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Pilot Trial of Ustekinumab for Primary Sjögren's Syndrome

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Sponsor: University of Rochester Medical Center
Funded by: Janssen Scientific Affairs Inc.

Definitions:

Company: Janssen Scientific Affairs Inc.
Institution: University of Rochester Medical Center

1. PURPOSE OF THE STUDY AND BACKGROUND

1.1 Purpose

Objectives: This pilot study will make a preliminary determination of the safety of ustekinumab in patients with Primary Sjogren's Syndrome (PSS) and assess the response of systemic measures of inflammation (biomarkers). If this study is successful we would anticipate applying for a moderate size phase IIa study where subjects would be randomized to ustekinumab or placebo.

Primary clinical objective: To examine the safety of ustekinumab in patients with PSS.

Secondary clinical objective: To assess the effect of ustekinumab on the subjective and objective clinical manifestations of PSS.

Primary Mechanistic objective: To determine whether the standard dosing schedule for ustekinumab lowers serum biomarkers of inflammation in patients with PSS.

1.2 Background

Sjogren's syndrome (SS) is a chronic systemic autoimmune disease, for which no treatment is available. For this trial, we propose to study the safety and clinical efficacy of ustekinumab, a human monoclonal antibody that works by inhibiting the p40 subunit of the proteins IL-12 and IL-23. Ustekinumab has been FDA approved for treatment of moderate–to-severe plaque psoriasis. Similar to psoriasis, T cells are central effectors in SS, as demonstrated by the T cell predominance of the salivary glands lymphocytic infiltrates, with a large predominance of CD4+ T cells [1]. Pathophysiologic models emphasize an "autoimmune epithelitis" [2], where the initial injury triggers a cytokine cascade leading to development of SS at the site of salivary epithelial cell. Recent studies indicate that IL-17 plays a critical role in epithelial defense, while IL-22 promotes keratinocyte proliferation and secretion of host defense protein [3]. Increased plasma levels of IL-6, IL-12, IL-23, and IL-17 have been observed in SS. Furthermore, cells staining for IL-6, IL-23, and IL-17 as well as IL12 and IFNγ are present in salivary glands from SS patients [4] and increased levels of IL17, IL23 and their receptors are expressed on these cells [5]. Most importantly, ustekinumab has a very favorable safety profile, making it an attractive therapeutic agent for a patient population that is "starving" for an effective treatment.

2. STUDY DESIGN

2.1. Overview

This is a single-center, open label, pilot trial of ustekinumab in patients with Primary Sjögren's Syndrome (PSS). Up to 15 subjects will receive an infusion loading dose of 6 mg/kg of ustekinumab at baseline, and 90 mg of ustekinumab subcutaneously at week 4, week 12 and week 20. Subjects will be followed for 24 weeks.

2.2. Endpoints

- The primary endpoint is a well-established, patient reported questionnaire for use in PSS, ESSPRI [6]. The reason we chose a patient-reported outcome is multifactorial. Prior study with rituximab in PSS has demonstrated modest improvements at week 26 in patient-reported symptoms of fatigue and oral dryness, with no significant improvement in the objective measures of lacrimal and salivary gland function [7]. As most patients with PSS report that dryness and fatigue are the two most bothersome health issues, we feel that focusing on this aspect of the illness will be most meaningful from a patient perspective.
- Secondary endpoints: Change between day 0 and week 24 in the following:
  - Subjective efficacy
    (1) Short Form-36 questionnaire (SF-36)
    (2) VAS global assessments of symptoms of oral and eye dryness
    (3) VAS global assessment of fatigue
    (4) VAS global assessment of joint pain
  - Objective efficacy
    (1) Unstimulated and stimulated salivary flow
    (2) European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI)
  - Mechanistic studies
    (1) Serum levels of TNFα, IL-6, IL17, IL17A, IL17F, IL22, IL12, IL23, BAFF (baseline, 12, 24 weeks)
    (2) B and T cell subsets analysis baseline, 12, 24 weeks
    (3) Peripheral blood interferon signature (baseline, 12, 24 weeks)
  - SS Disease Activity Labs
    (1) Autoantibodies: Anti-Ro (screening), ANA, anti-La, RF (baseline, 12, 24 weeks)
    (2) Inflammatory markers: CRP, ESR (baseline, 12, 24 weeks)
    (3) Markers of immunological activation : IgG, C3, and C4 (baseline, 12, 24 weeks)
  - Safety
    (1) Adverse events; serious adverse events
    (2) Total infections; serious infections
    (3) CBC with differential and chemistry panel at baseline, 4, 12, 20 and 24 weeks
    (4) SF-36.
    (5) Stimulated and unstimulated whole salivary flow

(6) ESSDAI
(7) VAS global assessments of symptoms of oral and eye dryness
(8) VAS global assessment of fatigue
(9) VAS global assessment of joint pain

2.3. **Rationale for Study Design**

Nothing is known about the potential benefits of ustekinumab therapy for PSS, although a scientific rationale does exist for hypothesizing that this drug may improve the signs and symptoms of this disease. As ustekinumab has not been previously tested in PSS population, we decided that a pilot study to assess safety and efficacy in a small group of subjects is the most appropriate design. The open label design makes it difficult to properly assess efficacy but can provide the necessary data and framework for a larger phase III randomized, double blind clinical trial. The objective of the study is to assess efficacy and safety of ustekinumab in patients with PSS. Each patient will be his/her own control, and we will look for the difference in the outcomes listed between baseline and 24 week end-point.

2.4. **Rationale for Dosage**

The efficacy and safety of ustekinumab (UST) in the treatment of lupus was evaluated in a global Phase 2, randomized, placebo-controlled trial in 102 adults with seropositive SLE by Systemic Lupus International Collaborating Clinics (SLICC) criteria and active disease despite ongoing standard of care therapy (steroid, antimalarial and/or immunosuppressive therapies) (https://www.jnj.com/media-center/press-releases/stelara-ustekinumab-shows-positive-resultsin-treatment-of-systemic-lupus-erythematosus-in-phase-2-trial). Patients were randomized (3:2) to receive intravenous (IV) STELARA® 6 mg/kg or placebo (PBO) at week 0, followed by subcutaneous (SC) injections of STELARA® 90 mg or placebo every eight weeks, both in addition to standard of care therapy for 24 weeks. At week 24, patients in the placebo arm crossed over to active study agent.

Systemic lupus erythematosus and PSS have very similar cytokine profiles, and there is a significant overlap in the cytokine disturbances. Therefore, it is mechanistically reasonable to use a similar dose for PSS. An infusion loading dose of 6mg/kg of ustekinumab will be administered, followed by 90mg subcutaneous injections of ustekinumab approximately every 4 to 8 weeks. We chose this dose based on recent evidence of ustekinumab efficacy in SLE.

2.5. **Rationale for Mechanistic Samples**

The purpose of the mechanistic studies is to examine the effects of ustekinumab therapy on the mechanisms of disease in PSS and on immunocompetence. The specific aims are to determine if ustekinumab treatment produces changes in systemic immune function, as evidenced by serum levels of acute phase reactants, serum levels of autoantibodies (including but not limited to antiSSA(Ro) and anti-SSB(La) antibodies, and rheumatoid factor (RF), serum level of cytokines and chemokines, peripheral blood T and B cell subsets, and the interferon signature in peripheral blood.

Although the pathogenesis of Primary Sjogren's Syndrome remains unclear, the disease has traditionally been believed to be T cell mediated. Histology suggests that in SS T cells tend to dominate the glandular lesions early on while B cells tend to dominate the late phase of the disease [11]. However, recent evidence indicates a major contribution of B cells [12]. Such abnormalities include B-cell hyperactivity manifested through hypergammaglobulinemia and a

constellation of autoantibodies including both organ-specific antibodies and systemic autoantibodies (anti-nuclear antibodies, anti-Ro and anti-La and rheumatoid factor) [13]. Interestingly, these autoantibodies may be present before obvious salivary dysfunction develops suggesting that they are not secondary to the tissue damage.
In this context, B cell activating factor belonging to the tumor necrosis factor (TNF) family (BAFF) was found to be strikingly associated with SS [14]. In mice, BAFF overexpression is responsible for B cell compartment expansion and autoimmune manifestations such as lupus-like disease and SS which progress with age [15]. BAFF overexpression is associated with autoantibody production in primary SS. Recombinant soluble BAFF co-stimulates B cells in vitro to proliferate and secrete Ig [16] and elevated levels of BAFF were found in sera from patients with SLE and primary SS [17, 18]. In primary SS, BAFF levels were higher in patients with antiSSA or anti-SSB Abs compared to patients without detectable levels of these autoantibodies [19]. One interesting feature of SS autoimmunity in both humans and animal models of SS is the high levels of IFN, both IFN-α/β and IFN-γ [11, 20]. SS, like systemic lupus erythematosus (SLE) [21] has been designated an autoimmune disease characterized by an "IFN-signature." models, based on the elevated levels of plasma IFNs in SS patients and the reported activation of multiple IRGs/ISGs seen in microarray studies [22].

The cytokine imbalance in SS has been long described. The peripheral blood is characterized by overexpression of the interferon regulated genes [23], high immunoglobulin levels and the presence of autoantibodies indicating concomitant activation of the innate and adaptive immune system. In the exocrine glands pro- inflammatory cytokines, such as Interferon (IFN)α and γ, tumor necrosis factor (TNF) α, interleukin (IL-)12 and IL-23 along with other cytokines important in T and B cell activation and autoantibody production, such as IL-6 and B cell activating factor (BAFF), are overexpressed [24]. Interleukin-12 (IL-12) is a heterodimeric cytokine produced predominantly by activated monocytes and dendritic cells. It enhances proliferation and cytolytic activity of natural killer (NK) and T cells, and stimulates their IFN-γ production [25]. An age-dependent increase in anti-SSB/La antibodies was observed in IL-12transgenic mice and was accompanied by an increase in antinuclear antibodies [26].

3. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1. Subject Characteristics

Patients fulfilling the 2016 ACR EULAR classification criteria for PSS (see below) who are stable in terms of their PSS and are otherwise in good health. Systemic manifestations of the disease (fatigue, joint pain, peripheral neuropathy, interstitial lung disease, leukocytoclastic vasculitis, renal tubular acidosis, significant parotid swelling) will be documented, but will not be a requirement for eligibility.

a) **Number of Subjects:** The first 15 subjects who meet all eligibility criteria will be enrolled into the treatment
b) **Gender and Age of Subjects:** This study will enroll adults, male and female, aged 18-75 years old.
c) **Racial and Ethnic Origin:** Racial and ethnic origin of subjects will be monitored to reflect the diversity of our community. Because of the epidemiology of PSS, we expect more women than men and more whites (non-Hispanic) in that population. However, no subjects will be excluded based on race or ethnic origin.

d) **Vulnerable Subjects:** Vulnerable subjects will not be targeted. The stipend is appropriate to the level of inconvenience and pain of the procedure and therefore should not be coercive. Subjects will be assured that they are free to not participate or to withdraw at any time, without risking loss of present or future care that they would otherwise receive.

3.2. **Inclusion and Exclusion Criteria**

Inclusion: A subject who has met all of the following criteria is **eligible** for participation in the study:

1) Has provided written informed consent
2) Between the ages of 18-75 years (inclusive)
3) Body weight ≥ 40 kg
4) Meets the 2016 ACR EULAR criteria (score ≥4)
    a. 3 points- Labial salivary gland with focal lymphocytic sialadenitis and focus score of >1 foci/4 mm2‡
    b. 3 Points- Anti-SSA/Ro positive
    c. 1 Point- Ocular Staining Score >5 in at least 1 eye
    d. 1 Point- Schirmer's test <5 mm/5 minutes in at least 1 eye
    e. 1 Point- Unstimulated whole saliva flow rate <0.1 ml/minute
5) If taking prednisone (or equivalent corticosteroid), the dose must be ≤ 10 mg/day and stable for at least 4 weeks prior to baseline visit
6) If taking hydroxychloroquine, the dose must be stable for at least 12 weeks prior to baseline.
7) If taking a cholinergic stimulant (e.g. pilocarpine, cevimeline), the dose must be stable for at least 4 weeks prior to baseline.
8) If a female of childbearing potential, must agree to practice two highly effective forms of contraception during the study (one of which must be a barrier method) and able to continue contraception for 20 weeks after her last dose of study agent.
9) If a male of reproductive potential, must agree to practice two highly effective forms of contraception during the study (one of which must be a barrier method) and be able to continue contraception for 20 weeks after his last dose of study agent. Subject must also agree not to donate sperm up to 20 weeks after his last dose of study drug.

Exclusion: A subject who meets any of the following criteria is **disqualified** from participation in the study:

1) Has a chronic or persistent infection that might be worsened by immunosuppressive treatment (e.g., HIV, hepatitis B, hepatitis C, or tuberculosis).
2) History of untreated TB or positive QuantiFERON TB-Gold during screening period. If a subject has previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug resistant TB infection are <5%) or active TB infection, a QuantiFERON TB-Gold test need not be obtained, but a chest radiograph or other appropriate image must still be obtained if not done so within the prior 3 months.
3) History of recurrent significant infections or occurrence of a serious local infection (e.g., cellulitis, abscess) or systemic infection (e.g., pneumonia, septicemia) within twelve weeks prior to Day 0.
4) Active symptomatic infection within two weeks prior to Day 0.
5) Receipt of live vaccine within four weeks prior to Day 0.
6) History or presence of primary or secondary immunodeficiency.
7) History of any life-threatening allergic reactions to pilocarpine, latex, or any components of ustekinumab. Pilocarpine will be used to stimulate salivary flow in order to assess flow rate. Latex is a component in the needle cover for the pre-filled syringes containing the study drug.

8) Is currently pregnant or nursing.
9) Concurrent use of anticholinergic agents, such as tricyclic antidepressants (i.e. amitriptyline, nortriptyline, imipramine), first generation antihistamines (including diphenhydramine and hydroxyzine), phenothiazines, antiparkinsonian drugs, anti-asthmatic drugs (i.e. ipratroprium), or gastrointestinal (GI) medications that cause xerostomia in more than 10% of patients.
10) Treatment with any of the following within the defined period prior to the screening and Day 0 visits:
    a. 12 months for rituximab
    b. 24 weeks for cyclophosphamide
    c. 8 weeks for azathioprine, cyclosporine, methotrexate, and mycophenolate mofetil
    d. 4 weeks for intravenous immunoglobulin
    e. 4 weeks for etanercept
    f. 8 weeks for adalimumab
    g. 12 weeks for infliximab
    h. 8 weeks Golimumab
    i. 8weeks Certolizumab pegol
    j. 16 weeks Abatacept
    k. 4 weeks Tocilizumab SQ
    l. 16 weeks Tocilizumab IV
    m. 4 weeks Tofacitinib and Tofacitinib XR
11) Prednisone (or equivalent corticosteroid) > 10 mg/day.
12) A definite diagnosis of RA, SLE, systemic sclerosis, or dermatomyositis.
13) A history of alcohol or substance abuse within 5 years of baseline.
14) A history of head and neck radiation therapy, sarcoidosis, or graft-versus-host disease.
15) A history of malignancy, except for a resected basal or major squamous cell carcinoma, cervical dysplasia, or in situ cervical cancer Grade I, within the last five years.
16) Abnormal laboratory results for the following parameters at the baseline visit:
    a. Absolute neutrophil count (ANC): < 1500/mm3
    b. Platelets: < 100,000/mm3
    c. Hemoglobin: < 9 grams (g)/deciliter (dL)
    d. Serum creatinine: ≥ 2.0 mg/dL
    e. AST: > 1.5x upper limit of normal
    f. ALT: > 1.5x upper limit of normal.
17) A psychiatric disorder rendering the subject incapable of providing informed consent.
18) Plans for foreign travel to countries other than Canada or Western Europe within the treatment period.
19) Inability or unwillingness to follow the protocol
20) Any condition or treatment that, in the opinion of the investigator, places the subject at an unacceptable risk as a participant in the trial.

3.3. **Discussion of Subject Population**

The criteria were selected, firstly, in order to minimize the risks and account for the subject's safety. The criteria was also designed to select a subject population characteristic of PSS patients while eliminating as many confounding variables as able.

4. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

4.1. Method Of Subject Identification And Recruitment

The investigators have a well-defined population of PSS patients in a repository (RSRB# 35516, STUDY 0276) who have consented to contact about future research. Subjects will be first recruited from the repository. Subjects will also be recruited by the medical staff at surrounding Allergy, Immunology and Rheumatology clinics. This study may also identify potential subjects for recruitment using the CTSI Research Participant Registry, RSRB#42818.

4.2. Process of Consent

Consent will be obtained by one of the investigators and/or study coordinators. A verbal consent will be obtained over the phone in order for potential subjects to hold salivary stimulant or tear production medications they might be taking as well as lubricating eye drops prior to screening. Subjects will also be asked via the verbal script to not wear eye make-up to the screening visit. Full informed consent will be obtained at the screening visit, prior to any study procedures. Subjects will be asked to sign a separate consent form for HIV testing. Female partners of male study subjects who become pregnant during the study or during 20 weeks after their partner's last study medication dose will be asked to sign a separate consent form to remain in contact, collect information regarding the pregnancy and to contact the childbirth doctor(s).

The study will be described orally and the subject will be given the opportunity to read the consent form and ask questions. The subject may also communicate with the study team member by writing back and forth. Those wishing to consider the study further or discuss it with their family members will be given a copy for review either through mail, email, or in person. They will also be informed that they are not required to participate in the study in order to receive care or treatment for their condition and that they may terminate their consent at any point. The signed consent form will be stored in a secure location.

5. METHODS AND STUDY PROCEDURES

Schedule of Activities

Procedures	Screening	Baseline	Week 4	Week 12	Week 20	Week 24/ ET	Unscheduled
Informed Consent	x						
Eligibility / Inclusion/Exclusion	x	x					
Medical History (complete)	x						
Medical History (Interval)		x	x	x	x	x	x
Concomitant Medication	x	x	x	x	x	x	x
Vital Signs, including weight	x	x	x	x	x	x	x
Complete Physical Exam	x						
Targeted Physical Exam		x	x	x	x	x	x
Schirmer's Test*	x						
AE Assessment	x	x	x	x	x	x	x
Salivary Flow (unstimulated)	x	x				x	

Salivary Flow (stimulated)		x				x	
Efficacy Assessments (ESSPRI, SF36, VAS global)		x				x	
ESSDAI		x				x	x
UA reflex to micro (ESSDAI)		x				x	x
CBC with Diff & Chem Panel	x	x	x	x	x	x	x
ANA, Anti-La (SSB), Anti-Ro (SSA) & RF	x	x				x	
CRP, ESR, C3, C4, IgG		x		x		x	
HIV, Hep B & C	x						
Serum Pregnancy Test	x						
QuantiFERON TB-Gold	x						
Mechanistic Samples (collection)		x		x		x	
POCT Pregnancy Test (UA)		x	x	x	x		
Drug Administration		x	x	x	x		
Total Volume of Blood Drawn per visit	28mL	120mL	9mL	120mL	9mL	120mL	9mL

*Schirmer's Test will only be done on subjects who do not meet the unstimulated whole saliva flow rate criteria value at screening.

┼ Female subjects of childbearing potential will also receive a phone call 20 weeks after their last dose of IP to see if they have become pregnant.

5.1. **Treatment Dosage and Administration**

All subjects will receive an intravenous loading dose of 6 mg/kg at their baseline visit. 650mg acetaminophen and 60mg allegra will be given as premedication 30-60 minutes prior to the infusion. Subjects with a history of an allergic reaction to either allegra or acetaminophen will be given an equivalent substitute. The intravenous loading dose and premedication will be administered to the subject by qualified personnel at the clinical research center over a period of at least 1 hour. Subjects will be asked to wait an additional hour at the study site to monitor for adverse reactions. All patients will receive 90mg ustekinumab by a subcutaneous injection at all subsequent dosing visits. Subcutaneous injections do not require any premedication. Drug will be administered by qualified personnel. Subjects will be asked to wait for 15 minutes after the subcutaneous injection to monitor for adverse reactions.

5.2. **Efficacy Assessments**

Patient Questionnaires

- European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index (ESSPRI)
- Short Form-36 questionnaire (SF-36)
- VAS global assessments of symptoms of oral and eye dryness
- VAS global assessment of fatigue
- VAS global assessment of joint pain

Coordinator or PI administered assessments

- Unstimulated and stimulated salivary flow ○ Salivary flow rate will be measured using the whole saliva technique. The subject will be asked to not eat or drink for 1 hour prior to the assessment and to not take medications to increase salivary flow for

48 hours prior to the visit. All subjects will have their unstimulated whole salivary flow measured for 15 minutes followed by administration of a single 5mg dose of Pilocarpine. The 15 minute measurement of the stimulated salivary flow rate will begin one hour after administering the Pilocarpine. The weight of the samples will be recorded and used to calculate volume. An average of each sample will be calculated in order to determine flow rate.

- Schirmer's Test
  - A Schirmer's thin filter paper strip will be inserted in the lower fornix of the eye and remain there for five minutes. When the strip is removed it will be read to determine the length of the strip that is wet (in mm), which is proportional to the quantity of tears produced.
- European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI)

SS Disease Activity Labs

- Serum levels of autoantibodies, inflammation, and immune activations.
  - Autoantibodies: ANA, anti-Ro, anti-La, RF ○ Inflammatory markers: CRP, ESR
  - Markers of immunological activation : IgG, C3, and C4

Mechanistic Studies

- Serum levels of TNFα, IL-6, IL17, IL17A, IL17F, IL22, IL12, IL23, BAFF
- B and T cell subsets analysis
- Peripheral blood interferon signature

5.3. **Safety Assessments**

- Adverse events; serious adverse events
- Total infections including serious and opportunistic infections
- CBC with differential and chemistry panel
- Serum pregnancy test at screening, for applicable subjects. Urine pregnancy test before drug administration on days of dosing, for applicable subjects. 20 week follow-up phone call for applicable subjects.
- Physical exam with vital signs– complete physical exam at screening. Targeted physical exams at all other visits.

5.4. **Data & Specimen Banking for Future Research Use**

The subjects will be given the option of allowing their blood samples to be stored frozen in our secure lab for future research, if there is remaining blood after the tests for this study. These samples will only be accessed by members of the research staff. If the subjects agree, we will preserve the blood samples and use them in future studies. The future testing will not include genetic studies.

Repository

The Allergy, Immunology and Rheumatology Division has a subject repository protocol (RSRB #35516, STUDY 0267). This protocol stores all research data obtained so that it may be analyzed in conjunction with other studies. It also allows us to collect the names and private health information (PHI) of people who have taken part in our research studies and who are interested in participating in future studies. Subjects will be asked whether they are interested in being contacted for future studies and those that agree will have their PHI entered into our repository

database. This repository protocol maintains samples from subjects who agree to store for future research any samples remaining after research assays are completed.

5.5. **Costs to the Subject**

There will be no cost to the subject. Some standard of care labs may be drawn at the same time as research blood for subject convenience. These standard of care labs will charged to third party providers. This will be discussed with the subject prior to drawing blood and the subject will have the option to decline this courtesy.

5.6. **Payment for Participation**

Subjects will be paid in petty cash at the end of each completed visit. Subjects may also be given the option to be paid by check. They will be paid $75 for each completed scheduled visit. They will also be given a parking pass for each visit. Subjects will not be paid for an unscheduled visit.

5.7. **Return of Individual Research Results**

Subjects with autoimmune diseases have lab tests performed regularly to monitor their disease. Clinical labs results conducted as part of the research study or standard of care labs drawn during the study visit for subject convenience, will be included in the subject's electronic medical record. Subjects with access to Mychart will receive results at the same time as the investigator. The mechanistic sample results will not be available to the subject. There is a remote chance that a previously unknown condition could be discovered while examining a subject's blood sample or during clinical assessments. Although unlikely, if this was to occur the investigator or study team member would contact the subject and suggest an appropriate medical referral. Subjects will be notified confidentially of their HIV testing results. Subjects who are found to be HIV positive will be notified confidentially by an Investigator and offered counseling about HIV infection and notification of any partners. If the subject prefers to receive counseling regarding their HIV status from their Primary Care Physician or another doctor, then the study team will arrange this.

6. CONCOMITANT AND DISALLOWED MEDICATIONS

6.1 Concomitant

- Prednisone (or equivalent corticosteroid) must be < 10 mg/ day and stable for at least 4 weeks prior to baseline.
- Hydroxychloroquine must be stable for at least 12 weeks.
- Cholinergic stimulant (e.g. pilocarpine, cevimeline) dose must be stable for at least 4 weeks.

6.2 Disallowed

- Anticholinergic agents (such as tricyclic antidepressants, antihistamines, phenothiazines, antiparkinsonian drugs, anti-asthmatic medications, or gastrointestinal (GI) medications that cause xerostomia in more than 10% of patients).
- Rituximab within 2 years of baseline
- Cyclophosphamide within 24 weeks of baseline.
- Azathioprine, cyclosporine, methotrexate, mycophenolate mofetil within 8 weeks of baseline.
- Etanercept within 4 weeks of baseline.
- Adalimumab within 8 weeks of baseline.
- Infliximab within 12 weeks of baseline.
- Golimumab within 8 weeks of baseline.
- Certolizumab pegol within 8 weeks of baseline.

- Abatacept within 16 weeks of baseline.
- Tocilizumab SQ within 4 weeks of baseline. Tocilizumab IV within 16 weeks of baseline.
- Tofacitinib or Tofacitinib XR within 4 weeks of baseline.

7. SUBJECT WITHDRAWALS

Subjects will be advised in the written informed consent that they have the right to withdraw from the study at any time without loss of benefit or medical care to which they are entitled to. Subjects may be withdrawn from the study without their consent at the discretion of the PI and/or Sponsor for any reason including: subject non-compliance, termination of funding, worsening of the disease under study, intercurrent illness, or a positive pregnancy test. Subjects who are withdrawn from the study after the baseline visit will not be replaced. They will be asked to return for an early termination visit for final assessments.

8. STUDY DRUG ADMINISTRATION

8.1. STELARA® (Ustekinumab)

Ustekinumab is FDA approved and marketed in the US for Crohn's disease, plaque psoriasis and psoriatic arthritis. This study will examine the efficacy of ustekinumab in patients that have been diagnosed with Sjogren's Syndrome. Sjogren's Syndrome is mechanistically similar to other autoimmune diseases for which ustekinmab is approved to treat, therefore there is no significant increase in risk in using ustekinmab in this population. Outcomes of this study will not be used to support significant change in labeling of the drug, advertising of the drug and are not intended to promote or commercialize the drug. The study will be conducted in compliance with the requirements for review by and IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50). Therefore, this study is IND exempt. Drug will be supplied, packaged and labeled by Janssen Pharmaceuticals.

8.2. Accountability of Investigational Supplies

Ustekinumab will be controlled and monitored in the Investigational Drug Pharmacy. A label will be developed for the drug and placed on the syringes for the study team. Ustekinumab will be disposed of following the Investigational Drug Pharmacy destruction of study drugs by the Investigational drug service SOP after expiration and at the end of the study.

9. SAFETY AND REPORTABLE EVENTS

9.1. 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 30 days after the last dose of study drug.

For the purposes of this study, the Janssen medicinal product is:
Stelara (ustekinumab)

9.2. **Definitions**

Adverse Event (AE):
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.

Adverse Events of Special Interest:
Events that the COMPANY is actively monitoring as a result of a previously identified signal (even if non-serious).

In addition to the usual expedited reporting of all "serious" adverse events (per ICH criteria), the following AEs of special interest must also be reported to Janssen in an expedited fashion, i.e., per SAE reporting timelines, even when not serious (AE does not meet any of the ICH serious AE criteria):

- All malignancies
- All cases of active tuberculosis (TB)

Special consideration should be given to reporting adverse events that are opportunistic infections and clinically significant as serious adverse events based on the "otherwise medically significant" criteria for seriousness, when they do not meet other Serious AE ICH criteria (e.g., hospitalization).

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

Product Quality Complaint (PQC):

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

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

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.

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.]

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.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

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. For Stelara (ustekinumab), the link to the package insert is: http://www.stelarahcp.com/pdf/PrescribingInformation.pdf

9.3. **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)
- 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 Serious Adverse Event Report Form and be reported to the COMPANY **within 24 hours of becoming aware of the event.**

9.4. **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 Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death,

stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the Janssen Medicinal Product may have an effect on sperm, pregnancies in partners of male subjects exposed to a Janssen Medicinal Product will be reported by the Investigator within twenty-four hours of their knowledge of the event using the Serious Adverse Event Form. Depending on local legislation, this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

9.5. **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.

9.6. **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.

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 Transmission Methods listed below, 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 or special situation is required.

- The INSTITUTION and/or 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 correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to the COMPANY using a transmission method listed below within 24 hours of such report or correspondence being sent to applicable health authorities.

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.

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.

9.7. **Transmission Methods**
The following methods are acceptable for transmission of safety information to the COMPANY:
- Electronically via Janssen SECURE Email service (preferred) IIS-BIO-VIROGCO@its.jnj.com

- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report to 1-866-451-0371 ○ Telephone (if fax is non-functional).

9.8. **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. SPONSOR and/or PRINCIPAL INVESTIGATOR will review this listing and will resolve any discrepancies with the data provided by the COMPANY.

9.9. **Recording Adverse Events**

At each subject visit, the site study staff will assess adverse events by recording all voluntary complaints of the subject and by assessment of clinical and laboratory features. At each study visit, the subject should be questioned directly regarding the occurrence of any adverse experience since his/ her last visit.

All adverse events, whether observed by the Investigator, elicited from or volunteered by the subject, should be documented. Each adverse event will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, the relationship to investigational product, contributing factors, and any action taken with respect to the study drug.

All adverse events will be recorded from the time the subject signs consent at the screening visit until the subject completes the study or withdraws from participation. Adverse events will be followed until the event is resolved or stabilized. These events will be reported to the PI who is a physician or another physician member of the study team. They will provide the necessary referral or follow-up for appropriate medical care and safety purposes. They will also determine if the adverse event is attributable to a study procedure. Adverse events attributable to a study procedure, other than those known and indicated in the Risk Section of the protocol, will be tracked and reported to the Research Subjects Review Board (RSRB) at the time of continuing review.

9.10. **Responsibilities for Reporting Serious Adverse Events to Local Regulatory Authorities**

Serious adverse events related to study procedures that occur between the baseline visit and subject completion of or withdrawal from the study, will be reported to the Research Subjects Review Board (RSRB) within 10 days of the study team learning of the event. Adverse events that are determined by the PI and physician investigator to increase risk to study subjects will be reported to the RSRB within 2 business days of that determination and the PI will voluntarily temporarily suspend enrollment of new subjects to that group of the study until appropriate changes to ensure adequate safety for the subjects have been implemented prior to continued enrollment. The study staff will record all serious adverse experiences that occur during the study period in the appropriate source documents and/or AE log as applicable.

10. RISK ASSESSMENT

10.1. **Potential Drug-Related Risks**

In this section, the following terms are used**:**

- Very common: affects more than 1 user in 10
- Common: affects 1 to 10 users in 100
- Uncommon: affects 1 to 10 users in 1,000
- Rare: affects 1 to 10 users in 10,000

Very Common:
- None

Common:
- Headache
- Dizziness
- Diarrhea
- Nausea
- Itchiness
- Infection of the throat, airway, or sinus
- Sore throat
- Fatigue
- Redness or pain at the drug injection site
- Back, joint or muscle pain
- Vomiting

Uncommon:
- Swelling, itching, hardness, bleeding, bruising and irritation where the injection is given. Shingles (a painful rash)
- Depression
- Inflammation of tissue under the skin. Signs include warmth, swelling, redness and pain
- nasal congestion
- a form of psoriasis with raised bumps on the skin that are filled with pus
- Allergic reactions including rash or raised, itchy bumps
- tooth infections
- acne
- feeling weak
- vaginal yeast infection
- chest infection

Rare:
- Serious allergic reactions, which could be life-threatening (including low blood pressure, trouble breathing, swollen face, lips, mouth and/or throat)
- A form of psoriasis with redness and scaling of a much larger area of your skin or your entire body (erythrodermic psoriasis)
- In rare cases, symptoms such as cough, shortness of breath, and fever may also be a sign of an allergic lung reaction to Ustekinumab
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis).

<u>Infections</u>
Ustekinumab is a drug that may change how the body fights infections.

Serious infections requiring hospitalization for medical observation and /or treatment have been seen in Ustekinumab studies. Some of these infections have also been life threatening. Subjects will be advised to tell a study doctor if they have a new infection, if an infection keeps coming back, or if they experience any signs of infection such as:

- fever
- chills
- headache coughing
- congestion
- chest tightness
- shortness of breath
- flu-like symptoms
- night sweats
- nausea
- vomiting
- diarrhea
- increased frequency or burning while passing urine
- redness warmth, tenderness or swelling of skin or joint
- cold sores
- new or worsening of pain in any location
- weight loss
- tiredness

Fungal infections have been reported in subjects taking Ustekinumab. Some of these fungal infections can be serious and involve internal organs Subjects will be advised which fungal infections are common where they live and/or travel and what symptoms they might cause. Subjects will be advised to tell a study doctor and their family physician right away if they develop symptoms of such illnesses.

It is unknown if Ustekinumab may stop the development of a fever in the event of an infection and therefore make an infection harder to diagnose.

Subjects who receive Ustekinumab may also be at a greater risk for certain serious infections such as tuberculosis. Subjects will be screened for tuberculosis via QuantiFERON TB-Gold blood test prior to administration of Ustekinumab. Subjects will be encouraged to tell a study doctor if they develop:

- a cough that does not go away
- coughing up blood
- shortness of breath
- fever
- night sweats
- weight loss

<u>Cancer</u>
Cancers have been reported in subjects who have received Ustekinumab but it is unknown whether taking Ustekinumab has increased their risk for developing cancer. Because Ustekinumab may suppress the immune system, it is possible that it may increase the risk of developing cancer, including skin cancers. Subjects who have been diagnosed with psoriasis have a higher chance of developing skin cancers.

It is known that people who have had inflammatory diseases (such as, Crohn's disease, Rheumatoid Arthritis, Ulcerative Colitis etc.) for a long time and who use immunosuppressive therapies (such as, azathioprine, methotrexate etc.) for a long time have a higher risk of developing cancer. These people get cancer of the lymph nodes more often than other people.

Infusion reactions, Injection Site Reactions and Allergic Reactions

Ustekinumab may cause an allergic reaction in some people. These reactions are usually mild to moderate. The following can be symptoms of an allergic reaction:

- Fever
- Chills
- Hives
- Rash
- Swelling
- Itching
- Headache
- Nausea
- Flushing
- Light headedness
- Chest pain or tightness
- Wheezing
- Difficulty in swallowing or breathing
- Decrease or increase in blood pressure
- Anaphylaxis (life-threatening allergic reaction

Serious allergic reactions have been reported in subjects taking Ustekinumab and can be life threatening. Signs of a serious allergic reaction include skin rash, swollen face, mouth, lips, and/or throat, and trouble breathing.

Another type of allergic reaction has occurred in some subjects 1-14 days after receiving similar medications. The symptoms of this type of allergic reaction may include fever, rash, muscle aches and joint pain.

Sometimes the body can make special antibodies that may increase the risk of an allergic reaction to either Ustekinumab or other antibody medicines.

Ustekinumab may affect the response to allergy injections.

Latex allergy

The needle cover for the prefilled syringe that contains study drug contains dry natural rubber (a form of latex). This may cause allergic reactions in people who are sensitive to latex.

Cardiac and Vascular

Heart attacks and strokes have been reported in subjects who have received Ustekinumab. These events have rarely resulted in death. It is unknown whether taking Ustekinumab increases the risk for developing these events.

People who have psoriasis, and certain other inflammatory diseases, have a higher risk of heart attacks. These people have heart attaches more often than other people.

Vaccination
Subjects cannot receive most kinds of live vaccines (for example, FluMist™, varicella) during the study or for 3 months after the last study injection. Subjects also cannot receive a BCG vaccine during this study or for 12 months after the last study injection. Other kinds of vaccines, like tetanus, flu shots, and COVID vaccines that are not live are allowed. It is not known if Ustekinumab may interfere with them from working.

Other Risks
Two cases of a very rare disease of the brain, posterior reversible encephalopathy syndrome (PRES), also known as Reversible Posterior Leukoencephalopathy Syndrome (RPLS), were reported in clinical studies with Ustekinumab. PRES is generally reversible and is not caused by an infection. It is unknown whether taking Ustekinumab increases your risk of developing PRES/RPLS. Symptoms of this condition are:

- Headache
- Seizures
- Confusion
- Loss of eyesight

10.2. **Other Potential Risks** Subcutaneous
Injection/ Infusion
Injection or infusion of a medication may cause temporary discomfort or pain, bleeding, bruising or phlebitis at the site. As with any insertion of a needle into the skin, there is a small risk of infection. The risks of injection and infusion will be reduced by its performance by a trained nurse. If subjects have a mild infusion reaction (such as itchy skin or back pain) the infusion will be paused and then restarted at a slower rate. If subjects have a serious allergic reaction the infusion will be stopped immediately and emergency medications will be administered as needed. The infusion center has a crash cart that will be available during all infusions.

Infusion Pre-Medication: Allegra may cause drowsiness. Acetaminophen may cause liver damage in high doses. Part of the screening bloodwork includes liver function tests (AST/ALT) to exclude anyone who may have impaired liver function and might be susceptible to acetaminophen side effects.

Blood Drawing
Blood drawing may cause momentary discomfort or pain, bleeding, bruising, or phlebitis at the site. As with any insertion of a needle into the skin, there is a small risk of infection. Occasionally the subject may become dizzy or even faint. The risks of phlebotomy will be reduced by its performance by trained phlebotomists. Subjects will be seated during the blood draw to minimize dizziness and any risk of falling.

Salivary Flow Assessments
PSS patients who stop taking their saliva stimulants 48 hours prior to their screening visit appointment may notice that their mouth will become drier than normal. Pilocarpine may cause flushing, sweating or abdominal discomfort.

Schirmer's Test
PSS patients who stop taking their medication for dry eyes or using lubricating eye drops prior to their screening visit appointment may experience some discomfort or itchiness in their eyes or increased redness. The paper placed in the subject's eye may cause some mild irritation or discomfort. There is very little chance of infection.

Breach of Confidentiality

To reduce the risk of a breach of confidentiality, data access will be restricted as described below.

11. POTENTIAL BENEFITS TO SUBJECTS

There is no data in the treatment of Primary Sjogren's Syndrome with ustekinumab, and the potential benefits are theoretical. The information learned from this study may aide in better understanding of the disease and future treatments of it.

12. REPRODUCTIVE

The effect of Ustekinumab on human sperm or unborn babies is not known.

Pregnant women and women who are making breast milk to feed infants cannot participate in this study. Female subjects must have a blood test when beginning this study that shows they are not pregnant.

During this study and for at least -15 weeks after the last dose of study drug, women of childbearing potential and men must use proven birth control methods. The study doctor will discuss effective birth control methods with the subject.

Female study subjects will not be permitted to donate eggs during the study and for at least 15 weeks after their last dose of study drug. Male subjects will not be permitted to donate sperm during the study and for at least 15 weeks after their last dose of study drug.

Female subjects of childbearing potential will have a serum pregnancy test done at screening and must have a negative result to be eligible. Urine pregnancy tests will be done on all dosing visit days and must have a negative result prior to receiving IP dose. Male subjects with a female partner of childbearing potential will be asked to confirm their birth control methods at each visit.

Subjects who become pregnant or may have fathered a child while taking part in the study or up to 15 weeks after their last dose of study drug, will be instructed to notify the study doctor immediately. In addition, a study team member will contact female subjects of childbearing potential and male subjects with a female of childbearing potential partner by phone 15 weeks after their last dose of study drug to see if they have become pregnant.

Male study subjects who father a child during their participation in this study or within 15 weeks after their last dose of study drug, will be asked by the study doctor for their partner's permission to stay in contact with her throughout the length of the pregnancy. The partners will be asked to attend a visit to sign a separate pregnant partner consent form.

If a subject or partner of a subject becomes pregnant during participation or within 15weeks after their last dose of study drug, a member of the study team will collect information such as estimated weeks of gestation, expected delivery date, and if the pregnancy is a result of contraceptive failure. The study doctor or team member will then notify the Company on the subject's or partner's behalf. With the subject's or partner's permission, the PI will reach out to the subject's or partner's childbirth doctor to notify them that the mother or father received an investigational drug (Ustekinumab).

Female study subjects who become pregnant during their participation in this study, will stop treatment with study drug and may be withdrawn from some of the study procedures. Any subject or partner of subject who becomes pregnant during the study or at any point before 15 weeks has passed since the last dose of study drug will be followed by the study team until delivery. A telephone contact will be

made to the subject or partner within 30 days after the anticipated due date to collect information about the outcome of the pregnancy. Data collected may include, but is not limited to, information about gestational age at birth, type of delivery as well as any abnormal outcomes (i.e. spontaneous abortion, fetal death, stillborn, congenital abnormality, ectopic pregnancy). If the pregnancy results in an abnormal outcome, the study doctor will follow SAE reporting procedures. Subjects or partner's will be encouraged to contact the study staff immediately if they do experience an abnormal pregnancy outcome.

13. CONFIDENTIALIATY OF DATA AND INFORMATION STORAGE

Patients will be assigned a unique study number to identify all samples and data forms. Consent forms and data sheets will be maintained in the locked office suite of the department of Allergy, Immunology and Rheumatology or in the office of the investigator. All computer entry and networking programs will be done with coded numbers only except for an investigator restricted database which will include subject's name and identifiers. Access will be restricted to the investigator and the study team. Deidentified information may be shared with collaborators at outside institutions.

14. RESEARCH INFORMATION IN MEDICAL RECORDS

Standard of care labs, safety labs and SS disease activity labs, will be resulted in the subject's medical record and will be available to the subject. Mechanistic sample results will not be entered into the subject's medical record and will not be available to the subject.

15. DATA ANALYSIS AND MONITORING

15.1. **Planned Statistical Analysis**

This study will be used assess the effect of ustekinumab on laboratory/mechanistic parameters, and to get a rough estimate of the effect size on clinical parameters. Since ustekinumab has not been used for treatment of PSS, and this is a pilot study, the sample size of 15 subjects was picked a priori.

Each subject will perform as its own comparison, baseline vs. week 24. The analysis will also capture changes in the measured parameters at week 4, week 12, and week 20.

All endpoint data will be summarized as a single group using appropriate descriptive statistics. For continuous variables, summaries will include the mean, standard deviation or standard error, median, minimum, maximum and number of subjects. For ordinal or categorical variables, frequencies and percents will be computed. Figures, plots, or other displays will be used as necessary to better clarify the nature of the data.

We assume no dropout rate, given the small sample size and the safety profile of the drug. All 15 subjects will be analyzed as one population; we do not plan on stratifying into sub-populations, as this is a very small study. However, if there is any unplanned dropout, we will use Intent-toTreat analysis. This will include all the study subjects who received at least one dose of study drug.

Statistical analysis will be performed with IBM SPSS Statistics V.20 (SPSS, Chicago, Illinois, USA). p value<0.05 will be considered statistically significant.

15.2. **Primary Endpoint Analysis**

The primary analysis of primary endpoint, change in ESSPRI between baseline Day 0 and Week 24 will test the null hypothesis of "no ESSPRI difference between baseline and week 24" using

the ITT sample. The primary analysis of treatment effect will be conducted under the ITT principle, whereby outcome data from all subjects in the ITT population will be included in the analysis regardless of treatment compliance or duration of study participation. As such, for subjects who have no assessment at Week 24, the last observation will be carried forward for primary analysis.

15.3. **Secondary Endpoint Analysis**

For the secondary efficacy endpoints, differences will be evaluated using p-values derived from appropriate test statistics.

- Analyses analogous to those for the primary endpoint will be completed for the following:
  - Changes in SF-36 between day 0 and weeks 24.
- Linear mixed models for repeated measures will be used to evaluate treatment effect between baseline and week 24 for the continuous scale assessments measured longitudinally including:
  - Stimulated and unstimulated whole salivary flow
  - ESSDAI
  - VAS global assessments of symptoms of oral and eye dryness ○ VAS global assessment of fatigue ○ VAS global assessment of joint pain

15.4. **Safety Analysis**

All safety analyses will be performed using the entire study population. Safety analyses will include separate tabulations of AEs occurring prior to treatment and after the first dose of study agent (i.e. treatment-emergent AEs). The number of events and number (%) of participants experiencing events will be summarized by system organ class and preferred term for each treatment group and overall. In addition, AEs will be summarize by a maximum severity and relationship to study agent. Separate summaries will also be provided for SAEs, treatmentemergent AEs leading to study treatment discontinuation, and treatment-emergent AEs that may be related to disease activity.

15.5. **Immunological Analysis**

Due to the exploratory nature of the analyses, descriptive statistics and plots will be used to gain an understanding of the data prior to developing any statistical models. Means, medians, standard deviations, minimums and maximums will be computed for each continuous mechanistic/ immunologic endpoint at each time point. For dichotomous endpoints, frequencies and percents will be computed at each time point by study arm and separately for responders and nonresponders.

15.6. **Interim Analysis**

No formal analyses are planned for efficacy. Statistical analysis will be performed with IBM SPSS Statistics V.20 (SPSS, Chicago, Illinois, USA). P value <0.05 will be considered statistically significant.

15.7. **Data and Safety Monitoring**

As this is a small pilot trial, there will not be a data monitoring committee. The PI will be responsible for monitoring the progress of the study by reviewing cumulative data throughout the study. The PI will review data in real time, but at least quarterly, to ensure the validity and

integrity of the data as well as the safety and welfare of the subjects. The PI will also review an adverse event log and respond accordingly (please refer to the Adverse Events section).

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