.
13. Prior history of guttate psoriasis.

# 8 CONCURRENT MEDICATIONS

## 8.1 Allowed Medications and Treatments

All prior concomitant medications must be on a stable dose for at least 4 weeks before the first study treatment administration. All subjects should be maintained on the same medications throughout the entire study period, as medically feasible. Any changes in medications and medication dosing will be recorded on the CRF. After the screening period, the use of concomitant medications for psoriasis in all body regions is restricted to bland emollients and other non-medicated interventions.

## 8.2 Prohibited Medications and Treatments

The following are prohibited during the study and prior to the study for a set duration as follows:

- Systemic anti-psoriatic treatments including methotrexate, cyclosporine, corticosteroids, and cyclophosphamide: 4 weeks
- Biological immunomodulating agents including infliximab, etanercept, and adalimumab: 12 weeks
- Any therapeutic agent directly targeted to IL-12, IL-17, or IL-23 (ustekinumab, Tildrakizumab, secukinumab, ixekizumab, or brodalumab): 3 months
- Other systemic psoriasis treatments including retinoids: 4 weeks
- Photochemotherapy: 4 weeks
- Phototherapy (UVA/UVB): 2 weeks

- Topical treatment that is likely to impact signs and symptoms of psoriasis such as corticosteroids, vitamin D analogues, pimecrolimus, retinoids, salicylic acid, lactic acid, tacrolimus, tar, urea, alpha-hydroxy or fruit acids: 2 weeks
- Live vaccinations: 6 weeks
- Any investigational treatment or participation in any interventional trial: 4 weeks or 5 half-lives, whichever is longer

# 9 STUDY TREATMENTS

## 9.1 Supply of Study Drug at the Site

Janssen will ship study drug to the investigational site. The initial study drug shipment will be shipped after site activation (i.e., all required regulatory documentation has been received by the Company and a contract has been executed). Subsequent study drug shipments will be made after site request for resupply. The study drug is supplied in a carton of one 100 mg/mL (1 mL) prefilled syringe. Each kit of study drug will be labeled with the protocol number.

## 9.2 Dosage/Dosage Regimen

Guselkumab will be administered at a dose of 100 mg subcutaneously throughout the study, which is the FDA-approved dose for the treatment of moderate-to-severe plaque psoriasis. There is no weight-based dosing. The dosing schedule will be as follows: guselkumab 100 mg subcutaneously at weeks 0, 4, and every 8 weeks thereafter until week 44, at which time partial responders will be continued on every 8 weeks dosing and responders will be withdrawn from therapy. Nonresponders will be removed from the study at week 44 and will no longer receive study drug. After withdrawal of therapy, any responders who subsequently lose 50% of their week 44 PASI response will be restarted on guselkumab 100 mg subcutaneously every 8 weeks until the end of the study.

## 9.3 Dispensing

Study drug shall be dispensed only by the primary investigator and designated sub-investigators.

## 9.4 Administration Instructions

All doses of guselkumab during the first 44 weeks of the study will be administered at the study site after the study assessments for the visit have been completed. After week 44, subjects continuing in the treatment arm will administer half of their injections at the study site and every other injection independently after they have shown the competency to self-administer. There will be no medication given after week 96.

The subjects will be instructed to contact the investigator if he/she is unable for any reason to attend a study visit as scheduled. All dates and times of injections done to the subject during this study will be recorded on the Dosage Administration Record CRF. The investigator will promote compliance by instructing the subject to attend the study visits as scheduled and by stating that compliance is necessary for the subject’s safety and the validity of the study.

## 9.5 Storage

Guselkumab prefilled syringes will be stored in accordance with the package insert. The medication will be kept in a temperature-monitored refrigerator at the study site and kept between 2 and 8 degrees Celsius (36 to 46 degrees Fahrenheit). It will be stored in the original carton until time of use and will be protected from light, not frozen, and not shaken.

## 9.6 Study Drug Accountability

The qualified site personnel will maintain an accurate record of the shipment and dispensing of study treatment in a treatment accountability log. All study treatment kits assigned to the subject during the study will be recorded.

### 9.7 Measures of Treatment Compliance

Subjects will be given scheduled doses of guselkumab at each visit from week 0 until week 44. After week 44, half of the injections will occur at the study site and half will occur at the patients' homes. Patients will record date of injection, time of injection and injection on the study drug box and will return the box with this information at the next scheduled visit. The dosing information will be recorded in the patient's record.

## 10 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

All clinical assessments will take place at the study site: 515 Spruce Street, San Francisco, California 94118.

All blood draws will take place at the UCSF Blood Draw Lab: UCSF Mount Zion Clinical Lab, Quest Diagnostics, LabCorp, or other qualified lab.

### 10.1 Participants will have the option to do virtual visits (by phone or online) for all study visits which do not require in person procedures such as skin biopsies, laboratory testing or photography.

#### 10.1.1 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

#### 10.1.2 Medical History

Relevant medical history, including history of current disease, and information regarding underlying diseases will be recorded at Screening.

#### 10.1.3 Concomitant Medications

All concomitant medications and concurrent therapies will be documented at Baseline/Screening, at every site visit, and at early termination when applicable. Dose, route, unit, frequency, indication, and dates of therapy for each concomitant medication will be captured.

#### 10.1.4 Physical Examination

A complete physical examination will be performed by either the investigator or a sub investigator who is a physician at Screening, all site visits, and early termination. New abnormal physical exam findings will be documented and followed by a physician or other qualified staff at the next scheduled visit.

#### 10.1.5 Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed after resting for 5 minutes at every site visit.

#### 10.1.6 Adverse Events

Information regarding the occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment, and relation to study drug will be recorded on the case report form (CRF).

#### 10.1.7 PASI and IGA

Psoriasis Area and Severity Index (PASI) and Investigator Global Assessment (IGA) will be completed at screening and every subsequent site visit.

#### 10.1.8 Photography

Photographs will be taken at weeks 0, 12, 28, 44, 68, 96, and early termination (if necessary). Responders who lose 50% of their week 44 PASI response will follow-up at 16-week intervals and will have photographs taken at the Loss of PASI visit and at study close out at week 96. Photographs will be obtained with a standard blue background and will include full anterior/posterior, anterior/posterior trunk, anterior/posterior legs and forearms (will not include face). As per our standard practice, patients will be photographed with garments covering their sensitive (e.g. breast, buttock, genital). Photos will be stored on an encrypted drive.

#### 10.1.9 Patient Questionnaires

Patient questionnaires including the PSSD, DLQI, and PHQ-9, SF-36 will be completed at every study visit following screening.

### 10.2 Clinical Laboratory Measurements

#### 10.2.1 Hematology

Blood will be obtained once at the beginning of the study and sent to the clinical hematology lab for a complete blood count with differential (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count) for assessment of systemic evidence for infection and/or inflammation.

#### 10.2.2 Blood Chemistry Profile

Blood will be obtained once at the beginning of the study and sent to the clinical chemistry lab for determination of BUN, creatinine, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), and alkaline phosphatase.

#### 10.2.3 Pregnancy Test

A urine pregnancy test will be obtained from female subjects who are of childbearing age at screening and every subsequent site visit.

#### 10.2.4 HIV Screening

Blood will be obtained and sent to the clinical lab for determination of HIV status at screening.

#### 10.2.5 Hepatitis B/C Monitoring

Blood will be obtained and sent to the clinical lab for determination of hepatitis B and C status at screening. Laboratory tests will include evaluation of hepatitis B core antibody, hepatitis B surface antibody, hepatitis B surface antigen, and hepatitis C antibody status.

#### 10.2.6 Quantiferon Gold Plus (TB)

Blood will be obtained and sent to the clinical lab for determination of tuberculosis infection/exposure status as screening.

#### 10.2.7 Group A Streptococcus monitoring

Blood will be obtained and sent to the clinical lab for determination of ASO titer and throat cultures for Group A Streptococcus will be completed at week 0, week 44, loss of PASI visits, and early termination visits.

### 10.3 Research Laboratory Measurements

#### 10.3.1 Skin Biopsies

Skin biopsies will occur in all study patients at weeks 0, 12, and 44. Nonresponders will be discontinued from the study after week 44 and will not undergo any other study procedures. Partial responders (PASI50 to PASI75 at week 44) will be biopsied at weeks 68 and 96. Responders (greater than PASI75 at week 44) whose study drug is discontinued will be biopsied

at their loss of PASI visit (if this occurs) and at week 96. Week 68 biopsies will not be done on patients who maintain their PASI response despite withdrawal of drug. Biopsies done at weeks 0 and 12 will be analyzed by single cell RNA-seq while biopsies done at weeks 44 and later may be banked for possible future analysis.

## 11 EVALUATIONS BY VISIT

See Appendix 1.

### 11.1 Visit 1 (Screening)

- Review the study with the subject and obtain written informed consent and HIPAA authorization
- Assign the subject a unique screening number
- Review inclusion/exclusion criteria
- Collect demographics data
- Review medical history
- Complete physical examination
- Assess vital signs
- Record PASI and IGA
- Complete blood draw for laboratory assessments
- Obtain urine pregnancy test if applicable
- Review concomitant medications

### 11.2 Visit 2 (Week 0)

- Complete physical examination
- Assess vital signs
- Record PASI and IGA
- Administer patient questionnaires
- Obtain urine pregnancy test if applicable
- Record adverse events
- Review concomitant medications
- Perform skin biopsy
- Perform blood draw for ASO titers and throat swab for GAS culture
- Obtain photographs
- Dispense study medication

### 11.3 Visit 3 (Week 4)

- Complete physical examination
- Assess vital signs
- Record PASI and IGA
- Administer patient questionnaires
- Obtain urine pregnancy test if applicable
- Record adverse events
- Review concomitant medications
- Dispense study medication

### 11.4 Visit 4 (Week 12)

- Complete physical examination

- Assess vital signs
- Record PASI and IGA
- Administer patient questionnaires
- Obtain urine pregnancy test if applicable
- Record adverse events
- Review concomitant medications
- Perform skin biopsy
- Obtain photographs
- Dispense study medication

### 11.5 Visit 5 (Week 20)

- Complete physical examination
- Assess vital signs
- Record PASI and IGA
- Administer patient questionnaires
- Obtain urine pregnancy test if applicable
- Record adverse events
- Review concomitant medications
- Dispense study medication

### 11.6 Visit 6 (Week 28)

- Complete physical examination
- Assess vital signs
- Record PASI and IGA
- Administer patient questionnaires
- Obtain urine pregnancy test if applicable
- Record adverse events
- Review concomitant medications
- Obtain photographs
- Dispense study medication

### 11.7 Visit 7 (Week 36)

- Complete physical examination
- Assess vital signs
- Record PASI and IGA
- Administer patient questionnaires
- Obtain urine pregnancy test if applicable
- Record adverse events
- Review concomitant medications
- Dispense study medication

### 11.8 Visit 8 (Week 44)

- Complete physical examination
- Assess vital signs
- Record PASI and IGA
- Administer patient questionnaires

- Obtain urine pregnancy test if applicable
- Record adverse events
- Review concomitant medications
- Perform skin biopsy
- Perform blood draw for ASO titers and throat swab for GAS culture
- Obtain photographs
- Dispense study medication

### 11.9 Visit 9 (Week 52*)

- Complete physical examination
- Assess vital signs
- Record PASI and IGA
- Administer patient questionnaires
- Obtain urine pregnancy test if applicable
- Record adverse events
- Review concomitant medications
- Dispense study medication

### 11.10 Visit 10 (Week 68*)

- Complete physical examination
- Assess vital signs
- Record PASI and IGA
- Administer patient questionnaires
- Obtain urine pregnancy test if applicable
- Record adverse events
- Review concomitant medications
- Perform skin biopsy
- Obtain photographs
- Dispense study medication

### 11.11 Visit 11 (Week 84*)

- Complete physical examination
- Assess vital signs
- Record PASI and IGA
- Administer patient questionnaires
- Obtain urine pregnancy test if applicable
- Record adverse events
- Review concomitant medications
- Dispense study medication

### 11.12 Visit 12 (Week 96*)

- Complete physical examination
- Assess vital signs
- Record PASI and IGA
- Administer patient questionnaires
- Obtain urine pregnancy test if applicable

- Record adverse events
- Review concomitant medications
- Perform skin biopsy
- Obtain photographs

### 11.13 Loss of PASI Visit

- Complete physical examination
- Assess vital signs
- Record PASI and IGA
- Administer patient questionnaires
- Obtain urine pregnancy test if applicable
- Record adverse events
- Review concomitant medications
- Perform skin biopsy
- Perform blood draw for ASO titers and throat swab for GAS culture
- Obtain photographs
- Dispense study medication to be injected at least 8 weeks after last dose.

### 11.14 Early Termination

- Complete physical examination
- Assess vital signs
- Record PASI and IGA
- Administer patient questionnaires
- Obtain urine pregnancy test if applicable
- Record adverse events
- Review concomitant medications
- Perform skin biopsy
- Perform blood draw for ASO titers and throat swab for GAS culture
- Obtain photographs

* Visits 9, 10, 11, and 12 may be at different weeks due to patients restarting guselkumab at different time points. Patients who restart treatment after losing 50% of their week 44 PASI response will follow up every 16 weeks after their loss of PASI visit and at week 96 to close out the study.

## 12 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

### 12.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse

events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause. Adverse events 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.

### 12.1.1 AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

| Grades | Description |
|---|---|
| Grade 1 | Mild; Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| Grade 2 | Moderate; Minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL* |
| Grade 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. |
| Grade 4 | Life-threatening consequences; urgent intervention indicated. |
| Grade 5 | Death Related to AE |

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

### 12.1.2 AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines.

Table 2. AE Relationship to Study Drug

| Relationship to Drug | Comment |
|---|---|
| Definitely | Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis. |
| Probably | An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions. |
| Possibly | An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors. |

| | |
|---|---|
| Unrelated | An event that can be determined with certainty to have no relationship to the study drug. |

#### 12.1.3 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

##### *12.1.3.1 Serious Adverse Experience Reporting*

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end 12 weeks after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

### 12.2 Interventional IIS COMPANY Requirements for Safety Data Collection and Reporting

#### 12.2.1 Overview

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

The INSTITUTION and PRINCIPAL INVESTIGATOR will provide safety information to the COMPANY on adverse events, special situations including pregnancies and product quality complaints as defined within this EXHIBIT.

#### 12.2.2 Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events for Janssen Medicinal Products regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this Exhibit 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 for 12 weeks after procedures for the final study visit have been completed.

For the purposes of this study, the Janssen medicinal product is guselkumab (Tremfya™)

#### 12.2.3 Definitions

##### *12.2.3.1 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 Harmonization [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.

#### *12.2.3.2 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.

#### *12.2.3.3 Individual Case Safety Report (ICSR)*

A valid ICSR must contain the four minimum criteria required 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 medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (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

#### *12.2.3.4 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., auto injector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

#### *12.2.3.5 Serious Adverse Event (SAE)*

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

- Results in death
- 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
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is 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.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

#### *12.2.3.6 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.

#### *12.2.3.7 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.

#### *12.2.3.8 Unlisted (Unexpected) Adverse Event/Reference Safety Information*

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

Link to Tremfya™ package insert: https://www.janssenmd.com/pdf/tremfya/tremfya_pi.pdf

### 12.2.4 Special Reporting Situations

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

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product

- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

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

Any special situation that meets the criteria of a serious adverse event should be recorded on a Janssen Serious Adverse Event Report Form and be reported to the COMPANY within 24 hours of becoming aware of the event.

#### 12.2.5 Pregnancy

All initial reports of pregnancy must be reported to the COMPANY by the PRINCIPAL INVESTIGATOR within 24 hours of becoming aware of the event using the Janssen 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 Janssen Serious Adverse Event Form.

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

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the PRINCIPAL INVESTIGATOR within 24 hours of their knowledge of the event using the Janssen 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 required.

#### 12.2.6 Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The INSTITUTION and PRINCIPAL INVESTIGATOR shall provide all adverse events, both serious and non-serious, in report format. 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 timeframe at the COMPANY's request.

#### 12.2.7 Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to the COMPANY

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

#### 12.2.8 SAEs, Adverse Events of Special Interest and Special Reporting Situations

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, must 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)

The INSTITUTION and the PRINCIPAL INVESTIGATOR) will transmit all SAEs, Adverse Events of Special Interest and special situations following exposure to a Janssen product under study in a form provided by the COMPANY in accordance with Section 12.2.11, Transmission Methods, in English within 24-hours of becoming aware of the event(s).

In the event the study is blinded, the PRINCIPAL INVESTIGATOR will submit an unblinded SAE or pregnancy exposure report to COMPANY.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the PRINCIPAL INVESTIGATOR, within 24 hours becoming aware, to the COMPANY using the COMPANY's 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 INSTITUTION and/or PRINCIPAL INVESTIGATOR 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 irrespective of association with the Janssen Product under study, are to be provided to the COMPANY using a transmission method in Section 12.2.11 within 24 hours of such report or correspondence being sent to applicable health authorities.

#### 12.2.9 Non-Serious AEs

All non-serious adverse events should be reported to COMPANY according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

#### 12.2.10 PQC Reporting

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 the COMPANY, and are mandated by regulatory agencies worldwide. The COMPANY 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 a Janssen medicinal product under study must be reported to the COMPANY by the PRINCIPAL INVESTIGATOR 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 medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PRINCIPAL INVESTIGATOR must report the PQC to the COMPANY according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the COMPANY.

#### 12.2.11 Transmission Methods

The following methods are acceptable for transmission of safety information to the COMPANY:

- 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).

Please use the contact information and process information provided by the COMPANY.

#### 12.2.12 SAEs Listing

At a minimum, on a semi-annual basis and at the end of the Study, COMPANY will provide to the INSTITUTION and/or PRINCIPAL INVESTIGATOR, a listing of all SAEs reported to the COMPANY. COMPANY and/or PRINCIPAL INVESTIGATOR will review this listing and will resolve any discrepancies with the data provided by the COMPANY.

#### 12.2.13 Dissemination of Safety Information from COMPANY to INSTITUTION/PRINCIPAL INVESTIGATORS

PRINCIPAL INVESTIGATOR will be responsible for submitting IND safety reports for the Study Product to INSTITUTION's IRB in accordance with Federal regulations 21 CFR 312.66. The PRINCIPAL INVESTIGATOR will provide a copy of each IND safety report to sub-investigators where the study design is either a multi-center or cooperative study.

COMPANY agrees to provide to the PRINCIPAL INVESTIGATOR IND safety reports for the Janssen Medicinal Product as they become available until all subjects in the Protocol have completed their last Study visit according to the Protocol (i.e. Last Subject Last Visit has occurred).

#### 12.2.14 Contacting COMPANY Regarding Safety

The names (and corresponding contact information) of the individuals who should be contacted regarding safety issues will be provided separately by the COMPANY.

#### 12.2.15 Final Study Report

The INSTITUTION/PRINCIPAL INVESTIGATOR 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 Research Funding Agreement.

#### 12.2.16 Discontinuation and Replacement of subjects

##### *12.2.16.1 Early Discontinuation of Study Drug*

A subject may be discontinued from study treatment at any time if the subject or the investigator, feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Company request for early termination of study
- Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. Refer to Section 10.13 for early termination procedures.

#### *12.2.16.2 Withdrawal of Subjects from the Study*

A subject may be withdrawn from the study at any time if the subject or the investigator feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Visit 12) should have an early discontinuation visit. Refer to Section 10.13 for early termination procedures. Subjects who withdraw after Visit 1 but prior to Visit 12 should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

### 12.2.17 Protocol Violations

A protocol violation occurs when the subject, investigator, or Company fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Noncompliance with study drug regimen
- Noncompliance with study visit procedures

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The PI will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Company's files.

## 13 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

### 13.1 Analysis of Primary Endpoint

The primary endpoint will be analyzed using a one sample paired t-test comparing mean change in lesional CD4+ and CD8+ T lymphocytes with IL-17A positivity compared to baseline.

### 13.2 Interim Analysis

Interim statistical analysis will be completed after 12 months. Efficacy and safety data from the first 12 weeks of the study as well as biomarker data from week 12 vs baseline will be analyzed.

### 13.3 Sample Size and Randomization

Empiric data from prior studies also informed the sample size. In ten psoriasis patients receiving anti-IL17 therapy, the percentage of IL-17 expressing CD4+ T-effector cells in lesional skin decreased from an average of 11.6% at week zero to 5.8% at week twelve, $p<0.05$.

## 14 DATA COLLECTION, RETENTION AND MONITORING

### 14.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug. Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the company.

For paper CRFs: If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

### 14.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

### 14.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis.

For paper studies: Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

### 14.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Company (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Company is required to maintain

study records and, therefore, the Company should be contacted prior to removing study records for any reason.

### 14.5 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Company. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

## 15 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

### 15.1 Protocol Amendments

Any amendment to the protocol will be written by the PI or a sub-investigator with the PI's approval. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days. Changes to the protocol will be reviewed and approved by Janssen prior to submitting to the IRB for approval.

### 15.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Company or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

### 15.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to Janssen for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to Janssen and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Company (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

### 15.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among Janssen and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

### 15.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying Janssen, except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to Janssen any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with Janssen.
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and Janssen all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

## APPENDIX 1. SCHEDULE OF STUDY VISITS (WEEKS 0-96)

| | | ACTIVE TREATMENT PERIOD | | | | | | | REASSESSMENT PERIOD[1] | | | | Loss of PASI Visit | Early Termination |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **9-12** | |
| Time of Visit | Screen visit | wk 0 | wk 4 | wk 12 | wk 20 | wk 28 | wk 36 | wk 44 | wk 52 | wk 68 | wk 84 | wk 96 | wk 45 - 95 | wk 0 - 96 |
| Inclusion / exclusion criteria | X | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | |
| Review medical history | X | | | | | | | | | | | | | |
| Demographic data collected | X | | | | | | | | | | | | | |
| Physical examination | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PASI and IGA | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Patient questionnaires[2] | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Screening lab assessments[3] | X | | | | | | | | | | | | | |
| Urine pregnancy | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse events | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Review con meds | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Skin biopsy[4] | | X[#] | | X[#] | | | | X[*] | | X[*] | | X[*] | X | X |
| Streptococcal assessment[5] | | X | | | | | | X | | | | | X | X |
| Photography | | X | | X | | X | | X | | X | | X | X | X |
| Dispense study drug | | X | X | X | X | X | X | X[†] | X[†] | X[†] | X[†] | | X[†] | |

[1] If a responder loses > 50% of their week 44 PASI response anytime during the withdrawal-retreatment period, they will be evaluated during a loss of PASI visit. If loss of response is confirmed, the patient will undergo skin biopsy and lab testing (ASOtiter and GAS culture) as well as re-start treatment with guselkumab 100 mg every 8 weeks. Responders who have restarted guselkumab due to loss of PASI response will follow up at 16 week intervals from their loss of PASI visit and at week 96. Theirfollow-up visits will correspond with study visits 9 through 11.

[2] PSSD, DLQI, PHQ-9, and SF-36 questionnaires
[3] Quantiferon Gold TB, Hepatitis Panel (Hep B core antibody, Hep B surface antibody, Hep B surface antigen, Hep C antibody) ,HIV screen, CBC with differential, BUN, Cr, AST/ALT/Alk Phos
[4] Skin biopsies will be done for all subjects at weeks 0, 12, and 44. Partial responders continuously on study drug will be biopsiedat week 68 and 96. Responders who lose their PASI response will be biopsied at their loss of PASI visit and at week 96. Responderswho maintain at least 50% of their week 44 PASI response will not be biopsied at week 68.
[5] ASO titer and GAS throat culture
[†]These procedures will only be done for subjects in the continued treatment group or in those responders who have restartedguselkumab due to loss of PASI response.
[#] Indicates biopsies that will be analyzed by single cell RNA-seq
[*] Indicates biopsies that will be banked for possible future analysis