Abbreviated Title: Anakinra in pustular dermatoses
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Title: A phase 2 study of anakinra in inflammatory pustular dermatoses: Evaluation of therapeutic efficacy and validation of pathogenic mechanisms

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PRÉCIS

Background:

- Inflammatory disorders that present with neutrophilic pustular skin lesions, including generalized pustular psoriasis, are characterized by severe cutaneous manifestations, generalized inflammation and significant morbidity.
- Recent studies in patients with phenotypically similar pustular diseases have identified two monogenic forms of neutrophilic pustular psoriasis implicating interleukin (IL)-1 in disease pathogenesis.
    - Deficiency of the IL-1 receptor antagonist (*IL1RN*, DIRA) is an autosomal recessive condition characterized by severe generalized pustular eruptions in the neonatal period, osteopenia, lytic bone lesions, joint pain, respiratory insufficiency, thrombosis, elevated acute phase reactants and significant mortality. Patients with this condition have responded rapidly to IL-1 receptor antagonist, anakinra.
    - Deficiency of IL-36 receptor antagonist (*IL-36RN*/*IL1F5,* DITRA) is an autosomal recessive condition with episodic widespread pustular skin lesions, fevers and systemic inflammation defined by marked leukocytosis and elevated c-reactive protein.
- Both *IL1RN* and *IL36RN/IL1F5* are highly expressed in epidermal keratinocytes, suggesting a role for keratinocytes in initiating innate immunity-mediated inflammatory skin diseases, and ultimately manifesting in a pustular phenotype.
- Patients with inflammatory pustular diseases often respond poorly to conventional treatment with methotrexate, cyclosporine and anti-TNF agents.
- Two recent case reports describe patients with pustular psoriasis unresponsive to TNF inhibition who responded to anti-IL-1 receptor therapy with anakinra.
- We hypothesize that monogenic and polygenic inflammatory pustular skin diseases share common pathogenic mechanisms mediated by IL-1.
- We propose a phase 2 study that will utilize a collaborative bench-to-bedside approach, applying targeted anti-IL-1 therapy, novel imaging modalities, and laboratory techniques including immunohistochemistry, gene expression and cytokine studies, and *in vitro* manipulations of skin to dissect and validate pathways in these complex diseases.

Objective:

- To characterize the clinical efficacy, optimal dosing and safety of anakinra in patients with pustular dermatoses.

Eligibility:

- Age ≥ 18 years.
- Active macroscopic noninfectious pustular skin lesions involving ≥ 5% of the total body surface area, or palmoplantar involvement.
- Histopathologic confirmation of epidermal neutrophilic pustulosis.
- Patients must have maintained a stable dose of immunosuppressant therapy, retinoids or anti-neutrophil therapy for 2 weeks prior to study initiation with resultant stable or worsening skin disease.

- Use of biologic agents requires a washout period of at least 3 half-lives prior to study initiation.
- Patients must have organ and marrow function as defined below:
  - leukocytes ≥3,000/mcL
  - absolute neutrophil count ≥1,500/mcL
  - platelets ≥100,000/mcL
  - creatinine within normal institutional limits
    OR
  - creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

Design:

- A 16-week, open-label phase 2 study.
- Patients will initially receive treatment with anakinra 100 mg/day by self-administered subcutaneous injection.
- Disease response will be assessed every 4 weeks, and determination of dose escalation will be made based on clinical assessment. Dose escalation can increase up to 200 mg/day, and for patients >75 kg up to 300 mg/day at the end of week 8.
- If a response is achieved with anakinra, other immunosuppressants administered for the purpose of treatment of pustular skin disease may be tapered per physician discretion.
- Clinical assessment, and laboratory and subjective data will be collected in-person every 4 weeks to determine disease response. Telephone assessments will be performed weekly.
- Twenty-five evaluable patients will be enrolled onto this trial. The accrual ceiling for this study will be set to 30.

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To assess the proportion of participants treated with anakinra who achieve 50% disease improvement by the end of week 12, as measured by total body surface area involvement (TBSAI50).

1.1.2 Secondary Objectives

Clinical Objectives

- To assess and characterize associations between inflammatory pustular dermatoses and systemic manifestations from ophthalmologic, cardiovascular, gastrointestinal, rheumatologic and immunologic perspectives.
- To assess the changes in quality of life and functional measures during the course of anakinra therapy.
- To determine adequate dosing and safety and assess toxicity with the use of anakinra in the management of inflammatory pustular dermatoses.

Laboratory Objectives

- To characterize and analyze inflammatory pathways in skin and peripheral blood mononuclear cells using immunohistochemistry, cytokine and gene expression studies.
- To evaluate systemic inflammation in patients with pustular dermatoses using novel imaging modalities, and assess biomarkers of cardiometabolic disease using novel techniques including nuclear magnetic resonance spectroscopy (NMR) and HDL cholesterol efflux capacity.
- To evaluate keratinocyte responses to targeted inflammatory stimuli including infectious agents and danger molecules.

1.2 BACKGROUND AND RATIONALE

Inflammatory disorders that present with neutrophilic pustular skin lesions, including generalized pustular psoriasis, are characterized by severe cutaneous manifestations, generalized inflammation and significant morbidity. Interestingly, several recent studies in patients with phenotypically similar pustular diseases have identified two monogenic forms of neutrophilic pustular psoriasis implicating interleukin (IL)-1 in disease pathogenesis (**Table 1**). Whereas dysregulated NFkB/TNF and IL-12/23 pathways have an established role in plaque-type psoriasis, these recent reports of monogenic pustular diseases have suggested a role for IL-1 in the development of pustular skin lesions.

Table 1: Identified monogenic pustular skin diseases

	Deficiency of IL-1 Receptor Antagonist (DIRA)	**Deficiency of IL-36 Receptor Antagonist (DITRA)**
Mutation	*IL1RN*	*IL-36RN/IL1F5*
Inheritance	Autosomal recessive	Autosomal recessive
Founder and type of mutation	Multiple founder deletion mutations described in Newfoundland, Puerto Rico, Lebanon, Holland and Brazil [1-4].	Single founder homozygous missense mutation described in 8 Tunisian families[5]. Two additional missense mutations found in 3 unrelated patients from England[6].
Biological consequence	Loss of function of IL1RA resulting in unopposed IL-1 activity	Decreased IL36RA protein resulting in increased inflammatory cytokines (ex vivo)
Clinical phenotype	Generalized pustules Lytic bone lesions Respiratory insufficiency Thrombosis Elevated acute phase reactants Significant mortality	Episodic widespread pustules Fevers Elevated acute phase reactants
Treatment	IL-1 receptor antagonist, anakinra	None described^

^Two patients with pustular psoriasis (but no mutation in IL-36RN) were successfully treated with IL-1 blockade[7].

Deficiency of the IL-1 receptor antagonist (*IL1RN*, DIRA) leads to a severe generalized pustular eruption in the neonatal period, osteopenia, lytic bone lesions, joint pain, respiratory insufficiency, thrombosis, elevated acute phase reactants and significant mortality [1-4]. Loss of function mutations in the IL-36 receptor antagonist (*IL-36RN,* another member of the IL-1 cytokine family, also known as *IL1F5*) were recently reported. These mutations lead to an autosomal recessive form of generalized pustular psoriasis called DITRA (deficiency of IL-36 receptor antagonist), a condition characterized by episodic widespread pustular skin lesions, fevers and systemic inflammation defined by marked leukocytosis and elevated c-reactive protein[5, 6]. Both DIRA and DITRA are associated with similar histologic findings including epidermal hyperplasia and epidermal and dermal accumulation of neutrophils, T lymphocytes and dendritic cells, suggesting a common underlying pathogenic pathway. Furthermore, both *IL1RN* and *IL36RN/IL1F5* are highly expressed in epidermal keratinocytes, suggesting a role for keratinocytes in initiating innate immunity-mediated inflammatory skin diseases[8, 9], and ultimately manifesting in a pustular phenotype.

The availability of biologics targeting IL-1 provides us with potent clinical tools to dissect and validate these pathways in inflammatory pustular skin diseases. Patients with pustular diseases often respond poorly to conventional treatment with systemic retinoids, methotrexate,

cyclosporine and anti-TNF agents. Two recent case reports, however, describe patients with generalized pustular psoriasis refractory to TNF inhibition who responded to anti-IL-1 receptor antagonist therapy with anakinra[7, 10]. However, beyond these case reports, the efficacy of IL-1 inhibition along the spectrum of neutrophilic and pustular skin conditions has not yet been systematically explored, and analysis of pathogenesis is lacking.

In light of these recent case reports and the efficacy of anakinra in other neutrophilic inflammatory diseases such as the periodic fever syndromes, we hypothesize that monogenic and polygenic pustular skin diseases share common pathogenic mechanisms mediated by IL-1. We aim to elucidate the shared inflammatory pathways that contribute to the development of neutrophilic pustular diseases. We propose a phase 2 study that will apply targeted anti-IL-1 therapy to dissect and validate the inflammatory pathways important in these complex diseases.

Published data and our preliminary studies provide support for common pathogenic pathways in pustular psoriasis. Keratinocyte dysregulation leads to the production of inflammatory chemokines and cytokines, suggesting a role for keratinocytes in the initiation of inflammatory skin disease[11]. DIRA and DITRA are caused by a mutation in IL-1 family members, IL1RN and IL36RN/IL1F5, which are highly expressed in the keratinocytes of the epidermis and suggest an important role of the innate immune system in disease development[6]. Activated keratinocytes recruit neutrophils into the skin, and ultimately manifest in a pustular phenotype.

Gene expression studies and therapeutic studies support an important contribution of the adaptive immune system in inflammatory diseases. Published data and preliminary data from our gene expression studies suggest that keratinocytes or macrophages carrying CARD14 mutations or lacking the IL-36 receptor antagonist produce chemokines IL-8, CCL2 and CCL20[6]. IL-23 derived from activated keratinocytes [11] or newly recruited myeloid dendritic cells [12] leads to IL-17 production. IL-17 promotes rapid neutrophil recruitment by inducing the secretion of proinflammatory mediators including IL-1, IL-6, IL-8, CXC ligand 1, TNF and GM-CSF, thus leading to a cycle of chronic inflammation [13].

Systemic inflammatory states are also associated with metabolic and cardiovascular risk factors. Psoriasis is an example of such an inflammatory state which has been shown to have an association with metabolic and cardiovascular disease. Experimentally induced *in vivo* inflammation in healthy humans is associated with robust activation of TNF-α and IL-6 followed by a systemic insulin-resistant state, metabolic dyslipidemia and decreased HDL function [14-17]. Additionally, acute inflammation is associated with mildly reduced HDL levels and increased triglycerides and small dense LDL particles [14, 18]. These lipoprotein responses may be designed to prevent cholesterol loss at a time of high cell turnover. However, sustained dyslipidemia due to chronic inflammation may be an important pro-atherogenic feature of systemic inflammatory conditions. The lipoprotein pattern observed in conditions like psoriasis (low HDL, reduced apo A-I) may be associated with reduction of macrophage cholesterol efflux and blunting of reverse cholesterol transport[19], an important anti-atherosclerotic pathway *in vivo*, recently shown to be associated with subclinical atherosclerosis and angiographic coronary artery disease [20]. The effect of inflammation-mediated macrophage efflux defects is poorly defined in inflammatory pustular diseases and may provide additional information about cardiovascular and metabolic diseases in systemic neutrophilic inflammatory states.

One innovative method to investigate the systemic inflammatory burden is with [18F]-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT).

FDG-PET/CT is a validated imaging technique that enables measurements of inflammation *in vivo*[21]. FDG uptake in the arterial walls reflects metabolic activity of inflammatory cells, particularly macrophages, involved in atherosclerotic lesions [22]. A recent study revealed that psoriasis is associated not only with clinically observed inflammation in the skin, but also foci of subclinical inflammation within the liver, joints, tendons, and aorta that were not explained by traditional cardiovascular risk factors or co-morbidities[23]. Importantly, vascular inflammation detected by PET/CT represents a stable, reproducible phenotype over time in control settings[24]. This modality can aid in detection of vascular inflammation, and has high inter-and intra-reader reliability[24]. Since vascular inflammation on FDG-PET/CT strongly predicted future major vascular events and responded to interventions for traditional CV risk factors [25-29], it may also serve as a useful marker for evaluating vascular inflammation, disease risk and disease response to therapy in a range of inflammatory conditions.

Chronic inflammatory states have also been associated with development and progression of malignancy. Notably, IL-1 is found in abundance at tumor sites and thought to play a role in carcinogenesis and tumor growth. IL-1 inhibition by IL-1ra may reduce tumor invasiveness, pointing to the potential role of IL-1 inhibition in cancer therapy[30, 31]. Although monoclonal gammopathies have been anecdotally associated with generalized pustular dermatoses[32, 33], the association between inflammatory pustular dermatoses and malignancy has not been systematically studied and this study may provide further insights into the relationship between innate immunity and neoplastic disease.

In this study, we intend to apply recent insights gained from monogenic disorders to understand the pathogenesis of neutrophilic pustular skin disorders. We will utilize a fully collaborative bench-to-bedside approach, including targeted therapeutic intervention with anakinra and powerful and novel clinical and laboratory techniques including immunohistochemistry, gene expression analysis, in vitro manipulations of skin cells, and FDG PET CT to dissect these complex diseases.

Anakinra is an IL-1 receptor 1 (IL-1R1) antagonist which competitively blocks the activity of IL-1. This agent was initially evaluated in sepsis patients, but is currently FDA approved for rheumatoid arthritis (RA)[34-36]. It is indicated for the management of signs and symptoms of moderately to severely active rheumatoid arthritis in patients 18 years of age or older who have failed 1 or more disease modifying antirheumatic drugs (DMARDs). Anakinra has been evaluated in over 1400 RA patients in four randomized, double-blind, placebo-controlled trials[37-42]. It is also effective in the management of monogenic autoinflammatory diseases including neonatal-onset multisystem inflammatory disease (NOMID)[43-45], as well as monogenic diseases with a pustular phenotype including DIRA[1].

The most common adverse event associated with anakinra is injection site reaction, which occurs in approximately 71% of patients and generally diminishes after 4-6 weeks of daily use. The most serious adverse events associated with anakinra include neutropenia, thrombocytopenia and infection. In placebo-controlled trials, 0.4% of patients treated with anakinra monotherapy developed neutropenia. Two percent of patients concurrently treated with anakinra and the anti-TNF agent etanercept developed neutropenia. Two percent of anakinra patients receiving anakinra alone developed a decreased platelet count (WHO toxicity grade 1) as compared with 0% of patients treated with placebo. In placebo-controlled trials in RA patients, the incidence of infection was 39% versus 37% in patients receiving anakinra versus placebo, respectively. The

incidence of serious infections was 2% versus 1% in patients treated with anakinra versus placebo, respectively. Serious infections consisted of bacterial cellulitis, pneumonia, and bone and joint infections. In patients receiving anakinra and etanercept concurrently for up to 24 weeks, serious infections were noted in 7% of patients, consisting primarily of bacterial pneumonia and cellulitis[42]. Although opportunistic infections were not observed in randomized, double-blind, placebo-controlled clinical trials, one case each of atypical mycobacterial infection, histoplasmosis and esophageal candidiasis were observed in an open-label extension study of 1346 RA patients[40].

Among 5300 RA patients treated with anakinra in clinical trials for a mean of 15 months, 8 lymphomas were observed[46]. This rate is similar to the rate expected for the RA patient population in which the rate of lymphoma is at least doubled[47, 48]. The most common other malignancies observed in clinical trials were breast, respiratory system, and digestive system malignancies. Four cases of melanoma were observed in one study and its long-term open-label extension, but none of the cases were attributed to anakinra[40]. The significance of these findings is unclear and the role of IL-1 antagonists in the development of malignancy is not known.

Patients with pustular psoriasis tend to respond poorly to anti-TNF agents and are typically excluded from clinical studies evaluating anti-TNF agents for psoriasis. Infectious, neoplastic and cardiac complications are associated with anti-TNF therapy. In 2002, the BIOBADASER (Base de Datos de Productos Biologicos de la Sociedad Espanola de Reumatologia) database reported 17 cases of tuberculosis among 1355 patients treated with infliximab. Eleven patients (65%) manifested extrapulmonary involvement and 2 deaths occurred (12% mortality rate), as compared with an expected 15% rate of extrapulmonary TB amongst patients with TB and 4.6% mortality in the general U.S. population at that time[49]. Serious bacterial and fungal opportunistic infections have also been reported in patients treated with anti-TNF agents[50]. An increased risk of worsening congestive heart failure (CHF) has been demonstrated with high-dose infliximab (all-cause mortality or CHF hospitalization: 16% at week 14, 26% at week 28)[51]. Adverse cardiac outcomes in patients with CHF are thought to be a class effect with anti-TNF agents. Data from the National Databank for Rheumatic Diseases also suggests a modest increase in lymphoma with TNF-blockers, with an incidence ratio of 2.6 (95% CI: 1.4-4.5) in patients treated with infliximab, 3.8 (95% CI: 1.9-7.5) in patients treated with etanercept and 1.9 (95% CI: 1.3-2.7) in the patient population overall[52]. Demyelinating disorders, liver toxicity and drug-induced systemic lupus erythematosus have also been described in association with anti-TNF agents[53, 54].

Anakinra use for this study is exempt from an investigational new drug (IND) application because this investigation:

1) Is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use of the drug product, nor intended to be used to support any other significant change in the labeling for the drug;
2) Is not intended to support a significant change in advertising to an existing lawfully marketed prescription drug product;
3) Does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

4) Will be conducted in compliance with the requirements for institutional review set forth in FDA regulations 21 CFR 56, and requirements for informed consent as set forth in FDA regulations 21 CFR 50.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Females and males, aged ≥18.

2.1.1.2 Patients must demonstrate active noninfectious inflammatory pustular skin lesions resembling pustular psoriasis and involving ≥ 5% total body surface area, or palmoplantar involvement. Conditions may include, but are not be limited to, pustular psoriasis, Sneddon-Wilkinson disease, subcorneal pustular dermatosis, reactive arthritis, palmoplantar pustulosis, acrodermatitis continua of Hallopeau and palmoplantar pustular psoriasis.

2.1.1.3 Patients must have histopathologic confirmation of epidermal neutrophilic pustular skin disease.

2.1.1.4 If taking immunosuppressants, retinoids or anti-neutrophil therapy, participants must maintain stable doses of these medications during the 2 weeks prior to study initiation.

2.1.1.5 Patients must have stable topical medication regimen for 2 weeks prior to study initiation

2.1.1.6 Patients must have normal organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– creatinine	within normal institutional limits OR
– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

2.1.1.7 Quantiferon TB Gold must be performed for screening for mycobacterium tuberculosis infection. However, a tuberculin skin test may be placed if the Quantiferon TB gold test is indeterminate (see below). Patients must have a negative Quantiferon TB Gold (or tuberculin skin test) or evidence of appropriate treatment prior to study entry (see below).

Negative Quantiferon TB gold	Begin study
Indeterminate Quantiferon TB gold	Place tuberculin skin test (TST). If negative, begin study.
Positive Quantiferon TB gold or TST	Negative CXR and ≥ 1month Tx prior to 1st dose of study drug

2.1.1.8 Patients must be able to understand and sign a written informed consent document and complete study-related procedures and questionnaires.

2.1.2 Exclusion Criteria

2.1.2.1 Enrollment in any other investigational treatment study or use of an investigational agent, or has not yet completed at least 3 half-lives since ending another investigational device or drug trial.

2.1.2.2 History of treatment with canakinumab within the 12 months prior to study initiation.

2.1.2.3 History of anakinra use.

2.1.2.4 History of phototherapy within 2 weeks prior to study initiation.

2.1.2.5 Patients may NOT concurrently be on biologic therapy such as etanercept, adalimumab, alefacept, infliximab, rituximab or rilonacept **(APPENDIX A: FORBIDDEN DRUGS)**. If there is a history of use of biologic agents, there must be a washout period of at least 3 half-lives prior to study initiation.

2.1.2.6 Subjects who experience a significant flare after discontinuation of a TNF inhibitor as part of this study that requires urgent medical management or hospitalization, or in the estimation of the principal investigator poses excessive risk to the patient to enter the study.

2.1.2.7 Other defined dermatologic conditions which may include pustules as part of the clinical presentation, but which clinically and/or histologically do not resemble pustular psoriasis. Examples include, but are not limited to acute generalized exanthematous pustulosis (AGEP, a drug-induced pustular dermatosis typically caused by beta-lactam antibiotics, tetracyclines, oral antifungals and other drugs), bacterial or fungal folliculitis, cutaneous candidiasis, tinea pedis, tinea corporis, neutrophilic eccrine hidradenitis or eosinophilic pustular folliculitis (Ofuji syndrome).

2.1.2.8 Known diagnosis of DIRA.

2.1.2.9 History of allergic reactions attributed to compounds of similar chemical or biologic composition to anakinra or other agents used in study. Known hypersensitivity to CHO-cell derived biologics or any components of anakinra.

2.1.2.10 Treatment with a live virus vaccine during the 3 months prior to baseline visit. No live vaccines will be allowed throughout the course of this study.

2.1.2.11 Patients with active or untreated malignancy-- with the exception of cutaneous basal or squamous cell carcinomas, or in situ cervical carcinoma-- are ineligible because of the immunomodulating effects of anakinra. The risk of recurrent malignancy secondary to this drug is unknown.

2.1.2.12 Presence of active infection. History of exposure to TB (positive PPD or Quantiferon TB gold) who have not been treated with a TB prophylaxis regimen for at least one month.

2.1.2.13 Chest x-ray (if Quantiferon TB Gold is positive) demonstrating pleural scarring and/or calcified granuloma consistent with prior or current untreated TB.

2.1.2.14 History of chronic or recurrent infection including but not limited to HIV, hepatitis B or hepatitis C.

2.1.2.15 Individuals with severe or uncontrolled recurrent cutaneous infections who are considered at elevated risk for serious infection on anakinra therapy will be excluded per physician discretion.

2.1.2.16 Presence of other known significant autoimmune or inflammatory disease. Examples include major chronic infectious/inflammatory/immunologic diseases such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome and periodic fever syndromes.

2.1.2.17 Other immunoregulatory or immunodeficiency diseases, such as multiple sclerosis.

2.1.2.18 Individuals with life-threatening or disabling inflammation of the eyes, gut or joints requiring urgent or immediate medical attention, or at the physician's discretion.

2.1.2.19 Subjects for whom there is concern about compliance with the protocol procedures.

2.1.2.20 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, uncontrolled or unmonitored psychiatric illness/social situations, or history of congestive heart failure, unstable angina pectoris or medically significant cardiac arrhythmia that would limit compliance with study requirements.

2.1.2.21 Presence of other severe acute or chronic medical or psychiatric condition, or significant laboratory abnormality requiring further investigation that may cause undue risk for the subject's safety, inhibit protocol participation, or interfere with interpretation of study results, and in the judgment of the investigator would make the subject enrollment inappropriate.

2.1.2.22 The effects of anakinra on the developing human fetus are unknown. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control or abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

Females of childbearing potential must have a negative serum pregnancy test at screening. Females must also have a negative serum pregnancy test at baseline and prior to performance of any radiologic procedure or administration of study medication and during each visit. Lactating mothers will discontinue breastfeeding prior to study enrollment.

2.1.2.23 Pregnant or lactating females. Women of non-childbearing potential is defined as women who are postmenopausal (no menses for > one year) or who have had a hysterectomy and will not require B-hCG testing.

2.1.3 Recruitment Strategies

Participants representing all ethnic groups and racial categories will be recruited for this study. Recruitment strategies may include a) referrals from NIH research physicians, b) referrals from non-NIH physicians, c) referrals from University of California, San Francisco (UCSF) and local area providers, d) NIH Patient Recruitment website, e) NIH Clinical Center Facebook page, f) print media including newspapers, specialized journals and magazines, g) advertisements posted on internet websites including Clinicaltrials.gov and ResearchMatch.org, local and regional dermatology association websites, h) interactions with patient and physician organizations in the local and national dermatology community including the National Psoriasis Foundation, i)

dissemination of IRB approved flyers at designated locations, j) dissemination of IRB-approved recruitment letters sent to potentially eligible participants identified by investigators via review of our patient database and charts.

2.2 SCREENING EVALUATION

- Assessments to be completed prior to enrollment
  - Skin biopsy for hematoxylin and eosin staining to confirm diagnosis if prior confirmational biopsy has not been performed
  - Microbiologic culture of pustule confirming noninfectious etiology
- Assessments to be completed within 8 weeks prior to enrollment
  - Quantiferon TB gold
    - Chest X-ray to ensure absence of radiographic evidence of tuberculosis only if Quantiferon TB gold or tuberculin skin test is positive
  - Medical history and medication review
  - CBC with differential
  - Serum B-hCG in females of childbearing potential. Not required for females who are status-post hysterectomy or postmenopausal (no menses for >one year).
  - Blood urea nitrogen and serum creatinine
  - Anti-HIV-1/2 screen
  - Viral Markers Hepatitis Screen (HBsAg and anti-HCV)

2.3 REGISTRATION PROCEDURES

2.3.1 Registration at the Clinical Center

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.3.2 For Participating Site Registration

A protocol registration form will be supplied by the NIAMS study coordinator and updates will be provided as needed. Subject eligibility and demographic information is required for registration. Once eligibility is confirmed, complete the protocol registration form which contains the eligibility checklist, indicating that the patient is being registered for treatment and send to NIAMS study coordinator. In addition, source documents supporting the eligibility criteria must be sent to the NIAMS study coordinator. The NIAMS study coordinator will notify you either by e-mail or fax that the protocol registration form has been received which will include the unique patient/subject ID number. Questions about eligibility should be directed to the study coordinator or PI. Questions related to registration should be directed to the study coordinator.

2.3.3 Treatment Assignment and Randomization/ Stratification Procedures

Cohort

Number	Name	Description
1	Cohort 1	Subjects with pustular skin disease

Arm

Number	Name	Description
1	Arm 1	An initial dose of anakinra 100 mg/day will be administered daily via self-administered subcutaneous injection. If active disease persists at this dose, anakinra dose may be escalated to 200 mg/day injected subcutaneously daily at week 4 and 300mg/day at week 8

Stratifications

None

Randomization and Arm Assignment

This is an open-label non-randomized study. All subjects in cohort 1 will be directly assigned to arm 1.

2.4 BASELINE EVALUATION

HISTORY AND PHYSICAL EXAMINATION

- Medication review
- Directed physical examination, including body mass index calculation
- Detailed skin examination including:
    - Total body surface area involvement (TBSAI)
    - Physician global assessment (PGA)
    - Pustular psoriasis assessment severity index (PPASI)
    - Palmoplantar psoriasis assessment severity index (PPPASI), if appropriate

BLOOD AND TISSUE

- Complete blood count with differential
- Serum creatinine and urea nitrogen
- Serum calcium, phosphorus
- Parathyroid hormone
- Serum 25-OH Vitamin D
- Hepatic panel including alkaline phosphatase
- Serum albumin and total protein
- Lipid Panel (total cholesterol, triglycerides, LDL, HDL)
- Serum insulin level

- Serum C-peptide
- Acute phase reactants: erythrocyte sedimentation rate, serum high-sensitivity C-reactive protein
- Serum ferritin
- Serologies: anti-nuclear antibody, anti-dsDNA antibodies, anti-ENA antibodies, rheumatoid factor, C3, C4, CH50.
- Quantitative serum immunoglobulins
- HLA class I and II typing
- Serum protein electrophoresis
- Anti-streptolysin O titer
- Viral Markers Hepatitis Screen (HbsAg, Anti-HCV)
- Skin biopsies: up to 3 (lesional x2, and non-lesional skin x1) (performed at the investigator's discretion)
- Serum, plasma and tissue cytokine levels
- Serum beta human chorionic gonadotropin (not required if females are status post hysterectomy or postmenopausal)
- Serum glucose
- Serum storage for research

URINE

- Urine protein electrophoresis
- Urinalysis
- Urine calcium, phosphorus

QUESTIONNAIRES/MEASUREMENTS

- Quality of life assessments/questionnaires including DLQI, SF-36, Pruritus VAS, Pain VAS, and Overall Disease Severity VAS (details in Section **3.4**)
- Total body photography (performed at the investigator's discretion)

CONSULTATIONS

The following consultations will be conducted at the investigator's discretion:

- Rheumatologic consultation including baseline joint examination with assessment by ACR criteria, including Health Assessment Questionnaire
- Cardiometabolic evaluation including baseline electrocardiogram
- Ophthalmologic examination
- Gastrointestinal consultation when indicated

RADIOLOGICAL

The following procedures will be conducted at the investigator's discretion:

- Total body research FDG-PET CT scan
- Joint MRI of affected joints

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This will be a phase 2, open label, prospective interventional 16-week dose titration study. Patients will complete a daily diary during the entire 16-week study course. Patients will be instructed to score the severity of rash, pustules, itch, skin pain, joint pain and overall well-being into their daily diaries. They will also document fever and doses of medications in their diaries. (**APPENDIX B: PATIENT**)

At the baseline visit, clinical assessments, and laboratory, histopathologic and subjective data will be collected. All enrolled patients will initially receive treatment with anakinra 100 mg/day via self-administered subcutaneous injection. The first dose of anakinra will be administered under supervision in the clinic.

At week 4, disease response will be assessed by clinical exam, laboratory markers and evaluation of patient diaries that are returned to clinic. Determination for dose escalation will be made based on week 4 assessments. Those patients who do not achieve complete disease clearance with initial anakinra dosing will be increased to the next incremental dose level (see Section **3.1.2**).

At week 8, patients will return for clinical evaluation and patients who do not achieve complete disease clearance on anakinra have the option of dose escalation up to the next incremental dose level. All patients will stop anakinra at week 12.

Patients will return for an Off Study visit at week 16, approximately 28 days after their final dose is administered. Considering personal/work/travel/other obligations, a period of no more than 1 week before or after the Week 4, 8, or 12 visits, and 2 weeks before or after the Week 16 visit may be permitted.

Total body photographs will be taken at baseline, week 4, week 8, week 12 and week 16 (at the investigator's discretion).

With the patient's consent, and at the discretion of the investigator, a skin biopsy for research will be taken at baseline and week 12. Skin biopsies will be taken from lesional and non-lesional skin. Non-lesional skin will be obtained for the purpose of comparison with lesional skin in immunohistochemistry, cytokine and gene expression studies, as well as in vitro keratinocytes studies.

Between scheduled clinic visits, disease status will be assessed by telephone at weeks 1-3, 5-7 and 9-11. Following discontinuation of anakinra at week 12, disease activity and adverse event monitoring will be assessed by telephone at weeks 13-15. A period of no more than 3 days before or after weeks 1-3, 5-7, 9-11, and 13-15 may be permitted. The completed patient diaries will be assessed upon their return to the clinic.

Once clinical disease is deemed to be quiescent, other immunosuppressants administered for the purpose of treatment of pustular skin disease may be tapered per physician discretion. Doses of anakinra and immunosuppressants will be recorded throughout the study period until week 12 in order to assess mean required dose of anakinra for maximum improvement of disease, and the number of participants who are able to taper other immunosuppressants while on anakinra therapy.

The primary outcome measure and all secondary outcome measures (see section **1.1.2**), will be assessed by the multidisciplinary study team at the conclusion of week 12.

Clinical assessment, and laboratory and subjective data will be collected monthly with the aid of primary care physicians during months when participants do not travel to the National Institutes of Health or participating site clinic. At any time during the study time period, serious adverse events grade 3 or greater that are possibly, probably or definitely related to the study drug will be reported to the IRB. Participants will hold therapy immediately and be evaluated emergently. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

A total of 25 participants will be recruited for this study. It is anticipated that 1-2 patients per month will enroll onto this trial. In order to allow for a small number of unevaluable patients, the accrual ceiling will be set at 30 patients. Accrual of 30 patients would be estimated to last up to 24 months. If 0 of the first 9 patients fail to respond to anakinra therapy by week 12, we will halt further patient recruitment.

3.1.1 Dose Limiting Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with anakinra until the end of study participation, regardless of inclusion in primary response evaluation.

This study will utilize version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) (http://ctep.cancer.gov/reporting/ctc.html) for toxicity and adverse event reporting. Only those adverse events deemed possibly, probably, or definitely related to anakinra will be used in the definition of dose-limiting toxicity. Greater or equal to CTCAE grade 3 toxicity in any enrolled subject thought to be possibly, probably or definitely associated with anakinra will be reported to the IRB. The adverse event will be presented to the IRB and safety monitor for review and consideration of protocol modification including possible trial termination. Events that are considered disease-related will not be considered dose limiting or medication-induced adverse events.

3.1.2 Dose Escalation

An initial dose of anakinra 100 mg/day will be administered daily via self-administered subcutaneous injection. If pustule formation persists at this dose, anakinra dose may be escalated up to 200 mg/day injected subcutaneously daily at week 4. Participants will be re-assessed at week 8, and if pustule formation persists and the patient weighs ≥75kg, the dose may be escalated up to a maximum 300 mg/day.

Dose Escalation Schedule	
Dose Level	Dose of anakinra
Level -1*	50mg SC daily
Level 1	100 mg SC daily
Level 2	200 mg SC daily
Level 3	300 mg SC daily (patients ≥75kg only)

*Patients who experience an adverse event on dose level 1 that requires dose reduction may be reduced to dose level -1, 50mg SC daily (see Section **3.3**). Patients who require dose reduction due to an adverse event at any point in this study will not be eligible for dose escalation.

Dose escalation will follow the rules outlined in the Table below.

Time of Assessment	Escalation Decision Rule
Baseline	• Enter each patient onto study at dose level 1
Week 4	• If patient has achieved complete clearance of pustular and plaque disease, remain at dose level 1 • If patient has not achieved complete pustule and plaque clearance, increase to next incremental dose level
Week 8	• If patient has achieved complete clearance of pustular and plaque disease, remain at current dose level • If patient has not achieved complete clearance of pustular and plaque disease AND patient weighs ≥75kg, increase to next incremental dose level

If a patient experiences a Grade 2 adverse event probably or definitely related to anakinra within 7 days prior to a scheduled dose escalation, dose escalation will be postponed until resolution of the adverse event or a maximum of 14 days, whichever is shorter.

3.2 DRUG ADMINISTRATION

Anakinra is supplied in single-use 1 ml prefilled glass syringes with 27 gauge needles as a sterile, clear, colorless-to-white, preservative-free solution for daily subcutaneous (SC) administration. Each 1 ml prefilled glass syringe contains: 0.67 ml (100 mg) of anakinra in a solution (pH 6.5) containing sodium citrate (1.29 mg), sodium chloride (5.48 mg), disodium EDTA (0.12 mg), and polysorbate 80 (0.70 mg) in water for injection, USP.

Patients will be instructed verbally and in writing that anakinra should be protected from light, stored in the refrigerator at 2ºC to 8ºC (36ºF to 46ºF) away from children, and never frozen. Patients will be instructed not to use any syringe if the solution appears discolored or cloudy or has been at room temperature ≥ 24 hours. Patients will be instructed to avoid shaking the pre-filled syringes, to use each syringe only once, and to inject the entire volume of solution. Patients will receive a diagram **(APPENDIX C: PATIENT HANDOUT)** of body sites where anakinra is to be injected, emphasizing the importance of avoiding veins, arteries and injecting into a new site each day. Self-injection demonstration and technique will be provided once the baseline visit has concluded.

All patients will be given a puncture-resistant container for proper disposal of syringes after use.

All patients will initiate anakinra therapy with one 1ml (100 mg) prefilled syringe injected subcutaneously daily. Those who achieve disease quiescence on this dose by week 4 will continue at this dose until week 12.

Those who do not demonstrate disease quiescence at week 4 will increase their dose to 2-1ml prefilled syringes (total of 200 mg) to be injected subcutaneously daily. Those individuals who weight >75kg and do not demonstrate disease quiescence by week 8 on anakinra 200 mg/day will be instructed to increase their dose to 3-1ml prefilled syringes (total of 300mg) injected subcutaneously daily.

Patients who miss a dose will be instructed to administer the dose as soon as they remember. However, if it is almost time to administer the next dose, the patient will be directed to skip the missed dose and proceed with their regularly scheduled dose. Patients will be reminded to avoid double-dosing in an effort to make up the missed dose.

If a patient misses a dose of study drug, it will be recorded in the medical record and on the CRF. Missed doses will not be reported to the IRB as a protocol deviation unless the patient misses >5 doses per month.

3.3 DOSE MODIFICATIONS

All dose modifications must be discussed with the PI. This study will utilize version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) (http://ctep.cancer.gov/reporting/ctc.html) for toxicity and adverse event reporting. Expected pre-existing or concurrent manifestations of inflammatory pustular dermatoses include fatigue, malaise, pain, pruritus, arthritis, enthesitis, alopecia, pustular and papular skin lesions, hypopigmentation, hyperpigmentation, skin dryness, nail changes, koebnerization at sites of trauma or injections, uveitis, conjunctivitis, rash, hypocalcemia, hypoalbuminemia and leukocytosis. Any of the above symptoms newly presenting after initiation of anakinra must be carefully evaluated for attribution, i.e., new skin rash may be biopsied to determine drug reaction versus pustular dermatosis. See **APPENDIX D: DOSE MODIFICATION FLOW CHART** for Dose Modification Flow Chart.

Adverse event	**CTCAE grade/attribution**	**Protocol Action**
Any adverse event (excluding infection, treatment-related malignancy)	Grade 2 >7 days that is probably or definitely related to anakinra.	Hold study drug; *If AE resolves to ≤ grade 1 or baseline within 14 days: resume dose at same dose level. ** If AE does not resolve to ≤ grade 1 or baseline within 14 days: patient comes off drug.
Any adverse event (excluding infection, treatment-related malignancy)	Same grade 2 >7 days recurs that is probably or definitely related to anakinra.	Hold study drug; *If AE resolves to ≤ grade 1 or baseline within 14 days: decrease dose by 1 dose level. **If AE does NOT

		resolve to ≤ grade 1 or baseline within 14 days: patient comes off drug.
Any adverse event (excluding infection, treatment-related malignancy)	Same grade 2 >7 days recurs after dose reduction that is probably or definitely related to anakinra.	Patient comes off drug.
Any adverse event (excluding infection, treatment-related malignancy)	Grade 3 that is probably or definitely related to anakinra.	Hold study drug; *If AE resolves to ≤ grade 1 or baseline within 14 days: decrease dose by 1 dose level. **If AE does NOT resolve to ≤ grade 1 or baseline within 14 days: patient comes off drug.
Any adverse event (excluding infection, treatment-related malignancy)	Same grade 3 recurs after dose reduction that is probably or definitely related to anakinra.	Patient comes off drug.
Any adverse event (excluding infection, treatment-related malignancy)	Grade 4 that is probably or definitely related to anakinra.	Patient comes off drug.
Infection	Grade 2 that is probably or definitely related to anakinra	Hold study drug until completion of antibiotic course and resolution of infection, then restart at same dose level.
Infection	Grade 2 recurs that is probably or definitely related to anakinra	Hold study drug until completion of antibiotic course and resolution of infection, then decrease dose by 1 dose level.
Infection	Grade 2 recurs after dose reduction that is probably or definitely related to anakinra	Patient comes off drug.
Infection	Grade 3 that is probably or definitely related to anakinra	Patient comes off drug.
Infection	Grade 4	Patient comes off drug.
Treatment-related malignancy	Grade 3	Patient comes off drug.
Treatment-related	Grade 4	Patient comes off drug.

malignancy		

Exceptions to the above treatment modifications:

1. Alopecia any grade
2. Grade 2 anorexia
3. Grade 2 fever
4. Grade 2 fatigue
5. Grade 2 flu-like symptoms
6. Grade 2 chills
7. Grade 2 headache
8. Grade 2 hypoalbuminemia
9. Hypocalcemia toxicity grade should be assigned based on the calcium level corrected for degree of hypoalbuminemia according to the following formula: albumin 1 gram/dL: total calcium 0.2 mmol/L. Ionized calcium can also be used to assess toxicity.
10. Grade 2 injection site reaction
11. Grade 2 malaise
12. Grade 2 nausea
13. Grade 2 dry skin
14. Grade 2 skin or soft tissue infection
15. Grade 2 paronychia
16. Basal cell carcinoma or squamous cell carcinoma of the skin

Doses withheld while recovering from an adverse event should not be made up.

3.4 QUALITY OF LIFE TOOLS/QUESTIONNAIRES

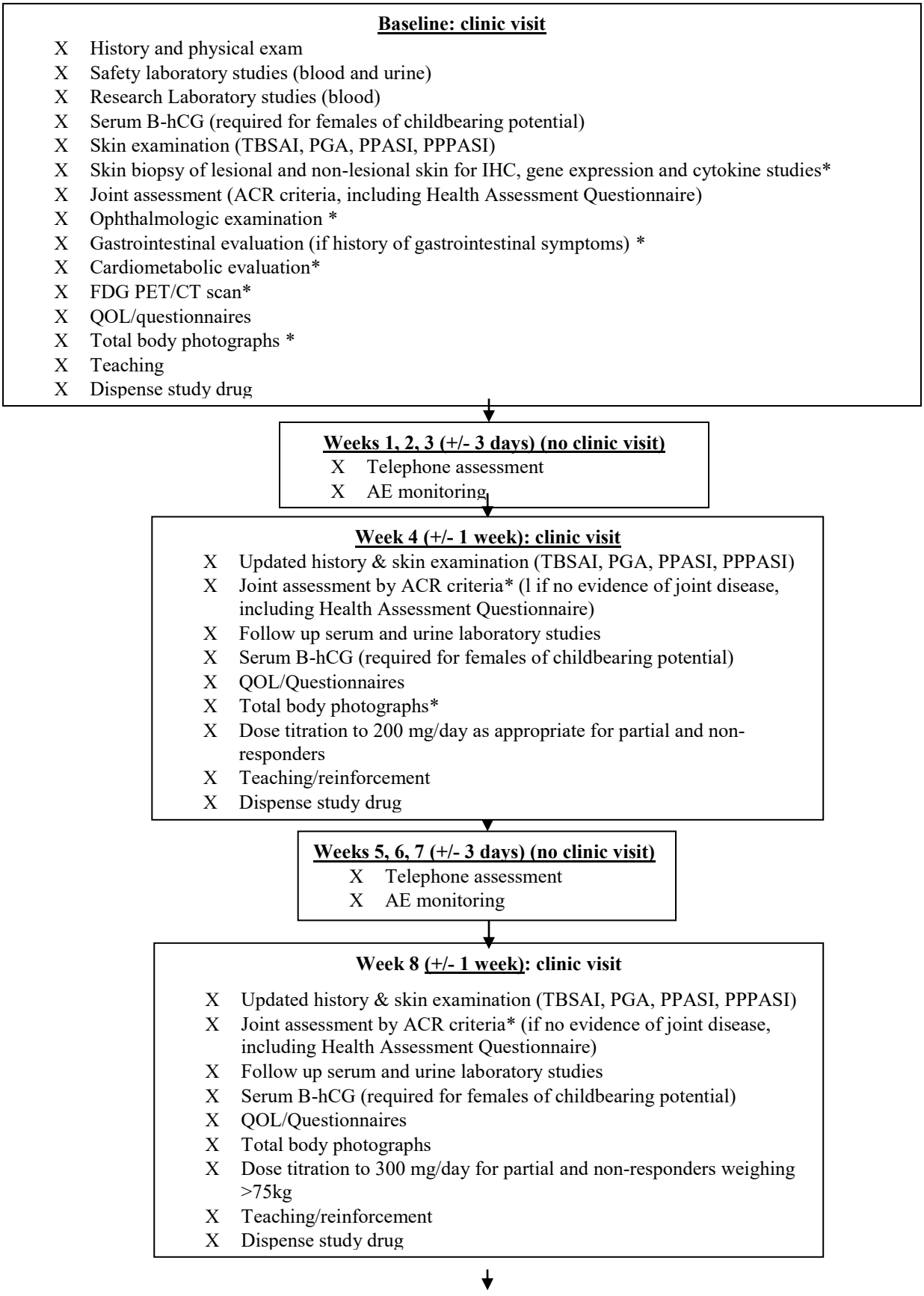
The following quality of life instruments will be administered at baseline, week 4, week 8 and week 12:

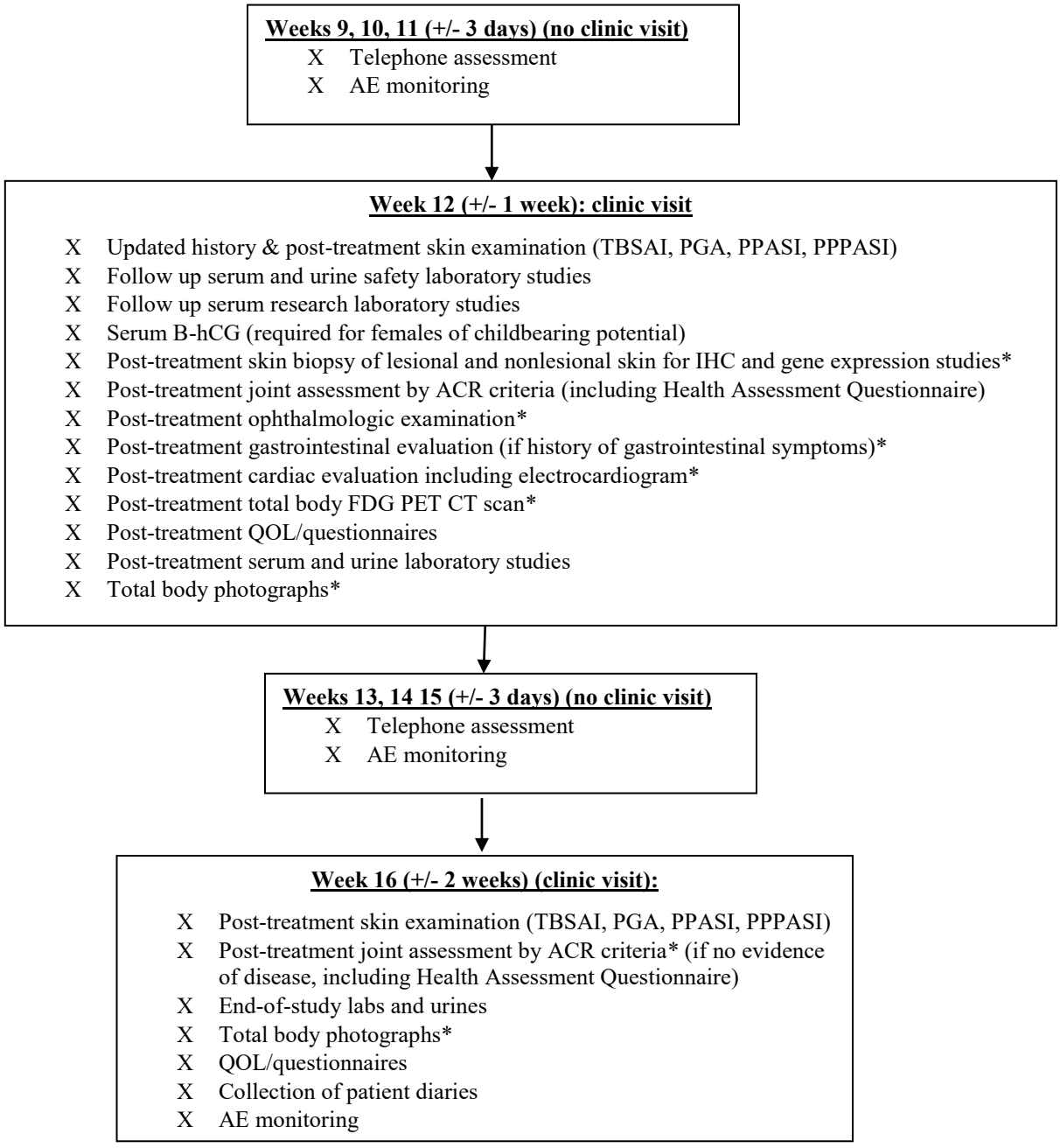
1. 36-item Short Form Health Survey is a self-administered multi-purpose, short-form health survey with 36 questions yielding an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure. This scale has been used for the measurement of general health status quality of life. This questionnaire will be administered at baseline, week 4, week 8, week 12 and week 16. (10-12 minutes) **(APPENDIX E: SHORT FORM 36 (ENGLISH AND SPANISH))**
2. Dermatology Life Quality Instrument (DLQI) is a 10-item questionnaire which assesses impact of skin disease on life quality. It is a validated questionnaire which has been used in 33 different skin conditions in 32 countries and is available in 55 languages. It is the most frequently used instrument in studies of randomized controlled trials in dermatology. This questionnaire will be administered at baseline, week 4, week 8, week 12 and week 16. (2 minutes) **(APPENDIX F: DERMATOLOGY LIFE QUALITY (ENGLISH AND SPANISH))**

3. Pruritus Visual Analog Scale is a self-administered psychometric response instrument which measures subjective characteristics or attitudes that cannot be directly measured. It ranges from 0-10. This scale has been used for measurement in a variety of dermatologic settings. This questionnaire will be administered at baseline, week 4, week 8, week 12 and week 16. (1 minute) (**APPENDIX H: PUSTULAR DERMATOSIS CLINICAL ASSESSMENT SCALE**)
4. Skin Pain Visual Analog Scale is a self-administered psychometric response instrument which measures subjective characteristics or attitudes that cannot be directly measured. It ranges from 0-10. This scale has been used for measurement in a variety of dermatologic settings. This questionnaire will be administered at baseline, week 4, week 8, week 12 and week 16. (1 minute) (**APPENDIX H: PUSTULAR DERMATOSIS CLINICAL ASSESSMENT SCALE**)
5. Joint Pain Visual Analog Scale is a self-administered psychometric response instrument which measures subjective characteristics or attitudes that cannot be directly measured. It ranges from 0-10. This scale has been used for measurement in a variety of dermatologic settings. This questionnaire will be administered at baseline, week 4, week 8, week 12 and week 16. (1 minute) (**APPENDIX H: PUSTULAR DERMATOSIS CLINICAL ASSESSMENT SCALE**)
6. Overall Disease Severity Visual Analog Scale is a self-administered psychometric response instrument which measures subjective characteristics or attitudes that cannot be directly measured. It ranges from 0-10. This scale has been used for measurement in a variety of health settings. This questionnaire will be administered at baseline, week 4, week 8, week 12 and week 16. (1 minute) (**APPENDIX H: PUSTULAR DERMATOSIS CLINICAL ASSESSMENT SCALE**)
7. Health Assessment Questionnaire (HAQ) is a self-administered questionnaire which aims to assess health-related quality of life longitudinally based on five patient-centered dimensions: disability, pain, medication effects, costs of care, and mortality. This instrument is used in the calculation of the ACR70. This questionnaire will be administered with each rheumatology evaluation. (5 minutes) **(APPENDIX I: HEALTH ASSESSMENT QUESTIONNAIRE)**

Completed questionnaires will be maintained in the subject's research chart until study analysis is completed.

3.5 STUDY FLOWCHART





*Denotes procedure/consultation that is to be performed at the discretion of the investigator.

3.6 STUDY CALENDAR

	Screening ≤8 weeks prior to enrollment	**Baseline-up to drug initiation** [a]	**Weeks 1, 2, 3 (+/- 3 days)**	**Week 4 (+/- 1 week)**	**Weeks 5, 6, 7 (+/- 3 days)**	**Week 8 (+/- 1 week)**	**Weeks 9, 10, 11 (+/- 3 days)**	**Week 12 (+/- 1 week): End of Treatment**	**Weeks 13, 14, 15 (+/- 3 days)**	**Week 16 (+/- 2 weeks): Post Therapy Follow-up** [a]
Eligibility	X	X-update		Clinic visit		Clinic visit		Clinic visit		
Consent		X								
H&P	X	X-update		X		X		X		X
NIH Advanced Directives Form[b]		X								
Medication review	X	X-update		X		X		X		X
Dose titration[c]				X		X				
Telephone surveillance			X		X		X		X	
Immunosuppressant drug taper (per MD discretion)					X	X	X	X		
CBC/diff, serum creatinine and urea nitrogen, hepatic panel with alk. phos, serum B-hCG	X	X		X		X		X		X

	Screening ≤8 weeks prior to enrollment	**Baseline- up to drug initiation [a]**	**Weeks 1, 2, 3 (+/- 3 days)**	**Week 4 (+/- 1 week)**	**Weeks 5, 6, 7 (+/- 3 days)**	**Week 8 (+/- 1 week)**	**Weeks 9, 10, 11 (+/- 3 days)**	**Week 12 (+/- 1 week): End of Treatment**	**Weeks 13, 14, 15 (+/- 3 days)**	**Week 16 (+/- 2 weeks): Post Therapy Follow-up[a]**
Blood sampling: calcium, phosphorus, albumin, total protein, ESR, hs-CRP, serum c-peptide		X		X		X		X		X
Urine sampling: UA, calcium, phosphorus		X		X		X		X		X
Ferritin, lipid panel, serum insulin, serum glucose		X								
Serum and urine protein electrophoresis, Parathyroid hormone, Serum 25-OH Vitamin D, anti-nuclear antibody, anti-dsDNA antibodies, anti-ENA antibodies, rheumatoid factor, C3, C4, CH50, HLA typing, quantitative serum immunoglobulins, anti-streptolysin O titer		X								
HIV screen and hepatitis screen	X									
Total body photographs		X		X		X		X		X

	Screening ≤8 weeks prior to enrollment	**Baseline-up to drug initiation [a]**	**Weeks 1, 2, 3 (+/- 3 days)**	**Week 4 (+/- 1 week)**	**Weeks 5, 6, 7 (+/- 3 days)**	**Week 8 (+/- 1 week)**	**Weeks 9, 10, 11 (+/- 3 days)**	**Week 12 (+/- 1 week): End of Treatment**	**Weeks 13, 14, 15 (+/- 3 days)**	**Week 16 (+/- 2 weeks): Post Therapy Follow-up[a]**
Total body surface area involvement measurement		X		X		X		X		X
PGA scoring		X		X		X		X		X
Skin biopsy	X[g]	X[h]						X[h]		
Quantiferon T gold	X[d]									
Chest X-ray if positive Quantiferon TB Gold	X[d]									
Microbiologic culture of pustule confirming noninfectious etiology	X									
FDG-PET CT scan		X						X		
Joint MRI		X						X		
Research blood sampling		X						X		
Rheumatology Consultation including ACR assessment[e]		X		X		X		X		X
Cardiometabolic evaluation including electrocardiogram		X						X		
Ophthalmologic examination		X						X		
Gastrointestinal consultation		X						X		

	Screening ≤8 weeks prior to enrollment	**Baseline- up to drug initiation [a]**	**Weeks 1, 2, 3 (+/- 3 days)**	**Week 4 (+/- 1 week)**	**Weeks 5, 6, 7 (+/- 3 days)**	**Week 8 (+/- 1 week)**	**Weeks 9, 10, 11 (+/- 3 days)**	**Week 12 (+/- 1 week): End of Treatment**	**Weeks 13, 14, 15 (+/- 3 days)**	**Week 16 (+/- 2 weeks): Post Therapy Follow-up[a]**
QOL/questionnaires[f]		X		X		X		X		X
Daily scoring diary		**Start Day 0**		X----------						----------X
AE Monitoring		START	X	X	X	X	X	X	X	X

[a] Additional clinical labs may be obtained as indicated at baseline and follow up visits

[b] As indicated in section **10.3**, all subjects at NIH will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

[c] If escalation criteria are met (see Section **3.2**)

[d] Within 8 weeks of enrollment

[e] If the rheumatology consult is done at Week 0, the patient will be seen again at Week 12. If there is evidence of joint disease, patients will be strongly encouraged to have rheumatology consult during all clinic visits (Weeks 0, 4,8, 12 and 16)

[f] QOL/questionnaires (see Section **3.4**)

[g] Skin biopsy for hematoxylin and eosin staining to confirm diagnosis if prior confirmational biopsy has not been performed

[h] Performed at the investigator's discretion for research purposes

3.7 SURGICAL GUIDELINES

Skin biopsies of lesional and nonlesional skin will be taken at baseline and week 12. Skin biopsy procedure will be explained to the patient and informed consent will be obtained. The risks of infection, scarring, nerve damage, pigment change, numbness, recurrence, bleeding, pain, and allergy to anesthesia will be reviewed. Sterile preparation of the proposed biopsy site will be performed. The biopsy site will be locally anesthetized. Size of punch biopsies will be up to 6mm. One punch biopsy will be performed from nonlesional skin, and up to two punch biopsies will be performed from lesional skin. We will place sutures for hemostasis. Petrolatum and bandage will be applied to the wound site and wound care will be reviewed. Written wound care instructions will be given. We will instruct the patient regarding suture removal.

3.8 OPHTHALMOLOGIC PROCEDURES

3.8.1 Ophthalmic Examination with Dilation

Dilation of the pupils will cause temporary glare and blurring of vision. Rarely an allergic reaction or infection secondary to contaminated drops can occur. Dilating drops can also cause a sudden increase of pressure (acute glaucoma) in eyes that are already predisposed to develop this condition. There is little risk of glaucoma being triggered in this way, but if it is, treatment will be available.

3.8.2 Fluorescein Angiography (if clinically indicated)

The participant's skin may turn yellow for several hours. The yellow color will disappear as the kidney filters the dye from the body. Because the dye passes through the kidneys, the urine will turn dark orange for up to 24 hours after the exam. Some participants may be slightly nauseous (upset stomach) during the exam, but their nausea usually lasts only a few seconds. If the dye leaks out of the vein during the injection, some of the skin around the injection site may feel mildly uncomfortable or become yellow. The mild discomfort usually lasts only a few minutes, and the yellow color goes away in a few days.

Sometimes participants have an allergic reaction to the dye, but this rarely happens. Oral antihistamines are usually used to treat this or the antihistamines may be injected if the symptoms are severe. Very rarely, a participant may have a severe allergic reaction that causes respiratory distress and shock ("anaphylaxis"), which can be life-threatening. Trained personnel with drugs or, possibly, surgery would treat this immediately.

3.8.3 Optical Coherence Tomography (OCT)

There is no medical risk from OCT.

3.8.4 Microperimetry

There is no medical risk from microperimetry.

3.9 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to documenting removal from study, effort must be made to have all subjects complete a safety visit approximately 28 days following the last dose of study therapy.

3.9.1 Criteria for removal from protocol therapy

- Completion of 12-week anakinra therapy
- Noncompliance with protocol procedures
- Pregnancy
- Participant requests to be withdrawn from active therapy
- Non-allergic toxicity or observed allergic reaction to anakinra
- Investigator discretion
- Positive pregnancy test
- Death

3.9.2 Off-Study Criteria

- Completion of post-treatment week 16 off-study visit
- Participant requests to be withdrawn from study
- Death

3.9.3 Off Protocol Therapy and Off Study Procedure

3.9.3.1 Clinical Center Off Protocol Therapy and Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Update Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

3.9.3.2 Participating Site Off Protocol Therapy and Off-Study Procedure

The Participant Status Update Form will be supplied by the NIAMS study coordinator. Send the completed form to the NIAMS study coordinator.

3.10 BASIC AND CLINICAL SCIENCE RESEARCH PLAN

3.10.1 Characterize and dissect inflammatory pathways in participant lesional skin and peripheral blood mononuclear cells

3.10.1.1 Immunohistochemical studies

Immunohistochemistry studies will be utilized to characterize the hematopoietic inflammatory infiltrate in lesional skin, including neutrophils (neutrophil elastase and CD15), myeloid dendritic cells (blood dendritic cell antigen [BDCA]-1, CD11c, BDCA-3), macrophages (CD163) and T lymphocytes (CD3).

Two-color immunofluorescence will be performed to determine $CARD14^{+}$ cells (e.g., CARD14 versus CD11c, CARD14 versus CD163)[55-57].

3.10.1.2 Global gene expression studies

Lesional and nonlesional skin biopsies obtained before and after treatment with anakinra will be assayed for gene expression profiles with microarray assays. Genes associated with immune dysregulation and cell differentiation will be assessed and compared between patients. Gene expression will be confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) and quantitative RT-PCR for low-expressing cytokines.

For patients with systemic inflammation characterized by fever, marked leukocytosis and/or elevated acute phase reactants, we will perform gene expression studies on peripheral blood mononuclear cells (PBMCs) before and after treatment with anakinra.

These profiles will be compared with gene expression profiles from lesional skin in patients with known DIRA (n=2), CARD14 mutations (n=3), and familial psoriasis (n=5). Additional analytic approaches will include Ingenuity Pathways Analysis (IPA), and Gene Set Enrichment Analysis (GSEA)[55, 58, 59].

Genomics studies will not be performed on this protocol. Genomics studies for pustular dermatoses will be performed on protocol 17-I-0016. At the time of enrollment, patients will be offered simultaneous enrollment in protocol 17-I-0016. (Section **5.2**)

3.10.1.3 Cytokine studies

We will perform skin and serum studies before and after anakinra therapy to assess levels of inflammatory cytokines including IL-1b, IL-6, IL-8, IL-17, IL-21, IL-22, IL-23, G-CSF and TNF using RT-PCR Luminex assay.

3.10.2 Evaluate systemic inflammation in participants with pustular dermatoses using imaging modalities and biomarkers of cardiometabolic disease

3.10.2.1 Fluoro-Deoxy-Glucose PET CT Imaging for Body Metabolism

We will utilize a technique for quantifying the extent of atherosclerosis in the aorta by combining standard uptake values (SUVs) in the aortic wall obtained using FDG-PET with volumetric data provided by CT [60, 61]. FDG uptake will be measured in all six segments of the aorta by calculating the mean combining SUVs for each segment. On each axial CT image, region-of-interest tracings along the inner and outer wall contours of the aorta are created. The average SUVs are then multiplied by the wall volume to calculate the total amount of vascular inflammation for each segment of the aorta. This total amount of vascular inflammation of each aortic segment can be used as an indicator of the extent of the atherosclerotic process by combining the functional and structural data provided by FDG-PET and CT.

Subjects will fast for six hours prior to imaging. Blood glucose will be checked and should be in the 100-160 mg/dL range to ensure an optimum study. The patient is injected with 10 mCi of 18-Fluoro-Deoxy glucose (FDG) and then rests for 60 minutes. The effective radiation dose of two 10 mCi injections of FDG is 2.6 rem. The subject will be positioned in a 16-slice PET CT scanner (GE, Discovery ST). The CT images acquired as part of the PET CT examination will be acquired using a low dose technique during quiet breathing. The CT images will allow for attenuation correction of the PET emission data, and will aid in the accurate anatomical

localization of sites of radiotracer uptake seen on PET images. The scanning time is typically 45 minutes. The CT and PET images are co-registered and can be viewed and interpreted.

The presence of brown fat is inferred from the following:

- FDG uptake in known usually symmetric distribution in the body
- Corresponding CT appearances consistent with fat at a site of FDG uptake

Whole body metabolism can be assessed by visual inspection of scout images and then quantified using standardized uptake volumes (SUV).

3.10.2.2 Evaluating biomarkers of cardiometabolic disease

We will evaluate biomarkers of cardiovascular disease by assaying pro-atherogenic lipoproteins via nuclear magnetic resonance spectroscopy (NMR), and high density lipoprotein (HDL) function via HDL cholesterol efflux capacity.

3.10.3 Evaluate keratinocyte responses to targeted inflammatory stimuli including infectious agents and danger molecules.

3.10.3.1 Characterize response to Toll-like receptor (TLR) stimulation

Our preliminary data shows that keratinocytes from patients with monogenic forms of pustular diseases not only produce higher levels of proinflammatory cytokines and chemokines in response to stimulation, but also demonstrate hyper- and parakeratosis histologically, thus indicating abnormal differentiation and abnormal apoptosis. We will create keratinocyte cell lines to assess whether keratinocytes from patients with pustular lesions have abnormal responses to TLR stimulation. We have made keratinocyte cell lines from skin biopsies from both healthy individuals and patients with monogenic pustular skin diseases (healthy controls, n=6; DIRA, n=2; CARD14, n=1). We will create keratinocyte cell lines from study participants with genetically-undefined pustular diseases. The keratinocyte cell lines will be immortalized as recently described in the presence of feeder cells and a ROCK-inhibitor.[62]

Keratinocytes from healthy controls, patients with monogenic forms of pustular disease, and patients with genetically-undefined pustular diseases will be exposed to a panel of TLR stimulants. We will use gene expression profiling to assess the impact of TLR stimulation on cell differentiation.

3.10.3.2 Compare affected and unaffected keratinocytes and fibroblasts with those of patients with monogenic pustular diseases and genetically-undefined pustular diseases in an organotypic raft culture system

We will study signaling pathway effects on keratinocyte proliferation and differentiation in an environment that closely mimics human epidermis. The organotypic raft culture system has been shown to mimic the functional alterations observed in inflammatory disease[63]. Immortalized keratinocytes (as described above) will be used to generate rafts to examine the response of these cells to stimuli from cytokines and TLR agonists.

We will evaluate inflammatory and differentiation properties in keratinocytes from study participants. Immunohistochemical techniques will be applied to raft cultures to evaluate alterations in markers of proliferation (PCNA, Ki67) and differentiation (epidermal differentiation markers including loricrin, filaggrin, involucrin, keratin 1, keratin 10) between unaffected controls and patient samples. Preliminary characterization by western blot analysis of immortalized keratinocytes from unaffected controls differentiated in culture with calcium[64] indicate that this methodology is also applicable for these samples.

4 CONCOMITANT MEDICATIONS/MEASURES

No drug-drug interaction studies with anakinra in human subjects have been conducted. Toxicological and toxicokinetic studies in rats did not demonstrate alterations in the clearance or toxicological profile of either methotrexate or anakinra when the two agents were administered together. In two studies of concurrent etanercept and anakinra therapy, patients were treated for up to 24 weeks and a 7% rate of serious infections was observed, which was higher than when either agent was used alone. Two percent of patients (3/139) treated concurrently with anakinra and etanercept developed neutropenia (ANC < 1 x 10^9/L). Patients enrolled into this study will be required to discontinue etanercept (Enbrel®), or other TNF-inhibitor therapy, including infliximab (Remicade®), golimumab (Simponi®) and adalimumab (Humira®), certolizumab (Cimzia®), and other TNF-inhibiting agents such as thalidomide at least three half lives prior to initiation of anakinra therapy because of a potential increased risk of infection (**APPENDIX A**: **FORBIDDEN DRUGS**). All medication changes will be recorded in the patient daily diary.

4.1 SUPPORTIVE CARE

Patients will be screened thoroughly and will be instructed by medical providers to detect and report early signs of side effects related to anakinra. Patients will receive instructions on monitoring, recording, and reporting side effects or adverse events. Should subjects experience an adverse event, they will be instructed to contact the study team immediately and to anticipate a clinic visit for evaluation and possible treatment.

4.1.1 NIH Patients

Communication and consultation with physicians and nurses is available 24 hours a day, 7 days a week through the nursing unit of the NIAMS Dermatology Clinic or the NIH page operator at (301) 496-1211. When possible, subjects requiring supportive care will be evaluated at the NIH. If a subject is unable to be seen at the NIH, telephone consultation will be available, as described above, to assist other practitioners involved in the patient's care.

4.1.2 UCSF Patients

Communication and consultation with physician and study coordinator is available 24 hours a day, 7 days a week through the UCSF Dermatology Clinic, the UCSF page operator or the confidential patient portal service, MyChart. When possible, subjects requiring supportive care will be evaluated at UCSF. If a subject is unable to be seen at UCSF, telephone consultation will be available, as described above, to assist other practitioners involved in the patient's care.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH

The research nurse will be responsible for coordinating transport of biospecimen samples collected throughout the study.

5.1.1 Blood (Clinical and Research Samples)

Blood will be obtained from each patient during the initial and subsequent visits. All blood volumes to be drawn will remain within the NIH Clinical Center guidelines for adult patients. Only clinical laboratory and/or microbiology results will be returned to the patient or their designated primary care provider (PCP). In rare instances, blood drawing limit may exceed the expected volume as a result of loss or damage of blood samples, repeating the tests in order to validate unusual or erroneous results, will not exceed the limits set forth by the NIH CC MEC policy. The amount of blood drawn from adults for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight week period. Additionally, aliquots of blood may be coded and shared with other collaborating researchers/investigators, under the auspices of appropriate material transfer agreements.

5.1.1.1 Clinical bloods

Blood samples will be analyzed for standard medical evaluations as outlined in Section **2**.

5.1.1.2 Research bloods

Research blood will be drawn to examine serologic and immunological markers, including but not limited to cytokines, cardiometabolic markers including fasting insulin and glucose and gene expression studies (see section **3.10.1.2**).

5.1.1.3 Research biopsies

At the investigator's discretion, research skin punch biopsies will be collected from lesional and nonlesional skin at baseline and week 12 to perform immunohistochemistry studies, cytokine studies and gene expression studies. Keratinocyte responses to infectious and inflammatory stimuli will be assessed. Keratinocytes will also be used to make cell lines which will then be used to study keratinocytes inflammatory and differentiation properties in vitro.

5.1.2 Research samples collected at UCSF

All blood (Sodium Heparin, SST, EDTA, Pax Gene tubes) and biopsy specimens in DMEM culture medium and biopsy specimens in RNAlater will be shipped to NIH in an ambient thermal container overnight to be received within 24 hours of collection. Specimens should be shipped to the below address:

Yan Huang
10 Center Dr., Room 11C-216
Bethesda, MD 20892
301-761-7637
yan.huang2@nih.gov

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

Please refer to protocol 17-I-0016 for details.

Whole blood, blood products, tissue, and RNA from all subjects will be stored indefinitely in the laboratories of Dr. Goldbach-Mansky and Dr. Nehal Mehta, and coded by study date and number. Patient samples will be identifiable using a database that is only accessible to the researchers intimately involved with the protocol. The samples themselves will not have direct patient identifiers.

Effective with amendment J, all patients will be offered simultaneous enrollment in protocol 17-I-0016, which aims to comprehensively evaluate patients with inflammatory multi-system diseases clinically, genetically, immunologically, and endocrinologically, and evaluate long term outcomes and biomarkers. If the patient consents to both studies, data collected on protocol 17-I-0016 will be correlated with data collected on our protocol.

NOTE: Prior to amendment J, subjects were offered simultaneous enrollment onto protocol 03-AR-0173, for the purposes described above. However, data from protocol 03-AR-0173 has been transferred to protocol 17-I-0016.

If the patient withdraws consent, the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will report any loss or destruction of samples to the NIH Intramural IRB as soon as he is made aware of such loss.

The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

Samples at NIH will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without IRB notification and an executed MTA.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

Data will be collected by investigators during visits and recorded in the patient's permanent medical record. Data will be entered into the C3D database. Protocol-specific case report forms will be developed and completed by the clinical teams. Data collection forms may include the clinical and laboratory information obtained from standard clinical evaluations at study entry,

organ-specific scales, selected research laboratory data and the follow-up outcomes that are necessary for determination of primary and secondary endpoints.

Personal identifiers will not be used when collecting and storing data. An enrollment log will be maintained in the regulatory binder/file which is the only location of personal identifiers with unique subject identification number.

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for 28 days after removal from study treatment or until off-study, whichever comes first.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

6.2 RESPONSE CRITERIA

6.2.1 Definitions

For the purposes of this study, patients will be evaluated for response every 4 weeks.

Response is defined by at least 50% reduction in TBSAI at week 12.

Partial Response is defined by 25-49% reduction in TBSAI at week 12.

No response to therapy is defined as stable or worsened (increase in total body surface area involvement) skin disease on anakinra.

Other parameters used to assess disease response include American College of Rheumatology criteria and other clinical markers. ACR20/50/70 is defined as 20%, 50% and 70% improvement in tender or swollen joint counts, respectively.

6.2.2 Disease Parameters

Measurable disease: Total body surface area involvement of pustules and erythematous plaques will be measured in this study. At the time of enrollment, all study participants will have active disease warranting systemic therapy, as defined by macroscopic non-infective pustular and inflammatory skin lesions involving ≥ 5% of the total body surface area, or palmoplantar involvement.

Joint involvement will also be assessed using criteria set forth by the American College of Rheumatology.

6.2.3 Methods for Evaluation of Measurable Disease

Plaque and pustular disease will be measured by Total Body Surface Area Involvement (TBSAI) as well as Physician Global Assessment (PGA). Additionally, Pustular Psoriasis Assessment Severity Index (PPASI) and Palmoplantar Psoriasis Assessment Severity Index (PPPASI) scores will be calculated for each patient (**APPENDIX H: PUSTULAR DERMATOSIS CLINICAL ASSESSMENT SCALE**). All baseline evaluations will be performed as closely as possible to the beginning of treatment and not more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize skin lesions at baseline and during follow-up.

Clinical lesions: Skin lesions will be documented using clinical examination and disposable ruler as needed, and color photography (at the investigator's discretion). Joint lesions will be documented by clinical examination as delineated by ACR guidelines, and joint imaging modalities. Ocular involvement will be assessed through a comprehensive ophthalmic exam including assessment for keratoconjunctivitis. Ocular exams will occur in the eye clinic at baseline and at completion of the study unless otherwise medically indicated. Specialized ophthalmic testing (i.e., optical coherence tomography, fluorescein angiography, fundus photos or visual fields) will only be performed if medically indicated and required to establish a diagnosis.

Histology: Histologic evaluation will be used to diagnose and characterize disease at the time of enrollment and completion of anakinra.

6.2.4 Response Criteria

6.2.4.1 Evaluation of Target Lesions

TBSAI50 is defined as 50% improvement in total body surface area involvement.

ACR20/50/70 is defined as 20%, 50% and 70% improvement in tender or swollen joint counts and other clinical markers, respectively.

No response to therapy is defined as stable or worsened (increase in total body surface area involvement) skin disease on anakinra.

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon

appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NIH INTRAMURAL IRB AND CLINICAL DIRECTOR REPORTING

7.2.1 NIH Intramural IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NIH Intramural IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.2.2 NIH Intramural IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NIH Intramural IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:

    - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
    - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
    - All Grade 5 events regardless of attribution;
    - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.3 NCI Guidance for Reporting Expedited Adverse Events for Multi-Center Trials

The site PI must immediately report to the coordinating center PI any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event within 24 hours of PI awareness of the event. The Site PI must also report any protocol deviations to the coordinating center PI within 7 days of PI awareness using the problem report form (See **APPENDIX L**: **CCR PROBLEM REPORT FORM**). A copy of this form can also be obtained from the NIAMS study coordinator. Participating centers must also submit the report to their IRB in accordance with their institutional policies.

7.4 Data and Safety Monitoring Plan

7.4.1 Principal Investigator/Research Team

The clinical research team will meet weekly when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.4.2 Safety Monitoring Committee (SMC)

This protocol will require oversight from the Safety Monitoring Committee (SMC). Initial review will occur as soon as possible after the annual NIH Intramural IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period. Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

8 STATISTICAL CONSIDERATIONS

The primary objective of this one-stage phase 2 study is to obtain an estimate of the response rate to treatment with anakinra for pustular dermatoses. Those patients who experience at least a 50% improvement in TBSAI will be considered responders. With 25 evaluable patients, the maximum width of a two-sided 95% confidence interval will be +/-20% if the response rate is 50%, and less wide if the response rate is either lower or higher than 50%. An early stopping rule will be implemented in order to guard against undue risk to enrolled subjects. If 0 of the first 9 patients fail to respond to anakinra therapy, there is a 95% probability that the true response rate is 28% or less, which is unacceptably low, and we will halt further patient recruitment.

All other biologic parameters will be evaluated using exploratory and descriptive methods, emphasizing non-parametric techniques.

It is anticipated that 1-2 patients per month may enroll onto this trial. In order to allow for a small number of unevaluable patients, the accrual ceiling will be set at 30 patients. Accrual would be estimated to last 18-24 months in order to enroll up to 30 patients.

9 COLLABORATIVE AGREEMENTS

9.1 AGREEMENT TYPE

9.1.1 Clinical Trials Agreement

Clinical Trials Agreement (CTA) # 924 has been executed for the transfer of anakinra from Biovitrum to NCI.

9.1.2 Material Transfer Agreement

A Material Transfer Agreement will be executed with Hailey Naik/ University of California, San Francisco for the transfer of blood specimens and patient data.

9.2 MULTI-INSTITUTIONAL GUIDELINES

9.2.1 IRB Approvals

The PI will provide the NIH Intramural IRB with a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NIH Intramural IRB.

9.2.2 Amendments and Consents

The NIAMS PI will provide the NIH Intramural IRB with copies of all amendments, consents and approvals from each participating institution.

10 HUMAN SUBJECTS PROTECTIONS

10.1 Rationale For Subject Selection

Subjects who have inflammatory pustular skin diseases will be enrolled. The gender, age and ethnic distribution is expected to represent the characteristics of the patients genetically predisposed to developing these conditions. This protocol intends to enroll an appropriately balanced study population consistent with the distribution of these diseases. No sex or racial/ethnic group will be specifically recruited or excluded for this study.

10.2 Participation of Children

Individuals under the age of 18 will not be eligible to participate in this study at this time due to discomfort of multiple injections and dose escalation nature of the study as well as the unknown safety of higher than FDA approved doses in children.

10.3 Participation of NIH Subjects Unable to Give Consent

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **10.5**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MAS Policy 87-4 and NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

10.3.1 For Participating Sites

Participating sites should follow local procedures regarding re-consent for subjects that become decisionally impaired.

10.4 Evaluation of Benefits and Risks/Discomforts

Subjects participating in this protocol may potentially benefit from an improvement in symptoms of neutrophilic pustular dermatosis. Potential risks include the range of side effects listed in

section **11.1.2**. Subjects will be evaluated medically throughout the protocol in order to minimize risk.

Blood Sampling
Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

Tissue Biopsy
All care will be taken to minimize risks that may be incurred by tissue sampling. However, there are procedure-related risks (such as bleeding, infection and scarring) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsies, medical treatment is available at the NIH's Clinical Center in Bethesda, Maryland or other participating site. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

10.5 Risks/Benefits Analysis

Inflammatory pustular dermatoses are associated with significant morbidity and mortality. Patients with generalized skin disease are subject to risk of infection. Many of the pustular dermatoses are refractory to currently-available therapies which fail to mitigate disease course and complications. Randomized controlled trials have not been undertaken due to rarity of disease and cost of such a study. An effective therapeutic agent for the management of this group of diseases would be both a significant contribution to clinical management and to our understanding of pathogenesis of neutrophilic and pustular disease. Based on current scientific knowledge, IL-1 plays a key role in pathogenesis of neutrophilic and pustular diseases. IL-1 antagonist anakinra has been safely and successfully used in children with autoinflammatory diseases including NOMID and DIRA, and we anticipate the drug will be similarly well-tolerated in adults with pustular diseases. We anticipate this study will be associated with more than minimal risk and offers the prospect of direct benefit due to protocol treatment for adult subjects, including those who are or may become unable to consent.

10.6 Consent Process and Documentation

Patients will meet with an associate or principal investigator on the trial in the NIH Dermatology Clinic or participating site clinic during the initial evaluation for this study. During that meeting, the investigator will inform patients of the purpose, alternatives, treatment plan, research objectives and follow-up of this trial. The investigator will then provide a copy of the IRB-approved informed consent document that is included in this protocol. The patient will be allowed to take as much time as he wishes, in deciding whether or not he wishes to participate. If a prolonged period of time expires during the decision-making process (several weeks, as an example), it may be necessary to reassess the patient for protocol eligibility. Subjects will consent to procedures performed at the investigator's discretion (biopsy, PET scan, CT scan, MRI scan) at the time of the procedure. If the subject refuses the optional procedure at that time, the refusal will be documented in the medical record and in the research record. The original signed consents go to Medical Records; and a copy of each will be placed in the research record (NIH policy).

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on the study.

10.6.1 Telephone Reconsent

Reconsent on this study may be obtained via telephone according to the following procedure: the informed consent document will be sent to the subject. An explanation of the change (s) in the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator.

10.6.2 Informed consent of non-English speaking subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation. Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

11 PHARMACEUTICAL INFORMATION

11.1 ANAKINRA

Please refer to package insert for complete information. This protocol is exempt from an IND in accordance with Title 21 of the Code of Federal Regulations, Part 312.2 (b) as it meets all of the following exemption criteria:

1. The investigational drug is lawfully marketed in the United States.
2. The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use of the drug product.

3. The investigation is not intended to support a significant change in advertising to an existing lawfully marketed prescription drug product.
4. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
5. The investigation will be conducted in compliance with the requirements for institutional review set forth in FDA regulations 21 CFR 56, and requirements for informed consent as set forth in FDA regulations 21 CFR 50.

11.1.1 Source: Biovitrum

Anakinra will be donated by the manufacturer. Anakinra may also be purchased directly through the NIH pharmacy for NIH patients.

11.1.2 Toxicity

The safety and efficacy of anakinra have been evaluated in 3 randomized, double-blind, placebo-controlled trials of 1392 patients ≥ 18 years of age with active RA[42]. An additional fourth study was conducted to assess drug safety.

Injection-site Reactions

The most common and consistently reported treatment-related adverse event associated with anakinra is injection-site reaction (ISR). Seventy-one percent of patients developed an ISR, which was typically reported within the first 4 weeks of therapy in clinical trials. The majority of ISRs were reported as mild (72.6% mild, 24.1% moderate and 3.2% severe). The ISRs typically lasted for 14 to 28 days and were characterized by 1 or more of the following: erythema, ecchymosis, inflammation, and pain.

Infections

In placebo-controlled trials, the incidence of infection was 39% in the anakinra-treated patients and 37% in placebo-treated patients during the first 6 months of blinded treatment. The incidence of serious infections in Studies 1 and 4 was 2% in anakinra-treated patients and 1% in patients receiving placebo over 6 months. The incidence of serious infection over 1 year was 3% in anakinra-treated patients and 2% in patients receiving placebo. These infections consisted primarily of bacterial events such as cellulitis, pneumonia, and bone and joint infections. The majority of patients (73%) continued on study drug after the infection resolved. No serious opportunistic infections were reported. Patients with asthma appeared to be at higher risk of developing serious infections when treated with anakinra (8 of 177 patients, 4.5%) compared to placebo (0 of 50 patients, 0%).

In open-label extension studies, the overall rate of serious infections was stable over time and comparable to that observed in controlled trials. In clinical studies and post marketing experience, cases of opportunistic infections have been observed and included fungal, mycobacterial and bacterial pathogens. Infections have been noted in all organ systems and have been reported in patients receiving anakinra alone or in combination with immunosuppressive agents.

In patients who received both anakinra and etanercept for up to 24 weeks, the incidence of serious infections was 7%. The most common infections consisted of bacterial pneumonia (4 cases) and cellulitis (4 cases). One patient with pulmonary fibrosis and pneumonia died due to respiratory failure.

Malignancies

Among 5300 RA patients treated with anakinra in clinical trials for a mean of 15 months (approximately 6400 patient years of treatment), 8 lymphomas were observed for a rate of 0.12 cases/100 patient years. This is 3.6 fold higher than the rate of lymphomas expected in the general population, based on the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database. However, reports indicate that the rate of lymphoma is doubled in the rheumatoid arthritis (RA) population, and may be further increased in patients with more severe disease activity[47, 48]. Thirty-seven malignancies other than lymphoma were observed. Of these, the most common were breast, respiratory system, and digestive system. There were 4 melanomas observed in one study and its long-term open-label extension, however these cases were not thought to be related to anakinra. The significance of this finding is not known. While patients with RA, particularly those with highly active disease, may be at a higher risk (up to several-fold) for the development of lymphoma, the role of IL-1 blockers in the development of malignancy is not known.

Hematologic Events

In placebo-controlled studies with anakinra, 8% of patients receiving anakinra had a decrease in total white blood counts of at least one WHO toxicity grade, compared with 2% of placebo patients. Nine anakinra-treated patients (0.4%) developed neutropenia (ANC < 1 x 10^9/L). Nine percent of patients receiving anakinra had increases in eosinophil differential percentage of at least one WHO toxicity grade, compared with 3 % of placebo patients. Of patients treated concurrently with anakinra and etanercept, 2% developed neutropenia (ANC < 1 x 10^9/L). One neutropenic patient developed cellulitis and recovered with antibiotic therapy. Two percent of patients receiving anakinra had decreased platelets, all of WHO toxicity grade one, compared to 0% of placebo patients.

Hypersensitivity Reactions

Hypersensitivity reactions including anaphylactic reactions, angioedema, urticaria, rash, and pruritus have been reported with anakinra.

Immunogenicity

In placebo-controlled studies, from which data is available for up to 36 months, 49% of patients tested positively at one or more time points for anti-anakinra antibodies in a highly sensitive, anakinra-binding biosensor assay. Of the 1615 patients with available data at Week 12 or later, 30 (2%) were seropositive in a cell-based bioassay for antibodies capable of neutralizing the biologic effects of Anakinra. Of the 13 patients with available follow-up data, 5 patients remained positive for neutralizing antibodies at the end of the studies. No correlation between antibody development and adverse events was observed.

Antibody assay results are highly dependent on the sensitivity and specificity of the assays. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, concomitant medications, and underlying disease.

For these reasons, comparison of the incidence of antibodies to anakinra with the incidence of antibodies to other products may be misleading.

Other Adverse Events

Other adverse events that occurred at similar rate to placebo included: URI, sinusitis, influenza like symptom, headache, nausea, diarrhea, sinusitis and abdominal pain.

Overdosage

There have been no cases of overdose reported with anakinra in clinical trials of rheumatoid arthritis. In sepsis trials, no serious toxicities attributed to anakinra were seen when administered at mean calculated doses of up to 35 times those given patients with RA over a 72-hour treatment period.

Experience in NOMID

In addition to the adverse events described in the package insert, our center has considerable experience in treating NOMID patients with anakinra. Our cohort of primarily pediatric patients has been treated with anakinra doses ranging from 1 mg/kg to 6.7 mg/kg daily. This practice is consistent with that of other specialty centers where doses as high as 10 mg/kg daily were used to control disease in the treatment of NOMID[65]. In our experience with 26 patients and 1494 patient-years (an average of 57.5 months / patient), the most frequently observed adverse events were upper respiratory infections 88.5%, gastroenteritis 46.2%, otitis media 38.5%, injection site reactions 34.6%, urinary tract infections 23.1%, transient transaminase elevation 15.4%, epistaxis 15.4%, otitis externa 11.6%, cellulitis 11.6%, and pneumonia 7.7%. One patient had an episode of viral meningitis, one had a catheter infection, and one had a recurrent bowel abscesses. Serious adverse events during this period included an ICU admission to evaluate for a post lumbar puncture bleed at 1 mg/kg/day, a wound infection with surrounding cellulitis at 3 mg/kg/day, and macrophage activation syndrome at 2 mg/kg/day. None of the adverse events required discontinuation of anakinra. In a cohort of 10 French NOMID patients treated with anakinra described with follow-up ranging from three months to twenty years, the only reported adverse events were injection site reactions[65].

11.1.3 Formulation and preparation

Anakinra is supplied in single use prefilled glass syringes with 27 gauge needles as a sterile, clear, colorless-to-white, preservative free solution for daily subcutaneous (SC) administration. The solution may contain trace amounts of small, translucent-to-white amorphous proteinaceous particles. Each prefilled glass syringe contains: 0.67 mL (100 mg) of anakinra in a solution (pH 6.5) containing disodium EDTA (0.12 mg), sodium chloride (5.48 mg), sodium citrate (1.29 mg), and polysorbate 80 (0.70 mg) in Water for Injection, USP.

11.1.4 Stability and Storage

Anakinra should not be shaken. Before using, the product should be checked visually for particles or discoloration. If either is present, the liquid should not be used. The medication should be warmed to room temperature for 60 to 90 minutes before injecting.

11.1.5 Administration procedures

This medication is injected subcutaneously once a day.

Before injecting each dose, the injection site should be cleaned with rubbing alcohol. It is important to change the location of the injection site daily. The medication should not be injected into an area that is tender, red, bruised, or hard or which has scars or stretch marks.

11.1.6 Incompatibilities

No drug-drug interaction studies in human subjects have been conducted. Toxicologic and toxicokinetic studies in rats did not demonstrate any alterations in the clearance or toxicologic profile of either methotrexate or anakinra when the two agents were administered together.

TNF Blocking Agents: A higher rate of serious infections has been observed in patients treated with concurrent anakinra and etanercept therapy than in patients treated with etanercept alone. Two percent of patients treated concurrently with anakinra and etanercept developed neutropenia (ANC< $1x10^9$/L). Use of anakinra in combination with TNF blocking agents is not recommended and use of TNF blocking agents is an exclusion criterion for study entry.

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13 APPENDIX A: FORBIDDEN DRUGS

Abatacept/Orencia

Adalimumab/Humira

Alefacept/Amevive

Canakinumab/Ilaris

Certolizumab/Cimzia

Etanercept/Enbrel

Golimumab/Simponi

Infliximab/Remicaide

Rilonacept/Arcalyst

Rituximab/Rituxan

Phototherapy

Live vaccines

14 APPENDIX B: PATIENT DIARY

PUSTULAR DERMATOSIS DIARY

Rate the symptoms from 0-3 to best describe the severity of the symptoms listed below
0=no symptoms
1=mild symptoms
2=moderate symptoms
3=severe symptoms (worst symptom observed)
Fever: list the actual temperature in degress farenheit
Overall-well being (0=poor, 1=fair, 2=good, 3=excellent)
Please list name of study drug: anakinra
Please list all steroid medications here:
Please list other immunosuppressive medications here:
Dilute bleach baths/hibiclens wash? Yes or No

Day	Date	Time Anakinra dose given	Fever	Rash	Pustules	Itching	Skin pain	Joint pain	Overall well-being	Dilute bleach bath/ hibiclens wash?
1										
2										
3										
4										
5										
6										
7										
8										
9										
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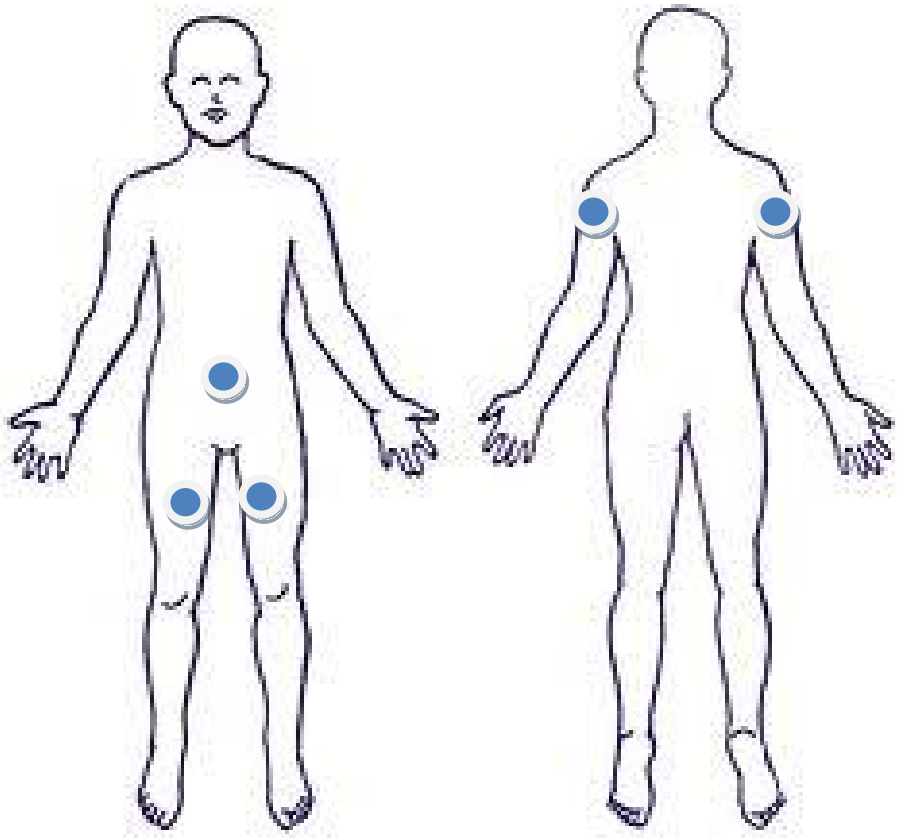
15 APPENDIX C: PATIENT HANDOUT

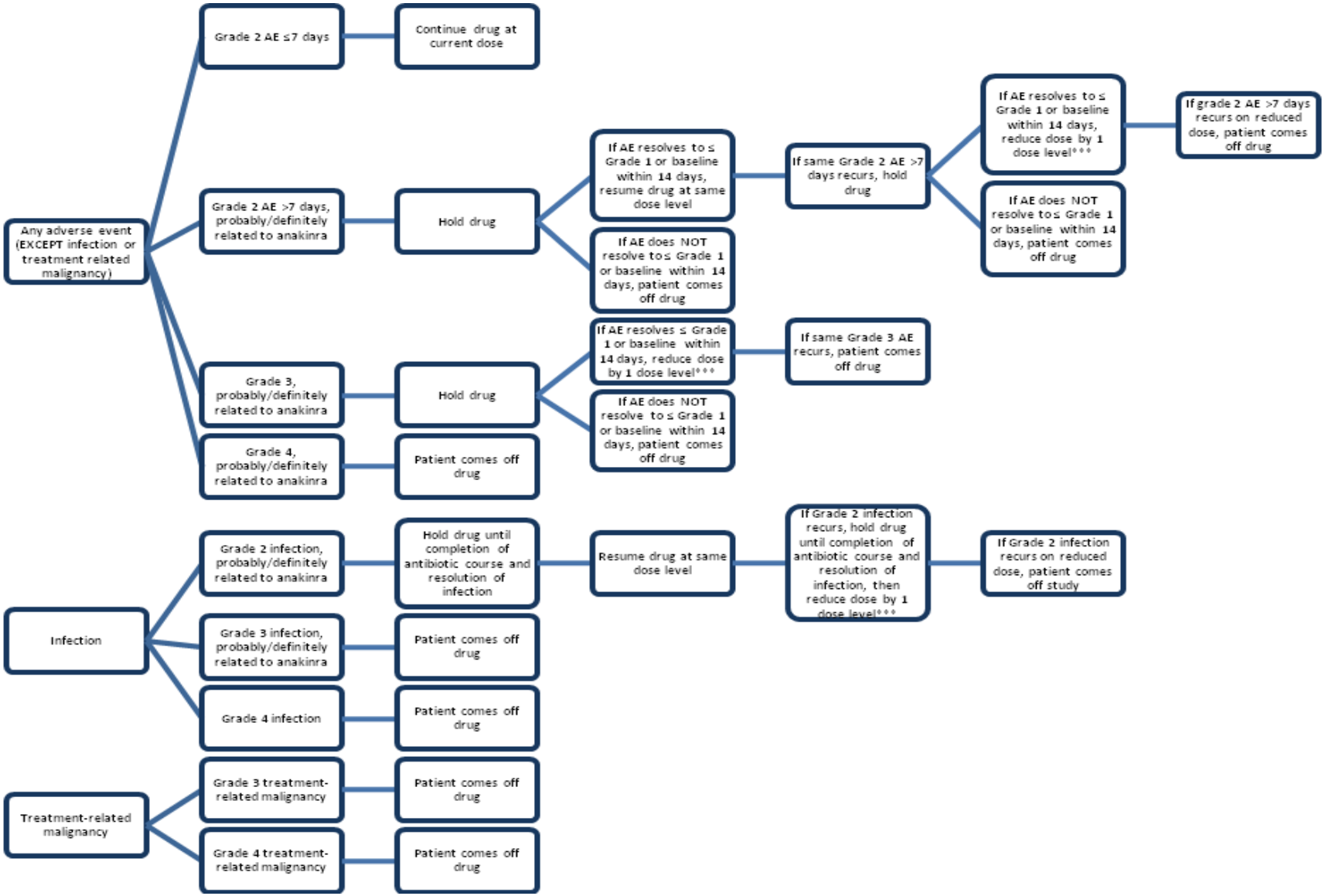
Where can I inject anakinra/Kineret®?

Upper arm
Abdomen
Thigh

Remember to rotate the injection site daily.



16 APPENDIX D: DOSE MODIFICATION FLOW CHART



17 APPENDIX E: SHORT FORM 36 (ENGLISH AND SPANISH)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b. Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f. Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g. Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h. Have you been happy?	☐1	☐2	☐3	☐4	☐5
i. Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b. I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c. I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d. My health is excellent	☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THESE QUESTIONS!

Collection of this information is authorized under 42 USC 285. The primary use of the information you provide is to assess your health and quality of life. The information may be disclosed to clinicians and researchers for research purposes and to monitor personnel to assure that safety standards are maintained. Submission of this information is voluntary.

Su Salud y Bienestar

Esta encuesta le pide sus opiniones acerca de su salud. Esta información permitirá saber cómo se siente y qué tan bien puede hacer usted sus actividades normales. ***¡Gracias por contestar estas preguntas!***

Para cada una de las siguientes preguntas, por favor marque con una ☒ la casilla que mejor describa su respuesta.

1. En general, ¿diría que su salud es:

Excelente	Muy buena	Buena	Pasable	Mala
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Comparando su salud con la de hace un año</u>, ¿cómo la calificaría en general <u>ahora</u>?

Mucho mejor ahora que hace un año	Algo mejor ahora que hace un año	Más o menos igual ahora que hace un año	Algo peor ahora que hace un año	Mucho peor ahora que hace un año
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. Las siguientes preguntas se refieren a actividades que usted podría hacer durante un día típico. ¿Su estado de salud actual lo/la limita para hacer estas actividades? Si es así, ¿cuánto?

		Sí, me limita mucho	Sí, me limita un poco	No, no me limita en absoluto
a	Actividades vigorosas, tales como correr, levantar objetos pesados, participar en deportes intensos	☐ 1	☐ 2	☐ 3
b	Actividades moderadas, tales como mover una mesa, empujar una aspiradora, jugar al bowling o al golf o trabajar en el jardín	☐ 1	☐ 2	☐ 3
c	Levantar o cargar las compras del mercado	☐ 1	☐ 2	☐ 3
d	Subir varios pisos por la escalera	☐ 1	☐ 2	☐ 3
e	Subir un piso por la escalera	☐ 1	☐ 2	☐ 3
f	Doblarse, arrodillarse o agacharse	☐ 1	☐ 2	☐ 3
g	Caminar más de una milla	☐ 1	☐ 2	☐ 3
h	Caminar varias cuadras (varios cientos de metros)	☐ 1	☐ 2	☐ 3
i	Caminar una cuadra (unos cien metros)	☐ 1	☐ 2	☐ 3
j	Bañarse o vestirse	☐ 1	☐ 2	☐ 3

4. Durante las <u>últimas 4 semanas</u>, ¿cuánto tiempo ha tenido usted alguno de los siguientes problemas con el trabajo u otras actividades diarias regulares <u>a causa de su salud física</u>?

	Siempre	Casi siempre	Algunas veces	Casi nunca	Nunca
a Ha reducido el <u>tiempo</u> que dedicaba al trabajo u otras actividades	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Ha logrado hacer menos</u> de lo que le hubiera gustado	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Ha tenido limitaciones en cuanto al <u>tipo</u> de trabajo u otras actividades	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Ha tenido <u>dificultades</u> en realizar el trabajo u otras actividades (por ejemplo, le ha costado más esfuerzo)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. Durante las <u>últimas 4 semanas</u>, ¿cuánto tiempo ha tenido usted alguno de los siguientes problemas con el trabajo u otras actividades diarias regulares <u>a causa de algún problema emocional</u> (como sentirse deprimido/a o ansioso/a)?

	Siempre	Casi siempre	Algunas veces	Casi nunca	Nunca
a Ha reducido el <u>tiempo</u> que dedicaba al trabajo u otras actividades	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Ha logrado hacer menos</u> de lo que le hubiera gustado	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Ha hecho el trabajo u otras actividades <u>con menos cuidado</u> de lo usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. Durante las <u>últimas 4 semanas</u>, ¿en qué medida su salud física o sus problemas emocionales han dificultado sus actividades sociales normales con la familia, amigos, vecinos o grupos?

Nada en absoluto	Ligeramente	Mediana-mente	Bastante	Extremada-mente
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. ¿Cuánto dolor <u>físico</u> ha tenido usted durante las <u>últimas 4 semanas</u>?

Ningún dolor	Muy poco	Poco	Moderado	Severo	Muy severo
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. Durante las <u>últimas 4 semanas</u>, ¿cuánto ha dificultado el <u>dolor</u> su trabajo normal (incluyendo tanto el trabajo fuera de casa como los quehaceres domésticos)?

Nada en absoluto	Un poco	Mediana-mente	Bastante	Extremada-mente
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. Estas preguntas se refieren a cómo se siente usted y a cómo le han ido las cosas durante las últimas 4 semanas. Para cada pregunta, por favor dé la respuesta que más se acerca a la manera como se ha sentido usted. ¿Cuánto tiempo durante las últimas 4 semanas…

	Siempre	Casi siempre	Algunas veces	Casi nunca	Nunca
a se ha sentido lleno/a de vida?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b se ha sentido muy nervioso/a?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c se ha sentido tan decaído/a de ánimo que nada podía alentarlo/la?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d se ha sentido tranquilo/a y sosegado/a?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e ha tenido mucha energía?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f se ha sentido desanimado/a y deprimido/a?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g se ha sentido agotado/a?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h se ha sentido feliz?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i se ha sentido cansado/a?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. Durante las últimas 4 semanas, ¿cuánto tiempo su salud física o sus problemas emocionales han dificultado sus actividades sociales (como visitar amigos, parientes, etc.)?

Siempre	Casi siempre	Algunas veces	Casi nunca	Nunca
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. ¿Qué tan CIERTA o FALSA es <u>cada una</u> de las siguientes frases para usted?

	Claramente cierta	Mayormente cierta	No sé	Mayormente falsa	Claramente falsa
a Parece que yo me enfermo un poco más fácilmente que otra gente	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Tengo tan buena salud como cualquiera que conozco	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Creo que mi salud va a empeorar	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Mi salud es excelente	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

¡Gracias por contestar estas preguntas!

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How to Score the Rand SF-36 Questionnaire

Step 1: Scoring Questions:

QUESTION NUMBER	ORIGINAL RESPONSE	RECORDED VALUE
1, 2, 20, 22, 34, 36	1	100
	2	75
	3	50
	4	25
	5	0
3, 4, 5, 6, 7, 8, 9, 10, 11, 12	1	0
	2	50
	3	100
13, 14, 15, 16, 17, 18, 19	1	0
	2	100
21, 23, 26, 27, 30	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
24, 25, 28, 29, 31	1	0
	2	20
	3	40
	4	60
	5	80
	6	100
32, 33, 35	1	0
	2	25
	3	50
	4	75
	5	100

Short Form-36 (SF-36) Health Survey continued.

Step 2: Averaging Items to Form 8 Scales:

SCALE	NUMBER OF ITEMS	AFTER RECORDING AS PER TABLE 1, AVERAGE THE FOLLOWING ITEMS
Physical functioning	10	3, 4, 5, 6, 7, 8, 9, 10, 11, 12
Role limitations due to physical health	4	13, 14, 15, 16
Role limitations due to emotional problems	3	17, 18, 19
Energy/fatigue	4	23, 27, 29, 31
Emotional well being	5	24, 25, 26, 28, 30
Social functioning	2	20, 32
Pain	2	21, 22
General health	5	1, 33, 34, 35, 36

Step 3: Figuring Scores:

RAND recommends the following straightforward approach to scoring the RAND 36-Item Health Survey.

All questions are scored on a scale from 0 to 100, with 100 representing the highest level of functioning possible. Aggregate scores are compiled as a percentage of the total points possible, using the RAND scoring table (STEP I chart).

The scores from those questions that address each specific area of functional health status (STEP II chart) are then averaged together, for a final score within each of the 8 dimensions measured. (eg pain, physical functioning etc.)

For example, to measure the patients energy/fatigue level, add the scores from questions 23, 27, 29, and 31. If a patient circled 4 on 23, 3 on 27, 3 on 29 and left 31 blank, use table 1 to score them.

An answer of 4 to Q23 is scored as 40, 3 to Q27 is scored as 60, and 3 to Q29 is scored as 40. Q31 is omitted. The score for this block is 40 + 60 + 40 = 140. Now we divide by the 3 answered questions to get a total of 46.7. Since a score of 100 represents high energy with no fatigue, the lower score of 46.7% suggests the patient is experiencing a loss of energy and is experiencing some fatigue.

All 8 categories are scored in the same way. Using this questionnaire at the beginning and during the course of care, we can track the progress of the 8 parameters mentioned in the STEP II chart.

References

Lansky D Butler JBV Waller FT. Using health status measures in the hospital setting. 1992; 30: MS57-MS73.

McDowell I Newell C. Measuring Health—A Guide to Rating Scales and Questionnaires Second Edition. Oxford Press. 1996. pages 446-456.

Ware JE Jr Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Medical Care. 1992; 30: 473-483.

Short Form-36 (SF-36) Health Survey.

18 APPENDIX F: DERMATOLOGY LIFE QUALITY (ENGLISH AND SPANISH)

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score: ☐
Address: Diagnosis:

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** or **self conscious** have you been because of your skin?	Very much ☐ A lot ☐ 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.

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CUESTIONARIO SOBRE LA CALIDAD DE VIDA – DERMATOLOGÍA

El objetivo de este cuestionario consiste en determinar qué efecto ha tenido su problema de la piel en su vida DURANTE LA ÚLTIMA SEMANA. Por favor marque con una "X" una casilla para cada pregunta.

1.	**Durante la última semana, ¿ha sentido** picazón**,** dolor **o** ardor **en la piel o la ha tenido** adolorida**?**	**Muchísimo** **Mucho** **Un poco** **Nada**	❑ ❑ ❑ ❑		
2.	**Durante la última semana, ¿se ha sentido** avergonzado/a **o** cohibido/a **debido a su piel?**	**Muchísimo** **Mucho** **Un poco** **Nada**	❑ ❑ ❑ ❑		
3.	**Durante la última semana, ¿le ha molestado su condición de la piel para hacer las** compras **u ocuparse de la** casa **o el** jardín**?**	**Muchísimo** **Mucho** **Un poco** **Nada**	❑ ❑ ❑ ❑	**Sin relación**	❑
4.	**Durante la última semana, ¿ha influido su condición de la piel en la elección de la** ropa **que lleva?**	**Muchísimo** **Mucho** **Un poco** **Nada**	❑ ❑ ❑ ❑	**Sin relación**	❑
5.	**Durante la última semana, ¿ha influido su condición de la piel en alguna actividad** social **o** recreativa**?**	**Muchísimo** **Mucho** **Un poco** **Nada**	❑ ❑ ❑ ❑	**Sin relación**	❑
6.	**Durante la última semana, ¿ha tenido dificultad para practicar** deportes **debido a su condición de la piel?**	**Muchísimo** **Mucho** **Un poco** **Nada**	❑ ❑ ❑ ❑	**Sin relación**	❑
7.	**Durante la última semana, ¿le ha impedido su condición de la piel** trabajar **o** estudiar**?**	**Sí** **No**	❑ ❑	**Sin relación**	❑
	Si la respuesta es "No", durante la última semana, ¿cuánta dificultad le ha ocasionado su condición de la piel en el trabajo **o en sus** estudios**?**	**Mucho** **Un poco** **Nada**	❑ ❑ ❑		
8.	**Durante la última semana, ¿su condición de la piel le ha ocasionado dificultades con su** pareja**,** amigos íntimos **o** familiares**?**	**Muchísimo** **Mucho** **Un poco** **Nada**	❑ ❑ ❑ ❑	**Sin relación**	❑
9.	**Durante la última semana, ¿cuánta dificultad le ha ocasionado su condición de la piel en**	**Muchísimo** **Mucho**	❑ ❑		

su vida sexual**?**	**Un poco**	❑		
	Nada	❑	**Sin relación**	❑

10. **Durante la última semana, ¿cuánta dificultad le ha ocasionado su** tratamiento **de la piel, por ejemplo, ocupándole tiempo o ensuciando o desordenando su casa?**	**Muchísimo**	❑		
	Mucho	❑		
	Un poco	❑		
	Nada	❑	**Sin relación**	❑

Por favor verifique que ha contestado a TODAS las preguntas. Muchas gracias.

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19 APPENDIX G: DERMATOLOGY LIFE QUALITY SCORING TOOL

http://www.dermatology.org.uk/quality/dlqi/quality-dlqi-faqs.html

The scoring of each answer is as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question unanswered	scored 0
Question 7: "prevented work or studying"	scored 3

The DLQI is calculated by adding the score of each question. The maximum score is 30 and the minimum is 0. The higher the score, the more quality of life is impaired. The DLQI can be expressed as a percentage of the maximum possible score of 30 but we do not recommend this because the "original" score is much easier to understand.

Please Note: The scores associated with the different answers should not be printed on the DLQI itself, as this might cause bias**.**

Meaning of DLQI Scores

0-1 = no effect at all on patient's life
2-5 = small effect on patient's life
6-10 = moderate effect on patient's life
11-20 = very large effect on patient's life
21-30 = extremely large effect on patient's life

Detailed analysis of the DLQI

The DLQI can also be analyzed under six headings or dimensions as follows:

- Symptoms and feelings Questions 1 and 2 Score maximum 6
- Daily activities Questions 3 and 4 Score maximum 6
- Leisure Questions 5 and 6 Score maximum 6
- Work and School Question 7 Score maximum 3

- Personal relationships Questions 8 and 9 Score maximum 6
- Treatment Question 10 Score maximum 3

The scores for each of these sections can also be expressed as a percentage of either 6 or 3.

Q. How do you handle missing data from DLQI?

There is a very high success rate of accurate completion of the DLQI. However, sometimes subjects do make mistakes.

- If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.

- If two or more questions are left unanswered the questionnaire is not scored.

- If question 7 is answered 'yes' this is scored 3 even if in the same question one of the other boxes is ticked.

- If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1.

- If two or more response options are ticked for one question, the response option with the highest score should be recorded.

- If there is a response between two tick boxes, the lower of the two score options should be recorded.

- The DLQI can be analyzed by calculating the score for each of its six sub-scales (see above). When using sub-scales, if the answer to one question in a sub-scale is missing, that sub-scale should not be scored.

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20 APPENDIX H: PUSTULAR DERMATOSIS CLINICAL ASSESSMENT SCALE

PUSTULAR PASI CALCULATION

PSORIASIS CHARACTERISTIC	RATING SCORE	HEAD	ARMS	TRUNK (including groin)	LEGS (including buttocks)
Erythema/redness (E) Lt red, red, v red, deep red	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very Severe				
Induration/thickness (I) 0.25, 0.5, 1, 1.25mm					
Desquamation/scaling (D) Fine, coarse fine, coarse thick, v thick					
Pustules (P) Few, scattered, dense, confluent					
SUM: E+I+D+P					
Modifier		x 0.1	x 0.2	x 0.3	x 0.4
Weighted plaque score = sum x modifier					
% affected body surface area					
AREA SCORE	0 = None 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%				
SUBTOTAL = Weighted plaque score x Area score					
PUSTULAR PASI SCORE					

Signature **Printed Name** **Date**

MODIFIED PALMOPLANTAR PASI CALCULATION

PSORIASIS CHARACTERISTIC	RATING SCORE	RIGHT PALM	LEFT PALM	RIGHT SOLE	LEFT SOLE
Erythema/redness (E) Lt red, red, v red, deep red	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very Severe				
Pustules (P) or Infiltration Few, scattered, dense, confluent					
Desquamation/scaling (D) Fine, coarse fine, coarse thick, v thick					
SUM: E+P+D					
Modifier		x 0.2	x 0.2	x 0.3	x 0.3
Weighted plaque score = sum x modifier					
% affected body surface area					
AREA SCORE	0 = None 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%				
SUBTOTAL = Weighted plaque score x Area score					
PALMOPLANTAR PASI SCORE					

Date of biopsy	**Clinical findings**	**Location of biopsy**	**Affected/Unaffected**	**Reason for biopsy (D, R, D/R*)**

*D- Diagnostic; R-Research, D/R- Diagnostic/Research

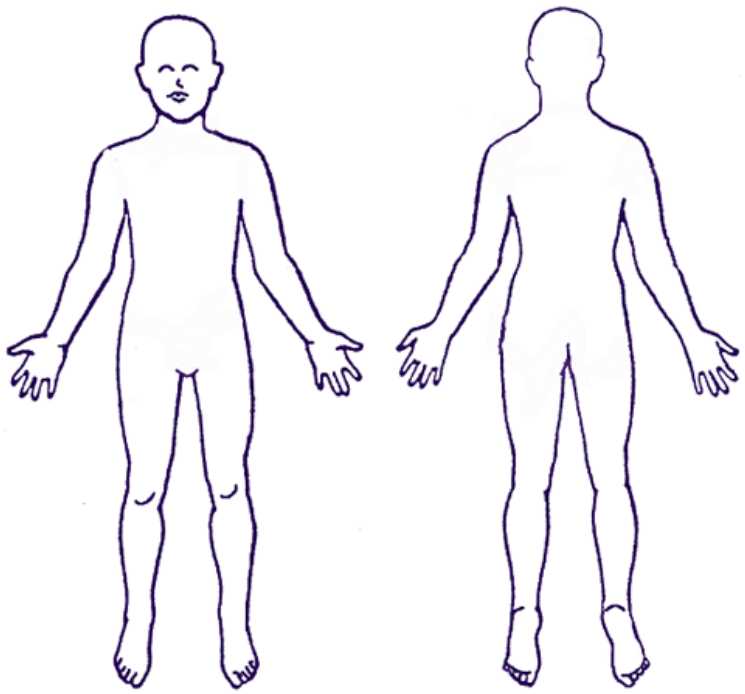
Signature **Printed Name** **Date**

TOTAL BODY SURFACE AREA INVOLVEMENT (TBSAI)

	HEAD	ARMS	TRUNK	LEGS	
% affected area (plaques & pustules)					
Body area: % affected area x modifier	x 0.1	x 0.2	x 0.3	x 0.4	**TOTAL**
Subtotal					

PHYSICIAN GLOBAL ASSESSMENT (PGA)

PGA RATING SCORE	**Plaque PGA score**	**Pustule PGA score**	**Overall PGA score**
0 = Clear 1 = Minimal 2 = Mild 3 = Moderate 4 = Severe 5 = Very severe			



Signature **Printed Name** **Date**

PATIENT VISUAL ANALOGUE SCALES

Skin pain due to skin disease: 0 (no pain) to 10 (worst imaginable pain)
Joint pain due to skin disease: 0 (no pain) to 10 (worst imaginable pain)
Itching: 0 (no itching) to 10 (worst imaginable itching)
Overall disease severity: your assessment of the degree of severity of your disease

SKIN PAIN (0-10)	JOINT PAIN (0-10)	PRURITUS (0-10)	OVERALL DISEASE SEVERITY (0-10)

Provider Signature **Printed Name** **Date**

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21 APPENDIX I: HEALTH ASSESSMENT QUESTIONNAIRE

THE STANFORD HEALTH ASSESSMENT QUESTIONNAIRE Visit #		
Subject Initials _____	Subject ID _____	Visit date _____ mm/dd/yyyy

The STANFORD HEALTH ASSESSMENT QUESTIONNAIRE ©
Stanford University School of Medicine, Division of Immunology & Rheumatology

HAQ Disability Index:
In this section we are interested in learning how your illness affects your ability to function in daily life.
Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities **OVER THE PAST WEEK:**

	Without ANY Difficulty[0]	With SOME Difficulty[1]	With MUCH Difficulty[2]	UNABLE To Do[3]
DRESSING & GROOMING				
Are you able to:				
- Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
- Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
-Stand up from a straight chair?	☐	☐	☐	☐
-Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
-Cut your meat?	☐	☐	☐	☐
-Lift a full cup or glass to your mouth?	☐	☐	☐	☐
-Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
-Walk outdoors on flat ground?	☐	☐	☐	☐
-Climb up five steps?	☐	☐	☐	☐

*** Please check any AIDS OR DEVICES that you usually use for any of these activities:**

- Cane ☐
- Walker ☐
- Crutches ☐
- Wheelchair ☐
- Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.) ☐
- Built up or special utensils ☐
- Special or built up chair ☐
- Other (Specify: _____) ☐

*** Please check any categories for which you usually need HELP FROM ANOTHER PERSON:**

- Eating ☐
- Walking ☐
- Dressing and Grooming ☐
- Arising ☐

Please check the response which best describes your usual abilities **OVER THE PAST WEEK:**

	Without ANY Difficulty[0]	With SOME Difficulty[1]	With MUCH Difficulty[2]	UNABLE To Do[3]
HYGIENE				
Are you able to:				
- Wash and dry your entire body?	☐	☐	☐	☐
- Take a bath (get in and get out)?	☐	☐	☐	☐
- Get on and off the toilet or potty?	☐	☐	☐	☐
REACH				
Are you able to:				
- Reach and get down a 5-pound object such as a bag of sugar from just above your head?	☐	☐	☐	☐
- Bend down to pick up clothing or a piece of paper from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
- Open car doors?	☐	☐	☐	☐
- Open jars,which have been previously opened?	☐	☐	☐	☐
- Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
- Run errands and shop?	☐	☐	☐	☐
- Get in and out of a car?	☐	☐	☐	☐
- Do household chores such as vacuuming or yard work?	☐	☐	☐	☐

*** Please check any AIDS or DEVICES that you usually use for any of these activities:**

- Raised toilet seat	☐	- Bathtub bar/rail	☐
- Bathtub seat	☐	- Long-handled appliances for reach	☐
- Jar opener (for jars previously opened)	☐	- Long-handled appliances in bathroom	☐
		- Other (Specify:_____)	☐

*** Please check any categories for which you usually need HELP FROM ANOTHER PERSON:**

- Hygiene	☐	- Gripping and opening things	☐
- Reach	☐	- Errands and chores	☐

PAIN: We are also interested in learning whether or not you are affected by pain because of your illness. How much pain have you had because of your illness **IN THE PAST WEEK?** Please mark a line below, to indicate the severity of the pain.

No Pain 0 ——— **100 Very Severe Pain**

GENERAL EVALUATION: Considering all the ways that your arthritis affects you, rate how you are doing by placing a single mark on the line below.

Very Well 0 ——— **100 Very Poor**

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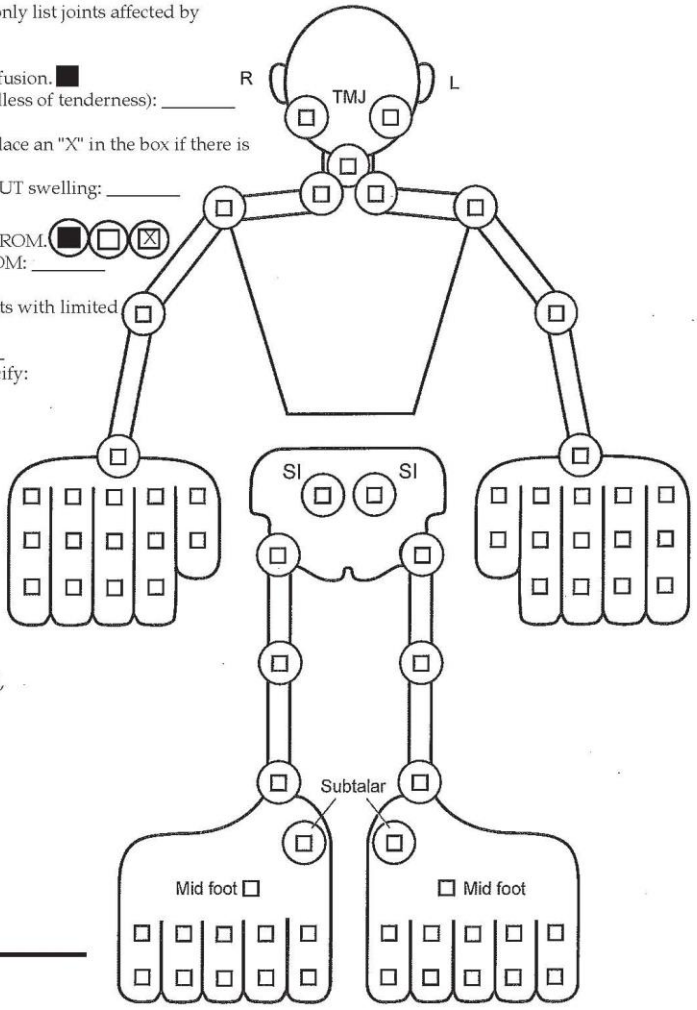
22 APPENDIX J: JOINT EXAM CLINICAL ASSESSMENT FORM

Pilot Study on Anakinra in Pustular Skin Disease: Joint Assessment

Visit Number		
Subject Initials	Subject ID	Visit Date

Joint exam

Instructions for each joint (box). Please only list joints affected by underlying inflammatory arthritis:
(1) Swollen joints
a. Fill in the box if there is swelling or effusion. ■
b. Total number of swollen joints (regardless of tenderness): _____
(2) Tender joints
a. In the absence of swelling/effusion, place an "X" in the box if there is tenderness or painful ROM. ☒
b. Total number of tender joints WITHOUT swelling: _____
(3) Limited ROM
a. Circle each box where there is limited ROM. ■ □ ☒
b. Total number of joints with limited ROM: _____
(4) Total number of active joints:
a. Add up #1 and #2, do NOT count joints with limited ROM but no swelling or tenderness
b. Total number of active joints: _____
(5) If any joints were NOT assessed, specify:



(6) If all joints were assessed and normal, check this box: □

MD Signature _____

MD Name _____

Collection of this information is authorized under 42 USC 285. The primary use of the information you provide is to assess your health and quality of life. The information may be disclosed to clinicians and researchers for research purposes and to monitor personnel to assure that safety standards are maintained. Submission of this information is voluntary.

23 APPENDIX K: REVIEW OF SYSTEMS

MEDICAL HISTORY

Do you have or have had any of the following medical conditions diagnosed by a physician? Please check all that apply.		
7	*Cardiovascular Diseases*	☐ High blood pressure requiring daily medication ☐ High cholesterol requiring daily medication ☐ Heart attack or coronary artery disease ☐ Heart failure (you may have been short of breath and the doctor may have told you that you have fluid in your lungs or that your heart was not pumping well) ☐ Needed an operation to unclog or bypass the arteries in your legs (peripheral vascular disease) ☐ Stroke, cerebrovascular accident, blood clot or bleeding in the brain, or transient ischemic attack (TIA) ☐ Other: _____ ☐ **No history of cardiovascular disease**
8	*Lung Disease*	☐ COPD (Emphysema or Chronic bronchitis) requiring daily treatment or treatment for flare ups ☐ Asthma requiring daily treatment or treatment for flare ups ☐ Other: _____ ☐ **No history of lung disease**
9	*Infection*	☐ HIV ☐ AIDS (CD4 count ≤200, History of opportunistic infection) ☐ Hepatitis B ☐ Hepatitis C ☐ Tuberculosis infection (with symptoms requiring treatment and/or hospitalization) ☐ Tuberculosis exposure (a positive TB test that may have required treatment, but no symptoms or need for hospitalization) ☐ Infection requiring hospitalization ever ☐ Infection requiring hospitalization within last 12 months ☐ One infection requiring oral antibiotics within last 12 months ☐ Two or more infections requiring oral antibiotics within last 12 months ☐ Other: _____ ☐ **No history of infection**
10	*Gastrointestinal Tract/Kidney*	☐ Stomach ulcer or peptic ulcer disease ☐ Mild liver disease (e.g. non-infectious hepatitis) ☐ Moderate to severe liver disease (e.g. cirrhosis or ascites) ☐ Chronic kidney disease ☐ Chronic kidney disease requiring dialysis or preparation for kidney replacement therapy ☐ Inflammatory bowel disease (e.g. Ulcerative colitis, Crohn's disease) ☐ Other: _____ ☐ **No history of gastrointestinal tract or kidney disease**

11	*Endocrine*	☐ Diabetes requiring medication by mouth or insulin injection ☐ Diabetes with complication (e.g. eye problems such as retinopathy, neuropathy, kidney disease) ☐ Other: _____ ☐ **No history of endocrine disease**
12	*Musculoskeletal*	☐ Osteoarthritis ☐ Gout ☐ Psoriatic arthritis diagnosed by rheumatologist ☐ Psoriatic arthritis diagnosed by different physician ☐ Other: _____ ☐ **No history of musculoskeletal disease**
13	*Psychiatric*	☐ Depression (requiring counseling and/or prescription medication) ☐ Anxiety (requiring counseling and/or prescription medication) ☐ Other: _____ ☐ **No history of psychiatric disease**
14	*Neurologic*	☐ Multiple sclerosis ☐ Optic Neuritis ☐ Parkinson's disease ☐ Dementia or Alzheimer's disease ☐ Paralysis ☐ Other: _____ ☐ **No history of neurologic disease**
15	*Cancer*	☐ History of any internal cancer (e.g. colon, lung, breast, prostate, leukemia, lymphoma) Please specify: _____ ☐ Any metastatic solid cancer ☐ Melanoma ☐ Non-melanoma skin cancer (Basal Cell or Squamous Cell Carcinoma) ☐ **No history of cancer**
16	*Autoimmune disease*	☐ Connective tissue disease (e.g. lupus, rheumatoid arthritis, dermatomyositis/polymyositis) If yes, please specify: _____ If yes – do you take medications for it daily? ☐ Yes ☐ No ☐ Other: _____ ☐ **No history of autoimmune disease**

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24 APPENDIX L: CCR PROBLEM REPORT FORM

CCR PROBLEM REPORT FORM

<table>
<tr><td>NCI Protocol #:</td><td colspan="2">Protocol Title:</td></tr>
<tr><td></td><td colspan="2">Report version: (select one)
____Initial Report
____Revised Report
____Follow-up</td></tr>
<tr><td>Site Principal Investigator:</td><td colspan="2"></td></tr>
<tr><td>Date of problem:</td><td colspan="2">Location of problem: (e.g., patient’s home, doctor’s office)</td></tr>
<tr><td colspan="3">Who identified the problem? (provide role (not name of person): nurse, investigator, monitor, etc…)</td></tr>
<tr><td>Brief Description of Subject (if applicable)
(Do NOT include personal identifiers)</td><td colspan="2">Sex: ___ Male ___ Female Age:
___ Not applicable (more than subject is involved)</td></tr>
<tr><td colspan="3">Diagnosis under study:</td></tr>
<tr><td colspan="3">Name the problem: (select all that apply)
[ ] Adverse drug reaction
[ ] Abnormal lab value
[ ] Death
[ ] Cardiac Arrest/ code
[ ] Anaphylaxis</td></tr>
</table>

[ ] Sepsis/Infection

[ ] Blood product reaction

[ ] Unanticipated surgery/procedure

[ ] Change in status (e.g. increased level of care required)

[ ] Allergy (non-medication)

[ ] Fall

[ ] Injury/Accident (not fall)

[ ] Specimen collection issue

[ ] Informed consent issue

[ ] Ineligible for enrollment

[ ] Breach of PII

[ ] Tests/procedures not performed on schedule

[ ] Other, brief 1-2 word description: _____

Detailed Description of the problem: (*Include any relevant treatment, outcomes or pertinent history*):

***Is this problem unexpected?** *(see the definition of unexpected in the protocol))* __YES __NO
Please explain:

***Is this problem related or possibly related to participation in the research?** __YES __NO
Please explain:

***Does the problem <u>suggest</u> the research places subjects or others at a greater risk of harm than was previously known or recognized?** __YES __NO **Please explain:**

Is this problem? (*select all that apply*)

[ ] An Unanticipated Problem* that is: [ ] Serious [ ] Not Serious

[ ] A Protocol Deviation that is: [ ] Serious [ ] Not Serious [ ] Non-compliance **Note if the 3 criteria starred above are answered, "YES", then this event is also a UP.*
Is the problem also *(select one)* [ ] AE [ ] Non-AE
Have similar problems occurred on this protocol at your site? __YES __NO **If "Yes", how many? ____ Please describe:**
Describe what steps you have already taken as a result of this problem:
In addition to the NIH Intramural IRB, this problem is also being reported to: (*select all that apply*) [ ] Local IRB [ ] Study Sponsor [ ] Manufacturer : _____ [ ] Institutional Biosafety Committee [ ] Data Safety Monitoring Board [ ] Other: _____ [ ] None of the above, not applicable

INVESTIGATOR'S SIGNATURE:	**DATE:**