1. TITLE PAGE

PCS499
PHASE 2 PROTOCOL
PCS499-NL01

An Open-Label Study to Evaluate the Safety and Tolerability of PCS499 for the treatment of Necrobiosis Lipoidica

VERSION 2.0 DATE: 02 November 2018

The Sponsor is Processa Pharmaceuticals, Inc.
7380 Coca Cola Drive, Suite 106
Hanover, MD 21076

2. INVESTIGATOR PROTOCOL AGREEMENT

PROTOCOL SIGNATURE PAGE

Protocol Title: An Open-Label Study to Evaluate the Safety and Tolerability of PCS499 for the treatment of Necrobiosis Lipoidica

Protocol Number: PCS499-NL01

02-Nov-2018

Maya Das
VP, Clinical Research
Processa Pharmaceuticals

Date

By my signature, I confirm that my staff and I have carefully read and understand this protocol or protocol amendment, and agree to comply with the conduct and terms of the study specified herein and with any other study conduct procedures provided. I agree to review and comply with all relevant regulations and guidance principles. I will not implement any protocol or protocol amendment without agreement from Processa Pharmaceuticals and prior submission to and written approval (where required) from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except when necessary to eliminate an immediate hazard to the patients or for administrative aspects of the study (where permitted by all applicable regulatory requirements).

Principal Investigator's Name and Signature Date

3. STUDY CONTACT

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4. SYNOPSIS

Name of Sponsor/Company: Processa Pharmaceuticals, Inc.	
Name of Investigational Product: PCS499	
Name of Active Ingredient: PCS499	
Title of Study: An Open-Label Study to Evaluate the Safety and Tolerability of PCS499 for the treatment of Necrobiosis Lipoidica	
Study center(s): Approximately 4 centers in the US	
Studied period (years): Estimated date first patient enrolls: To Be Determined Estimated date last patient enrolls: To Be Determined Estimated date last patient completes 1 year of treatment: To Be Determined	**Phase of development:** 2
OBJECTIVES: **Primary Objective:** To evaluate the safety and tolerability profile of PCS499 in patients with Necrobiosis Lipoidica **Exploratory Objectives:** To evaluate the efficacy of PCS499 on reducing clinical findings related to Necrobiosis Lipoidica To assess the pharmacodynamic activity of PCS499 on immunologic and inflammatory biomarkers	
Methodology: This is an open-label study that will evaluate the safety of PCS499 for the treatment of necrobiosis lipoidica (NL) and will inform the design of future studies. Based on previous experience with PCS499, a 1200 mg daily dose administered as 600 mg BID was well-tolerated in a study of patients with diabetic nephropathy, but had limited efficacy. A recent Phase 1 study in healthy volunteers found that daily doses of 1800 mg administered as 900 mg BID or 600 mg TID of PCS499 were safe and well tolerated. The study will consist of a 6 month treatment period followed by a 6 month extension period. Approximately 12 NL patients (6-9 patients without ulceration and 3-6 patients with ulceration) who also meet other inclusion/exclusion criteria will be enrolled in the study. Patients will be administered PCS499 900 mg BID. Primary safety and exploratory efficacy	

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analysis will be performed after the last patient completes the 6-month visit. Patients will have the option to continue dosing in an extension period for up to an additional 6 months.

All patients will take PCS499 300 mg BID with food for 1 week. Beginning at Week 2, patients will commence administration of twice daily dosing of three PCS499 300 mg tablets (900 mg BID) with food. Patients will continue at their assigned dose for the remainder of the study.

During the dosing period, if a patient receiving PCS499 900 mg BID experiences unacceptable toxicity (i.e., non-transient, moderate to severe limitation in activity) that is deemed by the Investigator to be related to study drug, his/her dose will be changed to PCS499 600 mg TID with food at the discretion of the Investigator in consultation with the Medical Monitor. If this dose is not tolerated, the dose will be further reduced to PCS499 600 mg BID with food at the discretion of the Investigator in consultation with the Medical Monitor. If 4 out of the first 6 patients dosed in this study require dose modification or discontinue from the study due to a drug-related adverse event within 1 month of dosing, consideration will be made to change the starting dose to 600 mg TID with food for all subsequent patients. Efficacy and safety data will be collected at regular intervals throughout the course of the study.

An analysis will be conducted to assess safety and exploratory efficacy after the last patient completes the 6-month visit. A final analysis of patients enrolled in the study will be conducted after the last patient completes the 12-month visit.

Number of patients (planned):

- Total number enrolled into this open label study: ~12 NL patients
  - 6-9 without ulcerations and 3-6 with ulcerations

Diagnosis and Main criteria for Eligibility:

Inclusion criteria:

1. Male or female patients age 18 to 80 years of age, inclusive, at Screening.
2. Biopsy-confirmed diagnosis of NL. Biopsies of continually active lesions performed outside of this clinical study will need to be reviewed and the diagnosis confirmed by the study pathologist. For patients with no previous history of biopsy, no biopsy within the previous 5 years, a biopsy that is not confirmed to be NL, or newly active lesion, a biopsy to confirm a diagnosis of NL will be performed at the Screening visit.

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3. Reference NL lesion with a score of 2 or greater on the IGA:NL Activity scale AND surface area with minimum size of 10 cm^2. If more than one lesion is present, the reference lesion area is the lesion with the highest disease severity.
4. Women of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Baseline before dosing.
5. Women of childbearing potential must use one of the following acceptable methods of contraception throughout the study: oral contraceptive medication, intrauterine device (IUD), hormonal implants, injectable contraceptive medications, double-barrier methods, or tubal ligation.
6. Females who are postmenopausal (age-related amenorrhea >= 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening) or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.
7. Male patients must be willing to use appropriate contraceptive measures and refrain from sexual activity with any female who is pregnant or lactating.
8. Patient must be willing and able to swallow whole tablets.
9. Patient must be willing and able to comply with study procedures.
10. Patient must be willing and able to provide signed, informed consent.

Exclusion criteria:

1. Current or previous (within 4 weeks of Baseline) treatment with:
    a. Oral, topical, or intralesional corticosteroids;
    b. Systemic pentoxifylline, theophylline, or cilostazol
    c. Oral or topical retinoid;
    d. Other systemic or topical immunosuppressant drugs, including but not limited to calcineurin inhibitors (e.g., tacrolimus), thalidomide, apremilast, anti-malarials (e.g., hydroxychloroquine, chloroquine), cyclosporine, mycophenolate mofetil, azathioprine, methotrexate, etc.
2. Current or previous (within 12 weeks of Baseline) treatment with any biologic therapy (e.g., adalimumab, etanercept, infliximab, anakinra, etc.).
3. Phototherapy/photochemotherapy (NBUVB, UVB, PUVA) within 6 weeks prior to Baseline.
4. Skin grafting, or other surgical procedure (other than debridement) within 6 weeks prior to Baseline.

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5. History of drug allergy, including but not limited to pentoxifylline or other xanthine derivatives, or other allergy, which in the opinion of the Investigator, contraindicates participation.
6. Anticipated concurrent use of a strong CYP1A2 inhibiting drug, including but not limited to cimetidine and/or fluvoxamine, during the course of the study (after Screening).
7. Fever (>38°C), or chronic, persistent, or recurring infection(s) at Screening or Baseline.
8. Any infection requiring oral antimicrobial therapy within 2 weeks prior to Baseline and/or any infection requiring parenteral antibiotics or hospitalization within 12 weeks prior to Baseline. Any treatment for such infections must have been completed and the infection cured for at least 2 weeks prior to Baseline.
9. History of sarcoidosis, pyoderma gangrenosum, or any other disorder (in the judgment of the Investigator) that would interfere with the evaluation of NL or require protocol prohibited medication.
10. History of any life threatening infection or sepsis within 12 months of Baseline.
11. Clinically significant cardiac disease including but not limited to unstable angina, acute myocardial infarction within 6 months of Baseline, and arrhythmia requiring therapy.
12. Patient has QTc interval ≥ 480 milliseconds on Screening ECG; a second Screening ECG may be done at investigator's discretion but the average of the two QTc screening intervals must not be ≥ 480 milliseconds.
13. History of cerebral hemorrhage, cerebrovascular accident, transient ischemic attack, gastrointestinal bleeding, or retinal hemorrhage within 6 months of Baseline.
14. Patient has active or history of neoplastic disease (except for adequately treated non-invasive basal cell and/or squamous cell carcinoma or carcinoma in situ of the cervix) within the past 5 years prior to Baseline.
15. Presence of clinically significant medical condition(s) including but not limited to: renal, hepatic, cardiovascular, hematological, gastrointestinal, endocrine, pulmonary, neurological, psychiatric, substance abuse, and/or any other clinically significant disease or disorder, which in the opinion of the Investigator (by its nature or by being inadequately controlled), may put the patient at risk due to participation in the study, influence the results of the study, and/or affect the patient's ability to complete the study.

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16. History of or current diagnosis of active tuberculosis (TB); undergoing treatment for latent TB infection (LTBI); untreated LTBI (as determined by documented results within 3 months of the Screening Visit of a positive TB skin test with purified protein derivative with induration >= 5 millimeter (mm), a positive QuantiFERON-TB test or positive or borderline T-SPOT [Elispot] test); or positive TB test at Screening. Subjects with documented completion of appropriate LTBI treatment would not be excluded and are not required to be tested.
17. Vaccination with live or live-attenuated virus vaccine within 1 month prior to Baseline.
18. The results of the following laboratory tests performed at the central laboratory at Screening meet any of the criteria below:
    a. Hemoglobin < 8.0 g/dL (International System of Units (SI): < 80 g/L);
    b. White blood cells < 3.0 x 10^3 cells/mm^3 (SI: < 3.0 x 10^9 cells/L);
    c. Neutrophils < 1.0 x 10^3 cells/mm^3 (SI: < 1.0 x 10^9 cells/L);
    d. Lymphocytes < 0.5 x 10^3 cells/mm^3 (SI: < 0.5 x 10^9 cells/L);
    e. Platelets < 100 x 10^3 cells/mm^3 (SI: < 100 x 10^9 cells/L)
    f. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or alkaline phosphatase (ALP) ≥ 2 x upper limit of normal (ULN);
    g. Total bilirubin level ≥ 2 x ULN unless the individual has been diagnosed with Gilbert's disease and this is clearly documented;
    h. Estimated glomerular filtration rate < 40 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease (MDRD) formula.
    i. Positive HIV serology
    j. Evidence of active Hepatitis B Virus (HBV) infection
    k. Evidence of active Hepatitis C Virus (HCV) infection
19. Women who are pregnant or breastfeeding.
20. Patient unwilling or unable to swallow tablets whole.
21. Any other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigator, would preclude participation in the study.
22. Use of any investigational product within 30 days prior to Baseline or currently enrolled in another study that involves clinical investigations.

Investigational product, dosage and mode of administration

Patients will take tablets twice daily by mouth with food.

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Group	Dosage Forms
PCS499 900 mg BID	3 x PCS499 300 mg tablets

Criteria for Evaluation:

Safety:

- Adverse Events (AEs) (by type, severity, and relatedness) at each visit.
- Changes in safety clinical laboratory testing and vital signs at each visit.
- Changes in electrocardiograms (ECGs) at Months 1, 3, 6, 9, and 12.

Exploratory Efficacy:

- Proportion of patients with scores of clear or almost clear (0 or 1) of the reference lesion on the Investigator Global Assessment: NL (IGA:NL) Activity Scale at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Proportion of patients with ≥ 1 point decrease in IGA:NL Activity score of the reference lesion at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Proportion of patients with ≥ 2 point decrease in IGA:NL Activity score of the reference lesion at Months 1, 2, 3, 4, 5, 6, 9, and 12
- Proportion of patients with ≥ 1 point decrease in the Color score on the Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS) of the reference lesion at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Change from Baseline in Physician Global Assessment (PGA) score at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Percent change from Baseline in reference lesion surface area of inflammation/erythema based on Investigator measurement at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Percent change from Baseline in total lesion(s) surface area of inflammation/erythema based on Investigator measurement at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Percent change from Baseline in reference lesion surface area of inflammation/erythema based on photograph at Months 1, 2, 3, 4, 5, 6, 9, and 12.

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- Change from Baseline in Dermatology Quality of Life Index (DLQI) score at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Change form Baseline in Skindex-29 score at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Change from Baseline in Patient Global Assessment (PtGA) visual analog scale (VAS) score at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Time to obtaining scores of clear or almost clear (0 or 1) of reference lesion on the IGA:NL Activity scale.
- Incidence of new ulceration (defined as a site with no previous ulceration) at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Time to new ulceration.

Patients with ulceration at Baseline only:

- Proportion of patients with ≥ 1 point decrease in the Ulcer score on the Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS) of the reference lesion at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Percent change from Baseline in reference ulcer surface area based on Investigator measurement at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Percent change from Baseline in total ulcer surface area based on Investigator measurement at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Percent change from Baseline in reference ulcer surface area based on photograph at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Incidence of complete wound closure of reference ulcer (defined as skin re-epithelialization without draining or dressing requirements confirmed at two consecutive study visits at least 2 weeks apart) at Months 2, 3, 4, 5, 6, 9, and 12.
- Time to complete wound closure of reference ulcer.
- Incidence of recurrence of reference ulcer after complete wound closure at Months 3, 4, 5, 6, 9, and 12.
- Time to recurrence of reference ulcer after complete wound closure.
- Change from Baseline in reference ulcer volume based on 3D scanning at Months 1, 2, 3, 4, 5, 6, 9, and 12.

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Exploratory Serum Biomarkers:

- Change from baseline in TNF-α, IFN-γ, IL-1β, IL-6, IL-12, IL-17, and MCP-1 at Months 1, 3, 6, 9 and 12.
- Change from baseline in C-peptide levels at Months 1, 3, 6, 9 and 12.

STATISTICAL ANALYSES:

Analysis Populations:

Patients will be analyzed by assigned treatment group. Analyses will be performed based on observed data, and missing values will not be imputed unless otherwise stated.

- Safety Population: Defined as all patients enrolled in the study who received at least 1 dose of treatment.
- Efficacy Population (Modified Intent to Treat (mITT)): Defined as all patients enrolled in the study who received at least 1 dose of treatment and has at least 1 post-baseline efficacy assessment.
- Per-Protocol Population: Defined as a subset of the Efficacy Population who did not have a major protocol violation as defined in the Statistical Analysis Plan.
- Biomarker Population: Defined as all patients enrolled in the study who received at least 1 dose of treatment, participated in biomarker evaluations, and have appropriate samples available for analysis.

Timing of Analyses:

All endpoints will be analyzed after the last patient completes the 3-month visit and the 6-month visit (primary). A final lock of the database and the final analyses will occur after the last patient completes the 12-month visit.

Patient Characteristics:

Baseline demographics and disease characteristics will be presented for each treatment group by descriptive statistics as well as for the combined active groups. All descriptive summary statistics of continuous variables will include: n, mean, median, standard deviation, minimum and maximum. All descriptive summaries presenting frequencies and incidences will include n, % and N, where N is the total number of patients with recorded values in the corresponding group. Patient completion status and exposure outcomes will be similarly presented.

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Safety Analyses:

The safety analyses will be performed using the Safety Population and include adverse events, changes in physical exam findings, vital signs, and clinical laboratory values.

Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA version 21.0 or higher). The number and percent of patients reporting at least one adverse event will be summarized by System Organ Class (SOC) and Preferred Term (PT) and presented by dose level, severity, relationship to study drug, amount of drug exposure, and time. Each patient will contribute only once (i.e., first occurrence) to each of the incidence rates, regardless of the number of occurrences. For reporting of adverse event severity in patients with more than one occurrence of the same adverse event, the patient will only be reported once based on the highest severity of the adverse event observed. Patients who have a serious adverse event (SAE) or who discontinue the study due to an adverse event deemed to be related to study drug will be described in patient narratives.

Vital signs, clinical laboratory, and ECG results will also be presented and summarized by dose level and summarized by descriptive statistics with change from Baseline values calculated. All safety data collected in the clinical database, including physical exam findings and abnormal ECG results, will be presented in data listings.

Efficacy Analyses:

Efficacy analyses will be performed using the Efficacy (mITT) Population. Efficacy endpoints will be summarized by descriptive statistics for each treatment group and by ulceration status. All descriptive summary statistics of continuous variables will include: n, mean, median, standard deviation, minimum and maximum. All descriptive summaries presenting frequencies and incidences will include n, % and N, where N is the total number of patients with recorded values in the corresponding group. Graphical representations will be presented, if appropriate. Efficacy data will also be presented in listings to assess changes within patients over time.

Exploratory Analyses:

Depending on the extent of the data, additional exploratory analyses may be performed to characterize relationships among variables, such as correlations among variables and trending, as well as further sub-group analyses, such as based on diabetic status and study completion status. Additional sensitivity analyses may include comparisons between observed values and imputed values for missing data using different methods (e.g., multiple imputation, last observation carried forward (LOCF).

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Biomarker Analyses: Analyses will be performed using the Biomarker Population. Biomarkers will be evaluated to assess changes within patients over time. Additional exploratory analyses may be performed depending on the extent of the data using appropriate statistical methods.
SAMPLE SIZE CALCULATION: As this is a pilot study, no formal sample size calculation was performed.

5. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

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6. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this study protocol.

Table 1: Abbreviations and Special Terms

Abbreviation or Special term	Explanation
3D	Three dimensional
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BID	Twice a day
BP	Blood pressure
Con med	Concomitant medications
CFR	Code of Federal Regulations
CKD	Chronic kidney disease
CRF	Case report form
CRO	Clinical research organization
CYP	Cytochrome P-450
DLQI	Dermatology Quality of Life Index
ECG/EKG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA1c	Glycosylated hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPMC	hydroxypropyl-methylcellulose
HRQL	Health related quality of life

Abbreviation or Special term	Explanation
IB	Investigational Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGA:NL	Investigator Global Assessment: Necrobiosis Lipoidica
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	Intrauterine device
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LTBI	Latent tuberculosis infection
MedDRA	Medical Dictionary for Regulatory Activities
MDRD formula	Modification of Diet in Renal Disease formula
mITT	Modified Intent to Treat
NBUVB	Narrow Band Ultraviolet B therapy
NL	Necrobiosis Lipoidica
NLCUS	Necrobiosis Lipoidica Color and Ulcer Scale
PCS499	(*S*)-1-(4,4,6,6,6-pentadeutero-5-hydroxyhexyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione.
PGA	Physicians Global Assessment
PIS	Patient Information Sheet(s)
PHI	Protected Health Information
PT	Preferred Term
PtGA	Patient Global Assessment
PTX	Pentoxifylline
PTX-M1	M1 metabolite of pentoxifylline: 1-((S)-5-hydroxyhexyl)-3,7-dimethylxanthine (Metabolite of PTX)
PTX-M2	M2 metabolite of pentoxifylline
PUVA	Photodynamic chemotherapy
SAE	Serious adverse event

Abbreviation or Special term	Explanation
SDV	Source document verification
SOC	System Organ Class
SOP	Standard operating procedure
TB	Tuberculosis
TGF-β	Transforming growth factor beta
TID	Three times a day
TNF	Tumor necrosis factor
TORO	Transfer of Regulatory Obligations
United States	US
ULN	Upper Limit of Normal
UVA/UVB	Ultraviolet A /Ultraviolet B phototherapy
VAS	Visual Analog Scale
VS	Vital Signs
WHO	World Health Organization
WOCBP	Women of Child Bearing Potential

7. INTRODUCTION

7.1. Background Information

Necrobiosis lipoidica (NL) is a rare, idiopathic granulomatous disease involving collagen degradation. It is a chronic, disfiguring skin condition that often develops on the pretibial region of the lower extremities but can also occur on other areas including the face, scalp, forearm, and trunk. NL usually presents initially as red papules that enlarge to form patches or plaques with an atrophic yellow center. Although more commonly found in diabetic patients, non-diabetic patients can also develop NL and the progression of the disease is not correlated with glycemic control. It is estimated that approximately 0.3% of the diabetic population has NL and that between 11-65% of the NL patients are diabetic (Muller, 1966; O'Toole, 1999). NL also occurs predominantly in women (3:1 female-to-male ratio). Ulceration occurs in approximately 30% of patients, which can lead to more severe complications, such as deep tissue infections that can threaten life of the limb (Muller, 1966; Erfurt-Berge, 2015). Rare cases of squamous cell carcinoma in the NL region have also been reported.

The earliest observed changes in NL involve small vessel vascular inflammation, progressing to larger vessel vasculitis, and collagen degeneration with septal fibrosis and fibrotic replacement of fat lobules (Muller, 1966). Interstitial and palisaded granulomas involving the dermis and subcutaneous tissues are usually present. Granulomas are composed primarily of histiocytes (macrophages) with lymphocytes and plasma cells. Palisaded histiocytes can be found near necrobiotic areas (especially in diabetics) with deposition of extracellular fat. Although the pathophysiology of NL is still unclear, various potential mechanisms for development and progression of NL have been proposed. Immune-complex deposition in blood vessels, abnormal collagen deposition/degradation and impaired neutrophil migration have all been suggested as possible causes of granuloma and necrobiotic collagen seen in the disease (Ullman, 1977; Oikarinen, 1987; Markey, 1988; Gange, 1979). Considering the strong association between NL and diabetics, diabetic microangiopathy (deposition of glycoprotein in blood vessels) has also been suggested to play an important role in the pathogenesis (Reid, 2013).

7.2. Preclinical Data

PCS499 is a methylxanthine derivative that is structurally identical to the pentoxifylline M1 metabolite (PTX-M1), except that several key hydrogen atoms have been replaced with deuterium. Pentoxifylline is the active ingredient in Trental® which is approved in the US for the treatment of intermittent claudication on the basis of occlusive arterial disease of the limbs. The extended release (ER) formulation of Trental was originally approved for use in Europe in 1972 and US FDA approval for the treatment of intermittent claudication due to chronic occlusive arterial disease of the limbs was granted in 1984. Metabolically, PTX and PTX-M1 are known to interconvert in erythrocytes and liver by carbonyl reductase and CYP enzymes and are subsequently metabolized to hydroxy, carboxy and demethylated metabolites (PTX-M2, PTX-M3, PTX-M4, PTX-M6 and PTX M7) as well as the terminal metabolite, M5 by various CYP enzymes and possibly carboxylase (Hinze, 1972; Lillibridge, 1996; Lee, 1997; Shin, 1998; Nicklasson, 2002; Peterson, 2004; Wyska, 2007).

PCS499 has a complex mechanism of action including anti-inflammatory, immunomodulatory, hemorheological and antifibrotic effects that potentially could benefit NL patients. PCS499 has

slightly more potent anti-inflammatory/immunosuppressive activities than PTX in inhibiting proinflammatory cytokines (TNF-α and IFN-γ) and neutrophil activation that drive granuloma formation and other inflammatory/autoimmune mechanisms underlying the pathogenesis of NL. In addition, PTX and PTX-M1 have *in vitro* hemorheological properties that increase red blood cell deformability and decrease platelet aggregation. These data suggested that PCS499 potentially could moderate hypoxia and platelet aggregation/coagulation associated with microangiopathy and antibody-mediated vasculitis in NL. Furthermore, PCS499 and PTX have similar activities in inhibiting *in vitro* the secretion of TGF-β, the master regulator of fibrosis, which could potentially modulate the fibrosis and increased collagen crossing linking in basement membranes in NL lesions.

Thus, PCS499 may benefit NL patients based on its slightly more potent inhibition of pro-inflammatory cytokines/chemoattractants and neutrophil activation that induce inflammation and granuloma formation, as well as its promoting effect on red blood cell deformability and platelet deaggregation, which can improve microcirculatory flow and hypoxia in NL lesions, plus its inhibitory effect on TGF-β which reduce fibrosis and other collagen abnormalities.

In terms of toxicology findings, there was no evidence of genetic toxicity *in vitro* or *in vivo*. PCS499 did not inhibit any of the major CYP450 isotypes in human liver microsomes; it exhibited low plasma protein binding and was permeable in CaCO-2 cells. The oral bioavailability of PCS499 was 37% in rats, and 62% and 25% in male and female dogs, respectively.

PCS499 was well-tolerated in single- and repeat-dose toxicity studies at dose levels that are above the anticipated human dose levels. Overall, none of preclinical results preclude the administration of PCS499 to humans and its development for the treatment of NL.

Full details regarding the preclinical program for PCS499 are provided in the Investigational Brochure (IB).

7.3. Clinical Data Summary

7.3.1. Previous Phase 1 and 2 Studies

PCS499 was previously being developed for the treatment of diabetic nephropathy. Six clinical trials with PCS499 have been completed including 4 studies in healthy volunteers and 2 studies in patients with chronic kidney disease (CKD).

Four Phase 1 clinical trials in healthy adult volunteers have been completed evaluating tablet formulations, different dose regimens and administration of PCS499 with and without food. PCS499 tablets provide for a controlled release of the drug over an extended period of time after dosing. The maximum concentration (Cmax) and area under the concentration vs time curve (AUC) of PCS499 increased approximately in proportion to dose across the range of tolerated doses. Single daily doses up to 2400 mg have been administered to healthy subjects and were well tolerated up to 1800 mg. A daily dose of 1800 mg administered as 900 mg BID or 600 mg TID in a multiple dose healthy volunteer study was also well tolerated. In healthy volunteers administered 900 mg BID or 600 mg TID, the most common adverse events were nausea and headache.

Trials in patients with CKD include a single Phase 1 study and a Phase 2, 48-week double-blind into 48-week open-label clinical trial in CKD patients with Type 2 diabetes. During the Phase 2 double-blind study, treatment with PCS499 was generally well tolerated. Gastrointestinal (GI) events were reported more frequently in the PCS499 arm. Nausea was the most commonly reported event in the PCS499 arm, with 12 (13.5%) PCS499 vs 5 (5.7%) placebo patients reporting the event. Influenza was reported in 9 (10.1%) PCS499 and 1 (1.1%) placebo patients, and peripheral oedema reported in 9 (10.1%) PCS499 and 4 (4.5%) placebo patients. Hypertension was reported in a greater proportion of placebo patients, with 6 (6.7%) PCS499 and 12 (13.6%) placebo patients experiencing the event. However, as only 6 patients required dose reduction, and only 4 patients were unable to tolerate PCS499 due to a GI event (and were forced to discontinue treatment), the 600 mg BID dosing regimen, following an initial 2 weeks of once daily (QD) dosing, appeared to be satisfactorily tolerated in this patient population.

Clinical safety data obtained to date in the 5 completed, Phase I clinical studies and the Phase 2 study indicate that PCS499 is well tolerated. There have been no serious adverse events (SAEs) that were considered by the Investigators to be related to study treatment. Further information regarding previous clinical studies can be found in the Investigator Brochure.

7.4. Dose Rationale

Previously, single oral doses of up to 1800 mg have been shown to be safe and well tolerated in a Phase 1 study with healthy volunteers.

PCS499 has been previously administered to CKD patients. Multiple doses of 600 mg QD for 2 weeks followed by 600 mg BID for an additional 2 weeks were administered to Stage 3 CKD patients. No significant AEs were observed in this study. Also, in a Phase 2 study (CP.505.2001), PCS499 was administered at a dose of 600 mg BID for up to 2 years in diabetic nephropathy patients. From the studies conducted to date, although tolerable, higher daily doses may be needed to further maximize the effects from PCS499.

A recent study (PCS499.1005) was performed to identify a formulation with target product profile characteristics of a delayed time to maximum concentration (Tmax), lower Cmax, and increased AUC. The PK and safety profile of the selected formulation was then assessed in a multiple dose study with a maximum daily dose of 1800 mg administered as 900 mg BID or 600 mg TID. Both the 900 mg BID and 600 mg TID dosing regimens were well-tolerated in healthy volunteers, although the 900 mg dose resulted in higher AUC and Cmax than the 600 mg dose. While the sample size was small with large variations among patients, an association may exist in certain subjects between the presence of AEs and a rapid drug absorption rate and higher maximum plasma concentrations.

Therefore, as the 900 mg BID dosing regimen of PCS499 results in a higher AUC and is generally well tolerated, this regimen was selected for this study. However, if a patient administered 900 mg BID has unacceptable toxicity, the dosing regimen will be changed to 600 mg TID.

7.5. Study Rationale

No approved therapies exist for NL. Current treatment approaches are based on empirical evidence, but generally produce unsatisfactory results. These include corticosteroids (topical,

intralesional, and systemic), topical calcineurin inhibitors, anti-platelet agents, various immunosuppressants (chloroquine, thalidomide, TNF-α blockers, etc.), UV phototherapy, and skin grafting. For ulcerated lesions, wound care involving moisture control, infection control, conservative debridement, and compression therapy is employed. Spontaneous resolution has been reported in 13-19% of patients after 6-12 years (Muller, 1966).

Clinically, multiple case reports have been published suggesting benefit from the use of pentoxifylline (PTX) in NL patients, possibly related to its vascular and anti-inflammatory effects (Littler, 1987; Noz, 1993; Basaria, 2003; Wee, 2017). PCS499 is an analog of pentoxifylline that provides an exposure profile of active molecules more favorable to inhibiting the secretion of TNF-α, IFN-γ, and other pro-inflammatory cytokines. Furthermore, PCS499 has been well tolerated in Phase 1 studies at higher doses, which may be due to the flatter slope in achieving maximum plasma concentrations (Cmax) of active metabolites, which would be consistent with published reports that equate a higher rate of adverse events with a rapid drug absorption rate and higher maximum plasma concentrations for PTX (Cleary, 1999). Thus, PCS499 may benefit NL patients based on its enhanced inhibition of cytokines (TNF-α, IFN-γ) that induce inflammation and granuloma formation as well as its effect on red blood cell deformability and promotion of platelet deaggregation, which can improve microcirculatory flow. Furthermore, higher doses of PCS499 can be administered with resulting higher exposures of active molecules with no observed increase in adverse effects.

8. STUDY OBJECTIVES AND PURPOSE

8.1. Objectives

Primary Objective:

- To evaluate the safety and tolerability profile of PCS499 in patients with Necrobiosis Lipoidica

Exploratory Objectives:

- To evaluate the efficacy of PCS499 on reducing clinical findings related to Necrobiosis Lipoidica
- To assess the pharmacodynamic activity of PCS499 on immunologic and inflammatory biomarkers

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan: Description

This is an open-label study that will evaluate the safety of PCS499 for the treatment of necrobiosis lipoidica (NL) and will inform the design of future studies.

The study will consist of a 6 month treatment period followed by a 6 month extension period.

Approximately 12 NL patients (6-9 patients without ulceration and 3-6 patients with ulceration) who also meet other inclusion/exclusion criteria will be enrolled in the study. Patients will be administered PCS499 900 mg BID. Primary safety and exploratory efficacy analysis will be performed after the last patient completes the 6-month visit. Patients will have the option to continue dosing in an extension period for up to an additional 6 months.

All patients will take PCS499 300 mg BID with food for 1 week. Beginning at Week 2, patients will commence administration of twice daily dosing of three PCS499 300 mg tablets (900 mg BID) with food. Patients will continue at their assigned dose for the remainder of the study.

During the dosing period, if a patient receiving PCS499 900 mg BID experiences unacceptable toxicity (i.e., non-transient, moderate to severe limitation in activity) that is deemed by the Investigator to be related to study drug, his/her dose will be changed to PCS499 600 mg TID with food at the discretion of the Investigator in consultation with the Medical Monitor. If this dose is not tolerated, the dose will be further reduced to PCS499 600 mg BID with food at the discretion of the Investigator in consultation with the Medical Monitor. If 4 out of the first 6 patients dosed in this study require dose modification or discontinue from the study due to a drug-related adverse event within 1 month of dosing, consideration will be made to change the starting dose to 600 mg TID with food for all subsequent patients. Efficacy and safety data will be collected at regular intervals throughout the course of the study.

An analysis will be conducted to assess safety and exploratory efficacy after the last patient completes the 6-month visit. A final analysis of patients enrolled in the study will be conducted after the last patient completes the 12-month visit.

9.2. Detailed Description of Study Visits

When assessments occur at the same visit, the order of assessments will be vital signs collection, 12-lead ECG then blood collection.

9.2.1. Screening Visit (Day -28 to Day -1, Clinic Visit)

The Screening visit will include:

- Patient informed consent, to be reviewed and signed by the patient.
- Review of demographics
- Review of medical history
- Review of Inclusion/Exclusion Criteria
- Concomitant medications taken in the last 30 days prior to Screening visit will be recorded.

- Vital Signs (BP, heart rate, respiratory rate and temperature) as well as height and weight for body mass index measurements will be assessed.
- A physical exam will be performed
- 12-lead ECG
- Blood and urine will be collected for safety testing
- HIV, hepatitis panel and QuantiFERON TB test
- Serum blood collection for pregnancy for women of child bearing potential (WOCBP)
- Investigator Global Assessment: Necrobiosis Lipoidica (IGA:NL)
- Skin/ulcer exam
- Photograph/3D scan of lesion(s)/ulcer
- Skin biopsy
    - **Note:** A skin biopsy is required if the patient has no previous history of biopsy, no biopsy within the previous 5 years, a biopsy that is not confirmed to be NL, or newly active lesion
- Study Drug instructions will be explained
- Assessment of any adverse events or tolerability issues the patient may have experienced as a result of screening procedures
- Any concomitant medications administered for adverse events or tolerability issues as a result of screening procedures will be solicited (if applicable)

9.2.2. Open-Label Study

Patients who satisfy the eligibility criteria will be enrolled into an approximately 12 month treatment period in which they will receive open-label PCS499, titrated from 300 mg twice daily (BID) for 1 week followed by 900 mg twice daily (BID) for the remainder of the study to determine safety and tolerability.

9.2.2.1. Day 0 (Baseline Visit)

Patients will begin the dosing of open-label PCS499 according to their dosing instructions. There is no study visit on Day 1. However, any adverse events the patients experience after their first dose should be reported at the next study contact (Phone Check in on Day 7).

- Review of Inclusion/Exclusion criteria
- Review of medical history and concomitant medications
- Vital signs
- Physical exam

- Skin/ulcer exam
- Photograph/3D scan of lesion(s)/ulcer
- The following scales will be performed:
  - Investigator Global Assessment: Necrobiosis Lipoidica (IGA:NL),
  - Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS),
  - Physician Global Assessment (PGA),
  - Skindex-29,
  - Dermatology Quality of Life Index (DLQI),
  - Patient Global Assessment (PtGA)
- 12-lead ECG
- Blood and urine will be collected for safety testing (including HbA1c and PT, aPTT and INR)
- Blood will be collected for biomarkers
- A urine pregnancy test will be performed on all WOCBP
- Patient will be given the first kit of study medication
- Assessment of any adverse events or tolerability issues the patient may have experienced during baseline visit procedures
- Any concomitant medications administered for adverse events or tolerability issues during baseline visit procedures will be solicited (if applicable)

9.2.2.2. Day 7 and Day 14 (Phone Checks, +/- 1 day)

The site will call the patient on Day 7 and Day 14 to assess for any adverse events or tolerability issues the patient may have experienced since starting dosing. A review of systems will be discussed and any changes in concomitant medications will also be solicited.

- If a patient reports satisfactory tolerability to study medication on the Day 7 Safety Check-in, they will be instructed to increase their morning dose to 3 tablets and their evening dose to 3 tablets.
- If a patient reports tolerability issues, an additional week of dosing with the morning dose of 1 tablet and evening dose of 1 tablet may be performed.
- Patients who are unable to tolerate even the single tablet after 2 weeks of dosing are to be discontinued from the study.

9.2.2.3. Day 28/Month 1 (Clinic Visit, +/- 3 days)

The following will be performed at this clinic visit:

- Vital signs

- Skin/ulcer exam
- Photograph/3D scan of lesion(s)/ulcer
- The following scales will be performed:
  - Investigator Global Assessment: Necrobiosis Lipoidica (IGA:NL),
  - Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS),
  - Physician Global Assessment (PGA),
  - Skindex-29,
  - Dermatology Quality of Life Index (DLQI),
  - Patient Global Assessment (PtGA)
- 12-lead ECG
- Blood and urine will be collected for safety testing (including PT, aPTT and INR)
- Blood will be collected for biomarkers
- A urine pregnancy test will be performed on all WOCBP
- Assessment of any adverse events or tolerability issues the patient may have experienced since the last visit
- Any changes in concomitant medications will also be solicited
- Drug accountability will be performed
- Patient will be given a new kit of study medication

9.2.2.4. Day 60/Month 2 (Clinic Visit, +/- 7 days)

The following will be performed at this clinic visit:

- Vital signs
- Skin/ulcer exam
- Photograph/3D scan of lesion(s)/wound
- The following scales will be performed:
  - Investigator Global Assessment: Necrobiosis Lipoidica (IGA:NL),
  - Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS),
  - Physician Global Assessment (PGA),
  - Skindex-29,
  - Dermatology Quality of Life Index (DLQI),
  - Patient Global Assessment (PtGA)
- Blood and urine will be collected for safety testing (including PT, aPTT and INR)

- A urine pregnancy test will be performed on all WOCBP
- Assessment of any adverse events or tolerability issues the patient may have experienced since the last visit
- Any changes in concomitant medications will also be solicited
- Drug accountability will be performed
- Patient will be given a new kit of study medication

9.2.2.5. Day 90/Month 3 (Clinic Visit, +/- 7 days)

The following will be performed at this clinic visit:

- Vital signs
- Physical exam
- Skin/ulcer exam
- Photograph/3D scan of lesion(s)/ulcer
- The following scales will be performed:
  - Investigator Global Assessment: Necrobiosis Lipoidica (IGA:NL),
  - Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS),
  - Physician Global Assessment (PGA),
  - Skindex-29,
  - Dermatology Quality of Life Index (DLQI),
  - Patient Global Assessment (PtGA)
- 12-lead ECG
- Blood and urine will be collected for safety testing (including HbA1c, PT, aPTT and INR)
- Blood will be collected for biomarkers
- A urine pregnancy test will be performed on all WOCBP
- Assessment of any adverse events or tolerability issues the patient may have experienced since the last visit
- Any changes in concomitant medications will also be solicited
- Drug accountability will be performed
- Patient will be given a new kit of study medication

9.2.2.6. Day 120/Month 4 (Clinic Visit, +/- 7 days)

The following will be performed at this clinic visit:

- Vital signs

- Skin/ulcer exam
- Photograph/3D scan of lesion(s)/ulcer
- The following scales will be performed:
  - Investigator Global Assessment: Necrobiosis Lipoidica (IGA:NL),
  - Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS),
  - Physician Global Assessment (PGA),
  - Skindex-29,
  - Dermatology Quality of Life Index (DLQI),
  - Patient Global Assessment (PtGA)
- Blood and urine will be collected for safety testing (including PT, aPTT, and INR)
- A urine pregnancy test will be performed on all WOCBP
- Assessment of any adverse events or tolerability issues the patient may have experienced since the last visit
- Any changes in concomitant medications will also be solicited
- Drug accountability will be performed
- Patient will be given a new kit of study medication

9.2.2.7. Day 150/Month 5 (Clinic Visit, +/- 7 days)

The following will be performed at this clinic visit:

- Vital signs
- Skin/ulcer exam
- Photograph/3D scan of lesion(s)/ulcer
- The following scales will be performed:
  - Investigator Global Assessment: Necrobiosis Lipoidica (IGA:NL),
  - Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS),
  - Physician Global Assessment (PGA),
  - Skindex-29,
  - Dermatology Quality of Life Index (DLQI),
  - Patient Global Assessment (PtGA)
- Blood and urine will be collected for safety testing (including PT, aPTT and INR)
- A urine pregnancy test will be performed on all WOCBP
- Assessment of any adverse events or tolerability issues the patient may have experienced since the last visit

- Any changes in concomitant medications will also be solicited
- Drug accountability will be performed
- Patient will be given a new kit of study medication

9.2.2.8. Day 180/Month 6 (Clinic Visit, +/- 7 days)

The following will be performed at this clinic visit:

- Vital signs
- Physical exam
- Skin/ulcer exam
- Photograph/3D scan of lesion(s)/ulcer
- The following scales will be performed:
  - Investigator Global Assessment: Necrobiosis Lipoidica (IGA:NL),
  - Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS),
  - Physician Global Assessment (PGA),
  - Skindex-29,
  - Dermatology Quality of Life Index (DLQI),
  - Patient Global Assessment (PtGA)
- 12-lead ECG
- Blood and urine will be collected for safety testing (including HbA1c, PT, aPTT and INR)
- Blood will be collected for biomarkers
- A urine pregnancy test will be performed on all WOCBP
- Assessment of any adverse events or tolerability issues the patient may have experienced since the last visit
- Any changes in concomitant medications will also be solicited
- Drug accountability will be performed
- If the patient chooses to continue into the Extension Period, the patient will be given a new kit of study medication

9.2.3. Extension Period

9.2.3.1. Day 270/Month 9 (Clinic Visit, +/- 10 days)

The following will be performed at this clinic visit:

- Vital signs
- Physical exam
- Skin/ulcer exam
- Photograph/3D scan of lesion(s)/ulcer
- The following scales will be performed:
  - Investigator Global Assessment: Necrobiosis Lipoidica (IGA:NL),
  - Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS),
  - Physician Global Assessment (PGA),
  - Skindex-29,
  - Dermatology Quality of Life Index (DLQI),
  - Patient Global Assessment (PtGA)
- 12-lead ECG
- Blood and urine will be collected for safety testing (including HbA1c, PT, aPTT and INR)
- Blood will be collected for biomarkers
- A urine pregnancy test will be performed on all WOCBP
- Assessment of any adverse events or tolerability issues the patient may have experienced since the last visit
- Any changes in concomitant medications will also be solicited
- Drug accountability will be performed
- The patient will be given a new kit of study medication

9.2.3.2. Day 360/Month 12 (Clinic Visit, +/- 10 days)

The following will be performed at this clinic visit:

- Vital signs
- Physical exam
- Skin/ulcer exam
- Photograph/3D scan of lesion(s)/ulcer
- The following scales will be performed:
  - Investigator Global Assessment: Necrobiosis Lipoidica (IGA:NL),
  - Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS),
  - Physician Global Assessment (PGA),
  - Skindex-29,

  - Dermatology Quality of Life Index (DLQI),
  - Patient Global Assessment (PtGA)
- 12-lead ECG
- Blood and urine will be collected for safety testing (including HbA1c, PT, aPTT and INR)
- Blood will be collected for biomarkers
- A urine pregnancy test will be performed on all WOCBP
- Assessment of any adverse events or tolerability issues the patient may have experienced since the last visit
- Any changes in concomitant medications will also be solicited
- Drug accountability will be performed

9.2.3.3. Early Discontinuation from Study Drug (Clinic Visit)

If a patient discontinues study drug prior to study termination, the patient will return to the clinic for an Early Discontinuation from Study Drug assessment, which will include:

- Vital signs
- Physical exam
- Skin/ulcer exam
- Photograph/3D scan of lesion(s)/ulcer
- The following scales will be performed:
  - Investigator Global Assessment: Necrobiosis Lipoidica (IGA:NL),
  - Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS),
  - Physician Global Assessment (PGA),
  - Skindex-29,
  - Dermatology Quality of Life Index (DLQI),
  - Patient Global Assessment (PtGA)
- 12-lead ECG
- Blood and urine will be collected for safety testing (including HbA1c, PT, aPTT and INR)
- Blood will be collected for biomarkers
- A urine pregnancy test will be performed on all WOCBP
- Assessment of any adverse events or tolerability issues the patient may have experienced since the last visit

- Any changes in concomitant medications will also be solicited
- Drug accountability will be performed

9.2.3.4. Unscheduled Visits

All attempts should be made to keep a patient on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, follow-up on adverse events or for other reasons, as warranted. Procedures that may be performed at the Unscheduled visit are as follows:

- Vital signs
- Physical exam
- Skin/ulcer exam
- 12-lead ECG
- Blood and/or urine collection for safety testing.

9.2.4. Schedule of Events

Table 2 provides detail on the schedule of assessments.

Table 2: Schedule of Events (Study PCS499-NL01)

Procedure	Screening (-28 to -1 days)	Dosing Visit 2 Day 0 (Baseline Visit)	Visit 3 Week 1 Day 7 (±1 day)	Visit 4 Week 2 Day 14 (±1 day)	Visit 5 Month 1 Day 28 (±3 days)	Visit 6 Month 2 Day 60 (±7 days)	Visit 7 Month 3 Day 90 (±7 days)	Visit 8 Month 4 Day 120 (±7 days)	Visit 9 Month 5 Day 150 (±7 days)	Visit 10 Month 6 Day 180 (±7 days)	Extension Period	
											Visit 11 Month 9 Day 270 (±10 days)	Visit 12 Month 12/ET Day 360 (±10 days)
PI/informed consent	•											
Demographic information	•											
Medical history	•											
Inclusion/ exclusion criteria	•	•										
Screening Laboratory Testing (Hep B/C, HIV, TB)	•											
Skin biopsy*	•*											
Medications	•	•	☎	☎	•	•	•	•	•	•	•	•
Vital signs	•	•			•	•	•	•	•	•	•	•
Physical exam	•	•					•			•	•	•
Skin/ulcer exam	•	•			•	•	•	•	•	•	•	•
Photograph/ 3D scan	•	•			•	•	•	•	•	•	•	•
IGA:NL	•	•			•	•	•	•	•	•	•	•
NLCUS		•			•	•	•	•	•	•	•	•
PGA		•			•	•	•	•	•	•	•	•

DLQI		•			•	•	•	•	•	•	•	•
Skindex-29		•			•	•	•	•	•	•	•	•
PtGA		•			•	•	•	•	•	•	•	•
Safety check-in			☎	☎								
Safety Laboratory testing* **	•	•			•	•	•	•	•	•	•	•
Blood for biomarkers		•			•		•			•	•	•
Pregnancy test**	•	•			•	•	•	•	•	•	•	•
ECG	•	•			•		•			•	•	•
Adverse Events	•	•	☎	☎	•	•	•	•	•	•	•	•
Drug Accountability					•	•	•	•	•	•	•	•
Study Drug Dispensed		•			•	•	•	•	•	•	•	
Study Drug Instructions	•	•										

*If no previous history of biopsy, no biopsy within the previous 5 years, a biopsy that is not confirmed to be NL, or newly active lesion.

**For WOCBP: Serum β-HCG at Screening; Urine pregnancy test at subsequent visits.

*** Additional hematology (PT, aPTT and INR) will be tested at every visit except Screening. HbA1c will be tested at Day 0 and Months 3, 6, 9 and 12.

9.3. Number of Subjects

The number of subjects estimated for this study is ~12 patients (6-9 patients without ulceration and 3-6 patients with ulceration) with Necrobiosis Lipoidica.

9.4. Treatment Assignment

This is an open label study where the ~12 patients with Necrobiosis Lipoidica will receive PCS499 900mg BID (3 x 300mg tablets) with food.

10. SELECTION AND WITHDRAWAL OF PATIENTS

This section describes the inclusion and exclusion criteria for entry into the study, as well as patient withdrawal criteria for patients who are enrolled into the study. Any exceptions to these inclusion or exclusion criteria for eligibility require approval of the Medical Monitor in advance.

10.1. Patient Inclusion Criteria

To participate in the study, **patients must meet all** the following inclusion criteria at screening:

1. Male or female patients age 18 to 80 years of age, inclusive, at Screening.
2. Biopsy-confirmed diagnosis of NL. Biopsies of continually active lesions performed outside of this clinical study will need to be reviewed and the diagnosis confirmed by the study pathologist. For patients with no previous history of biopsy, no biopsy within the previous 5 years, a biopsy that is not confirmed to be NL, or newly active lesion, a biopsy to confirm a diagnosis of NL will be performed at the Screening visit.
3. Reference NL lesion with a score of 2 or greater on the IGA:NL Activity scale AND surface area with minimum size of 10 cm^2. If more than one lesion is present, the reference lesion area is the lesion with the highest disease severity.
4. Women of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Baseline before dosing.
5. Women of childbearing potential must use one of the following acceptable methods of contraception throughout the study: oral contraceptive medication, intrauterine device (IUD), hormonal implants, injectable contraceptive medications, double-barrier methods, or tubal ligation.
6. Females who are postmenopausal (age-related amenorrhea >= 12 consecutive months and increased follicle-stimulating hormone [FSH] > 40 mIU/mL. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening) or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.
7. Male patients must be willing to use appropriate contraceptive measures and refrain from sexual activity with any female who is pregnant or lactating.
8. Patient must be willing and able to swallow whole tablets.
9. Patient must be willing and able to comply with study procedures.
10. Patient must be willing and able to provide signed, informed consent.

10.2. Patient Exclusion Criteria

Patients **will not be eligible** for entry into this study if they meet any of the following exclusion criteria:

1. Current or previous (within 4 weeks of Baseline) treatment with:
    a. Oral, topical, or intralesional corticosteroids;

b. Systemic pentoxifylline, theophylline, or cilostazol
c. Oral or topical retinoid;
d. Other systemic or topical immunosuppressant drugs, including but not limited to calcineurin inhibitors (e.g., tacrolimus), thalidomide, apremilast, anti-malarials (e.g., hydroxychloroquine, chloroquine), cyclosporine, mycophenolate mofetil, azathioprine, methotrexate, etc.

2. Current or previous (within 12 weeks of Baseline) treatment with any biologic therapy (e.g., adalimumab, etanercept, infliximab, anakinra, etc.).
3. Phototherapy/photochemotherapy (NBUVB, UVB, PUVA) within 6 weeks prior to Baseline
4. Skin grafting, or other surgical procedure (other than debridement) within 6 weeks prior to Baseline.
5. History of drug allergy, including but not limited to pentoxifylline or other xanthine derivatives, or other allergy, which in the opinion of the Investigator, contraindicates participation.
6. Anticipated concurrent use of a strong CYP1A2 inhibiting drug, including but not limited to cimetidine and/or fluvoxamine, during the course of the study (after Screening).
7. Fever (>38°C), or chronic, persistent, or recurring infection(s) at Screening or Baseline.
8. Any infection requiring oral antimicrobial therapy within 2 weeks prior to Baseline or any infection requiring parenteral antibiotics or hospitalization within 12 weeks prior to Baseline. Any treatment for such infections must have been completed and the infection cured for at least 2 weeks prior to Baseline.
9. History of sarcoidosis, pyoderma gangrenosum, or any other disorder (in the judgment of the Investigator) that would interfere with the evaluation of NL or require protocol prohibited medication.
10. History of any life threatening infection or sepsis within 12 months of Baseline:
11. Clinically significant cardiac disease including but not limited to unstable angina, acute myocardial infarction within 6 months of Baseline, and arrhythmia requiring therapy.
12. Patient has QTc interval ≥ 480 milliseconds on Screening ECG; a second Screening ECG may be done at investigator's discretion but the average of the two QTc screening intervals must not be ≥ 480 milliseconds.
13. History of cerebral hemorrhage, cerebrovascular accident, transient ischemic attack, gastrointestinal bleeding, or retinal hemorrhage within 6 months of Baseline.
14. Patient has active or history of neoplastic disease (except for adequately treated non-invasive basal cell and/or squamous cell carcinoma or carcinoma in situ of the cervix) within the past 5 years prior to Baseline.
15. Presence of clinically significant medical condition(s) including but not limited to: renal, hepatic, cardiovascular, hematological, gastrointestinal, endocrine, pulmonary, neurological, psychiatric, substance abuse, and/or any other clinically significant disease

or disorder, which in the opinion of the Investigator (by its nature or by being inadequately controlled), may put the patient at risk due to participation in the study, influence the results of the study, and/or affect the patient's ability to complete the study.

16. History of or current diagnosis of active tuberculosis (TB); undergoing treatment for latent TB infection (LTBI); untreated LTBI (as determined by documented results within 3 months of the Screening Visit of a positive TB skin test with purified protein derivative with induration >= 5 millimeter (mm), or a positive QuantiFERON-TB test or positive or borderline T-Spot [Elispot] test); or positive TB test at Screening. Subjects with documented completion of appropriate LTBI treatment would not be excluded and are not required to be tested.
17. Vaccination with live or live-attenuated virus vaccine within 1 month prior to Baseline.
18. The results of the following laboratory tests performed at the central laboratory at Screening meet any of the criteria below:
    a. Hemoglobin < 8.0 g/dL (International System of Units (SI): < 80 g/L);
    b. White blood cells < 3.0 x 10^3 cells/mm^3 (SI: < 3.0 x 10^9 cells/L);
    c. Neutrophils < 1.0 x 10^3 cells/mm^3 (SI: < 1.0 x 10^9 cells/L);
    d. Lymphocytes < 0.5 x 10^3 cells/mm^3 (SI: < 0.5 x 10^9 cells/L);
    e. Platelets < 100 x 10^3 cells/mm^3 (SI: < 100 x 10^9 cells/L)
    f. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or alkaline phosphatase (ALP) ≥ 2 x upper limit of normal (ULN);
    g. Total bilirubin level ≥ 2 x ULN unless the individual has been diagnosed with Gilbert's disease and this is clearly documented;
    h. Estimated glomerular filtration rate < 40 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease (MDRD) formula.
    i. Positive HIV serology
    j. Evidence of active Hepatitis B Virus (HBV) infection
    k. Evidence of active Hepatitis C Virus (HCV) infection
19. Women who are pregnant or breastfeeding.
20. Patient unwilling or unable to swallow tablets whole.
21. Any other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigator, would preclude participation in the study.
22. Use of any investigational product within 30 days prior to Baseline or currently enrolled in another study that involves clinical investigations.

10.3. Patient Withdrawal Criteria

The intent of this study is to follow all subjects until study termination unless the subject withdraws consent. Patients will be informed that they have the right to withdraw from the study

at any time for any reason without prejudice to their medical care. The Investigator also has the right to withdraw patients from the study if it is in their best interest. Patients may be withdrawn from the study if they:

- Have entered the study in violation of the protocol
- Require use of a prohibited concomitant medication
- Experience an AE that warrants premature withdrawal

All treated patients should be followed according to the Schedule of Assessments. All patients, even those who are withdrawn prematurely, should have all evaluations for the Month 12/ET Visit performed, if possible. All procedures required should be documented in the electronic case report form (eCRF). For all patients who withdraw prematurely, the Investigator will indicate one of the following reasons for withdrawal on the eCRF:

- Adverse event (AE)
- Death
- Protocol violation
- Lost to follow-up
- Patient's decision
- Other (reason to be specified by the Investigator)

In case of patients' withdrawal from the study due to an AE, such patients will be closely monitored until the resolution or stabilization of the AE. The Investigator should document the reason for withdrawal in the source documentation and eCRF.

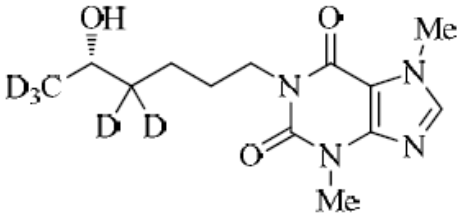
If a patient withdraws participation from the trial early, early withdrawal should be documented by the Investigator (or designee) in the appropriate eCRF pages and source documents when confirmed.

11. TREATMENT OF PATIENTS

11.1. Description of Study Drug

PCS499 is a stable, optically active, white-crystalline solid with the chemical name (*S*)-1-(4,4,6,6,6-pentadeutero-5-hydroxyhexyl)-3,7-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione. The structural formula is provided in Figure 1 .

Figure 1: Structural Formula for PCS499



The molecular formula is $C_{13}H_{15}D_5N_4O_3$.

The dosage form is a white tablet containing 300 mg of PCS499. The inactive ingredients are hydroxypropylmethylcellulose (HPMC), silicon dioxide, and magnesium stearate.

11.2. Concomitant Medications

At the discretion of the Investigator, over-the-counter (OTC) medications will be allowed for the management of a self-limiting indication (e.g., acetaminophen for headache). The use of concomitant OTC medications, including OTC herbals, must be approved by the Investigator before administration. All prescription medications must be approved by the Investigator throughout the active treatment period.

With the exception of PCS499, investigational drugs are not to be taken during the study.

IMPORTANT: Patients should be instructed to consult with the Investigator before taking any new medication or changing medications and/or dosing regimens throughout the study.

Drugs that are known to be strong inhibitors of CYP1A2 may increase exposure to the investigational product. The Investigator should contact the Medical Monitor prior to (if possible) the initiation of a CYP1A2 inhibiting drug, such as ciprofloxacin, cimetidine, fluvoxamine, etc.

Additional medication limitations are as follows:

- Topical skin treatments to the affected NL area are not permitted during the study.
- Systemic or topical immunosuppressive therapy, including but not limited to corticosteroids (excluding intraarticular injections, inhaled or nasal steroids), calcineurin inhibitors, thalidomide, apremilast, anti-malarials (e.g., hydroxychloroquine, chloroquine), cyclosporine, mycophenolate mofetil, azathioprine, methotrexate, and biologics (TNF-α blockers, anakinra, etc.) are not permitted during the study.

- Oral retinoids are not permitted during the study.
- Phototherapy (UVA/UVB) or photochemotherapy (PUVA) is not permitted during the study.
- Consumption of pentoxifylline, cilostazol, or a theophylline preparation is not permitted during the study.

11.3. Treatment Compliance

Patients will be instructed to bring their bottles, whether empty or containing unused study medication, with them for a compliance assessment during each clinic visit. Compliance will be assessed via tablet counts.

11.4. Randomization and Blinding

This is an open-label study which does not require a randomization list or blinding.

12. STUDY DRUG MATERIALS AND MANAGEMENT

12.1. Study Drug

The test article is PCS499 modified release 300mg tablets.

12.2. Study Drug Packaging and Labeling

PCS499 tablets will be packaged in high density polyethylene bottles respectively.

Each patient's study medication will be packaged in a study-specific box (kit) and shipped to the study site by a central distribution site.

12.3. Study Drug Storage

All investigational drug supplies should be stored in a secure, locked area, under the responsibility of the Investigator or other authorized individual. Study drug must be stored in the original packaging between 20 to 25°C (68 to 77°F), with deviations permitted between 15 to 30°C (59 to 86°F), and protected from extreme conditions of temperature, light, and humidity.

12.4. Study Drug Preparation

There is no study drug preparation needed for this study.

12.5. Administration

All patients will take PCS499 300 mg BID with food for 1 week. Beginning at Week 2, patients will commence administration of twice daily dosing of three PCS499 300 mg tablets (900 mg BID) with food. Patients will continue at their assigned dose for the remainder of the study.

Safety and tolerability will be assessed throughout study and the following steps may be taken:

- During the dosing period, if a patient receiving PCS499 900 mg BID experiences unacceptable toxicity (i.e., non-transient, moderate to severe limitation in activity) that is deemed by the Investigator to be related to study drug, his/her dose will be changed to PCS499 600 mg TID with food at the discretion of the Investigator in consultation with the Medical Monitor. If this dose is not tolerated, the dose will be further reduced to PCS499 600 mg BID with food at the discretion of the Investigator in consultation with the Medical Monitor. If 4 out of the first 6 patients dosed in this study require dose modification or discontinue from the study due to a drug-related adverse event within 1 month of dosing, consideration will be made to change the starting dose to 600 mg TID with food for all subsequent patients. If clinically indicated at any time during the study, study medication will be discontinued. However, patients will not be discontinued from the study due to cessation of study drug.

All changes in medication administration will also be noted in the eCRF.

Each kit will be clearly marked with dosage instructions.

Each subject's medication will be packaged for dispensing as described in the study manual.

12.6. Study Drug Accountability

The Investigator or designee must maintain accurate records of the receipt of all study drug, including date received, lot number, expiration date if applicable, amount received, condition of the package and the disposition of all study drug.

Patients will be instructed to bring their bottles, whether empty or containing unused study medication, with them for a compliance assessment during each clinic visit. Compliance will be assessed via tablet counts. Details of study medication compliance will be recorded on the eCRF. Investigational drug orders, records of receipt, dispensing records, and inventory forms will be examined and reconciled during and at the end of the study. Both the investigational drug that was used during the course of the study, as well as any remaining unused investigational drug, will be accounted for on a drug accountability record provided to the Investigator by Processa or its designee. In addition, a copy of all completed drug accountability records will be retained in the Investigators' Study Files, with a copy sent to Processa. The investigational drug will be kept in a locked area with limited access under controlled room temperature conditions.

12.7. Study Drug Handling and Disposal

Investigational drug orders, records of receipt, dispensing records and inventory forms will be examined and reconciled during and at the end of the study. Unless otherwise directed, at the end of the study, all unused and partially used containers of investigational drug must be returned as designated by the Sponsor.

In addition, a copy of all completed drug accountability records must be retained in the Investigators' Study Files, with a copy sent to the Trial Master File. The investigational drug shall be kept in a locked area with limited access under controlled room temperature conditions (see Section 12.3).

13. Demographics and Other Baseline Characteristics

Subject demographic characteristics (e.g., age, sex, and race) and baseline characteristics will be collected. Relevant NL-related as well as general medical history/current medical condition data until the start of study treatment will be collected, such as date of diagnosis of NL, previous treatments for NL, other skin disease history, and diabetic status.

14. ASSESSMENT OF EXPLORATORY EFFICACY

14.1. Exploratory Efficacy Variables

14.1.1. Investigator Global Assessment: Necrobiosis Lipoidica (IGA:NL)

The Investigator Global Assessment: Necrobiosis Lipoidica (IGA:NL) is a tool that has been adapted to assess the presence and severity of necrobiosis lesions. Adaptation of the scale was based on input from 4 dermatologists with expertise in granulomatous disorders, NL, and ulcers. The scale has face validity and has performed well in limited testing. The scale scores activity based on features of inflammation/erythema, induration, and ulceration (Table 3) and damage based on features of pigmentation, scarring, and atrophy (Table 4). Further validation of the scale is ongoing.

Instructions: Select (1) a numeric score that describes the activity and (2) a numeric score that describes the damage of the reference lesion*. (*Reference lesion is the most severely affected lesion.)

Table 3: IGA:NL Activity

Score	Definition	Description
0	Clear	No inflammation, induration or ulceration , but residual damage may be present.
1	Almost Clear	Minimal inflammation (faint erythema); essentially flat with possible trace induration; no ulceration present.
2	Mild	Mild inflammation (pink color) and/or slight induration; no ulceration present.
3	Moderate	Marked inflammation (dark pink, yellow-orange color) and/or moderate induration; no ulceration present.
4	Severe	Intense inflammation (red or orange color) and/or severe induration and/or 1-2 shallow ulcerations present, but underlying structures (muscle, bone) NOT visible.
5	Very Severe	Very intense inflammation (bright red/purple or deep orange color) and/or very severe induration and/or any deep ulceration present with underlying structures (muscle, bone) visible and/or more than 2 ulcerations.

Table 4: IGA:NL Damage

Score	Definition	Description
0	Absent	None

Score	Definition	Description
1	Dyspigmentation	Post-inflammatory hypo- or hyper- pigmentation
2	Scarring	Post-inflammatory scarring, including atrophic plaques

14.1.2. Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS)

A tool called the Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS) is also under development that separately assesses the color and ulcer of NL lesions. This tool includes domains to separately assess the color/inflammation (Table 5) and induration (Table 6) of NL lesions and the extent of ulceration, if present (Table 7). The scale was developed among 4 dermatologists with expertise in granulomatous disorders, NL, and ulcers, and has face validity and has performed well in limited pre-clinical testing. Further validation of the scale is ongoing.

Instructions: Select (1) a numeric score that describes the color and (2) a numeric score that describes the ulceration status of the reference lesion*. (*Reference lesion is the most severely affected lesion.)

Table 5: NLCUS: Color/Inflammation

Score	Color/Inflammation
0	None
1	Minimal inflammation (faint erythema)
2	Mild inflammation (pink)
3	Marked inflammation (dark pink/red, orange)
4	Intense inflammation (bright red/purple, deep orange)

Table 6: NLCUS: Induration

Score	Induration
0	None
1	Essentially flat with possible trace induration
2	Slight but definite induration
3	Moderate induration
4	Severe induration

Table 7: NLCUS: Ulcer

Score	Ulcer
0	None
1	1-2 shallow ulcerations, but underlying structures (muscle, bone) NOT visible.
2	Any deep ulceration with underlying structures (muscle, bone) visible and/or more than 2 ulcerations

14.1.3. Physician Global Assessment (PGA)

The physician's global assessment will be performed using a 10 cm VAS ranging from "none" to "extreme activity", after the question "Based on your assessment of the disease activity, draw a vertical mark (|) through the horizontal line for the level of disease activity that is present today."

14.1.4. Lesion/ulcer surface area

Surface area of the lesions(s)/ulcer will be measured by the Investigator and by photography. Lesion surface area is defined as the surface area of the lesion with active inflammation/erythema. The total lesion surface area (if more than one lesion is present), the reference lesion (defined as the lesion with the highest disease severity) surface area, reference ulcer surface area (defined as the ulcer with the highest disease severity within the reference lesion), and total ulcer surface area will be calculated. The longest length and width (measured perpendicular to the longest length) measurements taken by the Investigator with a ruler will be entered into the eCRF along with an assessment of the shape of the lesion (rectangular, circular, triangular, or elliptical).

Using the digital photograph/3D scan of the lesion, the Investigator will also electronically trace the perimeter of the reference lesion and reference ulcer (if present). Based on the tracing, the surface area of the reference lesion and the surface area and volume of the reference ulcer (if present) will be calculated.

14.1.5. Dermatology Quality of Life Index (DLQI)

The Dermatology Quality of Life Index (DLQI) is a self-administered, standard health-related quality of life (HRQL) instrument used in clinical trials related to skin diseases (Both, 2007). The DLQI consists of 10 items and covers six domains including: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Scores range from 0 to 30 with higher scores indicating poorer HRQL.

14.1.6. Skindex-29

Skindex-29 is another self-administered standard HRQL instrument that has been proposed to be comprehensive, but less used in clinical trials (Chren, 2012). It includes 29-items with 3 domains, symptoms, emotions and functioning. Each domain is scored from 0 to 100 with higher scores indicating lower quality of life. The domains can be combined and scored separately.

14.1.7. Patient Global Assessment (PtGA)

The patient's global assessment will be performed using a 10 cm VAS ranging from "very severe" to "not at all", after the question "Please indicate with a vertical mark (|) on the horizontal line, how does your skin condition affect you today?"

14.1.8. Exploratory Efficacy Variables in Ulcerated Patients

14.1.8.1. Closure of reference ulcer

Closure of reference ulcer is defined as skin re-epithelialization without drainage or dressing requirements confirmed at two consecutive study visits 2 weeks apart.

14.1.8.2. Ulcer volume

Ulcer volume will be assessed using via the use of a 3D-imaging system.

14.2. Biomarkers

Selected serum biomarkers related to the potential anti-inflammatory and/or immunosuppressive effects of PCS499 on NL will be measured. These include TNF-α, IFN-γ, IL-1β, IL-6, IL-12, IL-17 and MCP-1.

Additionally, an association between underlying autoimmunity and the development of NL has been suggested based on the higher than expected prevalence of the disease in patients with Type 1 diabetes (as compared to Type 2 diabetes) (Erfurt-Berge, 2015). C-peptide levels will be measured to assess whether there is any benefit of PCS499 in maintaining natural insulin production.

15. ASSESSMENT OF SAFETY

The safety parameters collected will include adverse events, vital signs, ECGs, physical examinations, and laboratory tests. In addition, concomitant medications will be recorded.

15.1. Safety Parameters

15.1.1. Vital Signs, Height, Weight, and Body Mass Index

Vital signs, including blood pressure, heart rate, respiratory rate, and oral temperature, will be measured. Height, weight and body mass index measurements will be collected at Screening only. Vital signs will be performed after the patient has been seated for at least 5 minutes.

15.1.2. Physical Examination

Full physical examinations will be performed. All abnormal findings will be documented in the eCRF.

15.1.3. Electrocardiogram

Standard resting 12-lead ECGs will be performed; ECGs will be performed after the patient has rested for at least 5 minutes.

15.1.4. Clinical Laboratory Assessments

Clinical Safety Laboratory assessments will include hematology, chemistry and urinalysis, coagulation, and HgbA1c.

Screening panels will include virus serology (HIV, and hepatitis B and C). Results must be available prior to dosing.

The list of clinical laboratory assessments is included in Appendix A.

15.1.4.1. Pregnancy Testing

PCS499 should not be administered to pregnant women. Effective methods of birth control must be used by WOCBP.

A serum β-HCG will be performed at Visit 1 (Screening). All WOCBP will have local urine pregnancy tests as indicated in the Schedule of Events (Table 2). A positive urine pregnancy test requires immediate interruption of study treatment until a serum β-HCG is performed and found to be negative. If positive, the subject must be discontinued from the study.

15.1.5. Concomitant Medications

Concomitant medications are defined as any medication taken by the patient during the course of the study following the first dose. Prior medications are defined as any medication taken by the patient within 30 days of their first dose of study medication. Prior and concomitant medications will be coded using the WHO Drug Dictionary.

15.2. Adverse Events and Reporting Procedures

15.2.1. Adverse Event Definition and Collection

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product whether or not considered drug-related. Adverse events may include safety findings considered to be clinically significant by the Investigator, Sponsor, or Medical Monitor. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is related to the medicinal product. Reporting an adverse event does not necessarily reflect a conclusion by the Investigator, Sponsor or Food and Drug Administration (FDA) that the event is causally related to the drug.

All adverse events should be captured and must be reported on the Adverse Event eCRF. Adverse events should be spontaneously reported or elicited by non-suggestive probing. All adverse event reports should contain the date the adverse event occurred, a brief description of the event (if the event consists of a cluster of signs and symptoms, record a diagnosis rather than each sign and symptom), onset date, the severity, the Investigator's assessment of the relationship to study drug, the study drug action taken, the outcome, date resolved, and whether or not the event was serious (and if so, why).

New information regarding signs and symptoms that occurred during the Screening phase and prior to the day of the first study medication dose on Day 1 of study that are related to screening procedures should be recorded on the Adverse Event log. Intercurrent illnesses or injuries should be regarded as AEs. Abnormal results of laboratory tests or diagnostic procedures are considered to be AEs if the abnormality:

- Is associated with clinical signs or symptoms
- Is considered by the Investigator to be of clinical significance
- Results in study withdrawal
- Fulfills any of the criteria for an SAE, as described in this section
- Requires intervention or further evaluation to determine the etiology of the abnormality and/or assess the risk to the patient
- Requires treatment

15.2.2. Categorizing Adverse Events in Relation to Study Phase

The relationship of each adverse event must be recorded on the Adverse Event eCRF as one of the choices provided on the scale that follows, where the temporal sequence is defined as an association between administration of a drug and the observed reaction or event such that the drug was present prior to the reaction or event:

The Investigator assesses the relationship between the AE and the study drug by using the following definitions:

- DEFINITELY RELATED – Onset of the event as relative to administration of the study drug is reasonable and there is no other cause to explain the event; or a re-challenge (if feasible) is positive.
- PROBABLY RELATED – Onset of the event as relative to administration of the study drug is reasonable and is more likely explained by the drug than by any other cause.
- POSSIBLY RELATED – Onset of the event as relative to administration of the study drug is reasonable; however, the event could have been due to another, equally likely, cause.
- UNLIKELY TO BE RELATED – Onset of the event as relative to administration of the study drug, is possible but another cause itself can explain the occurrence of the event or there are no reasonable grounds for suspecting that the product could have caused the event.
- NOT RELATED – Onset of the event as relative to administration of the study drug, is not reasonable; or, another cause itself can explain the occurrence of the event.

All AEs (regardless of seriousness or relationship to study drug) including those from the time of signing of the Informed Consent Form (ICF) through to the follow-up/early withdrawal visit are to be recorded in the patient's source documents and on the corresponding page(s) in the eCRF. Whenever possible, symptoms, signs, and laboratory abnormalities should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, intensity, action taken with respect to study drug, corrective treatment/therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study drug. All medications administered to treat an AE must be recorded in the patient's source documentation and documented in the eCRF.

15.2.3. Assigning Severity to Adverse Events

The severity of each adverse event must be recorded on the Adverse Event eCRF as one of the choices provided on the scale below:

- MILD: Awareness of sign or symptom, but easily tolerated.
- MODERATE: Discomfort enough to cause interference with usual activity.
- SEVERE: Incapacitating with inability to work or do usual activity.

15.2.4. Serious Adverse Event Definition and Collection

An adverse event is considered a serious adverse event (SAE) if, in the view of either the investigator or sponsor, it includes any untoward medical occurrence at any dose that:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.
- Results in a congenital anomaly/birth defect
- Is a medically important event that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed above.

The term “life threatening” in the definition of “serious” refers to an event in which the patient in the view of either the Investigator or Sponsor, was at risk of immediate death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Death is an outcome of an event. The event that resulted in death should be recorded and reported on the SAE form and documented in the eCRF.

Reporting serious adverse events to the Medical Monitor requires additional detailed reports and follow-up, depending upon the Investigator's (or in some cases the Sponsor's) estimate of a causal relationship between the test agent and the adverse event(s), and whether the adverse event(s) is identified in nature, severity, and frequency in the Investigator's Brochure or other risk information supplied to the Investigator.

In the event of a serious adverse event, the Investigator must notify the Medical Monitor immediately (within 24 hours). The SAE hotline telephone and SAE fax line numbers will be provided to each site and will be present also on the Serious Adverse Event Worksheet. Details of the serious adverse event must be documented on the Serious Adverse Event Worksheet by the site and faxed to the SAE fax line. The initial report should be as complete as possible. Information not available at the time of the initial report (e.g., an end date for the adverse event or discharge summary/testing/laboratory values received after the first report), must be documented on a follow-up Serious Adverse Event Worksheet. Sites must make an effort to obtain all hospital medical records including discharge summary confirming final diagnosis.

All serious adverse events (SAEs) should be submitted to the Institutional Review Board (IRB) as per the requirements of the IRB. The death of a patient must be immediately (within 24 hours of site awareness) reported to the IRB. All serious and non-serious adverse events should be thoroughly documented on the Adverse Event eCRF and followed out by the Investigator until the event resolves or until the termination visit. The event may be followed longer, if deemed necessary. Sites must ensure that the final SAE Worksheet captures the same information as the Adverse Event eCRF. For any death occurring during the trial, the medical condition that led to the death on the Adverse Event eCRF and also reported on the SAE Worksheet. The “outcome” status should be noted as “death” in these cases of SAEs that resulted in death. In addition, all SAEs that occur within 30 days after the last dose of study drug should be recorded and reported as noted previously.

16. ENDPOINTS

16.1. Primary Safety Endpoints

- Evaluation of AEs/SAEs (by type, severity, and relatedness) at each visit.
- Changes in safety clinical laboratory testing, vital signs at each visit.
- Changes in ECGs at Months 1, 3, 6, 9, and 12.

16.2. Exploratory Efficacy Endpoints

- Proportion of patients with scores of clear or almost clear (0 or 1) on the Investigator Global Assessment: NL (IGA:NL) Activity scale of the reference lesion at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Proportion of patients with ≥ 1 point decrease in IGA:NL Activity score of the reference lesion at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Proportion of patients with ≥ 2 point decrease in IGA:NL Activity score of the reference lesion at Months 1, 2, 3, 4, 5, 6, 9, and 12
- Proportion of patients with ≥ 1 point decrease in the Color score on the Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS) of the reference lesion at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Change from Baseline in Physician Global Assessment (PGA) score at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Percent change from Baseline in reference lesion surface area of inflammation/erythema based on Investigator measurement at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Percent change from Baseline in total lesion(s) surface area of inflammation/erythema based on Investigator measurement at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Percent change from Baseline in reference lesion surface area of inflammation/erythema based on photograph at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Change from Baseline in Dermatology Quality of Life Index (DLQI) score at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Change form Baseline in Skindex-29 score at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Change from Baseline in Patient Global Assessment (PtGA) visual analog scale (VAS) score at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Time to obtaining scores of clear or almost clear (0 or 1) of reference lesion on the IGA:NL Activity scale.

- Incidence of new ulceration (defined as a site with no previous ulceration) at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Time to new ulceration.

Patients with ulceration at Baseline only:

- Proportion of patients with ≥ 1 point decrease in the Ulcer score on the Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS) of the reference lesion at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Percent change from Baseline in reference ulcer surface area based on Investigator measurement at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Percent change from Baseline in total ulcer surface area based on Investigator measurement at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Percent change from Baseline in reference ulcer surface area based on photograph at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Incidence of complete wound closure of reference ulcer (defined as skin re-epithelialization without draining or dressing requirements confirmed at two consecutive study visits at least 2 weeks apart) at Months 2, 3, 4, 5, 6, 9, and 12.
- Time to complete wound closure of reference ulcer.
- Incidence of recurrence of reference ulcer after complete wound closure at Months 3, 4, 5, 6, 9, and 12.
- Time to recurrence of reference ulcer after complete wound closure.
- Change from Baseline in reference ulcer volume based on 3D scanning at Months 1, 2, 3, 4, 5, 6, 9, and 12.

16.3. Exploratory Serum Biomarkers

- Change from baseline in TNF-α, IFN-γ, IL-1β, IL-6, IL-12, IL-17 and MCP-1 at Months 1, 3, 6, 9 and 12.
- Change from baseline in C-peptide levels at Months 1, 3, 6, 9 and 12.

17. STATISTICAL METHODOLOGY

All endpoints will be analyzed after the last patient completes the 3-month visit and the 6- month visit (primary). A final lock of the database and the final analyses will occur after the last patient completes the 12-month visit.

17.1. Sample Size Determination

As this is a pilot study, no formal sample size calculation was performed.

17.2. General Statistical Methods

Patients will be analyzed by assigned treatment group. Analyses will be performed based on observed data, and missing values will not be imputed unless otherwise stated.

17.3. Analysis Populations

Safety Population: Defined as all patients enrolled in the study who received at least 1 dose of treatment.

Efficacy Population (Modified Intent to Treat (mITT)): Defined as all patients enrolled in the study who received at least 1 dose of treatment and has at least 1 post-baseline efficacy assessment.

Per-Protocol Population: Defined as a subset of the Efficacy Population who did not have a major protocol violation as defined in the Statistical Analysis Plan.

Biomarker Population: Defined as all patients enrolled in the study who received at least 1 dose of treatment, participated in biomarker evaluations, and have appropriate samples available for analysis.

17.4. Patient Characteristics

Baseline demographics and disease characteristics will be presented by descriptive statistics. All descriptive summary statistics of continuous variables will include: n, mean, median, standard deviation, minimum and maximum. All descriptive summaries presenting frequencies and incidences will include n, % and N, where N is the total number of patients with recorded values in the corresponding group. Patient completion status and exposure outcomes will be similarly presented.

17.5. Safety Analysis

The safety analyses will be performed using the Safety Population and include adverse events, changes in physical exam findings, vital signs, clinical laboratory values, and ECG results.

17.5.1. Adverse Events

Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA version 21.0 or higher). The number and percent of patients reporting at least one adverse event will be summarized by System Organ Class (SOC) and Preferred Term (PT) and presented by dose level, severity, relationship to study drug, amount of drug exposure,

and time. Each patient will contribute only once (i.e., first occurrence) to each of the incidence rates, regardless of the number of occurrences. For reporting of adverse event severity in patients with more than one occurrence of the same adverse event, the patient will only be reported once based on the highest severity of the adverse event observed. Patients who have a serious adverse event (SAE) or who discontinue the study due to an adverse event deemed to be related to study drug will be described in patient narratives.

17.5.2. Other Safety Analyses

Vital signs, clinical laboratory, and ECG results will also be presented and summarized by dose level and summarized by descriptive statistics with change from Baseline values calculated. All safety data collected in the clinical database, including physical exam findings and abnormal ECG results, will be presented in data listings.

17.6. Efficacy Analysis

Efficacy analyses will be performed using the Efficacy (mITT) Population. Efficacy endpoints will be summarized by descriptive statistics for each treatment group and by ulceration status. All descriptive summary statistics of continuous variables will include: n, mean, median, standard deviation, minimum and maximum. All descriptive summaries presenting frequencies and incidences will include n, % and N, where N is the total number of patients with recorded values in the corresponding group. Graphical representations will be presented, if appropriate. Efficacy data will also be presented in listings to assess changes within patients over time.

17.7. Biomarkers

Analyses will be performed using the Biomarker Population. Biomarkers will be evaluated to assess changes within patients over time. Additional exploratory analyses may be performed depending on the extent of the data using appropriate statistical methods.

17.8. Exploratory Associations among Outcomes

Depending on the extent of the data, additional exploratory analyses may be performed to characterize relationships among variables, such as correlations among variables and trending, as well as further sub-group analyses, such as based on diabetic status and study completion status. Additional sensitivity analyses may include comparisons between observed values and imputed values for missing data using different methods (e.g., multiple imputation, LOCF).

18. SAMPLE COLLECTION

18.1. Biomarker Sample Collection

Plasma and urine samples for all of these analytes will be collected as per the Schedule of Events (Table 2).

Additional instructions for sample preparation, labeling, storage and shipment will be provided in a separate lab manual.

18.2. Biomarker Sample Storage and Shipping

Instructions for sample preparation, storage, and shipping schedule and further instructions will be provided in a separate lab manual.

19. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

19.1. Study Monitoring

At regular intervals during the study, the site will be contacted through monitoring visits, letters, and telephone calls by a representative to review study progress, Investigator and subject compliance with study protocol requirements, and any emergent problems. During monitoring visits, the following points will be reviewed in accordance with all applicable regulatory requirements and standard operating procedures (SOPs): original medical records and other source documents, the Investigator site file, screening logs, subject informed consent, subject recruitment and follow-up, SAE documentation and reporting, documentation and reporting of endpoints, study drug allocation, subject compliance with the study drug regimen, study drug accountability, concomitant therapy use, and quality of data. In addition, other required regulatory documents will be reviewed, including but not limited to: IRB/IEC composition and correspondence, laboratory certification(s), delegation of authority, and Investigator and study personnel curricula vitae.

19.2. Sponsor's Responsibility

Processa Pharmaceuticals or its designee is responsible for the following:

1. Selecting qualified Investigators
2. Providing Investigators with the information they need to properly conduct an investigation
3. Ensuring proper monitoring of the investigation
4. Ensuring that the applicable regulatory authorities, and all participating Investigators are properly informed of significant new information regarding AEs or risks associated with the medication being studied

As the sponsor, Processa Pharmaceuticals has delegated some responsibilities to external vendors and Contract Research Organizations (CROs). These will be detailed in a Transfer of Regulatory Obligations (TORO) per Processa SOPs.

19.3. Audits and Inspections

Processa Pharmaceuticals (or representative) may conduct audits at the study site(s). Audits will include, but are not limited to: drug supply, presence of required documents, the informed consent process, laboratory specimen processing, and comparison of eCRFs with source documents. The Investigator agrees to cooperate with audits conducted at a reasonable time and in a reasonable manner.

Regulatory authorities worldwide may also audit the Investigator during or after the study. The Investigator should contact Processa Pharmaceuticals immediately if this occurs, and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

The Investigator is required to make all study documentation promptly available for inspection, review or audit at the study site upon request by sponsor, its representatives, or any appropriate regulatory agencies.

19.4. Institutional Review Board (IRB)

Some centers in this study may utilize a central IRB that meets the requirements of 21 CFR Part 56. Those centers not using the central IRB will use their local institutional review board as applicable.

19.5. Criteria for Study Termination

19.5.1. Sponsor Termination

If Processa Pharmaceuticals, Inc., their Study Representative (e.g., Contract Research Organization), or the Investigator discovers conditions arising during the study which indicate that the clinical investigation should be halted, the study must be terminated after appropriate consultation between the Study Sponsor, Agent and Investigator. Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence to protocol requirements, or;
- A decision on the part of Processa Pharmaceuticals, Inc. to suspend or discontinue development of the drug.

19.5.2. Patient Discontinuation

If a patient is discontinued from the study prematurely, the Investigator must select a reason for discontinuation on the termination page (End of Study Phase Status) eCRF. In addition, every effort should be made to complete the assessments listed under the early termination study visit. Patients withdrawn from the study will be considered evaluable for analysis.

A patient may be removed from the study for the following medical or administrative reasons:

- Adverse Event: If a patient experiences an adverse event that the patient finds unacceptable or that, in the judgment of the Principal Investigator, Processa Pharmaceuticals, Inc., or the Medical Monitor presents an unacceptable consequence or risk to the patient, the patient may be discontinued from further participation in the study.
- Administrative Discontinuation: After consultation with the Sponsor or Medical Monitor, a patient may be discontinued from the study for failure to comply with protocol requirements. All instances of noncompliance must be documented in the eCRF.
- Refusal of Treatment: If for any reason the patient refuses treatment during the study, the patient shall be discontinued from the study and the reasons for refusal documented on the eCRF. Reasonable efforts shall be made to monitor the patient for adverse events following such discontinuation. Such efforts shall be documented on the eCRF.

20. QUALITY CONTROL AND QUALITY ASSURANCE

A quality control and quality assurance plan, addressing aspects of the trial that may affect data integrity or the protection of human subjects, may be instituted for this study. All audit findings will be summarized and placed on file with appropriate documentation of response/resolution.

21. ETHICS

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and the Investigator abide by Good Clinical Practice (GCP), including but not limited to Title 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312 and the International Conference on Harmonisation (ICH) guidelines and directives. Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki, Tokyo 2004, Korea 2008 and applicable local regulatory requirements and law.

Copies of these materials are available from Processa Pharmaceuticals and the CRO designee by request. The purpose of these regulations, legal obligations, and guidances is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

1. Human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not.
2. The study is conducted with diligence and in conformance with the protocol in such a way as to protect subject safety and ensure the integrity of the findings.
3. The potential benefits of the research justify the risks.

The Investigator is responsible for protecting the rights, safety, and welfare of subjects under his/her care, and for the control of the medications under investigation.

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study drug, and their study-related duties and functions. The Investigator will maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties. Individuals ineligible to conduct or work on clinical studies, including those ineligible as a result of debarment under the Generic Drug Enforcement Act of 1992, will not be allowed to conduct or work on studies sponsored by Processa Pharmaceuticals. The Investigator is required to immediately disclose to Processa Pharmaceuticals in writing, if any person involved in the conduct of the study is debarred pursuant to a hearing by US FDA under this anti-fraud law, or if any proceeding for debarment is pending, or is (to the best of the Investigator's knowledge) threatened.

The rest of this section of the protocol describes in more detail the specific GCP-defined responsibilities the Investigator assumes by agreeing to participate in this study.

21.1. Ethics Review

The Investigator (or designee) must submit this study protocol, the Processa Pharmaceuticals approved informed consent form (ICF), patient information sheets (PISs), subject recruitment materials, and other appropriate documents to the appropriate IRB or IEC, and following review of the submitted materials is required to forward to Processa Pharmaceuticals (or designee) a

copy of the written and dated approval/favorable opinion signed by the IRB Chairman, along with a list of the IRB/IEC composition.

The approval/favorable opinion should clearly state the trial (study number, protocol title, and version number), the documents reviewed (Protocol, ICF, IB, etc.) and the date of the review. The study will not commence at the study site until Processa Pharmaceuticals has received a copy of this written and dated approval/favorable opinion.

During the trial, any amendment to the protocol and the ICF (as appropriate) should be submitted to the IRB/IEC. The IRB/IEC should also be informed of any event likely to affect the safety of subjects or the continued conduct of the trial, in particular any change in safety. Additionally, all updates to the IB will be sent to the IRB/IEC. A progress report will be sent to the IRB/IEC and the protocol will be reviewed annually or more frequently, as required by IRB/IEC or local regulations.

The Investigator will notify the IRB/IEC of the conclusion of the clinical study within 1 month of completion or termination of the study. The final report sent to the IRB/IEC will also be sent to Processa Pharmaceuticals, along with the completed eCRFs and all necessary regulatory documents, thereby fulfilling the Investigator's regulatory responsibility.

The Investigator will maintain a copy of all correspondence with the IRB/IEC, including copies of approved documents. The Investigator will also maintain a copy of the IRB/IEC membership list, including members' occupation and qualifications (or a statement confirming compliance with GCP requirements for committee composition). An IRB or IEC General Assurance Number may be accepted in lieu of a membership roster.

21.2. Ethical Conduct of the Study

This study will be conducted in accordance with GCP as delineated by Title 21 CFR Parts 50, 56, and 312, and the ICH guidelines and directives. Participating Investigators, including members of the Committees and National Coordinators, will receive compensation for their time but will receive no financial profit from their activities related to the trial.

Before the first subject is enrolled in the study, all ethical, regulatory, and legal requirements must be met.

An Investigator participating in this study is required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable local regulations related to the conduct of a clinical study.

21.3. Written Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations. Written informed consent must be obtained from all subjects participating in a clinical study conducted by Processa Pharmaceuticals.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject. The subject must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the subject, must be given to the subject. Confirmation of a subject's informed consent must also be documented in the subject's source documentation prior to any testing under this protocol, including screening tests and assessments.

Each consent form should contain an authorization allowing the Principal Investigator(s) and Processa Pharmaceuticals to use and disclose patient health information (PHI) in compliance with local law.

The original signed consent form will be retained with the study records.

22. DATA HANDLING AND RECORDKEEPING

22.1. Data Collection

Electronic Case Report Forms (eCRFs) will be provided to the study site by Processa or its designee. All protocol-required information collected during the study must be recorded by the Investigator or designated representative in the source documentation for the study. The source documentation will then be used to enter the protocol required information onto the eCRF. The Investigator may authorize other persons to make entries in the eCRF, provided that the names, positions, signatures and initials of these persons are supplied in a delegation of authority log actively maintained at the site and reviewed by the Study Monitor. The Investigator or designated representative should enter source document data for enrolled patients into the eCRF as soon as possible once the information has been collected. All changes to data will be collected electronically through a computerized system for electronic data capture. Changes or corrections to electronic case report forms will be documented by use of audit trails and include identification of the person making a change or correction, and will be time/date stamped. The eCRF for each patient will be checked against source documents by the Study Monitor. eCRFs will be stored on an appropriate storage media at the Investigator's site and the data management center.

Prior to the start of the study, the Principal Investigator will complete a Delegation of Authority form (Site Signature and Delegation Log), showing the signatures and handwritten initials of all individuals and the delegation of responsibilities, such as identifying those individuals who are authorized to make or change entries on eCRFs.

22.2. Case Report Form Completion

Data within the eCRF will be monitored by the Clinical Research Associate according to a Clinical Monitoring Plan. Queries will be generated based on discrepancies found while monitoring. Site personnel will review and respond to these queries appropriately. Additionally, CRO and Processa Pharmaceuticals may periodically perform aggregate data reviews, which could result in queries being generated for site personnel resolution. The final, completed eCRF for each subject must be electronically signed and dated by the Principal Investigator to signify that the Principal Investigator has reviewed the eCRF and certifies it to be complete and accurate.

22.3. Database Management, Data Clarification, and Quality Assurance

A designated CRO will be responsible for data management. Data Management will develop a Data Management Plan document and provide it to Processa Pharmaceuticals for approval. The DMP document will define all activities in the data collection and cleaning process. The detailed DMP will be based on the protocol, work scope, contract, analysis plans, data-flows, eCRFs, data cleaning procedures, other supporting documents, and data management standards and practices.

Programmed data validation edit checks will be run to check for database completeness and consistency, and queries will be generated upon data entry or via review by a Clinical Data Manager after entry. The sites will respond to the data queries in a timely manner.

Concurrent medications entered into the database will be coded using a WHO Anatomical Therapeutic Chemical dictionary. Coexistent diseases and AEs will be coded using MedDRA.

Quality control procedures will be conducted prior to database lock according to the designated CRO SOPs.

When the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time will only be made by joint written agreement between Processa Pharmaceuticals, the Trial Statistician, the Data Manager, and the Quality Assurance Auditor according to designated CRO SOPs.

22.4. Inspection of Records/Source Documents

According to the ICH guidelines for GCP, the sponsor or designee must verify data entered in the eCRF entries against the source documents, except for the pre-identified source data directly documented in the eCRF (if applicable). The ICF will include a statement by which the subject allows the sponsor's duly authorized personnel, the IRB/IEC, and the regulatory authorities to have direct access to source data that supports the data in the eCRF (e.g., subject's medical file, appointment books, and original laboratory records). These personnel, bound by professional secrecy, must keep confidential all personal medical information.

The objective of source document verification (SDV) is to comply with GCP and international regulatory requirements and to reduce the risks of fraud. Source document verification means ensuring that the source documents are an accurate and verifiable reflection of the subject's participation in the study and that all relevant information that is recorded in the source document is accurately entered into the eCRF.

Where source documents serve as the basis for deriving data for the trial, SDV should ensure that these documents are correctly labeled and filed and that the data derived from them are correct.

All source documents pertaining to this study will be maintained by the Investigator and made available for inspection by authorized persons. If electronic progress notes and other electronic source documents are not Title 21 CFR Part 11 compliant, they are not considered a valid source for this study. All progress notes must be dated and signed by the Investigator or sub-Investigator at the time of the visit. Processa Pharmaceuticals reserves the right to terminate the study for refusal of the Investigator to supply original source documentation for this clinical study.

The Investigator will note in a source independent from the eCRF the following information:

1. Information to confirm that the subject exists (e.g., initials, date of birth, sex)
2. Confirmation that the subject satisfies the inclusion/exclusion criteria
3. Confirmation that the subject is taking part in the clinical trial
4. Confirmation of the informed consent process
5. Visit dates and documentation of protocol assessments and procedures
6. Information concerning all AEs
7. Details of concomitant and investigational medications

Source document verification is not a substitute for clinical trial monitoring, the purpose of which is to ensure that the protocol has been followed correctly, the eCRF has been fully and accurately completed, SDV has been carried out, and the study timelines and enrollment goals and requirements have been met.

22.5. Retention of Records

The Investigator must maintain all study documentation as confidential, and take measures to prevent accidental or premature destruction of these documents.

The Investigator must retain the study documents at least 2 years after the approval of a marketing application/new drug application for the indication investigated or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product (e.g., the Investigational New Drug application is withdrawn). These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Processa Pharmaceuticals.

The Investigator must notify Processa Pharmaceuticals prior to destroying any study essential documents.

If the Investigator can no longer ensure archiving, he/she shall inform Processa Pharmaceuticals. The relevant records shall be transferred to a mutually agreed upon designee.

23. CONFIDENTIALITY, AMENDMENTS, AND PUBLICATIONS

All information disclosed or provided by Processa Pharmaceuticals (or designee) or produced during the trial including, but not limited to, the protocol, the eCRFs, the IB, and the results obtained during the course of the trial (if applicable), are confidential. The Investigator or any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of Processa Pharmaceuticals.

However, submission of this protocol and any other necessary documentation to the IRB/IEC is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from Processa Pharmaceuticals. However, authorized regulatory officials and sponsor personnel (or designee) will be allowed full access to inspect and copy the records. The copied and inspected records will remain at the site and will not be transmitted or removed from the site. All study drug, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by Processa Pharmaceuticals and responsible ethics committee(s) or regulatory authorities.

Photographs from this study may be used for the further development of clinical tools to evaluate the disease activity in patients with Necrobiosis Lipoidica (e.g. the IGA:NL scale and the NLCUS). If photographs are used, they will only include unidentifiable images, meaning that the patient will not be able to be identified from these photographs.

Subjects will be identified only by unique subject numbers in eCRFs. Their full names may, however, be made known to a regulatory agency or other authorized officials in the event of inspections. Documents containing the full name or other personally identifiable information of the subject are to remain at the site. This information will not be transferred to Processa Pharmaceuticals nor be contained in regulatory filings. In the event of inspections by authorized agencies, this subject identification may be disclosed.

23.1. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., PHI authorization in North America).

The subject will not be identified by name in the eCRF or in any study reports and these reports will be used for research purposes only. Processa Pharmaceuticals, its partner(s) and designee(s), and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

Processa Pharmaceuticals will protect individual subject information to the fullest extent possible during this trial. At no time will a subject become identified in any publication or presentation. However, the subject may have to become identified in the event of a regulatory authority audit or inspection in order to verify the accuracy of the data. Access to subject information is at the discretion of Processa Pharmaceuticals and cannot occur prior to database lock or other specified events as determined solely by the discretion of Processa Pharmaceuticals.

23.2. Study Protocol Amendments

The Investigator will not make any changes to this protocol without prior written consent from Processa Pharmaceuticals and subsequent approval by the IRB/IEC. Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol that appears necessary as the study progresses will be fully discussed by the Investigator(s) and Processa Pharmaceuticals. If agreement is reached regarding the need for an amendment, it will be written by Processa Pharmaceuticals. The written amendment must be submitted to the chairman of the IRB/IEC identified with this responsibility. Except for administrative amendments, Investigators must await IRB/IEC approval of protocol amendments before implementing the change(s). Administrative amendments are defined as having no effect on the safety of the research subjects, scope of the investigation, or quality of the trial. However, a protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, and the IRB/IEC notified within 5 days. Processa Pharmaceuticals will ensure submission of any protocol amendments to the appropriate regulatory agencies.

When, in the judgment of the chairman of the local IRB/IEC, the Investigators, and/or Processa Pharmaceuticals, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, the Investigator will obtain repeat informed consent from subjects enrolled in the study before expecting continued participation.

23.3. Publication

All information concerning the product as well as any information such as clinical indications for the study drugs, their formula, their formulation, methods of manufacture and other scientific data relating to it, that have been provided by Processa Pharmaceuticals or designee, and are unpublished, are confidential and must remain the sole property of Processa Pharmaceuticals. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from Processa Pharmaceuticals is obtained. Processa Pharmaceuticals has full ownership of the eCRFs completed as part of the study.

By signing the study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by Processa Pharmaceuticals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

Processa Pharmaceuticals or designee will prepare a final report on the study. The Investigator may not publish or present any information on this study without first presenting the information to Processa Pharmaceuticals for review.

24. REFERENCES

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APPENDIX A. LABORATORY ASSESSMENTS

Hematology Panel	Clinical Chemistry	Urinalysis
Hemoglobin (Hgb) Hematocrit (Hct) Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Total Neutrophils) Mean Corpuscle Volume (MCV) Mean Corpuscle Hemoglobin (MCH) Mean Corpuscle Hemoglobin Concentration (MCHC) Red cell Distribution Width (RDW) Mean Platelet Volume (MPV)	Alanine Aminotransferase (ALT) Albumin Alkaline Phosphatase (ALP) Aspartate Aminotransferase (AST) Bicarbonate (Carbon Dioxide) Bilirubin, Direct Bilirubin, Indirect Bilirubin, Total Calcium Chloride Cholesterol, Total Creatinine eGFR Gamma Glutamyl Transferase (GGT) Glucose HDL LDL Magnesium Phosphorus Potassium Protein, Total Sodium Triglyceride Urea, Blood Nitrogen (BUN) Uric Acid	Appearance Bilirubin Blood Color Glucose, Urine Ketone Leukocyte Esterase (LE) Nitrite pH Protein Specific Gravity Urobilinogen
Additional Hematology	**Serology Screen**	**Other Labs**
Prothrombin time test (PT) Activated partial prothrombin time test (aPTT) INR Hemoglobin A1c (HbA1c)	Human Immunodeficiency Virus (HIV) 1 and 2 antibody; confirmatory testing to be performed if indicated Hepatitis B surface Antigen (HBsAg) Hepatitis C virus antibody (HCV); confirmatory testing to be performed if indicated QuantiFeron Gold TB test	Follicle Stimulating Hormone (FSH) if indicated Serum β-HCG pregnancy test (at Screening) if indicated Urine Pregnancy test (in WOCBP) C-Peptide Cytokines (TNF-α, IFN-γ, IL-1β, IL-6, IL-12, IL-17, MCP-1)

APPENDIX B. LIST OF BIOMARKERS

- TNFα (plasma)
- IFN-γ (plasma)
- IL-1β (plasma)
- IL-6 (plasma)
- IL-12 (plasma)
- IL-17 (plasma)
- MCP-1 (plasma)
- C-peptide (serum)

APPENDIX C. SCALES (DLQI AND SKINDEX-29)

Dermatology Quality of Life Index (DLQI)

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.

Skindex-29

DERMATOLOGY SURVEY

This survey concerns the skin condition which has bothered you the most during the past four weeks.

Skindex29

These questions concern your feelings over the past 4 weeks about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST FOUR WEEKS DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My skin hurts	☐1	☐2	☐3	☐4	☐5
2. My skin condition affects how well I sleep	☐1	☐2	☐3	☐4	☐5
3. I worry that my skin condition may be serious	☐1	☐2	☐3	☐4	☐5
4. My skin condition makes it hard to work or do hobbies	☐1	☐2	☐3	☐4	☐5
5. My skin condition affects my social life	☐1	☐2	☐3	☐4	☐5
6. My skin condition makes me feel depressed	☐1	☐2	☐3	☐4	☐5
7. My skin condition burns or stings	☐1	☐2	☐3	☐4	☐5
8. I tend to stay at home because of my skin condition	☐1	☐2	☐3	☐4	☐5
9. I worry about getting scars from my skin condition	☐1	☐2	☐3	☐4	☐5
10. My skin itches	☐1	☐2	☐3	☐4	☐5
11. My skin condition affects how close I can be with those I love	☐1	☐2	☐3	☐4	☐5
12. I am ashamed of my skin condition	☐1	☐2	☐3	☐4	☐5
13. I worry that my skin condition may get worse	☐1	☐2	☐3	☐4	☐5
14. I tend to do things by myself because of my skin condition	☐1	☐2	☐3	☐4	☐5
15. I am angry about my skin condition	☐1	☐2	☐3	☐4	☐5
16. Water bothers my skin condition (bathing, washing hands)	☐1	☐2	☐3	☐4	☐5
17. My skin condition makes showing affection difficult	☐1	☐2	☐3	☐4	☐5
18. I worry about side-effects from skin medications / treatments	☐1	☐2	☐3	☐4	☐5
19. My skin is irritated	☐1	☐2	☐3	☐4	☐5
20. My skin condition affects my interactions with others	☐1	☐2	☐3	☐4	☐5

Please turn to next page

Skindex29

These questions concern your feelings over the past 4 week about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST 4 WEEK DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
21. I am embarrassed by my skin condition	☐1	☐2	☐3	☐4	☐5
22. My skin condition is a problem for the people I love . . .	☐1	☐2	☐3	☐4	☐5
23. I am frustrated by my skin condition	☐1	☐2	☐3	☐4	☐5
24. My skin is sensitive	☐1	☐2	☐3	☐4	☐5
25. My skin condition affects my desire to be with people . .	☐1	☐2	☐3	☐4	☐5
26. I am humiliated by my skin condition	☐1	☐2	☐3	☐4	☐5
27. My skin condition bleeds	☐1	☐2	☐3	☐4	☐5
28. I am annoyed by my skin condition	☐1	☐2	☐3	☐4	☐5
29. My skin condition interferes with my sex life	☐1	☐2	☐3	☐4	☐5
30. My skin condition makes me tired	☐1	☐2	☐3	☐4	☐5