STUDY SYNOPSIS

Title:	**An Open-Label, Proof-Of-Concept, Study of Ixekizumab in the Treatment of Pyoderma Gangrenosum**
Protocol number:	
Phase:	II
Indication:	Pyoderma Gangrenosum
Study drug and comparator:	Ixekizumab SQ No comparator is used in this study.
Main Objectives:	**Primary Objective**: the proportion of subjects achieving a two point reduction in the five-point investigator global assessment (IGA) for the target ulcer from baseline to week 12 **Secondary Objectives**: -Analysis of frequency of total closure of target/total ulcers from baseline to week 12 -Analysis of change in total surface area of target/total ulcers from baseline to week 12 -Analysis of change Patient Global Assessment (PGA) from baseline until week 12 -Analysis of change in patient pain perception using 10-point visual analog scale from baseline to week 12 -Analysis of change in patient quality of life using the dermatology life quality index (DLQI) from baseline to week 12
Study design:	This is a Phase II study that will be open label and include a total of five patients who will receive the investigational product. These patients will have histological testing to rule out competing etiologies and require 3rd party adjudication/confirmation on agreement of the diagnosis. These patients will undergo 12 weeks of ixekizumab dosed every 2 weeks with follow-up until week 16.
Major inclusion/exclusion criteria:	For the complete list of inclusion/exclusion, criteria refer to Section 4. <u>Major inclusion criteria:</u> - Have a clinical diagnosis of classic PG for at least 3 months as determined by the investigator and an external reviewer on the basis of results from clinical, histological and laboratory assessments - At screening, have a PG ulcer characterized by 'item a' AND 3/5 features in 'item b' OR 2/5 features in 'item b' with support from one of the conditions listed in c. a. Stable or increasing size within 2 months preceding screening by patient report or documentation

	b. Features such as violaceous border, undermining, cribriform scarring, pustules, peristomal location c. Identifiable secondary systemic condition, such as IBD, arthritis, MGUS, noncancerous hematologic disease, streptococcal carriage, levamisole-tainted cocaine, Bruton's agammaglobulinemia - Have a PG target ulcer that has an area ≥ 2 cm^2 and $\leq$ 200 cm^2 at screening - Initial IGA of 3 or higher on a 5 point scale (0-4) <u>Major exclusion criteria:</u> 1. Any condition (e.g., psychiatric illness, severe alcoholism, or drug abuse) or situation that may compromise the ability of the subject to give written informed consent, may put the subject at significant risk, may jeopardize the subject's safety after exposure to the study drug, may confound the study results, or may interfere significantly with the subject's participation in the study 2. History of malignancy within 2 years of screening other than carcinoma in situ of the cervix or adequately treated, non-metastatic, squamous or basal cell carcinoma of the skin 3. History of seropositivity for HIV antibody; active or carrier status of hepatitis B [surface antigen (HBsAg) positive, or core antibody (anti-HBc) positive with negative surface antibody]; active hepatitis C (i.e. not treated or not cleared spontaneously, as confirmed by HCV PCR) 4. History of severe allergic or anaphylactic reaction to monoclonal antibodies 5. Systemic infection (excluding wound colonization) requiring oral antibiotics within 2 weeks of Day 0 6. History of the following treatments: a. Anti-TNF or other biologic therapies within 5 half-lives of screening b. Changes (addition, discontinuation, or changes in dose) in immunosuppressive medication (including cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, apremilast, dapsone, or corticosteroids) within 2 months of Day 0 c. Systemic corticosteroids > 20 mg per day (prednisone or prednisone equivalent) within 8 weeks of Day 0, or change in dose within 8

	weeks of Day 0. Steroids may be tapered (although not increased above the Day 0 dose) during the trial as determined by the investigator. d. Intralesional corticosteroids within 8 weeks of day 0; topical immunomodulators are permitted. e. Wound debridement within 2 weeks of Day 0; dressing changes allowed per investigator discretion. g. Systemic antibiotics within 2 weeks of Day 0 h. Live, attenuated vaccines within 3 months of Day 0; or live, seasonal-flu- or H1N1 vaccines within 2 weeks of Day 0. Note: recombinant- and/or killed vaccines are permitted. i. Hyperbaric treatment within 4 weeks of Day 0 j. Investigational drug or investigational device within 30 days or 5 half-lives of Day 0, whichever is longer k. Prior exposure to ixekizumab l. Other treatments not described above should be maintained at a stable dose and frequency throughout the study as best as possible 13. Major, general surgery within 3 months of screening, or anticipated general surgery during the study period 14. Pregnancy, plans to become pregnant during the course of the study, delivery within 3 months of screening, or breast-feeding 15. If previous use of cyclosporine or systemic corticosteroids, failure to have any stabilization/response is exclusionary. This potentially indicates the disease is not PG.
Endpoints:	• Change in IGA between baseline and week 12
Safety plan:	Enrollment and toxicities on this trial will be monitored by the principal investigator and the OSU Data and Safety Monitoring Committee (DSMC)
Study treatment:	Ixekizumab subcutaneous injection 160 mg at d0, 80 mg q 2 weeks with the last dose at week 12.
Concomitant therapy and clinical practice:	As PG is a disease responsive to immunosuppression, use of concomitant medications will be carefully monitored, and patents will be required to have stable or worsening disease on a consistent dose of immunosuppression at screening. 1. Mycophenolate mofetil, azathioprine, cyclosporine, leflunomide, dapsone, apremilast and methotrexate will be allowed, but the patient is required to have stable/worsening disease for 4 weeks prior to screening,

	while on a stable dose of immunosuppression for > 8 weeks prior to baseline. 2. Anti-TNF or other biologic therapies will not be allowed within 5 half-lives before screening, or during the study. 3. Oral corticosteroids above 20 mg daily of prednisone (or equivalent) are excluded. Lower doses are allowed provided they are prescribed at stable doses for two months prior to baseline and are 20 mg or less per day of prednisone or other equivalently-dosed corticosteroids. 4. Intralesional corticosteroids within 4 weeks of screening and during the study are not permitted 5. Other therapies that are non-immunosuppressive and non-investigational can be started or continued at physician discretion provided the medicine has no history of association with progressive multifocal leukoencephalopathy. Antibiotics may be used as needed for evidence of superinfection, positive culture results, malodor, green discharge, etc.
Statistical methods:	The primary objective of a two-point IGA decrease in the target ulcer will be analyzed as the difference from baseline, with the null hypothesis that no patients will obtain the specified improvement if the investigational product does not have efficacy. The endpoint will be analyzed using the Fisher Exact test. The secondary and exploratory objectives will be analyzed in comparison to baseline measurements and at each time point to evaluate for efficacy using either the Fisher Exact test/Chi-square test or the Wilcoxon Rank Sums test. We anticipate that the basic statistics will be completed within 1-2 months of the last patient completing his/her week 12 visit. Analyzing the interferon multiplex assay and microbiome will take longer, but will primarily be descriptive at the different time points and be analyzed by T-testing for continuous variables.

1.0 BACKGROUND INFORMATION

Pyoderma Gangrenosum (PG) (Figure 1) is a neutrophilic inflammatory condition that results in ulcerations, classically over the lower extremity, which can be disfiguring and disabling. Most often, this disease is associated with inflammatory bowel disease or hematologic diseases such as MGUS, myelodysplastic syndrome, multiple myeloma, or acute myelogeneous leukemia[1]. Less frequently, it has been associated with underlying conditions such as streptococcal infections/carriage, seronegative arthritis, hidradenitis suppurativa, and Bruton's agammaglobulinemia.

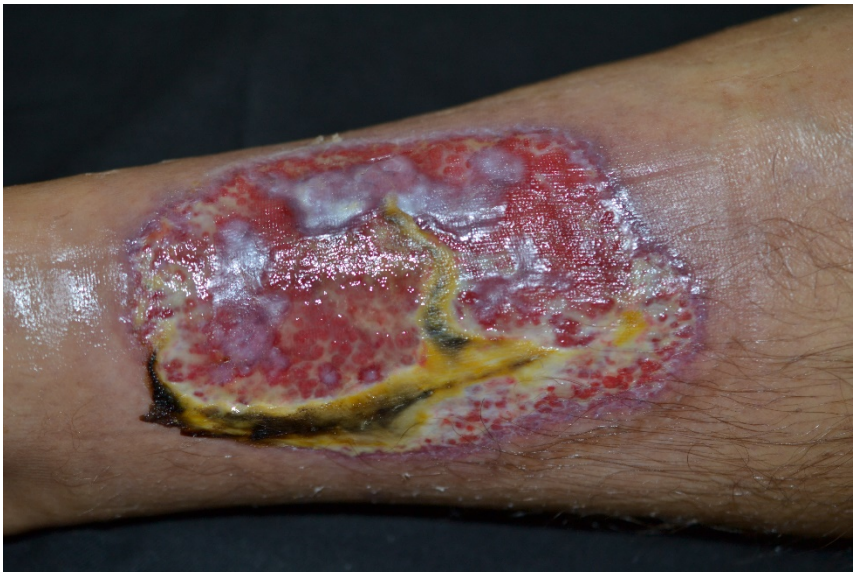


Figure 1 Classic Pyoderma Gangrenosum associated with undiagnosed and asymptomatic inflammatory bowel disease on the tibia

Unlike most dermatologic diseases, PG poses a significant mortality risk, with an 8-year mortality rate as high as 16%[1]. IL-1, IL-6, TNF, and other acute phase inflammatory cytokines have been shown to be elevated[2] and, consequently, biologics targeting the acute phase reactants such as IL-1 and TNF have demonstrated efficacy in treating pyoderma gangrenosum[3,4]. These cytokines are elevated in a wide variety of inflammatory skin diseases though. More specific cytokines, such as Interleukin-23, a critical cytokine for T-helper 17 cell (Th17) expression, has been found to be elevated in patients with pyoderma gangrenosum[5]. Furthermore, in a study of 15 patients with PG, not only was Th17 expression found to be elevated, but also regulatory T-cells were decreased[6]. Thus, there is basic science to suggest a benefit of IL-17 inhibition in patients with pyoderma gangrenosum.

Currently, PG is a disease without a preferred steroid-sparing option. Numerous options are available but no clearly effective low-risk agent is favored[7]. Corticosteroids are generally the first line treatment, patients with PG typically tend to have incurable comorbidities that are driving their disease (i.e. if immunosuppression is withdrawn, the underlying disease will worsen and PG will intensify concurrently). Further, when corticosteroids were compared with cyclosporine, neither was shown to be superior, although corticosteroids were shown to be associated with more infectious side-effects[8]. Both therapies ultimately take effect in PG similarly to how they modulate psoriasis; they are effective treatments but they are overly broad in their immunosuppression, less specific to the disease and, therefore, may present a greater than needed patient risk when compared to new biologic therapies. *Based on the chronic nature of the disease, the*

recrudescence upon stopping immunomodulating treatments and the associated mortality risk, new treatment options are urgently needed.

The proposed study is not starting at ground zero. Multiple clinical trials worldwide have successfully been completed, with others still in progress. There is an IL-1 modulator still in progress (MABp1), as well as a secukinumab investigator-initiated trial (IIT) in progress in Europe (ClinicalTrials.Gov). While the data are not published for these trials, or for a recently terminated IL-1 modulator trial (gevokizumab), several randomized controlled trials have been previously conducted. In the IBD patient, infliximab has been compared to placebo and was shown to successfully treat PG[3]. Similarly to this current proposed study, the infliximab trial did not use complete closure, but rather an investigator global scale as the primary endpoint[3]. A recently published British study compared cyclosporine to prednisolone but did not determine a difference in improvement between the groups, although more infections in the were noted in the prednisolone group[8]. Despite these trials, PG is in the same position that that psoriasis was 20 years ago before the advent of biologic agents, with clinicians choosing between two nonspecific immunosuppression agents. Thus, further treatment options are still needed.

The principle investigator is an assistant professor of dermatology at Ohio State University with a specific interest in neutrophilic disease and pyoderma gangrenosum. He has experience in clinical trials, with four currently active, industry-sponsored clinical trials and two investigator-initiated trials. His site has three research coordinators and a clinical trial fellow. Despite PG being a rare disease, the *principle investigator was the leading enroller nationwide for patients with pyoderma gangrenosum in two separate industry-sponsored clinical* investigating the biologics MABp1 and gevokizumab in 2015-2016. These trials have ended/are ending, so no competing trials are anticipated.

1.1 STATEMENT ON COMPLIANCE

This study will be conducted in compliance with this protocol, GCP, Declaration of Helsinki, and all applicable national and local regulations governing clinical studies.

2.0 STUDY OBJECTIVES AND PURPOSE

2.1 STUDY PURPOSE

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis with a multitude of presentations extending from pustules to vegetative lesions. It most consistently presents as an ulceration of the lower extremities with deep, undermining, and violaceous borders. The disease is an orphan disease without any FDA approved treatments. Classically, it is associated with inflammatory bowel disease (IBD), chronic streptococcal infections, acute myelogeneous leukemia (AML), myelodysplastic syndrome, or monoclonal gammopathy of unknown significance (MGUS). Corticosteroids and cyclosporine have been the primary treatments for patients; however, biologics also appear to be effective. The most closely studied is infliximab, an inhibitor of tumor necrosis factor (TNF)[3]. A subcutaneous injection of an interleukin-1 (IL-1) modulator recently went through a pivotal trial to obtain FDA approval for the treatment of PG; however, the trial was stopped short and the data has not been published, leaving an open horizon for finding the

ideal steroid-sparing treatment for this disease. New options are needed. IL-17 inhibition has demonstrated an effect on neutrophil numbers and function, suggesting the likely benefit of ixekizumab. Similarly, secukinumab, an alternate IL-17 inhibitory monoclonal antibody is currently being studied for the treatment of PG in an ongoing trial in Germany (ClinicalTrials.Gov).

Methodologically, this study will be conducted as an open-label, non-randomized, proof-of-concept study in patients with confirmed pyoderma gangrenosum. Patients will be initiated with psoriasis dosing of ixekizumab and will continue q2 week dosing to week 12. The primary endpoint for this study will be the proportion of subjects achieving a two-point improvement in the five-point investigator global scale (IGA). This is a simpler endpoint than the use of complete resolution of target ulcers and will allow for demonstration of benefit in a much shorter interval than complete resolution of ulcers. In addition, this endpoint may be more familiar to clinicians because dermatologists implicitly perform this grading every office visit as opposed to measuring and mathematically calculating an improvement with each visit.

2.2 OBJECTIVES

PRIMARY OBJECTIVE
The primary objective of this study is the proportion of subjects achieving a two point reduction in the five-point investigator global assessment (IGA) for the target ulcer from baseline to week 12. We hypothesize that ixekizumab, started at psoriasis dosing until ulcer closure will allow for healing of target and additional ulcers. However, 12 weeks is a short period to allow for complete ulcer resolution. Because of this, the use of an IGA endpoint was chosen as opposed to complete target ulcer healing. Thus, target and total ulcer complete healing between week 0 and 12 will be secondary objectives. There is no comparative group as this is a proof-of-concept study without a placebo.

SECONDARY OBJECTIVES
In addition to the primary objective, further secondary objectives include:
-Analysis of frequency of total closure of target and total ulcers from baseline to week 12
-Analysis of change in total surface area of target/total ulcers from baseline to week 12
-Analysis of change Patient Global Assessment (PGA) from baseline until week 12
-Analysis of change in patient pain perception using 10-point visual analog scale from baseline to week 12
-Analysis of change in patient quality of life using the dermatology life quality index (DLQI) from baseline to week 12

EXPLORATORY OUTCOMES
-Evaluation of an [IGA x Ulcer Area] scoring metric for target ulcer at each time-point
-Change in microbiome of ulcer between baseline and week 12
-Change in inflammatory markers between baseline and week 12: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), absolute neutrophils and total leukocytes in serum; IL-1, IL-6, IL-8, and TNF in target lesion tissue.
-Change in serum biomarker (if can be ascertained), depending on underlying cause (i.e. perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and anti-saccharomyces cerevisiae antibodies (ASCA) in patients with IBD, anti-streptolysin-O (ASO) in patients

with streptococcus- driven disease, or levels of monoclonal/polyclonal protein in patients with MGUS/elevated IgA levels.

3.0 STUDY DESIGN

1. Intent:

The intent of this study is to demonstrate evidence for the use of ixekizumab in the treatment of PG. Ixekizumab is an IL-17 inhibitor that is currently FDA approved for the treatment of psoriasis. There is evidence to suggest targeting the IL-17 cytokine pathway will be valuable in treating PG: IL-23, a critical cytokine for activation of Th17 and subsequent IL-17 production, has been found to be elevated in patients with pyoderma gangrenosum[5], as has the expression of Th17 cells themselves[6].

2. Location

The study will be conducted in Columbus, OH, at The Ohio State University (OSU) dermatology clinical trials center. Both the principal investigator and the OSU dermatology center have extensive experience with industry-sponsored clinical trials in PG, having completing two trials in 2015-16. At this time, we anticipate no competing trials in PG, and we estimate that 8-9 cases of classic PG are diagnosed by or referred to the investigator every year. Further, the investigator currently has 5 patients with chronic, active PG in need of new, potential treatment options. He will have additional support from an agreement with Dr. Jeff Callen at the University of Louisville, who will serve as an unbiased expert and who will have the opportunity to agree or disagree that alternate diagnoses have been properly excluded (i.e. trigger a screen failure). This is an important step because PG is a diagnosis of exclusion that even experts can misdiagnose and, subsequently, potentially publish data erroneously[9]. Having the unbiased expert agree to the diagnosis will not only add credibility to both the trial and the eventual publication, but it will also ensure validity and the homogeneity of pathogenesis among the patients enrolled. Dr. Callen will not be sent PHI. Laboratory results will be obtained through the OSU Wexner Medical Center at predefined research discounts in the budget. Complications, unforeseen events or additionally-needed hospitalizations, medicines, or office visits will be outside of the scope of the trial and will be funded by the patient's health insurance. Institutional Review Board approval will be obtained from the OSU Biomedical IRB.

3. Population

Patients with a diagnosis of pyoderma gangrenosum for at least 3 months, on a stable dose of medications listed in the inclusion and exclusion criteria, and with agreement of an external expert medical dermatologist may be enrolled in the study. Prisoners, children < 18 years of age, women who are breast-feeding, pregnant women or those desiring to become pregnant will not be included in the study population.

4. Subject Recruitment:

Patients will be recruited to this trial based on the diagnosis of pyoderma gangrenosum from the principle investigator's clinic, as well as through the use of the OSU Wexner Medical Center patient database for patients who have been seen in the past four years with an encounter diagnosis code of 686.01. Specific advertisement will be targeted towards local community dermatologists, and will consist of letters and emails for

notification of the study and referral options. Once patients are identified through the information query or through investigator records, the investigator will review the patient's chart from multiple encounters to ensure that the patient has the diagnosis of PG (per chart review), as the diagnosis can be difficult even for expert clinicians[9]. After the screening visit, an unassociated expert (Dr. Callen) will confirm the diagnosis before patients undergo a baseline visit or start the investigational medicine.

5. Treatment Groups:
We have received funding for only a small pilot study to prove a benefit from IL-17 inhibition in PG. Therefore, there is only one treatment arm. The primary outcome will be a comparison of week 12 to baseline regarding a two-point improvement in the IGA.

6. Assignment strategy:
There will be only one treatment group, so there is no assignment strategy.

7. Subjects per Treatment Group:
We anticipate consenting and screening a maximum of 8 patients will yield 5 eligible subjects who will continue on to receive the investigational product.

3.1 PRIMARY ENDPOINTS

The proportion of subjects achieving a two point reduction in the five-point investigator global assessment (IGA) for the target ulcer from baseline to week 12.

3.2 SECONDARY ENDPOINTS

-Frequency of total closure of target and total ulcers from baseline to week 12
-Change in total surface area of target and total ulcers from baseline to week 12
-Change Patient Global Assessment (PGA) from baseline until week 12
-Change in patient pain perception using 10-point visual analog scale from baseline to week 12
-Change in patient quality of life using the dermatology life quality index (DLQI) from baseline to week 12

3.3 EXPLORATORY ENDPOINT

-Evaluation of an [IGA x Ulcer Area] scoring metric for target ulcer at each time-point
-Change in microbiome of target ulcer between baseline and week 12
-Change in inflammatory markers between baseline and week 12: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), absolute neutrophils and total leukocytes in serum; IL-1, IL-6, IL-8, and TNF in target lesion tissue.
-Change in serum biomarker (if can be ascertained), depending on underlying cause (i.e. perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and anti-saccharomyces cerevisiae antibodies (ASCA) in patients with IBD, anti-streptolysin-O (ASO) in patients with streptococcus- driven disease, or levels of monoclonal/polyclonal protein in patients with MGUS/elevated IgA levels).

4.0 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 INCLUSION CRITERIA

Inclusion:

1. Have given written informed consent before participating in any study-specific activity
2. Have a clinical diagnosis of classic PG as determined by the investigator and an external reviewer on the basis of results from clinical, histological and laboratory assessments
3. Have a PG ulcer characterized by 'item a' AND 3/5 features in 'item b' OR 2/5 features in 'item b' with support from one of the conditions listed in c.
    a. Stable or increasing size within 2 months preceding screening by patient report or documentation
    b. Features such as violaceous border, undermining, cribriform scarring, pustules, peristomal location
    c. Identifiable secondary systemic condition, such as IBD, arthritis, MGUS, noncancerous hematologic disease, streptococcal carriage, levamisole-tainted cocaine, Bruton's agammaglobulinemia

4. Have a PG target ulcer that has an area ≥ 2 cm^2 and ≤ 200 cm^2 at screening
5. Initial IGA of 3 or higher on a 5 point scale (0-4) at screening 6. Age at least 18 years at screening
7. Negative quantiferon tuberculosis (TB) test, or normal chest x-ray with previous treatment for latent TB in the previous 12 months prior to screening
8. A negative pregnancy test (for females of childbearing potential) at both screening and at Day 0
9. For subjects with reproductive potential, a willingness to use methods* of contraception that will prevent the subject or the subject's partner from becoming pregnant during the study.

*Acceptable methods of contraception include proper use of condoms, cervical caps, diaphragms, hormonal contraceptive pills, contraceptive implants, intrauterine devices, or total abstinence

4.2 EXCLUSION CRITERIA

1. Any condition (e.g., psychiatric illness, severe alcoholism, or drug abuse) or situation that may compromise the ability of the subject to give written informed consent, may put the subject at significant risk, may jeopardize the subject's safety after exposure to the study drug, may confound the study results, or may interfere significantly with the subject's participation in the study
2. History of malignancy within 2 years of screening other than carcinoma in situ of the cervix or adequately treated, non-metastatic, squamous or basal cell carcinoma of the skin
3. History of seropositivity for HIV antibody; active or carrier status of hepatitis B [surface antigen (HBsAg) positive, or core antibody (anti-HBc) positive with negative surface antibody]; active hepatitis C (i.e. not treated or not cleared spontaneously, as confirmed by HCV PCR)

4. History of severe allergic or anaphylactic reaction to monoclonal antibodies
5. Systemic infection (excluding wound colonization) requiring oral antibiotics within 2 weeks of Day 0
6. History of the following treatments:
    a. Anti-TNF or other biologic therapies within 5 half-lives of screening
    b. Changes (addition, discontinuation, or changes in dose) in immunosuppressive medication (including cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, apremilast, dapsone, or corticosteroids within 2 months of Day 0
    c. Systemic corticosteroids > 20 mg per day (prednisone or prednisone equivalent) within 8 weeks of Day 0, or change in dose within 8 weeks of Day 0. Steroids may be tapered (although not increased above the Day 0 dose) during the trial as determined by the investigator.
    d. Intralesional corticosteroids within 8 weeks of day 0; topical immunomodulators are permitted.
    e. Wound debridement within 2 weeks of Day 0; dressing changes allowed per investigator discretion.
    g. Systemic antibiotics within 2 weeks of Day 0
    h. Live, attenuated vaccines within 3 months of Day 0; or live, seasonal-flu- or H1N1 vaccines within 2 weeks of Day 0. Note: recombinant- and/or killed vaccines are permitted.
    i. Hyperbaric treatment within 4 weeks of Day 0
    j. Investigational drug or investigational device within 30 days or 5 half-lives of Day 0, whichever is longer
    k. Prior exposure to ixekizumab
    l. Other treatments not described above should be maintained at a stable dose and frequency throughout the study as best as possible
13. Major, general surgery within 3 months of screening, or anticipated general surgery during the study period
14. Pregnancy, plans to become pregnant during the course of the study, delivery within 3 months of screening, or breast-feeding
15. If previous use of cyclosporine or systemic corticosteroids, failure to have any stabilization/response is exclusionary. This potentially indicates the disease is not PG.

4.3 SUBJECT WITHDRAWAL FROM TREATMENT OR FOLLOW UP

Patients will be withdrawn at his/her request at any point during the study. Patients becoming pregnant on therapy or no longer agreeing to contraception will be withdrawn from the study. Patients with SAEs will be withdrawn with the exception of patients admitted for pain control/pain management or wound infections at the discretion of the investigator, as these are both known complications of severe PG and do not necessarily represent worsening of disease.

5.0 TREATMENT OF SUBJECTS

5.1 RANDOMIZATION AND BLINDING

Subjects enrolled will receive open-label ixekizumab as such no blinding procedures occur during this study. All subjects will receive the same study regimen and as such there will be no randomization during this study.

5.2 CONCOMITANT THERAPY

5.2.1 Permitted Concomitant Therapy

As PG is a disease responsive to immunosuppression, use of concomitant medications will be carefully monitored, and patients will be required to have stable or worsening disease on a consistent dose of immunosuppression at screening.

1. Mycophenolate mofetil, azathioprine, cyclosporine, leflunomide, dapsone, apremilast and methotrexate are allowed if the dosage has been stable for >8 weeks prior to screening and the patient has had stable/worsening disease for 4 weeks prior to screening.
2. Oral corticosteroids up to 20 mg daily of prednisone (or equivalent) are allowed if the dosage has been stable for >8 weeks prior to screening and the patient has had stable/worsening disease for 4 weeks prior to screening.
3. Other therapies that are non-immunosuppressive and non-investigational may be started or continued at physician discretion. Antibiotics may be used as needed for evidence of superinfection, positive culture results, malodor, green discharge, etc.

5.2.2 Prohibited Concomitant Therapy

1. Intralesional corticosteroids are not permitted within 4 weeks prior to screening and/or during the study.
2. Anti-TNF or other biologic therapies are not permitted within 5 half-lives prior to screening or during the study.
3. Oral corticosteroids above 20mg daily of prednisone (or equivalent) are not permitted during the study.

Aside from that which is administered during the study, any chemotherapy, immunotherapy, medications associated with PML, experimental therapy, or radiotherapy are prohibited.

6.0 STUDY PROCEDURES

The schedules of events are shown in Table 6.1. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 5.0.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated.

Table 6-1. Schedule of Assessments

		Treatment Period							Follow Up
	Screening	**Baseline**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 16**
Windows (Days)	**-28 to -1**	**0**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**
Informed consent	X								
Medical History	X								
Disease History	X								
Inclusion and Exclusion Criteria	X								
Demographics	X								
Study Drug Dispensation*		X	X	X	X	X	X	X	
Confirm PG Diagnosis	X								
Investigator Global Scale of PG severity		X						X	X
VAS		X						X	X
DLQI		X						X	X
PGA		X						X	X
Lesion Assessment	X	X	X	X	X	X	X	X	X
Adverse Events	X		X	X	X	X	X	X	X
Con Meds	X		X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X	X	X
Photography	X	X			X			X	X

		Treatment Period							Follow Up
	Screening	**Baseline**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 16**
Windows (Days)	**-28 to -1**	**0**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**
General Labs if not < x mo									
Biopsy for exclusion if <12 mo	X								
CBC and Edif =1 mo	X	X		X		X		X	
Complete Metabolic Panel = 1 mo	X								
HIV = 12 mo	X								
Hepatitis Panel = 12 mo	X								
Quantiferon TB-Gold = 12 mo	X								
General Bacterial Culture	X	X			X				
Urine hCG (if of childbearing potential) = 1mo	X	X		X		X		X	
End Point Related Labs									
C-Reactive Protein**	X	X			X			X	
Erythrocyte Sedimentation Rate**	X	X			X			X	
Saccharomyces Cervisae Antibodies**	X	X			X				
Antistreptolysin-O**	X	X			X				
Rheumatoid Factor**	X	X			X				
Serum protein electrophoresis**	X	X						X	
Serum protein immunofixation**	X	X						X	
Biopsy for Analysis of Th17 and Inflammatory Cytokines ***		X						X	
Microbiome of target ulcer		X			X			X	

*Drug dispensation: 160mg at Week 0, then 80mg at subsequent dosing visits.
**End-point related labs: only repeat after baseline if baseline labs are elevated.
***Includes immunohistochemistry of tissue expression; Inflammatory cytokines include IL-1, IL-6, IL-8 and TNF

6.1 DESCRIPTION OF PROCEDURES

Informed Consent and HIPAA Authorization

Screening

Before initiating any screening or treatment activity that is not standard of care, the subject must read, understand, and sign the Institutional Review Board (IRB)-approved combined informed consent form (ICF) and HIPAA authorization to confirm his or her willingness to participate in this study and grant permission to use protected health information, respectively.

Medical History

Screening

The subject's complete history through review of medical records and by interview must be collected and recorded. Concurrent medical signs and symptoms must be documented to establish baseline severities. All medications and therapies administered within the past 14 days and a lifetime history of previous treatments must be recorded as part of the medical history. A disease history, including the date of initial diagnosis and list of prior treatments, and responses and duration of response to these treatments (if available), will also be recorded.

Adverse Events

At all visits

The accepted regulatory definition for an AE is provided in Section 7. All medical occurrences from the time of signing the informed consent that meet this definition must be recorded. SAEs occurring prior to therapy will not be considered dose-limiting toxicities (DLTs). Important additional requirements for reporting SAEs are explained in Section 7 as well.

Physical Examination & Vital Signs & Weight

At all visits

The physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, as well as examination of the skin, nose, throat, lungs, heart, abdomen, extremities, and lymphatic system.

Symptom-directed physical exams will be done during the treatment period and at the termination and safety follow-up visit.

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be measured at every visit.

Urine Pregnancy Test

Monthly (Females of Pregnancy Potential)

Pregnancy tests are required only for women with childbearing potential at screening, and Weeks 0, 4, 8, 12.

Lesion Assessment

Ulcerative lesions will be examined and measured during each study visit. The length and width of up to 5 ulcers will be measured at each study visit and the total surface area will be calculated. Additional assessment will include:

- **Photography-** Ulcers will be imaged by photography at Screening, and Weeks 0, 6, 12 and 16.
- **Biopsy-** Biopsy will be performed of an inflammatory edge of the target ulcer. A 4mm punch biopsy will be used under local anesthesia, and the site will be closed with gel foam. This procedure is considered minimal risk by the IRB. Immunohistochemistry for Th17 and related inflammatory

cytokines will be performed on biopsied tissue collected during Weeks 0 and 12. Biopsy may also be performed during screening to rule out other possible etiologies of the ulcer.

- **Swab-** General culture swabs will be performed at Screening, and Weeks 0 and 6. The microbiome analysis will be performed from swabs of the target ulcer and utilize bacterial DNA as a proxy to estimate organismal identity and abundance. Microbiome analysis will be performed at Weeks 0, 6 and 12.

Blood Draws

Routine blood draws will be performed by a phlebotomy laboratory at Screening and during Weeks 0, 4, 6, 8, and 12.

7.0 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

7.1.1 Serious Adverse Event

The terms "severe*"* and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). "Serious" is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities.

An AE should be classified as an SAE if it meets any 1 of the following criteria:

- It results in death (i.e. the AE actually causes or leads to death).
- It is life-threatening (i.e. the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs inpatient hospitalization. Exception will be admission due to inability to complete therapy as a consequence of limited clinic hours.
- It results in persistent or significant disability/incapacity (i.e. the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (i.e. may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

7.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the electronic CRF (eCRF). All SAEs also must be reported within 24 hours.

7.2.1 Adverse Event Reporting Period

The AE reporting period for this study, including SAEs, begins when the subject signs informed consent and ends with the safety follow-up visit.

7.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, clinically significant laboratory test, or other means will be recorded in the subject's medical record and on the AE eCRF and, when applicable, on an SAE/Product Compliant form.

Each recorded AE or SAE will be described by its duration (i.e. start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the investigational product (see following guidance), and any actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Fatal:	Adverse event resulted in death.
Unrelated:	Another cause of the adverse event is more plausible; a temporal sequence cannot be established with the onset of the adverse event and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Possibly Related:	There is a clinically plausible time sequence between onset of the adverse event and administration of the investigational product, but the adverse event could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible adverse event causes.
Definitely Related:	The adverse event is clearly related to use of the investigational product.

7.2.3 Pregnancy

A subject must immediately inform the investigator if the subject or subject's partner becomes pregnant from the time of consent to 30 days after the last dose of study drug. Abortion, whether therapeutic, elective or spontaneous, will be reported as an SAE.

Any female subjects receiving ixekizumab who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

7.2.4 Type and Duration of Follow-up of Subjects After Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the subject as stable, a new pyoderma gangrenosum therapy is initiated, or the subject is lost to follow-up or withdraws consent.

8.0 STATISTICAL CONSIDERATIONS

8.1 OVERVIEW

The primary objective of a two-point IGA decrease in the target ulcer will be analyzed as the difference from baseline, with the null hypothesis that no patients will obtain the specified improvement if the

investigational product does not have efficacy. The endpoint will be analyzed using the Fisher Exact test. The secondary and exploratory objectives will be analyzed in comparison to baseline measurements and at each time point to evaluate for efficacy using either the Fisher Exact test/Chi-square test or the Wilcoxon Rank Sums test. We anticipate that the basic statistics will be completed within 1-2 months of the last patient completing his/her week 12 visit. Analyzing the interferon multiplex assay and microbiome will take longer, but will primarily be descriptive at the different time points and be analyzed by T-testing for continuous variables.

8.2 ANALYSIS AND PUBLICATION PLAN:

The goal of the study will be a publication in a high-impact international dermatology journal such as the *Journal of the American Academy of Dermatology*, *JAMA Dermatology* or *British Journal of Dermatology*. We aim for a national level presentation at the American Academy of Dermatology annual meeting.

Sample Size: 8 with 3 anticipated screen failures

Proposed Enrollment and Study Completion Plan:

Total number of patients to be enrolled	8 with 3 anticipated screen failures
Number of investigative sites	1
Total study length	up to 20 weeks, including up to 4 weeks for screening
Enrollment period	Up to 6 weeks
Treatment period	12 weeks
Anticipated date of first patient visit	3/1/17
Anticipated date of the last patient visit	3/1/18
Anticipated date of final study report submission to Lilly	5/31/18
Anticipated publication date	12/31/2018

9.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

This study will be performed with support from Eli Lilly and Company. Eli Lilly and Company retains the right to terminate the study from the study site at any time. Specific circumstances that may precipitate such termination are:

- Unsatisfactory subject enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects and maintain adequate study records
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment.

9.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

The protocol, informed consent, prescribing information, and any other relevant supporting information (i.e. recruitment and advertising materials) will be submitted to the IRB for review and approval before study initiation. A letter confirming IRB approval of the protocol and informed consent, and a statement that the IRB is organized and operates according to GCP and the applicable laws and regulations **must** be forwarded to Eli Lilly and Company **before** screening subjects for the study. Amendments to the protocol must also be approved by the IRB and local regulatory agency, as appropriate, before the implementation of changes in this study.

9.2 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

A copy of the IRB-approved informed consent must be forwarded to Eli Lilly and Company for regulatory purposes. The investigator, or designee **must** explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in § 21CFR Part 50, and other applicable national and local regulations governing informed consent. Each subject must provide a signed and dated informed consent before enrollment into this study. Subjects who are incapable of providing informed consent will be ineligible for the study.
In accordance to individual local and national subject privacy regulations, the investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Eli Lilly and Company and its designees, regulatory agencies, and IRBs. Eli Lilly and Company will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

9.3 RECORD RETENTION

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each FDA Form 1572, IRB approval letters, signed ICFs, drug accountability records, SAE forms transmitted to Eli Lilly and Company, subject files (source documentation) that substantiate entries in eCRFs, all relevant correspondence and other documents pertaining to the conduct of the study.

An investigator shall retain records for a period of at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The investigator must notify Eli Lilly and Company and obtain written approval from Eli Lilly and Company before destroying any clinical study records at any time. Eli Lilly and Company will inform the investigator of the date that study records may be destroyed or return to Eli Lilly and Company.

Eli Lilly and Company must be notified in advance of, and Eli Lilly and Company must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes

to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Eli Lilly and Company to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

9.4 PROTOCOL AMENDMENTS

The investigators will initiate any change to the protocol in a protocol amendment document. Prior to IRB submission, this will be reviewed by Eli Lilly and Company. The amendment will be submitted to the IRB together with, if applicable, a revised model ICF. Additionally under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised ICF confirming willingness to remain in the trial.

9.5 PUBLICATION OF STUDY RESULTS

Eli Lilly and Company may use the results of this clinical study in registration documents for regulatory authorities in the United States or abroad. The results may also be used for papers, abstracts, posters or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by the OSU investigators. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, Eli Lilly and Company reserves the right to preview all manuscripts and abstracts related to this study, allowing Eli Lilly and Company sufficient time to make appropriate comments before submission for publication.

GENERAL INVESTIGATOR RESPONSIBILITIES

The principal investigator must ensure that:

1. He or she will personally conduct or supervise the study.
2. His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Delegation of Authority Log.
3. The study is conducted according to the protocol and all applicable regulations.
4. The protection of each subject's rights and welfare is maintained.
5. Signed and dated informed consent and permission to use protected health information are obtained from each subject before conducting nonstandard of care study procedures. If a subject or subject's legal guardian withdraws permission to use protected health information, the investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no further data be collected from the subject.
6. The consent process is conducted in compliance with all applicable regulations and privacy acts.
7. The IRB complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
8. Any amendment to the protocol is submitted promptly to the IRB.
9. Any significant protocol deviations are reported to Eli Lilly and Company and the IRB according to the guidelines at each study site.
10. All IND Safety Reports are submitted promptly to the IRB.
11. All SAEs are reported to Eli Lilly and Company Drug Safety/Designee within 24 hours of knowledge and to the IRB per their requirements.

10.0 REFERENCES

1. Binus AM, Qureshi AA, Li VW, Winterfield LS. Pyoderma gangrenosum: A retrospective review of patient characteristics, comorbidities and therapy in 103 patients. *Br J Dermatol*. 2011;165(6):1244-1250.
2. Marzano A V, Ceccherini I, Gattorno M, et al. Association of pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH) shares genetic and cytokine profiles with other autoinflammatory diseases. *Medicine (Baltimore)*. 2014;93(27):e187.
3. Brooklyn TN, Dunnill MGS, Shetty A, et al. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. *Gut*. 2006;55(4):505-509.
4. Kolios AGA, Maul JT, Meier B, et al. Canakinumab in adults with steroid-refractory pyoderma gangrenosum. *Br J Dermatol*. 2015;173(5):1216-1223.
5. Guenova E. Interleukin 23 Expression in Pyoderma Gangrenosum and Targeted Therapy With Ustekinumab. *Arch Dermatol*. 2011;147(10):1203.
6. Caproni M, Antiga E, Volpi W, et al. The Treg/Th17 cell ratio is reduced in the skin lesions of patients with pyoderma gangrenosum. *Br J Dermatol*. 2015;173(1):275-278.
7. Al Ghazal P, Dissemond J. Therapy of pyoderma gangrenosum in Germany: results of a survey among wound experts. *J Dtsch Dermatol Ges*. 2015;13(4):317-324.
8. Ormerod AD, Thomas KS, Craig FE, et al. Comparison of the two most commonly used treatments for pyoderma gangrenosum: results of the STOP GAP randomised controlled trial. *BMJ*. 2015;350:h2958.
9. Weenig RH, Davis MDP, Dahl PR, Su WPD. Skin ulcers misdiagnosed as pyoderma gangrenosum. *N Engl J Med*. 2002;347(18):1412-1418.

Appendix 1 VAS

Visual Analogue Scale

What has been the typical level of pain over the past 24 hours, where 0 equals no pain and 10 equals the most pain you have ever experienced?

Make a mark on the line which best correlates with your pain level.

Appendix 2 DQLI

DERMATOLOGY LIFE QUALITY INDEX

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ⇛ one box for each question.

1. Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?

Very much ❒
A lot ❒
A little ❒
Not at all ❒

2. Over the last week, how **embarrassed** **self conscious** have you been because skin?

Very much ❒ or
A lot ❒ of your
A little ❒
Not at all ❒

3. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?

Very much ❒
A lot ❒
A little ❒
Not at all ❒
Not relevant ❒

4. Over the last week, how much has your skin influenced the **clothes** you wear?

Very much ❒
A lot ❒
A little ❒
Not at all ❒
Not relevant ❒

5. Over the last week, how much has your skin affected any **social** or **leisure** activities?

Very much ❒
A lot ❒
A little ❒
Not at all ❒
Not relevant ❒

6. Over the last week, how much has your skin made it difficult for you to do any **sport**?

Very much ❒
A lot ❒
A little ❒
Not at all ❒

Not relevant ❒

7. Over the last week, has your skin prevented you from **working** or **studying**?

Yes ❒
No ❒
Not relevant ❒

If "No", over the last week how much has your skin been a problem at **work** or **studying**?

A lot ❒
A little ❒
Not at all ❒

8. Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?

Very much ❒
A lot ❒
A little ❒
Not at all ❒
Not relevant ❒

9. Over the last week, how much has your skin caused any **sexual difficulties**?

Very much ❒
A lot ❒
A little ❒
Not at all ❒
Not relevant ❒

10. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?

Very much ❒
A lot ❒
A little ❒
Not at all ❒
Not relevant ❒

Please check you have answered EVERY question. Thank you.

Appendix 3 Investigator Global Assessment

INVESTIGATOR'S GLOBAL ASSESSMENT (IGA)

How you would assess the Subject's current level of pyoderma gangrenosum disease activity?

☐ None (0)

☐ Mild (1)

☐ Moderate (2)

☐ Severe (3)

☐ Extreme (4)

Grade	Improvement from Baseline
0	Total resolution of ulcers with no sign of active PG
1	Almost completely healed ulcers with only minimal signs of active PG
2	Evidence of ulcer healing which involves >50% of ulcer/margin
3	Evidence of ulcer healing which involve 25-50% of ulcer/margin
4	Evidence of ulcer healing which involves <25% of ulcer/margin
5	No evidence of ulcer healing

Appendix 4 Lesion Assessment

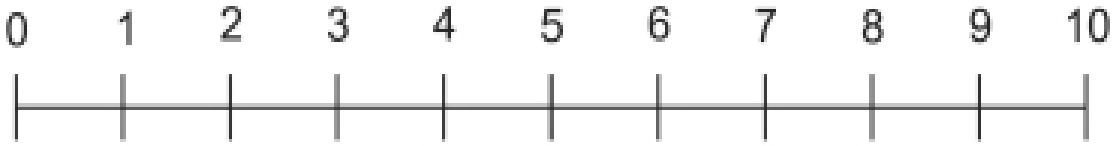
PG Lesion #	Location and Description
1	
2	
3	
4	
5	

Lesion #	1	2	3	4	5
Length (cm)					
Width (cm)					
Surface Area (cm^2)					

Appendix 5 Patient Global Assessment

Patient Global Assessment

How do you feel your pyoderma gangrenosum is doing overall, where 0 equals remission of disease and 10 equals very severe disease?



Make a mark on the line which best correlates with your disease severity.

Protocol: Taltz for Pyoderma Gangrenosum,
PI: Dr. Benjamin Kaffenberger
Protocol number: 2017H0045
Trial Type: OSU-IIT
Date document written: May 14, 2018
End of Study Report

Summary of Patients Screened/Enrolled

Pt	Age	Sex	Comorbidity	Disease length	Previous Treatments	Concomitant Treatments	Enrolled?
01	62	M	MGUS	2yrs	Cyclosporine, gevokizumab, prednisone, RA-18C3	ASA, atorvastatin, carvedilol, cilostazol, clopidogrel, mupirocin, omeprazole, oxycodone, prednisone, spironolactone, triamcinolone, Bactrim DS.	Yes
02	23	M	Bruton's agammaglobulinemia	2yrs	Prednisone, gevokizumab	Ibuprofen, vancomycin, Zosyn, morphine, Levaquin, Motrin, Benadryl, ampicillin, APAP, prednisone, Hizentra, Claritin D, Asmanex, tramadol, Paxil, omeprazole	Yes
03	55	F	+ASO, minor MGUS	20yrs	Debridement, prednisone, vein ablation	Tramadol, Zosyn, dilaudid, vancomycin, cefepime, KCl, Hylenex, gadoterate meglumine, minocycline, senokot, naproxen, morphine, metronidazole, heparin, Ca-VitD, docusate, pentoxifylline, maxipime, APAP, doxycycline, prednisone	Yes
04	49	F	IgA vasculitis	3yrs	Debridement, dapsone, MMF, fluocinonide, silversulfadiazene		No

05	58	M	Presumptive Crohns (based on Prometheus testing)	50yrs	Skin grafting, hyperbaric tx, debridement, collagen/silver dressings, mafenide cream	Lipitor, dexamethasone, Benadryl, Allegra, Lopid, Norco, Combivent, Syntroid, multiVit, probiotic, Januvia, Cozaar, mafenide, Metformin, Actos, Dakins soln, APAP, Immodium, Flonase, lidocaine 1% inj, fluconazole, meropenem, docusate-senna, GoLytley, daptomycin, vancomycin, Alteplase, metronidazole, MgSO4, heparin, Lispro, gadoterate meglumine, dilaudid,	Yes

1.1 PRIMARY ENDPOINTS

The proportion of subjects achieving a two point reduction in the five-point investigator global assessment (IGA) for the target ulcer from baseline to week 12.

Pt	Baseline IGA	Completion IGA	Notes (or completion wk)
01	3	3	
02	3	N/A (not captured at Wk 2)	Lost to FU after Wk 2
03	3	4	EOT visit at Week 6
05	4	4	EOT visit at Week 6
Mean	3.25	3.67	

1.2 SECONDARY ENDPOINTS

-Frequency of total closure of target and total ulcers from baseline to week 12

Pt	Closure of Target?	Closure of Any?	Notes (or completion wk)

01	No	No	
02	No	No	Lost to FU after Wk 2
03	No	No	ET visit at Week 6
05	No	No	ET visit at Week 6
Mean	No	No	

-Change in total surface area of target/total ulcers from baseline to week 12

Pt	Baseline Area	Completion Area	Notes (or completion wk)
01	14.56 cm^2	19.38 cm^2	
02	2.28 cm^2	3.96 cm^2	Lost to FU after Wk 2
03	23.4 cm^2	41.4 cm^2	ET visit at Week 6
05	20.48 cm^2	32 cm^2	ET visit at Week 6
Mean	15.18 cm^2	24.19 cm^2	

-Change Patient Global Assessment (PGA) from baseline until week 12

Pt	Baseline PGA	Completion PGA	Notes (or completion wk)
01	3	3	
02	3	N/A (not captured at Wk 2)	Lost to FU after Wk 2
03	8	7	ET visit at Week 6
05	10	6	ET visit at Week 6
Mean		5.33	

-Change in patient pain perception using 10-point visual analog scale from baseline to week 12

Pt	Baseline Pain VAS	Completion Pain VAS	Notes (or completion wk)
01	6	6	
02	5	N/A (not captured at Wk 2)	Lost to FU after Wk 2

03	10	8	ET visit at Week 6
05	4.5	4	ET visit at Week 6
Mean	6.37	6	

-Change in patient quality of life using the dermatology life quality index (DLQI) from baseline to week 12

Pt	Baseline DLQI	Completion DLQI	Notes (or completion wk)
01	6	7	
02	3	3	Lost to FU after Wk 2
03	15	17	ET visit at Week 6
05	18	6	ET visit at Week 6
Mean	10.5	5.75	

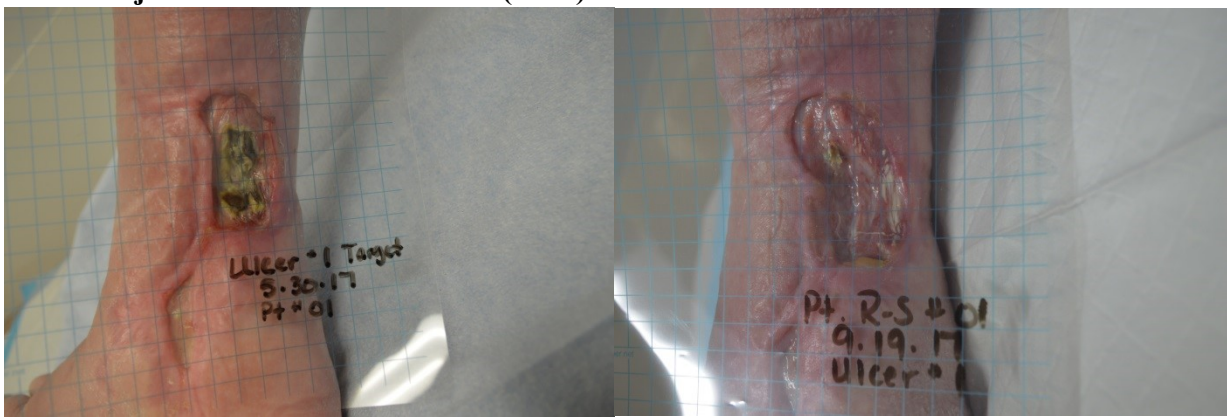
1.3 EXPLORATORY ENDPOINT

-Evaluation of an [IGA x Ulcer Area] scoring metric for target ulcer at each time-point
-Change in microbiome of ulcer between baseline and week 12
-Change in inflammatory markers between baseline and week 12 – C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), absolute neutrophils, total leukocytes, IL-1, IL-6, IL-8, and TNF in serum.
-Change in serum biomarker (if can be ascertained), depending on underlying cause (i.e. perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and anti-saccharomyces cerevisiae antibodies (ASCA) in patients with IBD, anti-streptolysin-O (ASO) in patients with streptococcus- driven disease, or levels of monoclonal/polyclonal protein in patients with MGUS/elevated IgA levels.

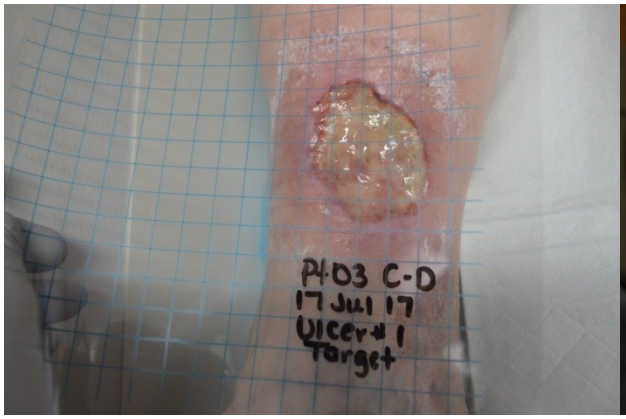
Due to few patients and only one patient completing a full 12 weeks of the study, the exploratory endpoints were not further assessed and rather nanostring technology was performed to evaluate whether there were gene expression markers of the biopsy prepost treatment in the skin demonstrating diminished inflammatory pathways. Data attached. Unfortunately, there were very few genes showing consistent changes in regulation and of those, the change in expression was small.

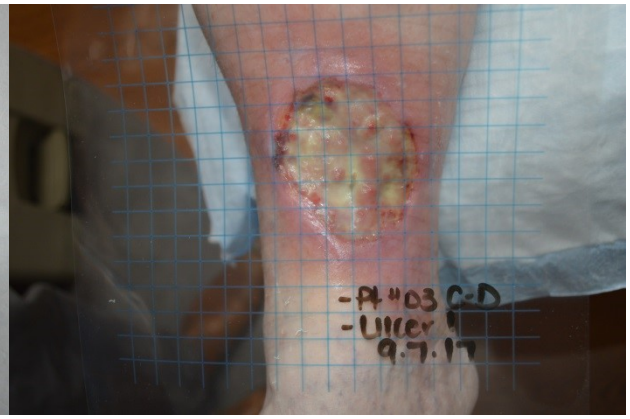
Clinical Image and Timeline:
(Note: As Subject 02 only completed visit 2, there are no photographs to compare to baseline)

BASLINE **Subject 01** **EOT (W16)**

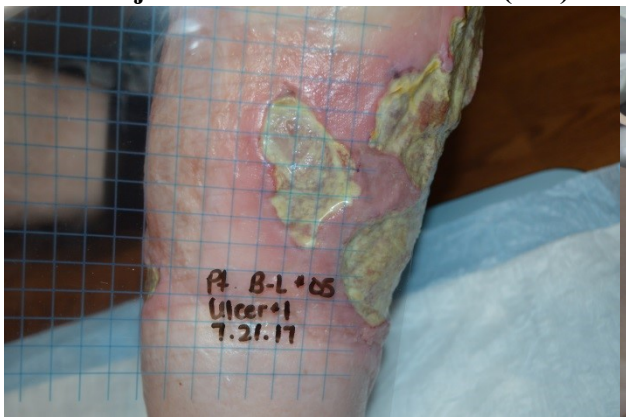


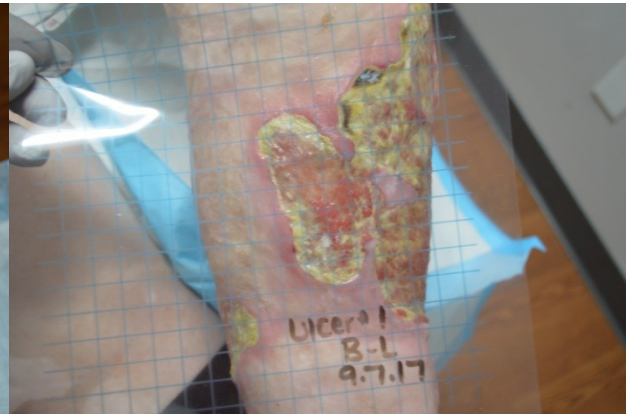
BASLINE **Subject 03** **EOT (W6)**





BASLINE **Subject 05** **EOT (W6)**





ANALYSIS AND PUBLICATION PLAN:

The goal of the study will be a publication in a high-impact international dermatology journal such as the *Journal of the American Academy of Dermatology*, *JAMA Dermatology* or *British Journal of Dermatology*. We aim for a national level presentation at the American Academy of Dermatology annual meeting.

Sample Size: 5

Proposed Enrollment and Study Completion Plan:

Total number of patients to be enrolled	5
Number of investigative sites	1
Total study length	16 weeks
Enrollment period	Up to 6 weeks
Treatment period	12 weeks
Anticipated date of first patient visit	3/1/17
Anticipated date of the last patient visit	3/1/18
Anticipated date of final study report submission to Lilly	5/31/18
Anticipated publication date	12/31/2018

STUDY SYNOPSIS

Study Synopsis:

Title:	**An Open-Label, Proof-Of-Concept, Study of Ixekizumab in the Treatment of Pyoderma Gangrenosum**
Protocol number:	
Phase:	II
Indication:	Pyoderma Gangrenosum
Study drug and comparator:	Ixekizumab SQ No comparator is used in this study.

Main Objectives:	**Primary Objective**: the proportion of subjects achieving a two point reduction in the five-point investigator global assessment (IGA) for the target ulcer from baseline to week 12 **Secondary Objectives**: -Analysis of frequency of total closure of target and total ulcers from baseline to week 12 -Analysis of change in total surface area of target/total ulcers from baseline to week 12 -Analysis of change Patient Global Assessment (PGA) from baseline until week 12 -Analysis of change in patient pain perception using 10point visual analog scale from baseline to week 12 -Analysis of change in patient quality of life using the dermatology life quality index (DLQI) from baseline to week 12
Study design:	This is a Phase II study that will be open label and enroll a total of five patients. These patients will have histological testing to rule out competing etiologies and require 3rd

	party adjudication/confirmation on agreement of the diagnosis. These patients will undergo 12 weeks of ixekizumab dosed every 2 weeks with follow-up until week 16.

Major inclusion/exclusion criteria:	For the complete list of inclusion/exclusion, criteria refer to Section 4. <u>Major inclusion criteria:</u> Have a clinical diagnosis of classic PG for at least 3 months as determined by the investigator and an external reviewer on the basis of results from clinical, histological and laboratory assessments At screening, have a PG ulcer characterized by 'item a' AND 3/5 features in 'item b' OR 2/5 features in 'item b' with support from one of the conditions listed in c. a. Stable or increasing size within 2 months preceding screening by patient report or documentation b. Features such as violaceous border, undermining, cribriform scarring, pustules, peristomal location c. Identifiable secondary systemic condition, such as IBD, arthritis, MGUS, noncancerous hematologic disease, streptococcal carriage, levamisole-tainted cocaine, Bruton's agammaglobulinemia Have a PG target ulcer that has an area ≥ 2 cm^2 and ≤ 200 cm^2 at screening Initial IGA of 3 or higher on a 5 point scale (0-4) <u>Major exclusion criteria:</u> 1. Any condition (e.g., psychiatric illness, severe alcoholism, or drug abuse) or situation that may compromise the ability of the subject to give written informed consent, may put the subject at significant risk, may jeopardize the subject's safety after exposure to the study drug, may confound the study results, or may interfere significantly with the subject's participation in the study 2. History of malignancy within 2 years of screening other than carcinoma in situ of the cervix or adequately treated, non-metastatic, squamous or basal cell carcinoma of the skin

	3. History of seropositivity for HIV antibody; active or carrier status of hepatitis B [surface antigen (HBsAg) positive, or core antibody (anti-HBc) positive with negative surface antibody]; active hepatitis C (i.e. not treated or not cleared spontaneously, as confirmed by HCV PCR) 4. History of severe allergic or anaphylactic reaction to

	monoclonal antibodies 5. Systemic infection (excluding wound colonization) requiring oral antibiotics within 2 weeks of Day 0 6. History of the following treatments: a. Anti-TNF or other biologic therapies within 5 half-lives of screening b. Changes (addition, discontinuation, or changes in dose) in immunosuppressive medication (including cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, apremilast, dapsone, or corticosteroids within 2 months of Day 0 c. Systemic corticosteroids > 20 mg per day (prednisone or prednisone equivalent) within 8 weeks of Day 0, or change in dose within 8 weeks of Day 0. Steroids may be tapered (although not increased above the Day 0 dose) during the trial as determined by the investigator. d. Intralesional corticosteroids within 8 weeks of day 0; topical immunomodulators are permitted. e. Wound debridement within 2 weeks of Day 0; dressing changes allowed per investigator discretion. g. Systemic antibiotics within 2 weeks of Day 0 h. Live, attenuated vaccines within 3 months of Day 0; or live, seasonal-flu- or H1N1 vaccines within 2 weeks of Day 0. Note: recombinant- and/or killed vaccines are permitted. i. Hyperbaric treatment within 4 weeks of Day 0 j. Investigational drug or investigational device within 30 days or 5 half-lives of Day 0, whichever is longer k. Prior exposure to ixekizumab

	l. Other treatments not described above should be maintained at a stable dose and frequency throughout the study as best as possible 13. Major, general surgery within 3 months of screening, or anticipated general surgery during the study period 14. Pregnancy, plans to become pregnant during the course of the study, delivery within 3 months of screening, or breast-feeding 15. If previous use of cyclosporine or systemic corticosteroids, failure to have any stabilization/response is exclusionary. This potentially indicates the disease is not PG.

Endpoints:	• Change in IGA between baseline and week 12
Safety plan:	Enrollment and toxicities on this trial will be monitored by
	the principal investigator and the OSU Data and Safety Monitoring Committee (DSMC)
Study treatment:	Ixekizumab subcutaneous injection 160 mg at d0, 80 mg q 2 weeks with the last dose at week 12.
Concomitant therapy and clinical practice:	As PG is a disease responsive to immunosuppression, use of concomitant medications will be carefully monitored, and patents will be required to have stable or worsening disease on a consistent dose of immunosuppression at screening. 1. Mycophenolate mofetil, azathioprine, cyclosporine, leflunomide, dapsone, apremilast and methotrexate will be allowed, but the patient is required to have stable/worsening disease for 4 weeks prior to screening, while on a stable dose of immunosuppression for > 8 weeks prior to baseline. 2. Anti-TNF or other biologic therapies will not be allowed within 5 half-lives before screening, or during the study. Oral corticosteroids above 20 mg daily of prednisone (or equivalent) are excluded. Lower doses are allowed provided they are prescribed at stable doses for two months prior to baseline and are 20 mg or less per day of prednisone or other equivalently-dosed corticosteroids. Intralesional corticosteroids within 4 weeks of screening and during the study are not permitted Other therapies that are non-immunosuppressive and noninvestigational can be started or continued at physician discretion provided the medicine has no history of association with progressive multifocal leukencephalopathy. Antibiotics may be used as needed for evidence of superinfection, positive culture results, malodor, green discharge, etc.

Statistical methods:	The primary objective of a two-point IGA decrease in the target ulcer will be analyzed as the difference from baseline, with the null hypothesis that no patients will obtain the specified improvement if the investigational product does not have efficacy. The endpoint will be analyzed using the Fisher Exact test. The secondary and exploratory objectives will be analyzed in comparison to baseline measurements and at each time point to evaluate for efficacy using either the Fisher Exact test/Chi-square test or the Wilcoxon Rank Sums test. We anticipate that the basic statistics will be completed within 1-2 months of the last patient completing his/her week 12 visit. Analyzing the interferon multiplex assay and microbiome will take longer, but will primarily be descriptive at the different time points and be analyzed by T-testing for continuous variables