Taltz (ixekizumab) in the Treatment of Bullous Pemphigoid

NCT# 03099538

April 26, 2018

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Document Type: Clinical Study Protocol
Version: 1.6
Date: 04/26/2018

Project Overview/Summary:

Title of study: Taltz (ixekizumab) in the Treatment of Bullous Pemphigoid (BP)

Purpose and rationale: BP is the most common auto-immune blistering disease of the skin and causes significant morbidity. BP disproportionally affects the elderly population and the current, non-specific immunosuppressive therapies, in addition to patient comorbidities, are associated with a high risk of infection related mortality. (1) Neutrophils and their proteases have been shown to play a major role in the cleavage of Bullous Pemphigoid 180 Antigen (BP180) in BP. (2) Mast cells and other cellular mediators also contribute to the pro-inflammatory environment within and surrounding blisters of BP. (3) However, the prior targeting of mast cells and basophils has resulted in unpredictable disease control. (4) Recently, IL-17 has been identified as a key driver of chronic inflammation in BP. (5) With the increasing aged population in the United States, BP will increase in prevalence and the development of a more targeted approach will be necessary to decrease morbidity and mortality. IL-17 inhibition with Taltz (ixekizumab) may have targeted, disease-modifying effects on BP.

Objectives: The primary objective is to test the effect of Taltz (ixekizumab) in the treatment of the autoimmune blistering disease, BP. The effect will be accessed by the change in blister formation, bullous pemphigoid disease activity index (BPDAI) (6), and the total dose of prednisone while on therapy. The primary endpoint is the median time from first dose of Taltz (ixekizumab) to cessation of new blister formation. Secondary objectives include the examination serological markers of BP and correlation with disease activity and the safety of Taltz (ixekizumab) in BP patients.

Population: BP patients (treatment naïve and treatment refractory) meeting clinical, histological and immunologic criteria for the disease will be enrolled.

Inclusion/Exclusion criteria:

Inclusion: Non-pregnant adults with BP.

Investigational and reference therapy:

Investigational: Taltz (ixekizumab) 80mg subcutaneous (160mg week 0, then 80mg weeks 2, 4, 6, 8, 10, & 12)(7)

Control (prior to washout): Standard of care therapy prior to washout

Rescue Therapy: Prednisone (see Supplement 4)

Study design: This is a single center, exploratory, open-label, single-arm design study of 12 patients. Treatment naïve and treatment refractory patients will be treated with Taltz (Ixekizumab). Patients who are non-responders, to physician choice standard of care, will undergo a washout period and will be enrolled in the study. The study consists of 3 epochs: screening/washout period (of at least 1 week and up to 4 weeks), treatment epoch (of 12 weeks from screen/washout), and follow up epoch (of 6 weeks). The screening and washout period will allow for treatment naïve/ new diagnosis BP to undergo evaluation and diagnosis and for treatment refractory to undergo a washout. The total duration of the study will be 18 weeks.

Primary Endpoint:

Median time from first dose of Taltz (ixekizumab) treatment to cessation of new blisters.

Secondary Endpoints:

Change in BPDAI (6) on Day 0 to Week 12

Total dose of prednisone required during each epoch

Changes in disease activity after discontinuation of Taltz (Ixekizumab) (week 12 to 18)

Clinical safety of Taltz (Ixekizumab)

Data analysis:

This study is exploratory in nature. We will access for the effects of Taltz (ixekizumab) on new blister formation as well, BDAI, and corticosteroid usage.

Introduction:

Bullous Pemphigoid (BP) is an autoimmune blistering disease that affects the elderly population. Nearly 3,000 to 5,000 new cases of BP will be diagnosed in the United States each year. (8, 9) The incidence of BP has nearly doubled in the last decade. (9) The risk of BP increases significantly with age where individuals over the age of 90, relative to those 60 or younger, are at a 300 fold increased risk of developing BP. (8) BP is characterized clinically by: skin blistering, severe pruritus or itch, and a decreased quality of life. Due to increased life expectancy in the United States, the rates of BP will likely rise in the future.

The pathogenesis of BP is due to antibodies that target the 180kD and 230kD BP proteins, BPAG2 and BPAG1 respectively. BPAG2 is felt to be the key mediator of disease activity in BP. (10) Neutrophils and their proteases have been shown to play a critical role in the cleavage of BPAG2. (2) Mast cells and other cellular mediators also contribute to the pro-inflammatory environment within and surrounding blisters of BP. (3) However, the prior targeting of mast cells and basophils has resulted in unpredictable disease control. (4) The current treatment for BP is most commonly non-specific immunosuppression, which improves the morbidity but may contribute to sepsis related mortality. (1) One study found that nearly 56% percent of individuals with BP developed infection related complications. (1) The aim of therapy is to either decrease the levels of pathogenic antibody or to decrease the inflammatory response.

The current therapeutic hierarchy, based upon randomized controlled trials (RCTs), for BP is largely reliant upon oral (up to 0.75mg/kg of prednisolone or prednisone) and topical (up to 40g of clobetasol daily) corticosteroids as well as adjuvant steroid sparing agents (azathioprine or mycophenolate mofetil). (11-14) A slow taper of oral corticosteroids is considered first-line for disease requiring systemic therapy. Therefore, the use of prednisone as a rescue therapy will allow for the assessment of Taltz (Ixekizumab) as a steroid sparing agent. Non-RCT based immunosuppression with rituximab and methotrexate have also been reported to be successful. (15, 16) Non-immunosuppressive agents including doxycycline, tetracycline, and niacinamide are reported to improve disease; however, only tetracycline and niacinamide have been compared to immunosuppressive agents. (17) There is one ongoing trial comparing doxycycline to prednisone in BP. (18)

Recently, IL-17 has been identified as a key driver of chronic inflammation in BP. (5) IL-17 inhibition may provide a much needed and more targeted treatment, with a better side effect profile. Taltz (ixekizumab) is a recombinant high-affinity fully human monoclonal antibody that targets IL-17A IgG1/kappa-class. Taltz (ixekizumab) neutralizes IL-17A and targets the Th17 pathway, which has been clearly shown to be involved in the pathogenesis of psoriasis with unprecedented responses. (7) In addition, the safety profile of Taltz (ixekizumab) is similar to that of etanercept with rare infectious complications. The clinical effects of targeting Th17 cells through IL-17A neutralization remain an unknown but attractive therapy in BP. The timing of targeting is paramount as prior studies in psoriasis often involve individuals with chronic plaque psoriasis in which there may be a larger percentage of Th17 cells. Therefore, the effects of Taltz (ixekizumab) in BP may be dependent upon the duration of disease prior to the institution of therapy.

The purpose of this study is to determine the effect of Taltz (ixekizumab) on BP patients as assessed by new blister formation, BPDAI, and prednisone usage. IL-17 inhibition with Taltz (ixekizumab) may have a targeted, disease-modifying effect on BP. This study will examine treatment naïve as well as treatment refractory BP. This will allow for the establishment of proper timing and usage of Taltz (ixekizumab) in BP, i.e. treatment naïve (acute onset) and treatment refractory disease (chronic). Additional serological disease markers, some well-established and some exploratory in nature, will be followed to correlate with disease activity.

Primary Objectives and Secondary Objectives:

Primary Objectives: The primary objective is to test the effect of Taltz (Ixekizumab) in the treatment of BP as assessed by cessation of blister formation. The primary endpoint of the study will be to determine the median time from first dose of Taltz (Ixekizumab) to cessation of new blisters.

Secondary Objectives: The secondary objectives will examine the efficacy of Taltz (Ixekizumab) by ancillary measures including BPDAI and prednisone use. Additionally, we aim to determine possible serological

predictors of response of BP to Taltz (Ixekizumab) and to assess the safety of Taltz (Ixekizumab) in BP patients.
Exploratory Objectives: Based upon prior published research, we will examine possible predictors of response using multiplex cytokine and RNA analysis. Samples will be stored at Mayo Clinic for future research.

Research Design:
This is a single center, exploratory, open-label, single-arm design study of 12 patients with BP. Treatment naïve and treatment refractory patients with BP will be treated with Taltz (Ixekizumab). Patients who are non-responders, to physician choice standard of care, will undergo a washout period and will be enrolled in the study. The washout period is 2 weeks for systemic non-immunosuppressive agents, topical steroids, and topical calcineurin inhibitors. A 4-week washout period will be used for systemic systemic immunosuppressive agents or 5 half-lives, whichever is longer, and no live vaccines should be administered within 12 weeks of the study drug. (**Table-1**) The study consists of 3 epochs: screening/washout period (of at least 1 week and up to 4 weeks), treatment epoch (of 12 weeks from screen/washout), and follow up epoch (of 6 weeks). The screening and washout period will allow for treatment naïve/ new diagnosis BP to undergo evaluation and diagnosis and for treatment refractory to undergo a washout. The total duration of the study will be 18 weeks.

The duration of treatment, 12 weeks, is based upon the maximal efficacy and dosing regimen of Taltz (Ixekizumab) in psoriasis.(7) Although psoriasis and BP are different disease processes, we would expect a response by 12 weeks of treatment. The open-label, single-arm design will allow for the assessment of the effects of Taltz (Ixekizumab) monotherapy in patients with acute and chronic disease in a relatively short time frame and will minimize study costs. This is critical as there may be a significant benefit either earlier or later in the disease course. This design will also allow for more patients to undergo targeted, serological analysis, which will provide in-vivo evidence of the pathogenesis of disease as well as the changes that occur during treatment. The open-label design of this study will have assessment bias on the part of the patient as well as the physician. The single-arm design will not allow for blinded assessment. In order to mitigate these issues, we will be using objective and validated methods of clinical assessment, which should be robust including: new blister formation, BPDAI, and prednisone usage. Additionally, the serological markers, which are secondary endpoints, will be assessed as an unbiased corollary to the primary effects of Taltz (Ixekizumab) on BP patients.

Our laboratory will perform a multiplex cytokine analysis on serum and blister fluid for Interleukin (IL)-6, -17, -22, -23 on an ELISA assay. Similar array based ELISAs will be used for Transforming Growth Factor beta (TGFb) and matrix-metalloprotease-9 (MMP-9) expression. The serum, cell pellet, and blister fluid will be stored per protocol and a single batch of samples from weeks 0, 4, 8, and 12 weeks will be run in parallel and in duplicate at the end of the study. The array-based kits are standardized and the dilutions of the serum and blister fluid will be optimized prior using the ELISA arrays. Additionally, we will perform analysis of RNA levels in the blister and serum. Finally, we will perform RNA analysis on archival biopsy tissue from each subject to correlate with the changes in the blood and serum.

Concomitant Medications:

Concomitant medications are allowed if not listed in **Table-1**. Oral corticosteroids will be allowed as a rescue medication. Stable doses of oral corticosteroids will be permitted at enrollment of the study, with a maximum dose not to exceed 20mg/day of prednisone or its equivalent. For patients on oral corticosteroids, Calcium 1200mg and Vitamin D 800 IU will be prescribed. For individuals with recurrent cellulitis or recurrent candidiasis, antimicrobials will be prescribed (see Exclusion Criteria). Dose adjustments of these medications should be avoided during the study. Drug-induced cases of BP will be excluded. Subjects who are receiving treatments known to worsen BP (angiotensin converting enzyme inhibitors & furosemide) must be on stable dose for at least 4 weeks prior to enrollment. Topical corticosteroids (TCS) are not allowed during the entirety of the study. Oral corticosteroids, as a rescue means (see Supplemental 4), will be allowed. After the screening period, the use of concomitant medication for BP in all body regions is restricted to bland emollients and other non-medicated interventions (not listed in **Table-1**) Use of bland emollients must be recorded. Preferred

emollients include Vaseline, Vanicream, and Vaniply. The definition of "bland" excludes all topical medications that contain pharmacologically active ingredients. Once the subject is screened and if the subject has intolerable blistering, scaling, and/or itching, the use of bland emollients is permitted. The use of bland emollients should be avoided during the 12 hours preceding a scheduled study visit.

Inclusion/Exclusion Criteria:

Subjects eligible for inclusion in this study have to fulfill **all** of the following criteria:

- Subjects must be able to understand and comply with the requirements of the study and communicate with the investigator. Subjects must give written, signed, and dated informed consent before any study related activity is performed. When appropriate, a legal representative will sign the informed consent according to local laws and regulation
- Both men and women must be at least 18 years of age at the time of screening
- Subjects must have clinical, histological, and serological features of BP
    - Urticarial plaques and/or vesicles and bullae
    - Characteristic eosinophilic spongiosis and/or subepidermal separation of the skin
    - Positive direct immunofluorescence (IgG and/or C3 at the basement membrane zone) or indirect immunofluorescence (IgG on the roof of salt- split skin) or positive serologies on ELISA for BPAG1 or BPAG2
- Subjects must have treatment naïve BP or treatment refractory disease, as defined by failure of at least one established treatment for BP
- Candidate for systemic therapy, defined by
    - Involvement of greater than 5% body surface area or moderate to extensive disease as defined by: the mean number of new bullae and urticarial plaques that have appeared over the course of 3 days as determined by the investigator or referring physician (moderate disease defined by > 1 and ≤ 10 new bullae and ≥ 5 urticarial plaques and extensive disease by >10 new bullae)
    - Failure of prior therapy
        - Topical treatment
        - Systemic immunosuppressant
        - Oral antibiotics and/or niacinamide

Subjects fulfilling **any** of the following criteria are not eligible for inclusion in this study. In order to ensure the recruitment of a representative sample of all eligible subjects, the investigator may apply no additional exclusions.

- Forms of BP other than classic BP (e.g. mucous membrane BP, Brunsting-Perry BP, p200 BP, p105 BP, or BP with concomitant pemphigus vulgaris
- Drug-induced BP (e.g., new onset or current exacerbation from angiotensin converting enzyme inhibitors, penicillamine, furosemide, phenacetin)
- Subjects who are receiving treatments known to worsen BP and use of penicillamine or phenacetin and those on angiotensin converting enzyme inhibitors or furosemide who have not been on a stable dose at least 4 weeks prior to enrollment.
- Ongoing use of prohibited treatments. Washout periods detailed in **Table-1**.
- Previous exposure to Taltz (Ixekizumab) or any other biologic drug directly targeting IL-17A or IL-17RA
- Use of any other investigational drugs within 5 half-lives of the investigational treatment before study drug initiation or until the pharmacodynamics effect has returned to baseline, whichever is longer
- Previous use of IL-20 monoclonal antibody
- Pregnant or nursing (lactating) women (pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test)
- Women of childbearing potential [Post-menopausal or not of child-bearing potential is defined by: 1 year of natural (spontaneous) amenorrhea or Surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. Oophorectomy alone must confirmed by follow up hormone level assessment to be considered not of child-bearing potential, defined as all women

physiologically capable of becoming pregnant, unless they are using basic methods of contraception which includes:

- Total abstinence (Periodic abstinence and withdrawal are not acceptable methods of contraception)
- Female sterilization (bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least 6 weeks before taking study treatment. Oophorectomy alone requires follow up hormone level assessment for fertility.
- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject.
- Barrier methods of contraception: condom or occlusive cap.
- Use of oral, injected or implanted hormonal methods of contraception or other forms or hormonal contraception that have complete efficacy (failure <1%). (The dose of the contraceptive should be stable for 3 months)

- Active ongoing inflammatory diseases of the skin other than BP that might confound the evaluation of the benefit of Taltz (Ixekizumab)
- Underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions) which, in the opinion of the investigator, significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy
- Investigator discretion should be used for subjects with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders
- Significant medical problems, including but not limited to the following: uncontrolled hypertension, congestive heart failure (New York Heart Association [NYHA] status of class III or IV)
- Serum creatinine level exceeding 2.0 mg/dL (176.8 µmol/L) **at screening**
- Total white blood cell (WBC) count <2,500/µL, platelets <100,000/µL, neutrophils <1500/µL or hemoglobin <8.5 g/dL, **at screening**
- Active systemic infections during the 2 weeks prior to randomization (common cold viruses not included) or any infection that reoccurs on a regular basis.
    - All patients should be specifically questioned in regards to a history of recurrent cellulitis or recurrent bacterial skin infections.
        - A history of recurrent cellulitis
            - Swab for MRSA carrier status
                - If positive, decolonization
                    - Intranasal mupirocin 2% twice daily for 5 days
                    - Chlorohexidine 2-4% wash daily for 5 days
            - Anti-streptolysin O (ASO) & Anti-DNA B (ADB) testing to be performed
                - If positive, place patient on prophylactic oral antibiotics for the duration of the study
                    - Penicillin non-allergic
                        - Penicillin VK 250mg BID (19)
                    - Penicillin allergic
                        - Clindamycin 150mg daily (20)
    - All patients should be screened for a history of oral, vaginal, or cutaneous candidiasis
        - A history of recurrent, clinically significant disease
            - Swab affected area for candida culture
                - If positive, prophylactic dosing of oral antifungals for the duration of the study
                    - 150mg fluconazole weekly (21, 22)
    - Investigator discretion should be used regarding subjects who have traveled or resided in areas of endemic mycoses, such as histoplasmosis, coccidioidomycosis or blastomycosis and for subjects with underlying conditions that may predispose them to infection, such as advanced or inadequately controlled diabetes. Due to its endemic nature in Arizona, coccidioidomycosis screening is

performed at baseline. A history of a disseminated coccidioidomycosis infection will exclude subjects.
    - Positive coccidioidomycosis Enzyme Immunoassay (EIA) IgG and/or IgM with positive complement fixation **at screening** and deemed by infectious disease to be inappropriate for therapy
        - Subjects with a positive coccidioidomycosis should undergo a full coccidioidomycosis work up and treatment should not be initiated until infectious disease specialists clear the subject.
- History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive or indeterminate QuantiFERON TB-Gold test (QFT) **at screening.**
    - Subjects with a positive QFT test may participate in the study if a full tuberculosis work up (according to local practice/guidelines) is completed within 12 weeks prior to establishes conclusively that the subject has no evidence of active tuberculosis.
    - If the presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to local country guidelines for at least 4 weeks prior to randomization.
- Past medical history of, or current infection with, human immunodeficiency virus (HIV), hepatitis B or hepatitis C prior to new diagnosis **at screening**
- History of lymphoproliferative disease and/or any known malignancy and/or history of malignancy of any organ system within the past 5 years
    - Exceptions include:
        - For skin squamous cell carcinoma in situ and/or well differentiate squamous cell carcinoma and/or basal cell carcinoma and/or actinic keratosis and/or melanoma in situ that have been treated with no evidence of recurrence
        - For the cervix carcinoma that has been removed
        - For the colon non-invasive malignant colon polyps that have been removed
- Current severe progressive or uncontrolled disease which the investigator renders the subject unsuitable for the trial or puts the subject at increased risk
- Inability or unwillingness to undergo repeated venipuncture
- Any medical or psychiatric condition which, in the investigator's opinion, would keep the subject from adhering to the protocol or completing the study per protocol
- History or evidence of ongoing alcohol or drug abuse, within the last 6 months prior to the initiation of therapy
- Plans for administration of live vaccines during the study period or in the 12 weeks prior to the initiation of therapy
- BCG vaccination within 12 months of starting the study or with 12 months after completing the study

Primary and Secondary Measures:

All efficacy assessments will be performed prior to the administration of study treatment at each visit. The recommended order and the overall outline of measurements for the efficacy assessments are described below.

Efficacy measures:

- Cessation of new blisters.
- BPDAI (6)
- Total dose of prednisone required during phases of treatment
- anti-BP180 IgG and anti-BP230 IgG levels by ELISA
- Neutrophil and eosinophil counts
- IL-6, -17, -22. -23, TGFb, and MMP-9 levels in the serum and blister fluid

Primary Outcome Measures:

Median time from first dose of Taltz (Ixekizumab) treatment to cessation of new blisters. The study subject will undergo physical examination and assessment for cessation of new blister formation via physical examination and standard full body photography.

Secondary Outcome Measures:

- Change in BPDAI (6) on day 0 to week 12.
- BPDAI on Day 0, Week 2, 4, 6, 8, 10, 12
- Total dose of prednisone required during phases of treatment
    - Treatment Epoch 1 (weeks 0-12)
- Anti-BP180 IgG and anti-BP230 IgG levels by ELISA assay at weeks 0, 4, 8, 12
- Change in neutrophil and eosinophil counts at weeks 0, 4, 8, 12
- Changes in disease activity after discontinuation of Taltz (Ixekizumab)
    - First onset of new blisters
    - BPDAI (week 12 to week 18)
- Clinical safety of Taltz (Ixekizumab) as assessed by vital signs, clinical laboratory variables, and adverse events monitoring

Exploratory Outcome Measures: Interleukin (IL)-6, -17, -22, -23, Transforming Growth Factor beta (TGFb), and matrix-metalloprotease-9 (MMP-9) expression in serum and blister fluid at weeks 0, 4, 8, 12). RNA changes in the blood, blister fluid, and archival tissue biopsy.

For more details on measures rationale see **Supplemental 1: Appropriateness of Measures**

Safety Measures:

A thorough baseline screening will be followed for all patients and is outlined in Table-2. A detailed list of the methods in which baseline screening will be performed is outlined in Supplemental 2. All blood draws and safety assessments must be performed **prior** to study treatment administration. Appropriate safety assessments (e.g., evaluation of AEs and SAEs) should be repeated after dosing with study treatment. A physical examination, including general appearance and vital signs, will be performed as indicated in Table-2. If indicated, based on medical history and/or symptoms, additional exams will be performed at the discretion of the investigator. If possible, the same member of the study site staff throughout the study will perform assessments for an individual subject. Information for all physical examinations will be included in the source documentation at the study site. Significant findings that are present prior to the subject signing informed consent will be included in the Medical History. Significant findings made after the signing of the informed consent, which meet the definition of an AE, must be recorded as an AE. Vital signs (blood pressure, pulse, height, weight) will be assessed at each physical examination as indicated in Table-2 (see Supplemental 2 for details on how to acquire vital signs). Whether action needs to be taken to address notable vital signs will be decided by the investigator, taking into account the overall status of the subject. Laboratory studies will be drawn as indicated in Table-2. Whether action needs to be taken to address notable laboratory values will be decided by the investigator, taking into account the overall status of the subject. Hematology assessments will be measured at all scheduled study visits specified in Table-2. Serum chemistry will be a comprehensive metabolic panel will be measured at all scheduled study visits specified in Table-2.

Safety Monitoring:

The occurrence of adverse events will be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when the patient volunteers them during or between visits or through physical examination, laboratory test, or other assessments. Please see Supplemental 3 for a detailed description of safety monitoring. Clinically significant abnormal laboratory values or test results will be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included determined by the Mayo Clinic Arizona and Mayo Medical Laboratory. Adverse events will be recorded in the Adverse Events Case Report Form (CRF) under the signs, symptoms or diagnosis associated with them, and severity. All adverse events will be treated appropriately. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the

outcome (see Supplemental 3). Information about common side effects already known about the investigational drug can be found in the package insert. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. The investigator will also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE. To ensure patient safety, every SAE (see Supplemental 3 for definition), regardless of suspected causality, occurring after the patient has provided informed consent and after the patient begins taking study drug and until 30 days after the patient has stopped study participation will be recorded and reported to Lilly. Any SAEs experienced after this 30-day period should only be reported to Lilly if the investigator suspects a causal relationship to the study drug. All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met. Medical and scientific judgment will be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the outcomes listed in SAE. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction. All AEs (serious and non-serious) are captured and recorded, SAEs also require individual reporting (see Supplemental 3). To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to the sponsor-investigator within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

Sample Size Computation and Power Analysis:
The sample size for this pilot study is set at 12 patients for logistical and financial reasons. This is similar in size to other exploratory studies and will provide adequate data for estimation purposes for planning future studies. With 12 patients, the study is intended to be for estimation purposes only.

Statistical Analysis Plan:
Design: This is an exploratory single center, open-label design study in approximately 12 patients. Safety of Taltz (Ixekizumab) in the treatment of the autoimmune blistering disease, BP will be evaluated. Changes in new blister formation will also be explored.
Primary Endpoint: The primary endpoint will be median time from first dose of Taltz (Ixekizumab) treatment to cessation of any new blisters.
Secondary Endpoint(s): The secondary endpoints will include change in BPDAI from day 0 to week 12, total dose of prednisone required during the therapeutic time period at weeks 0-12. Additional analysis will be performed on serological markers, disease activity after drug discontinuation, and safety monitoring. Descriptive statistics and graphical plots will be mainly used to summarize the data and estimate primary and secondary endpoints.
Primary Analysis: Calculation of the time from first dose of treatment until cessation of any new blisters will be conducted and summarized using means, standard deviations and 95% confidence intervals. Blister formation will be summarized at baseline and subsequent time points (using means, standard deviations and 95% confidence intervals). Change in blister formation (any new blisters) from baseline will be calculated by subtracting the baseline number of blisters from the number of blisters at each evaluation. Graphical displays will be produced; such as mean profile plots or bar charts.
Secondary Analyses: Analyses for secondary endpoints will also be descriptive in nature. Adjustment for multiple comparisons for the secondary analyses will not be done due to the exploratory nature of this research. Calculation of the change in BPDAI score from baseline to week 12 will be conducted and summarized using means, standard deviations and 95% confidence intervals. Graphical displays will be produced; such as mean profile plots or bar charts.

Publication Strategy:

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

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Tables:

Table-1: Prohibited treatment

Prohibited treatments[†, ‡]	**Washout period (before Randomization Visit)**
Taltz (Ixekizumab)	No prior use allowed
Any biologic drug directly targeting IL-17 or the IL-17 receptor (other than Taltz (Ixekizumab), e.g., brodalumab, secukinumab)	No prior use allowed
Other systemic immunomodulating treatments[§] [e.g., methotrexate, cyclosporine A, corticosteroids (oral, i.v., intramuscular, s.c., intra-articular, transdermal)[1], mycophenolate mofetil, azathioprine]	4 weeks
Topical treatment that is likely to impact signs and symptoms of BP (e.g., pimecrolimus, tacrolimus)	2 weeks
Live virus vaccinations	6 weeks
Non-immunosuppressive agents (tetracycline antibiotics & niacinamide)	2 weeks
Prohibited regimen of Topical Corticosteroids (TCS)	
TCS on any location on body (including face, scalp and/or genitoanal area)	2 weeks
Non-BP Therapy	**Stable period (before Randomization Visit)**
Any other treatment known to worsen BP (angiotensin converting enzyme inhibitors & furosemide)	Stable at least 4 weeks before randomization

[1]-subjects may be on up to 20mg of oral prednisone but must be on a stable dose prior to initiation of ixekizumab

[†] If the prohibited treatment is being used during the study for any indication, the subject must discontinue use of the prohibited treatment if he/she wishes to continue in the study.

[‡] In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator/qualified site staff. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment.

[§]Inhalative CS with only a topical effect (e.g., to treat asthma) are not considered "**systemic** immunomodulating treatments" and are therefore acceptable as co-medication.

Table-2: Screening and Visits

	Screening	Day 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 18
Ixekizumab		X	X	X	X	X	X	X	
Physical Exam	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X
Chest X-ray	X								
BPDAI		X	X	X	X	X	X	X	X
Photographer		X	X	X	X	X	X	X	X
ECG	X								
Venipuncture	X	X		X		X		X	
Serum Pregnancy Test	X								
anti-BMZ autoantibodies	X								
CRP-C reactive protein	X								
anti-BP230 IgG	X	X		X		X		X	
anti-BP180 IgG	X	X		X		X		X	
CMP	X					X			
CBC	X	X		X		X		X	
Quantiferon Gold	X								
Hepatitis B	X								
Hepatitis C	X								
HIV	X								
Coccidioidomycosis	X								
HbA1c	X								
Interleukin 6, 17, 22, 23		X		X		X		X	
TGFb- Transforming growth factor beta		X		X		X		X	
MMP-9 Matrix-metalloprotease-9		X		X		X		X	

Supplementals:

Supplemental 1: Appropriateness of Measures

According to expert consensus guidelines on BP, new blister formation is a defining feature of disease activity. (6) Disease control is defined as the cessation of new blister formation. The consolidation phase is defined as the phase with no new blister formation in 2 weeks and healing of lesions. Transient lesions heal within 1 week and non-transient lesions are does not heal within 1 week. Complete remission is defined by, no new blisters within 2 months, on or off therapy. Partial remission is defined by transient lesion formation. New, mild disease activity is defined by the formation of less than 3 lesions per month and a disease flare is defined by 3 or more lesions in a month. Therefore, we will be required to monitor for the time to cessation of new blisters as surrogate for disease control as well as the formation of new blisters throughout the study.

BPDAI will be used for calculation of the overall disease activity in BP. The BPDAI is a standard, objective and subjective scoring system for cutaneous disease activity and pruritus respectively in BP. The pemphigus disease activity index (PDAI) has been validated in a different auto-immune blistering disease which shares some characteristics with BP. (23) Currently, the BPDAI is undergoing validation studies and it represents the most current method of objectively scoring BP. (24) The two BPDAI indices capture disease activity and quality of life. Additionally, current studies have found that the degree of cutaneous involvement at initial diagnosis, which would be captured by the BPDAI, is predictive of the likelihood of a subsequent flare. (25) Therefore, the data collected by the BPDAI is useful in the analysis of flares in the follow up phase. The BPDAI consists of scoring various types of lesions and creates a score out of 120 (see below left). A score of greater than 56, on the objective portion, has been considered severe disease. (24) Note that we will be using 5% body surface area (BSA) of disease or moderate to extensive disease (Moderate to extensive Bullous Pemphigoid defined by the mean number of new bullae and urticarial plaques that have appeared over the course of 3 days as determined by the investigator or referring physician (moderate disease defined by > 1 and $\leq$ 10 new bullae and ≥ 5 urticarial plaques and extensive disease by >10 new bullae)) as our initial criteria for enrollment in the study. In our clinical experience, 5% BSA represents a simple, clinical cutoff for disease requiring systemic agents. Formal BPDAI will not be conducted prior to enrollment.

BPDAI					
SKIN	ACTIVITY		ACTIVITY		DAMAGE
Anatomical location	Erosions/Blisters	Number of Lesions if <3	Urticaria/ Erythema / Other	Number of Lesions if <3	Pigmentation / Other
	0 absent		0 absent		Absent 0, present 1
	1 1-3 lesions, none > 1 cm diameter		1 1-3 lesions, none >6 cm diameter		
	2 1-3 lesions, at least one > 1 cm diameter		2 1-3 lesions, at least one lesion > 6 cm diameter		
	3 >3 lesions, none > 2 cm diameter		3 >3 lesions, or at least one lesion > 10 cm		
	5 >3 lesions, and at least one >2 cm		5 >3 lesions and at least one lesion > 25 cm		
	10 >3 lesions, and at least one lesion >5 cm diameter or entire area		10 >3 lesions and at least one lesion > 50 cm diameter or entire area		
Head					
Neck					
Chest					
Left arm					
Right arm					
Hands					
Abdomen					
Genitals					
Back/Buttocks					
Left leg					
Right leg					
Feet					
Total skin	/120		/120		
MUCOSA	Erosions/Blisters				
	1 1 lesion				
	2 2-3 lesions				
	5 >3 lesions, or 2 lesions >2cm				
	10 entire area				
Eyes					
Nose					
Buccal mucosa					
Hard palate					
Soft palate					
Upper gingiva					
Lower gingiva					
Tongue					
Floor of Mouth					
Labial Mucosa					
Posterior Pharynx					
Anogenital					
Total Mucosa	/120				

BPDAI PRURITUS COMPONENT - VAS

DATE: ……..

☐**Baseline** ☐ **Beginning Consolidation**
☐**Consolidation phase** ☐**End of Consolidation**
☐**Tapering phase** ☐**Partial remission on minimal therapy**
☐**Complete remission on minimal therapy** ☐**Partial remission off therapy**
☐**Complete remission off therapy** ☐**Flare**

A. How severe has your itching been over the last 24 hours?

0 1 2 3 4 5 6 7 8 9 10
None Severe

Score out of 10 =

B. How severe has your itching been the past week?

0 1 2 3 4 5 6 7 8 9 10
None Severe

Score out of 10 =

C. How severe has your itching been in the past month?

0 1 2 3 4 5 6 7 8 9 10
None Severe

Score out of 10 =

Average INTENSITY SCORE FOR PAST MONTH = (A+B+C) = /30

OR

For BP patients with impaired mental functioning:

	No evidence of itch (no excoriations)	0
	Mild itch (isolated excoriations up to two body sites)	10
	Moderate itch (excoriations on ≥ 3 body sites, impairment of daily activity	20
	Severe itch (generalized excoriation, sleep impairment)	30
	TOTAL SCORE	/30

Adapted from: (6)

The subjective portion of the BPDAI is the pruritus component (see above right). This component is key to document as one of the major causes of morbidity in BP, in addition to the blistering, is the diffuse pruritus. Again, this test is undergoing validation currently and represents the most up to date measure for itch in BP.

Prednisone is the mainstay of therapy in BP and the dosage of prednisone correlates with disease activity. (11, 13, 18, 24) In this study, prednisone will be offered as a rescue therapy throughout the study (see Supplemental 4). This allows for examine the efficacy of Taltz (Ixekizumab) as a monotherapy, as well as its efficacy as a steroid-sparing agent. Oral corticosteroids will provide comfort, if needed, during the initiation phase of Taltz (Ixekizumab). All individuals on prednisone will be placed on Calcium 1200mg and Vitamin D 800IU.

ELISA Measurements for BPAG1 and 2 are the standard of care for diagnosis of BP. This test will be run centrally at the Mayo Medical Laboratory (MML) in Rochester Minnesota. The antibody levels, of BPAG2, correlate with disease activity. (26) Therefore, it is critical to monitor these antibody levels as this is a marker of disease severity and may be important in judging both a cutaneous and serological response to Taltz (Ixekizumab).

The exploratory variables examined in this study will aim to correlate the clinical responses in BP patients with both systemic and local changes in the cytokine milieu. The Th17 inflammatory response is a key pathway in autoimmune, inflammatory diseases. (27) The most efficacious therapies in psoriasis target the Th17 pathway with IL-17 and IL-23 blockade. (28-30) The key cytokines in the Th17 pathway are IL-6, -17, -22, -23, and TGFb. These cytokines play a complex role in the pro- and anti-inflammatory response. (27) IL-6 is a pro-inflammatory cytokine that, when present with IL-23, leads to Th17 polarization. Th17 cells release IL-17 which produces a biological cascade of inflammatory molecules including: tumor necrosis factor alpha (TNFa),

IL1-b, GM-CSF, IL-6, IL-8, and MMP-9. (31) MMP-9 is elevated in blister fluid and serum of patients with BP and IL-17 is elevated in the blister fluid. (5, 32) Treatment with topical corticosteroids has been shown to decrease lesional MMP-9 and IL-17 levels, which correlated better with clinical improvement than did the BPAG1 and 2. (33) Therefore, following these IL-6, -17, -22, -23, TGFb, and MMP-9 during therapy in treatment naïve and refractory disease may provide insight into the early and late pathogenesis in BP. Additionally, our findings may support the use of other serological biomarkers for monitoring disease activity as well as predicting therapeutic success in BP with the targeting of IL-17.

TGFb plays a particularly complex role in the pro- and anti-inflammatory response. TGFb, when present in the absence of IL-6, -17, and -23, generates T-regulatory cells. The pathogenesis of T-regulatory cell generation and the resolution phase of inflammatory diseases have remained unclear; however, recent studies suggest that there may be a process of trans-differentation of Th17 cells into T-regulatory cells. (34, 35) While the mechanism is still being deciphered, it appears that IL-17A receptor plays a key role in the formation of T-regulatory cells and it may be possible that IL-17A blockade is efficacious by not only down-regulating the Th17 response but by also up-regulating the T-regulatory response. A recent article in the journal, Nature, found that the Th17 cells themselves might be transdifferentiating into T-regulatory cells. (34) This has tremendous implications and may suggest the broad utility of IL-17A blockade in inflammatory diseases. However, more studies are needed to confirm these findings as well as the extent of plasticity of Th17 cells in inflammatory disease. If this current study is funded by Lilly, our group will be submitting for additional funding to examine the T-cell population during therapy to determine if the role that IL-17A blockade plays in T-regulatory cell formation and disease response.

In order to assess the inflammatory mileau of the blister and serum, a routine blood draw prior to drug therapy will be performed on the designated days and the serum will be stored for future use. The peripheral blood will be drawn and stored according to prior established protocols. Additionally, one active, tense blister will be drained using a needle and syringe. A minimum of 0.5cc of blister fluid and a maximum of 5cc of blister fluid will be stored via a simplified version of the serum protocol.

Our laboratory will perform a multiplex cytokine analysis on serum and blister fluid for Interleukin (IL)-6, -17, -22, -23 on an ELISA assay. Similar array based assays will be used for Transforming Growth Factor beta (TGFb) and matrix-metalloprotease-9 (MMP-9) expression. The serum and blister fluid will be stored per protocol and a single batch of samples at weeks 0, 4, 8, 12 will be run in parallel and in duplicate at the end of the study.

Finally, we will use RNA sequencing by Nanostring technology to examine the Gene expression changes in inflammatory pathways and correlate these changes with the cytokine analysis. We will examine the gene expression changes in the blister fluid, blood, and archival tissue samples. For archival tissue samples from each subject, we will use up to 100 microns of tissue to extract RNA.

Supplemental 2: Safety Measures
Baseline Screening:
A QuantiFERON® TB-Gold In-Tube assay will be performed to assess the TB status at screening for all subjects. This test will only be used to determine subject's eligibility for the trial. The test will be used to screen the subject population for latent tuberculosis infection. This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous Bacillus Calmette-Guérin vaccination or exposure to other Mycobacteria species. This test, in contrast to the purified protein derivative (PPD) skin test, is also insensitive to a booster effect since the subject is not exposed to the vaccine. The assay measures the production of interferon-gamma and presents it relative to a negative and a positive control sample. (36)

- If the test result is negative, the subject may be enrolled in the study
- If the test result is positive, the investigator should perform workup for the test result as per local procedures

    - Subjects **positive** for latent TB per workup may enter the study if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration
    - Subjects **positive** for active TB per workup are not eligible for the study
    - Subjects **negative** for TB (no signs of latent or active TB) per workup may be enrolled in the study
- If the test result is **indeterminate**, it is **recommended to repeat the test once**. If a TB workup was conducted prior to the screening the subject, results of the workup can be used to assess eligibility if the workup was conducted within 12 weeks prior to enrollment.
    - If the second test is **negative**, the subject may be enrolled
    - If the second test is **positive or indeterminate**, the investigator should perform workup as per local guidelines.
        - Subjects **positive** for latent TB per workup may enter the study if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration
        - Subjects **positive** for active TB per workup are not eligible for the study
        - Subjects **negative** for TB (no signs of latent or active TB) per workup may be enrolled in the study

According to the current CDC and United States Preventative Task Force (USPTF), HIV testing is a routine "opt-out" test. (37) Routine two-step HIV testing will be performed according to Mayo Medical Laboratories protocol. The testing involves antibody screening of HIV-1/-2. (38) If non-reactive in a low-risk group no further testing is needed. If reactive, a confirmatory test is performed with Western blot analysis. In indeterminate cases, repeat testing is performed as well as immunofluorescence and antibody confirmation testing. If a subject tests positive to HIV they will not be enrolled in the study and will be referred for management of their HIV.

- If the HIV-1/-2 antibody test result is **negative** and the patient is not suspected to have an acute HIV infection, the subject may be enrolled in the study
- If the HIV -1/-2 test result is **positive**, the investigator should perform workup for the confirmation of the result as per guidelines
    - Subjects **positive** for HIV per workup are not eligible for the study
    - Subjects **negative** for HIV per workup may be enrolled in the study
- If the test result is **indeterminate or unreadable**, **further analysis is recommended**.
    - Secondary testing may be performed with repeated testing in 3 months, immunofluorescence, HIV quantitation
    - If the second test is **negative**, the subject may be enrolled
    - If the second test is **positive or indeterminate**, the investigator should perform workup as per guidelines.
        - Subjects **positive** for HIV are not eligible
        - Subjects **negative** for HIV per workup may be enrolled in the study

Hepatitis B screening will be performed on all patients. Initial screening will be performed following the Mayo Medical Laboratory Protocol with Hepatitis B surface antigen (HBAG), Hepatitis B surface antibody (HBAB), Hepatitis B Core antibody (HBcAB) as screening tests with reflex testing with Hepatitis B DNA detection and quantitation by PCR.

Hepatitis C screening will be performed on all patients. Initial screening will be performed following Mayo Medical Laboratory Protocol with Hepatitic C antibody screening with reflex Hepatitis C RNA detection and quantitation by PCR.

Coccidioidomycosis (cocci) is a fungus that is endemic to the southwest United States, with Phoenix and Tucson having some of the highest rates of cocci in the entire world. (39) It is our standard of practice to test for

cocci prior to prescribing any immunosuppressive medications. Cocci disseminates in less than 0.5% of individuals. However, dissemination in the immune-compromised population can occur in up to half of cases. (40) Therefore, individuals with untreated cocci will be excluded from this study.
We utilize a two-step testing process that involves an enzyme immunoassay (EIA), which tests for Immunoglobulin G (IgG) and IgM for an acute cocci infection as well as a chest x-ray (CXR) to assess for pulmonary infiltrates. (41) If the EIA is positive, a second confirmatory test with a complement fixation assay will be performed. If the test is negative, but there is a high index of suspicious (i.e. a distinct rash, cough symptoms, or an abnormal CXR) repeat cocci testing should be performed in 2-3 weeks. All of these laboratory studies are done routinely at Mayo Clinic Arizona Laboratory.

- If the EIA test result is **negative**, the CXR is normal, and there are no constitutional symptoms, the subject may be enrolled in the study
- If the test result is **positive**, the investigator should perform workup for the test result as per local procedures
    - Subjects **positive** for active cocci per workup are not eligible for the study
    - Subjects **negative** for cocci per workup may be enrolled in the study
- If the test result is **indeterminate** (i.e. constitutional symptoms with a negative EIA), it is recommended to **repeat the test once in 2-3 weeks**.
    - If the second test is **negative**, the subject may be enrolled
    - If the second test is **positive or indeterminate**, the investigator should perform workup as per local guidelines.
        - Subjects **positive** for cocci are not eligible
        - Subjects **negative** for cocci per workup may be enrolled in the study

A standard 12-lead ECG will be performed at screening. The investigator/qualified site staff must review and initial the tracing. The tracing must then be stored with the subject's source documents. If the ECG findings are clinically relevant and would prevent the subject from participating in the study (taking into account the subject's overall status as well as the medication profile), the subject should be recorded a screen failure and should not receive treatment.

A serum β-hCG test will be performed in all pre-menopausal women as indicated. All pre-menopausal women who are not sterile at screening will also have a serum pregnancy test performed locally as indicated. Any woman with a confirmed positive pregnancy test during screening is not eligible for the study. A positive urine pregnancy test during the treatment periods of the study requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If the serum β-hCG test is positive, study treatment must be definitively discontinued.

Blood Pressure and Pulse:
After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic **blood pressure will be measured twice** (measurements separated by 1 to 2 minutes) using a validated device with an appropriately sized cuff and each BP measurement will be recorded. (42) In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. The average of the two measurements will be recorded. If possible, the same study site staff member throughout the study should perform assessments.

Normal blood pressure will be defined as a systolic pressure of 90 to <120 mmHg, and a diastolic blood pressure of 60 to <80 mmHg under the measurement conditions outlined above. Notable blood pressure will be hypertension (systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg) or hypotension (systolic blood pressure of <90 mmHg and/or a diastolic blood pressure of <60 mmHg). A blood pressure indicative of prehypertension (systolic blood pressure of 120 to <140 mmHg and/or diastolic blood pressure of 80 to <90 mmHg) will not be regarded as notable. (43)

A normal pulse rate will be defined as a rate of 60 to 100 beats per minute (bpm) under the measurement conditions outlined above. Notable pulse rates are a rate below 60 bpm (bradycardia) or above 100 bpm (tachycardia).

Height and Weight:
Height and body weight will be measured in indoor clothing, but without shoes. If possible, body weight assessments should be performed by the same study site staff member and using the same scale throughout the study.

Blood Draws:
Subjects should avoid smoking within the hour preceding the blood draws. All laboratory studies will be conducted within the Mayo Clinic Health Systems (Mayo Clinic Arizona and Mayo Clinic Rochester). Details on the collections, shipment of samples and reporting of results will follow Mayo Clinic's current protocols. For the identification of notable values, the Mayo Clinic reference laboratory should be consulted.

Supplemental 3: Safety Monitoring
Infection monitoring:
Study subjects will be evaluated at each visit for signs or symptoms of infection.

- Vitals signs as well as constitutional symptoms will be assessed.
- Assessment for common infections such as cellulitis as well as oral, vaginal, and cutaneous candidiasis will be performed

Steroid monitoring:
Study subject given prednisone will be assessed at each visit for signs of infection as well as elevated blood glucose.

- Unless contraindicated, all study subjects on prednisone will be placed on calcium 1200mg and vitamin D 800 IU daily.
- An endocrinologist will monitor those individuals with a history of diabetes.

Abnormal Labs:
Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Adverse Events (AE):
The severity grade/Common Toxicity Criteria (CTC) AE grade

- Mild: usually transient in nature and generally not interfering with normal activities
- Moderate: sufficiently discomforting to interfere with normal activities
- Severe: prevents normal activities

If CTCAE grading does not exist for an adverse event, use
1=mild, 2=moderate, 3=severe, 4=life-threatening, CTCAE Grade 5 (death) is not used, but is collected in other CRFs (Study Completion, Death/Survival).

AE Reporting:
Its relationship to the:

- Study treatment (no/yes), or
- Investigational treatment (no/yes), or
- The other study treatment (non-investigational) (no/yes), or

- Both or indistinguishable

The relationship will be categorized as follows:

- Unrelated- Clearly due only to extraneous causes, and does not meet criteria listed under possible or probable.
- Unlikely- Does not follow a reasonable temporal sequence from administration. May have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- Possible- Follows a reasonable temporal sequence from administration, but may have been also produced by the patient's clinical state, environmental factors or other therapies administered.
- Probable- Clear-cut temporal association with administration with improvement on cessation of investigational medicinal product or reduction in dose. Reappears upon rechallenge. Follows a known pattern of response to the investigational medicinal product.

Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
Whether it constitutes a serious adverse event(SAE)
Action taken regarding treatment

AE Action:

All adverse events should be treated appropriately. Treatment may include one or more of the following:

- No action taken (i.e. further observation only)
- [study/investigational] treatment dosage adjusted/temporarily interrupted
- [study/investigational] treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged

AE Outcome:

- All AE outcomes should be recorded (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Serious Adverse Events (SAE)

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria (Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.):

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

SAE Reporting:

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30-days after the subject stopped study participation must be reported to the Lilly as soon as

possible but no later than 5 days from learning of its occurrence according to the Mayo Clinic IRB policy. Any SAEs experienced after the 30-days period should only be reported to Lilly and the Mayo Clinic IRB if the investigator suspects a causal relationship to study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted as soon as possible but no later than 5 days from the investigator receiving the follow-up information. SAE should be followed up until resolution or until it is judged to be permanent. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information collected on the adverse event worksheet (and entered in the research database):

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event:
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

If the SAE is not previously documented in the Package Insert (new occurrence) and is thought to be related to the investigational treatment further reporting by the investigator to the Health Authority may be required

Supplemental 4: Corticosteroid Rescue

Subjects will be evaluated at baseline and at 2 week follow ups for disease activity and severity. Those individuals scoring greater than 20 on the BPDAI pruritus component- VAS will be offered oral corticosteroids as follows:

- Corticosteroid Taper
    - Baseline
        - If BPDAI pruritus component- VAS greater than 20
            - Offer oral prednisone 20mg daily
            - If patient declines prednisone for any reason other than disease control this should be documented in the eCRF
    - At 2 week follow ups
        - If BPDAI pruritus component- VAS greater than 20
            - If prednisone naive
                - Offer to continue prednisone at 20mg daily
                - If patient declines prednisone for any reason other than disease control this should be documented in the eCRF
            - If currently on prednisone 20mg daily
                - Maintain on 20mg prednisone daily
                - If patient declines or decides to stop prednisone for any reason other than disease control this should be documented in the eCRF
            - If currently on 20mg prednisone every other day
                - Offer to increase prednisone at 20mg daily
                - If patient declines or decides to stop prednisone for any reason other than disease control this should be documented in the eCRF
        - If BPDAI pruritus component- VAS less than 20
            - If at 20mg daily
                - Taper prednisone to 20mg every other day

        - If patient declines or decides to stop prednisone for any reason other than disease control this should be documented in the eCRF
    - If at tapered dose of 20mg every other day
        - Stop prednisone
        - If patient declines or decides to stop prednisone for any reason other than disease control this should be documented in the eCRF
- Calcium 1200mg and Vitamin D 800 IU will be prescribed along with oral corticosteroids and will be continued for the duration of the study once initiated