PROTOCOL DOCUMENT WITH STATISTICAL ANALYSIS INCLUDED

Title: Secukinumab for NLD (Cosentyx) in Patients With Necrobiosis Lipoidica Diabeticorum (NLD)

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PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	An open-label proof of concept study regarding the use of Secukinumab (Cosentyx) in patients with necrobiosis lipoidica diabeticorum (NLD)
Principal Investigator	Martina Porter, MD

B1. PURPOSE OF PROTOCOL

The objective of this study is to evaluate whether the IL-17 inhibitor, secukinumab shows evidence of efficacy in the treatment of Necrobiosis Lipoidica Diabeticorum (NLD).

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Background:

Necrobiosis lipoidica diabeticorum (NLD) is a rare granulomatous condition of the skin that is over-represented in patients with diabetes. Classically, this condition presents with papules and plaques, most commonly on the distal extensor lower extremities. These plaques can become atrophic over time displaying a characteristic yellow hue, and may subsequently ulcerate. Although in many patients the lesions are not painful, in approximately 25% of patients the lesions can be very painful, particularly among patients who develop ulcerations.

The nature of the relationship between NLD and diabetes mellitus is poorly understood. The incidence of NLD in people with diabetes mellitus is estimated to be 0.3% to 1.2%. Initial studies from the 1960's suggested that approximately 60% of patients with NLD also had diabetes, however subsequent studies reported lower estimates of diabetes in patients with NLD (11%), and further epidemiologic studies have not been performed.

The condition may be challenging to manage, as currently no FDA-approved treatment exists, and no well-established treatment algorithm has been described. Reports on successful therapeutic interventions have generally been small and inconsistent.

The pathogenesis of NLD is poorly understood, however associations with vascular changes and immune dysregulation have been explored. Recent literature has suggested a potential role for IL-17 in the development of this condition. In 2012, Wakusawa et al reported a case of a 37 year old woman with NLD and insulin dependent diabetes mellitus. Immunohistochemical staining was performed on a biopsy specimen and revealed a significant number of IL-17 positive cells present throughout the granuloma. [1]

Kato et al subsequently reported a 66 year old woman with typical clinical and histopathological features of NLD without diabetes mellitus. [2] In their report, immunohistochemical staining found IL-17 expression present in lymphocytes, macrophages, multinucleated giant cells, and a high density of IL-17 expressing T-cells in granulomatous regions and around blood vessels. Together these cases suggest that NLD may be an inflammatory disorder involving TH17 cells and that vessels may be the target of inflammation. This may, in part explain, previous reports of patients with NLD who have been successfully treated with TNF-alpha antagonists. Finally, Wakatsuki has reported a patient with concurrent NLD and palmoplantar pustulosis (PPP). Immunohistochemistry performed on biopsy specimens found IL-17 producing cells densely associated with NLD lesions, as well as PPP lesions.

Rationale:
The reports described above suggest a possible role for IL-17 in the pathogenesis of NLD, and raise the possibility that blockade of IL-17 may be a potential therapeutic strategy in patients with NLD. Secukinumab is a human monoclonal antibody that targets IL-17a, approved by the FDA for the treatment of psoriasis. Several phase III studies have found this medication to be largely safe with nasopharyngitis and headache reported as the most frequently observed adverse events.

An open-label proof of concept study regarding the use of secukinumab in patients with NLD may be a first step in elucidating and defining a definitive treatment for this chronic and potentially debilitating condition for which no FDA approved treatment currently exists.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Study Design

This study is a non-randomized, open-label, proof of concept study. Eighteen patients aged 18 and over with histopathologically-proven NLD will be included in a prospective non-controlled study. Dosage of Secukinumab will be given according to the standard therapy regimen for psoriasis (300 mg q weekly for 5 weeks followed by 300 mg q 4 weeks). The study compromises a 2-week screening period, a 24-week open-label study period, and a 12-week follow-up period. The follow-up period consists of a phone call 16 weeks after the last study drug dose.

Population

Patients potentially eligible for this study are at least 18 years of age and have histologically confirmed necrobiosis lipoidica diabeticorum. A total of 18 subjects will be enrolled in the study. Potential patients will be assessed for eligibility to participate in this clinical study using the criteria for inclusion and exclusion listed under “Subject Selection” section.

Methods

Study Endpoints:

1. Primary Endpoint

- Proportion of patients achieving remission or clinical improvement based on Investigator Global Assessment Score as measured at week 24.

2. Secondary Endpoints

- Proportion of subjects achieving improvement based upon histological score

- Proportion of subjects improving based upon patient-reported outcomes (pain score and Dermatology Quality of Life Index Score)

Investigator Global Assessment (IGA) of Efficacy Score (See Investigator Global Assessment of Efficacy Score)

(adapted from scoring system for published pyoderma gangrenosum trials)

Score	Description
0	Completely clear: except for possible residual hyperpigmentation
1	Almost clear: very significant clearance (about 90%); however, patchy remnants of dusky erythema and/or very small ulcerations
2	Marked improvement: significant improvement (about 75%); however, a small amount of disease remaining (i.e. remaining ulcers, although have decreased in size, minimal erythema and/or active boarder)
3	Moderate improvement: intermediate between slight and marked; representing about 50% improvement
4	Slight improvement: some improvement (about 25%); however, significant disease remaining (i.e. remaining ulcers with only minor decrease in size, erythema or boarder activity)
5	No change from baseline
6	Worse

Scoring system based on the following trial [4]:

An open-label pilot study of alefacept for the treatment of pyoderma gangrenosum. European Academy of Dermatology and Venereology 2008 22, pp943–949

Histological Score

a. Inflammatory infiltrate (0, none; 1, slight; 2, moderate; 3, severe)
b. collagen degeneration (0, none; 1, slight; 2, moderate; 3, severe)
c. epithelioid histiocytes, (0, none; 1, slight; 2, moderate; 3, severe)
d. qualitative expression of IL-17 (0, none; 1, slight; 2 moderate; 3, severe)

Scoring system based on the following trial [5]:

Fumaric acid esters in necrobiosis lipoidica: results of a prospective noncontrolled study. British

Journal of Dermatology 2005 153, pp802–807

Patient-Reported Outcomes

Pain Score

(i) Resolved

(ii) Improved

(iii) Stable

(iv) Worsened

Dermatology Life Quality Index (DLQI)

A Quality of Life Score will be calculated based upon the Dermatology Life Quality Index (DLQI). The DLQI is a validated general dermatology questionnaire that consists of 10 items that assess subject health-related quality of life (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment) (See Dermatology Life Quality Index). [7] It has been extensively used in dermatology clinical trials for AD. The DLQI is a psychometrically valid and reliable instrument that has been translated into several languages, and the DLQI total scores have been shown to be responsive to change. The minimally important difference for the DLQI has been estimated as a 2 to 5 point change from baseline.

Other study parameters

Safety Parameters

Safety evaluations include adverse event (AE) monitoring, physical examinations, vital sign measurements, and clinical laboratory testing (hematology and chemistry) as a measure of safety and tolerability for the entire study duration.

At every visit adverse events will be registered.

Randomization, blinding and treatment allocation

This is an open-label proof of concept study. There will be no randomization or blinding. All subjects will receive study treatment.

Study Procedures

Prior to performing any study related procedures, the investigator will discuss with each subject the nature of the study, its requirements and its restrictions. A written informed consent form will be obtained from each participant prior to any procedure.

Each subject with a signed informed consent form will be screened at the first visit, to ensure all the inclusion criteria are met and none of the exclusion criteria.

Study procedures are described in detail below and an overview of the study procedures during each visit.

Medical history

- A complete medical history, including history of diabetes, will be taken at screening. The subject's medical history will be updated at the Baseline visit. This updated medical history will serve as the baseline for clinical assessment.

- Demographic information, including subject self-reported gender, race, age, ethnicity, and child-bearing potential will be recorded.

- Nicotine and alcohol history will be obtained

- NLD history: Date of onset of NLD, all previous and current medical and procedural treatments for NLD, and reasons for discontinuation or outcomes of previous treatments will be obtained.

Vital signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, and body temperature will be obtained at visits as specified in the Overview of Study Procedures. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes.

Complete Physical exam, including height and weight.

Height will be measured at screening only. Body weight will be measured at all scheduled visits as specified in Overview of Study Procedures. The subject will wear lightweight clothing and no shoes

during weighing. A complete physical examination, including cutaneous examination to evaluate for skin malignancies, will be performed at the designated study visits as specified in Overview of Study Procedures. The physical examination performed on Study Day 0 will serve as the baseline physical examination for the entire study. If appropriate, a targeted physical exam should be performed at any other visit (e.g., to evaluate a reported adverse event). Any significant physical examination findings after the first dose will be recorded as adverse events, while any findings prior to the first dose will be recorded as medical history. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate AE report form. At any time, a symptom-directed physical examination can be performed as deemed necessary by the Investigator.

Efficacy assessment:

IGA of Disease Severity will be performed by the investigator. Patient-reported outcomes, including DLQI and Pain score, will be administered to subjects as subject questionnaires prior to any assessment of disease severity or laboratory testing. See Overview of Study Procedures for schedule and Study Parameters for further details on efficacy assessments.

Laboratory Testing

Blood samples will be collected at scheduled visits as listed in Overview of Study Procedures. A certified laboratory at Beth Israel Deaconess Medical Center (BIDMC) through the Clinical Research Center will be utilized to process and provide results for the clinical laboratory tests.
Laboratory reference ranges will be obtained prior to the initiation of the study. The Baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

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.

The following laboratory tests will be performed according to the study procedures schedule listed in Overview of Study Procedures:

- Complete Blood Count (CBC): automated WBC, RBC, hemoglobin, hematocrit, platelet count

and RBC indices

- Complete Metabolic Panel (CMP): Sodium, Potassium, Chloride, Bicarbonate, BUN, Creatinine, Glucose, Alk Phos, ALT, AST, Total Bilirubin, GGT, Albumin, Albumin/Globulin Ratio (calculated), BUN/Creatinine Ratio (calculated), Calcium, Globulin (calculated), Total Protein
- HIV: HIV1&2 Antibody/Antigen Combo Assay
- Hepatitis B: Hep B Core Ab (Hep B Cab), Hep B Surface Antigen (Hep B Sag), and Hep B surface antibody (Hep B Sab)
- Hepatitis C: Hepatitis C antibody
- Tuberculosis: Quantiferon-TB Gold

Subjects who test positive for TB (quantiferon gold), Hepatitis C antibody, or Hepatitis B Sag or Hepatitis B Core antibody will be excluded from the study. Patients with a positive quantiferon gold will be referred to ID. If a patient has an indeterminate quantiferon gold that test will be repeated. If there are two indeterminate quantiferon gold results, then the patient will be referred to ID. If ID thinks the patient (with an indeterminate quant gold) needs to be treated for latent TB, then the patient will be treated for latent TB (see below). If ID does not think the patient (with an indeterminate quant gold) needs treatment for latent TB then the patient will be eligible to enroll in the clinical trial

After one month of treatment for latent TB, a subject would be considered eligible for participation in the trial.

Skin Biopsy

A 4 mm punch biopsy will be obtained from lesional skin at the baseline and week 26 visit. Skin biopsy location will be determined by the investigator and standard procedures for skin biopsy will be employed. Subjects may have lesions closed with suture or gelfoam, depending on nature of lesion and biopsy.

Skin biopsies will be sent to Dermatopathology lab at BIDMC for further Immunohistochemistry analysis as below. Samples will be preserved in formalin jars and sent to the histology lab to be processed within 48 hours. The paraffin blocks will be sectioned and stained at the histology lab, and then blocks and slides will be returned to the Dermatopathologist and stored securely at BIDMC, Dept of Pathology. Samples are retained for the duration of the project, through publication. If all

members of the study team deem they are no longer needed, they will then be destroyed.

Immunohistochemistry

Each biopsy will be fixed in formalin, bisected vertically, dehydrated by routine histologic methods, and embedded in a paraffin block. 5-µm-thick surface sections will be cut, mounted on glass slides, and baked for 60 minutes at 60C. The first slide will be stained with Hematoxylin and Eosin. The next slide will be loaded into the Bond III staining platform and antigen retrieved by immersion in Bond Epitope Retrieval 2 for 30 minutes. It will then incubated at room temperature for 30 minutes with Anti-Human IL17A antibody [Abcam 4K5F6] at a concentration of 0.5–10 µg/ml. After appropriate washes, antibody detection will be performed using Bond Polymer Refine Detection kit. Slides will be developed in DAB, then dehydrated and coverslipped. A biopsy of an active psoriatic skin lesion and a slide of the case with no antibody applied will be run in parallel as positive and negative controls, respectively.

Evaluation of immunohistochemistry

IL-17A expression levels will be scored as follows: A three tier stratification threshold for percentage of positive lymphocytes will be established after review of the pre-treatment biopsies, and classified as absent, low, or high. Cellular staining intensity will be scored as 0 (no staining), 1 (weak staining), 2 (moderate staining), or 3 (strong staining).

Pre- and post-treatment expression levels will be compared using Fisher's exact test. Pre-treatment IL17A expression level will be compared with clinical response parameters and evaluated as a possible predictor of response to therapy.

In case of an adverse event or disease progression, patients are instructed to call and/or visit the clinic trials unit at Beth Israel Deaconess Medical Center. Any visits will be recorded on source documentation as Unscheduled Visits. Any o fthe procedures may be performed at an unscheduled visit at the discretion of the investigator.

<u>Follow up phone call at Week 36</u>

Study personnel will call subjects to collect information regarding the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs since last study visit.

EARLY TERMINATION VISIT

If a subject is withdrawn from the study for any reason, including withdrawing informed consent, he/she will be asked to return for an early termination visit within 2 weeks of being withdrawn from the study. Procedures performed at Early Termination Visit will be identical to Week 26 visit.

Treatment of Subjects

Investigational Treatment: Secukinumab (Cosentyx)

Secukinumab (Cosentyx) is a human monoclonal antibody that targets IL-17a and is FDA-approved for the treatment of psoriasis, psoriatic arthritis, and ankylosing spondylitis. Recent literature expanding on the previously poorly understood pathogenesis of NLD has suggested a potential role for IL-17 in the development of this condition. Thus blockade of IL-17 may be a potential therapeutic strategy in patients with NLD

Dosage

Dosage of Secukinumab will be given according to the standard therapy regimen for psoriasis and administered for 24 weeks. Each subject will receive 300mg of Secukinumab by using 2 syringes of 150mg each as a subcutaneous injection at weeks 0,1,2,3,4 then every 4 weeks for a total of 9 doses over 24 weeks. Medication will be administered during scheduled study visits by study personnel.

Use of Co-intervention

Co-medication

A full list of current medication, including over-the counter medicines, will be noted for each subject at time of screening visit and will updated at each visit in their medical chart/report form.

Analgesic Therapy

If a subject develops more than transient pain or the subject's pain increases after starting treatment, they are allowed to start analgesic therapy. In case of NLD-related pain, the subject will be asked to report this at the next visit.

Exacerbation/Intervention

In case exacerbations of NLD lesions occur in the treatment areas and an intervention is required, the investigator may decide to treat with standard therapies not anticipated to decrease size of active areas such as antibiotics. Use of any of the prohibited treatments listed below could that could

confound the efficacy assessment are NOT allowed during the study. If the subject requires treatment with any of the prohibited treatments listed below, the subject should be discontinued from the study treatment will proceed to an early termination visit.

Any medication or surgical treatment that will be used to treat AEs will be recorded on the electronic case report forms (eCRF).

Prohibited Therapy

The treatments listed below are prohibited for all subjects during the study:

- Any investigational agent
- Any immunosuppressive systemic therapy started within 28 days prior to baseline, including but not limited to oral corticosteroids, adalimumab or other biologic agent, etc.
- Surgical intervention on the treatment areas

Investigational Product/Study Drug

Secukinumab (Cosentyx)

Secukinumab (Cosentyx) is a human monoclonal antibody that targets IL-17a and is FDA approved for the treatment of psoriasis, psoriatic arthritis, and ankylosing spondylitis.

COSENTYX injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution. COSENTYX is supplied in a single-use Sensoready pen with a 27-gauge fixed ½-inch needle, or a single-use prefilled syringe with a 27-gauge fixed ½-inch needle. The removable cap of the COSENTYX Sensoready pen or prefilled syringe contains natural rubber latex.

Each COSENTYX Sensoready pen or prefilled syringe contains 150 mg of secukinumab formulated in: Lhistidine/histidine hydrochloride monohydrate (3.103 mg), L-methionine (0.746 mg), polysorbate 80 (0.2 mg), trehalose dihydrate (75.67 mg), and Sterile Water for Injection, USP, at pH of 5.8.

Secukinumab will be supplied by the sponsor, Novartis, and will be packaged in quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label in their original packaging and kept in a secure location. A temperature log will be maintained for documentation in the research pharmacy. Administration of the study drug will be recorded by study

personnel at scheduled study visits.

Summary of findings from clinical and non-clinical studies

Secukinumab is a recombinant human monoclonal IgG1/κ antibody that binds specifically to IL-17A. It is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line. Secukinumab has a molecular mass of approximately 151 kDa; both heavy chains of secukinumab contain oligosaccharide chains. Please refer to the local label available to you for information regarding the efficacy and safety of this product.

Overview of Study Procedures:
Evaluation Schedule:

Activity	Screening	BASELINE/WK0	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24	Wk26*	Follow Up Call (Wk 36)
Informed consent	✓												
Demographics	✓												
Medical history	✓	✓											
Nicotine use and alcohol history	✓												
NLD history	✓												
Eligibility criteria	✓	✓											
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Complete Physical Exam, including height and weight	✓	✓					✓				✓		
Adverse event assessment		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
IGA of disease severity	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Pain Score		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
DLQI		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Urine pregnancy test for women of childbearing potential	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
CMP & CBC	✓	✓				✓	✓	✓	✓	✓	✓		
TB Screening	✓												
HIV, Hepatitis B (Hep B Sag, Hep B Sab, Hep B Cab) and Hepatitis C Screening (Hep C ab)	✓												
Digital photography of		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		

Skin biopsy		✓									✓		
Suture removal*				✓								✓	
Administer Secukinumab		✓	✓	✓	✓	✓	✓	✓	✓	✓			

* = if suture is placed following skin biopsy

Multi-Site: Joslin Diabetes Center

The Co-Investigator at Joslin Dr. Giulio Romeo will be responsible for generating a list of patient MRNs with NLD diagnosis in their records. The list will generate a list of patients seen at Joslin as well as BIDMC. The list will be shared with BIDMC study team, who will then contact the patients via letters. Patients will be pre-screened by BIDMC study team only. Patient study visits will take place at BIDMC and Dr. Romeo will not be involved in the study visits at BIDMC. Patients study related records will only be stored at BIDMC and not shared with Joslin or Dr. Romeo.

After study completion follow up call:

We want to call patients who have completed the study (n=3) and had an early termination (n=1) for a follow up call. We will ask them general question about well-being, any side effects, and option to send photos of their NLD lesions. Patients can send photo to secure telederm or clinical trials email account.

B. Statistical Considerations

Sample Size Calculation

A sample size calculation is not applicable, for this is an early feasibility and tolerability pilot study.

Data/statistical analysis

Study Parameters

The clinical efficacy will be measured by physician assessments and standardized scoring tools as noted in Main Study Parameters and Secondary Parameters. Because of the small number of patients in the study, and absence of a control group, primarily descriptive statistics will be used to report data from measured endpoints.

Main Study parameters

Primary Endpoint

- Proportion of patients achieving remission or clinical improvement based on Investigator Global Assessment Score as measured at week 24.

We will assess the proportion of patients achieving remission or clinical improvement based upon the previously published Investigator Global Assessment Score. Remission correlates with a score of 0 or 1 and clinical improvement correlates with at least a -1 change from baseline.

Secondary study parameters

Secondary Endpoints

Because of the small sample size, primarily descriptive statistics will be used.

- Proportion of subjects achieving improvement based upon histological score
- Proportion of subjects achieving improvement based upon patient-reported outcomes (pain score and Dermatology Quality of Life Index Score)

Other study parameter(s)

Patient characteristics and demographic data will be presented using descriptive statistics.

Histological Score

In addition, a histological score will be calculated as a secondary endpoint. The score is calculated by adding sub scores as listed below, which will be evaluated by the dermatopathologist. Average of pre and post scores and overall change in score will be calculated and compared using a paired T-test. See Secondary Study Parameters for details regarding histologic analysis.

Pain Score

A Pain Score will be calculated based upon the Wong-Baker 10-point pain score, which has been widely used to rate pain in both children and adults and has also been used in dermatology clinical trials.[6]

Response based on an improvement from baseline in the Wong-Baker pain score at all scheduled time points will be calculated. We will compare pre and post treatment pain values and categorize patients as

Dermatology Life Quality Index (DLQI)

A Quality of Life Score will be calculated based upon the Dermatology Life Quality Index (DLQI).

C. Subject Selection

Inclusion Criteria

A subject must meet all of the following criteria in order to be eligible to participate in this study:

1. Adults, age 18 and over
2. Previous diagnosis of biopsy-proven NLD
3. Active NLD lesions, defined as
   (i) clinical signs of inflammation, for example erythematous margins, sensations of itch, pain, dysaesthesia
   (ii) lesions increasing in size or appearance of new lesions within the last 3 months
   (iii) ulcerations
4. Subjects must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study related activity is performed.

Exclusion Criteria

Eligible subjects will be excluded from participation if they meet any of the following criteria:

1. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive QuantiFERON TB-Gold test at screening.
2. Are currently pregnant, breastfeeding, or planning to get pregnant during the study.
3. Previous hypersensitivity reaction to secukinumab or to any of the components.
4. History of Inflammatory Bowel Disease (Crohn's Disease or Ulcerative Colitis)
5. Allergy to Latex
6. Currently on any other immunosuppressant systemic medication or within 28 days of baseline visit
7. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unwilling to use effective contraception during the study and for 16 weeks after stopping treatment. Methods of acceptable birth control are listed below under "Women of Childbearing Potential"
8. Subjects with a serum creatinine level exceeding 176.8 µmol/L (2.0 mg/dL)
9. Screening total WBC count <2,500/µL, or platelets <100,000/µL or neutrophils <1,500/µL or hemoglobin <8.5 g/dL
10. Known infection with HIV, hepatitis B or hepatitis C at screening or randomization. Patients who are Hepatitis B Core antibody and/or Hep B Surface Antigen positive will be excluded from this study. Patients who are Hepatitis C ab positive will also be excluded from this study.
11. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for non-melanoma skin cancer and carcinoma in situ of the cervix)
12. Are participating in another study using an investigational agent or procedure during participation in this study or within 28 days prior to baseline visit.
13. Plans for administration of live vaccines during the study period or 6 weeks prior to randomization
14. Any other procedural treatment for NLD with 28 days prior to baseline visit, including phototherapy, surgical intervention, laser therapy, or cryotherapy.
15. Any other active skin disease or condition (e.g., bacterial, fungal or viral infection) that may interfere with assessment of NLD;
16. Underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the

opinion of the investigator significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy

Women of Childbearing Potential

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unwilling to use effective contraception during the study and for 16 weeks after stopping treatment. Effective contraception is defined as one of the following:

- Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal) associated with inhibition of ovulation
- Progestogen-only hormonal birth control (oral, injectable, transdermal) associated with inhibition of ovulation
- Bilateral tubal occlusion/ligation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS).
- Vasectomized sexual partner(s) (the vasectomized partner should have received medical assessment of the surgical success and is the sole sexual partner of the trial participant).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

B4. POSSIBLE BENEFITS

It is not possible to predict whether you will benefit directly from participation in this study. However, your participation may help others in the future as a result of knowledge gained from the research.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

RISKS AND DISCOMFORTS

Summary of known and potential risks and benefits.

Benefits: there are no FDA-approved treatments for NLD. Subjects enrolled in this study may improve with study treatment. It is not possible to predict whether subjects will benefit directly from participation in this study. However, subject participation may help others in the future as a result of knowledge gained from the research.

Infections

Cosentyx may increase the risk of infections. In clinical trials, a higher rate of infections was observed in Cosentyx treated subjects compared to placebo-treated subjects. In placebo-controlled clinical trials in patients with moderate to severe plaque psoriasis, higher rates of common infections such as

nasopharyngitis (11.4% versus 8.6%), upper respiratory tract infection (2.5% versus 0.7%) and mucocutaneous infections with candida (1.2% versus 0.3%) were observed with COSENTYX compared with placebo. A similar increase in risk of infection was seen in placebo-controlled trials in patients with psoriatic arthritis and ankylosing spondylitis. The incidence of some types of infections appeared to be dose-dependent in clinical studies.

We will evaluate patients for tuberculosis (TB) infection prior to initiating treatment with COSENTYX. A positive TB test would lead to exclusion from the trial.

Inflammatory Bowel Disease
Exacerbations of inflammatory bowel disease (IBD), in some cases serious, occurred in COSENTYX treated patients during clinical trials in plaque psoriasis, psoriatic arthritis and ankylosing spondylitis. In addition, new onset inflammatory bowel disease cases occurred in clinical trials with COSENTYX. In an exploratory study in 59 patients with active Crohn's disease, there were trends toward greater disease activity and increased adverse events in the secukinumab group as compared to the placebo group.

Patients will be screened prior to inclusion in trial for a history of IBD. Patients who are treated with Cosentyx should be monitored for signs and symptoms of inflammatory bowel disease.

Hypersensitivity Reaction
Anaphylaxis and cases of urticaria occurred in Cosentyx treated patients in clinical trials. If an anaphylactic or other serious allergic reaction occurs, administration of Cosentyx should be discontinued immediately and appropriate therapy initiated.

Risk of Hypersensitivity in Latex-sensitive Individuals
The removable cap of the Cosentyx Sensoready pen and the Cosentyx prefilled syringe contains natural rubber latex which may cause an allergic reaction in latex-sensitive individuals. The safe use of Cosentyx Sensoready pen or prefilled syringe in latex-sensitive individuals has not been studied.

Vaccinations
Patients treated with Cosentyx should not receive live vaccines. Prior to initiating therapy with Cosentyx, we will consider completion of all age appropriate immunizations according to current immunization guidelines.

Non-live vaccinations received during a course of Cosentyx may not elicit an immune response sufficient to prevent disease.

Risks listed in the consent form are the following:

<u>Common</u>

- Sore throat and stuffy nose (upper respiratory tract infection, nasopharyngitis),
- Runny nose (rhinitis), diarrhea
- Cold sores (oral herpes)

<u>Rare</u>

- Oral thrush (oral candidiasis),
- signs of low levels of white blood cells, such as fever, sore throat or mouth ulcers due to infections (neutropenia),

- athlete's foot (tinea pedis),
- infection of the external ear (otitis externa),
- discharge from the eye with itching,
- redness and swelling (conjunctivitis),
- itchy rash (urticaria)

Other Risks Related to Study Procedures:

- **Blood Tests:** The risks and discomforts of blood draws
- **Subcutaneous (SC) Injection:** discomfort, infections, and/or pain at the site of the injection.
  Skin Biopsy: bleeding, pain, infection, scar

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

Dermatologists and Dermatopathologists from Beth Israel Deaconess Medical Center will be informed using IRB approved recruitment letters of this study and asked to refer eligible patients to our research unit. These letters will explain the purpose of the research, including a brief description of the nature and extent of involvement, and the investigator's email and phone number will be included. A research advertisement will also be posted in the dermatology clinic.

A list of potential subjects will be compiled from all BIDMC Dermatology physicians' patient population using ICD codes for necrobiosis lipoidica diabeticorum. These identified patients will be sent recruitment letters informing them of the study and to contact Dr. Porter if they are interested.

The study will also be placed on TrialX as well as skinstudies.com, craigslist, twitter and BU quickie jobs. TrialX will use clinicaltrials.gov information; skinstudies.com, craigslist, twitter and BU quickie jobs will use the recruitment flyer and language from the targeted provider email.

We will advertise the study on Twitter as well with the following posting: "Do you have necrobiosis lipoidica diabeticorum? You may be eligible to participate in a clinical trial. If you are interested visit our website skintudies.com, email us at clears@bidmc.harvard.edu or call at 617-667-5834."

The flyer will also be posted at the Dimock Center.

Joslin will generate a list of patient with NLD diagnosis in their records.

Consent

Prior to entering the study, a licensed physician investigator will explain to the potential subject the nature of the study, its purpose, procedures, expected duration, and the benefits and risks involved in study participation. The licensed physician will explain the main study.

Subjects will be given the opportunity to ask questions and be informed of their right of study withdrawal. After this explanation and before any study-specific procedures have been performed, the potential subject may voluntarily sign and date the informed consent form, thereby giving permission for the subject to enter the study.

Prior to participation in the study, the subject will receive a copy of the signed and dated written informed consent form and any other written information provided to the subject. If, for any reason, the subject desires more time to consider the decision, the subject will be given a copy of the unsigned consent form for reference and instructed to call the office if they decide to participate in the study.

Subject Protection

In order to address the issue of patients feeling pressured to participate, a standard approach was developed and implemented years ago. This gives the patient the opportunity to actively demonstrate their interest before enrolling in the study. If a discussion about the study presents itself during a clinical encounter, the patient is offered to take the consent home and read and then asked to follow up with the clinic if they are interested. It is also attempted to have a physician who is not involved in their clinical care go over their consent form in order to provide further separation.

B7. STUDY LOCATION

Privacy

Subject visits will be conducted in the CRC at BIDMC or, rarely, in private patient exam rooms in the dermatology clinic if the CRC is not available at the time of subject visits. Both locations should ensure adequate privacy for patients. Patients will complete all study related procedures in these private settings, including questionnaires. Questionnaires will be in written form and returned directly to the investigators or study staff.

Pre-screening telephone calls and subject visits will be limited only to the minimum amount of data necessary to accomplish the research purposes. No sensitive questions will be discussed by telephone.

Physical Setting

Subject visits will be conducted in the CRC at BIDMC or, rarely, in private patient exam rooms in the dermatology clinic if the CRC is not available at the time of subject visits. Both locations should ensure adequate privacy for patients. Patients will complete all study related procedures in these private settings, including questionnaires.

B8. DATA SECURITY

All subjects will be assigned a subject number at their screening visit. Only investigators and study staff at BIDMC will have access to the subject's identifiable health information. To ensure appropriate privacy and confidentiality, any paper source documentation and questionnaires will be stored in a locked cabinet. Only the PI, sub-investigator, and study staff will have access to this locked cabinet. This documentation will all be coded. Subject's identifiable health information will be kept separate from coded documentation. Any electronic data containing PHI will be stored on a password protected computer in a locked office and on a secure server behind the BIDMC firewall.

The Investigator will maintain adequate records for the study, including source documentation, Informed Consent documents, drug dispensing and disposition records, information regarding participants who discontinued, adverse events, and other pertinent data. All essential documents will retained by the Investigators for at least 10 years in a long-term storage facility as arranged through the CTO.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☒ Yes ☐ No

Is the BIDMC PI the lead investigator of the multi-site study? ☒ Yes ☐ No

B10 Dissemination of Research Results

Subjects will be thanked for their participation in the study immediately following their last visit. Because we are not able to anticipate the final completion date of the study, which may take years, and because we are not primarily responsible for analyzing and publishing the data, it will not be feasible for investigators to provide results to individual subjects. Subjects may contact the PI following their completion of the study to inquire about the final findings of the study, if available to the investigators, at that time.

Planned dissemination of research results may include abstract presentations at dermatology conferences and submission of data for publication in academic journals as an original research article.