INTEGRIUM, LLC
BIOMETRICS DEPARTMENT

Clinical Study Protocol: PCS499-NL01

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

Statistical Analysis Plan (SAP) Documentation

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Statistical Analysis Plan for Clinical Study Protocol: PCS499-NL01

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Document History

Version Number	Author	Date	Change
1.0	O. Lopez	18DEC2019	Initial version
2.0	O. Lopez	10AUG2020	Updated changes and promoted document version to an intermediate draft between versions 1.0 and 2.0 of this document. Changes include: - Update drug accountability definition for expected number of tablets and percentage of tables taken - Updated the scoring scheme for Skindex-29 outcomes - Updated the calculations of the difference between dates to not include an additional day - Split table 14.2.01.1 into two tables, Lesions and Ulcers separately - Reordered table output related to lesions and ulcers, moving ulcers specific output before lesion specific output - Removed table 14.1.4.1 since data was not coded - Defined the derivation for QTcF as an additional ECG parameter to summarize - Updated table output count - Removed tables - Removed all figures - Incorporated sponsor commentary

Glossary of Abbreviations

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
CKD	Chronic kidney disease
CYP	Cytochrome P-450
DLQI	Dermatology Quality of Life Index
ECG/EKG	Electrocardiogram
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
HRQL	Health related quality of life
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
NBUVB	Narrow Band Ultraviolet B therapy
NL	Necrobiosis Lipoidica
NLCUS	Necrobiosis Lipoidica Color and Ulcer Scale
PGA	Physicians Global Assessment
PHI	Protected Health Information
PtGA	Patient Global Assessment
SAE	Serious adverse event
SOC	System Organ Class
TB	Tuberculosis
TGF-β	Transforming growth factor beta
TID	Three times a day
TNF	Tumor necrosis factor
TORO	Transfer of Regulatory Obligations
ULN	Upper Limit of Normal
UVA/UVB	Ultraviolet A /Ultraviolet B phototherapy
VAS	Visual Analog Scale
WHO	World Health Organization
WOCBP	Women of Child-Bearing Potential

Table of Contents

1. Introduction

1.1. Scope

This document contains detailed information to aid the production of the Clinical Study Report (CSR) including summary tables and listings for trial PCS499-NL01. The contents of this document were reviewed by the sponsor, Processa Pharmaceuticals, Inc., and the trial biostatistician at Integrium.

1.2. Study Background/Plan

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. The test article is PCS499 modified release 300mg tablets.

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 Visit 2/Day 0 (Baseline). At the Visit3/Day 7 and Visit4/Day 14 phone Safety Check-in, patients will be instructed to increase their morning dose to 3 tablets and their evening dose to 3 tablets (PCS499 900 mg BID with food) if satisfactory tolerability to PCS499 300 mg BID is reported. 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. 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. 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 3-month visit and then again when 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.

1.3. Study Objectives

1.3.1. Primary Objective

The primary objective of this study is:

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

1.3.2. Secondary Objective

There are no secondary objectives defined for this study.

1.3.3. Exploratory Objectives

The exploratory objectives for this study are:

- 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.

1.4. Study Endpoints

1.4.1. Primary Endpoints

The following safety parameters will be recorded at regular intervals during the study:

- 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.

1.4.2. Secondary Endpoint

There are no secondary endpoints defined for this study

1.4.3. Exploratory Endpoints

The exploratory endpoints are:

- 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.
- 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.

<u>Patients with ulceration at Baseline only:</u>

- 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.

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.

2. Detailed Statistical Methods

2.1. General Statistical Methods

The statistical analysis of the data obtained from this study will be the responsibility of the study biostatistician. If, after the study has begun, changes are made to the statistical analysis plan, these deviations will be listed in the Documentation of Statistical Decisions document, along with an explanation as to why they occurred.

Continuous data will be summarized using descriptive statistics (number, mean, median, standard deviation, minimum, and maximum values). Categorical data will be summarized using frequency tables (frequency and percent).

If at the end of the study the Efficacy Population and the Per Protocol Population include the same patients, then only table and figure output for the Efficacy Population will be produced.

2.2. Study Populations

Safety Population
All patients enrolled in the study who received at least 1 dose of treatment.

Efficacy Population (mITT)
All patients enrolled in the study who received at least 1 dose of treatment and have at least 1 post-baseline efficacy assessment.

Per-Protocol Population (PP)
All patients enrolled in the study who received at least one dose of study treatment, have at least 1 post-baseline efficacy assessment, and did not have a major protocol violation.

Biomarker Population
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.

2.3. Disposition of Patients

The number and percentage of patients entering, discontinuing or completing the study will be presented. Reasons for withdrawal pre- and post-randomization will also be summarized.

2.4. Demographics and Patient Baseline Characteristics

Demographic data (age, sex, race, and ethnicity), baseline characteristics (age, weight, height, and body mass index), and general medical history will be summarized by means of descriptive statistics or frequency tables.

2.5. Study Drug Accountability

Treatment compliance will be assessed via tablet counts. Patients will be dispensed kits of study medication and dose and frequency will be recorded starting at Visit2/Day 0 (Baseline) and at every clinic visit starting at Month 1/Day 28 through Month 11/Day 270. The number of tablets returned will be captured starting at Month 1/Day 28 and repeated at every clinic visit through Month 12/Day 360.

The actual number of tablets taken, expected number of tablets taken based on the dose and frequency assigned, and percentage of tablets taken will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum) by clinic visit and overall.

The dose and frequency of dosage will be listed and summarized in frequency tables by clinic visit.

Actual number of tablets taken will be defined as the difference between the number of tablets dispensed and the number of tablets returned for each clinic visit and overall. Expected number of tablets number of tablets will be calculated as the maximum number of tablets based on the number of days between dispensation and collection of study drug, and the expected study dose and regimen for that particular study month. The percentage of tablets taken will be the ratio of actual number of tablets taken and expected number of tablets taken multiplied by 100.

2.6. Prior and Concomitant Medications

Prior and concomitant medications will be identified using the September 2018 release version of the World Health Organization (WHO) Drug dictionary.

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.

Section 2.15 describes the imputation rules for partial dates. All medications will be presented in a data listing and summarized by frequency counts.

2.7. Pregnancy Test

The results of the pregnancy tests will be listed separately from hematology and urinalysis laboratory results. A serum pregnancy test will be administered at the screening visit and urine pregnancy tests will be administered at subsequent visits.

2.8. Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be listed and summarized.

2.9. Safety Evaluations

All safety summaries will be presented for the Safety Population.

2.9.1. Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.

AEs occurring on or before Visit 2/Day 0 (Baseline) prior to drug administration will be regarded as "pre-treatment" and will not be included in the treatment emergent AE tabulations.

Treatment Emergent Adverse Events (TEAEs) are defined as any AE that starts or increases in severity after drug administration at Visit 2/Day 0 and will be summarized.

Listings of all AEs will be provided and separately by:

- Treatment Emergent AEs
- AEs leading to discontinuation of study
- Serious AEs

An overall summary table will be provided showing the number and percentage of patients with any:

- Pre-Treatment AEs
- TEAE
- Severe TEAE
- Serious TEAE
- Drug-related TEAE
- Drug-related severe TEAE
- Drug-related serious TEAE
- TEAE leading to withdrawal of study drug
- TEAE leading to change in study drug dose
- TEAE with outcome death

The number of reported AEs will also be shown in this summary table.

Summary tables for the following will also be presented:

- Summary of TEAEs by Body System and Preferred term,

- Summary of TEAEs by Severity,
    - If a patient has reported the same treatment emergent adverse event multiple times then the adverse event with the highest severity will be summarized.
- Summary of Drug-related TEAEs, and
- Summary of Drug-related TEAEs by Severity.
    - If a patient has reported the same drug-related treatment emergent adverse event multiple times, then the adverse event with the highest severity will be summarized.

Inferential statistical analysis comparing the AE data between active and placebo is not planned.

2.9.2. Laboratory Parameters

Clinical Safety Laboratory assessments will include hematology, chemistry and urinalysis, coagulation, and HgbA1c. Screening panels will include virus serology (HIV, hepatitis B and C, and TB) and FSH (to confirm post-menopausal status).

Observed values of continuous safety laboratory parameters and corresponding changes from baseline will be summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum) by visit. Categorical safety laboratory parameters will be summarized by frequency tables.

A clinically significant change from baseline (Visit 2/Day 0) will be recorded as an AE if deemed appropriate by the Investigator.

All laboratory outcomes will be listed.

2.9.3. Vital Signs

Observed values of vital sign parameters (temperature, SBP/DBP, heart rate, and respiration rate) and corresponding changes from baseline (Visit 2/Day 0) will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum) by visit.

A clinically significant change from baseline (Visit 2/Day 0) will be recorded as a TEAE if deemed appropriate by the Investigator.

2.9.4. Physical Examination

Individual physical examination findings will be listed by visit. A clinically significant change from Baseline (Visit 2/Day 0) will be recorded as a TEAE if deemed appropriate by the Investigator.

Results of the physical examination will be listed and summarized in frequency tables by body system.

A clinically significant change from Screening will be recorded as an AE if deemed appropriate by the Investigator.

2.9.5. Electrocardiogram

Observed values of continuous ECG parameters and corresponding changes Visit 2/Day 0 will be summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum). Results of ECG measurements will be summarized in frequency tables by visit.

A clinically significant change from baseline (Visit 2/Day 0) will be recorded as an AE if deemed appropriate by the Investigator.

Fridericia's formula will be used to derive the QT correction, QTcF parameter. QTcF is defined as the QT interval divided by the cubed root of the RR interval ($QTcF = QT / \sqrt[3]{RR}$).

2.10. Exploratory Efficacy Analyses

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

The IGA:NL will be assessed at every visit the patient visits the clinic (i.e. excluding Visit 3 and 4). The IGA:NL will be used to assess the presence and severity of necrobiosis lesions. The two scales that will be determined are Activity and Damage. Activity has a 6-point scale (0-5) and Damage a 3-point scale (0-2).

The outcomes from this assessment will treated as categorical and will be listed and summarized by frequency tables.

The outcomes detailed below will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum) by visit.

- Proportion of patients with scores of clear or almost clear (0 or 1) of the reference lesion on the Activity Scale at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Proportion of patients with ≥ 1-point decrease in 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 Activity score of the reference lesion 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.

Proportion of subjects with >= 1 point decrease or >=2 decrease in Activity score will be determined from the baseline Visit 2/Day 0.

Time to obtaining scores of clear or almost clear (0 or 1) will be defined as the difference between the date when this outcome of interest is determined and the date of first study drug exposure.

2.10.2.Necrobiosis Lipoidica Color and Ulcer Scale (NLCUS)

The NLCUS will be assessed starting at Visit 2/Day 0 and at every clinic visit through Month 12. The NLCUS will be used to assess the color and ulcer of necrobiosis lesions. The three scales that will be determined are Color/Inflammation, Induration, and Ulcer. Color/Inflammation has a 5-point scale (0-4), Induration a 5-point scale (0-4), and Ulcer a 3-point scale (0-2).

The outcomes from this assessment will treated as categorical and will be listed and summarized by frequency tables.

The outcomes detailed below will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum) by visit.

- Proportion of patients with ≥ 1-point decrease in the Color score of the reference lesion at Months 1, 2, 3, 4, 5, 6, 9, and 12.
- Among patients with ulceration at Baseline only: Proportion of patients with ≥ 1-point decrease in the Ulcer score on the Color and Ulcer Scale (NLCUS) of the reference lesion at Months 1, 2, 3, 4, 5, 6, 9, and 12.

2.10.3.Physician Global Assessment (PGA)

The PGA will be assessed using a 10 cm VAS ranging from “none” to “extreme activity”. The distance marked in centimeters from “none” to “extreme activity” and the change from baseline (Visit 2/Day 0) will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum) by visit.

2.10.4.Patient Global Assessment (PtGA)

The PtGA will be assessed using a 10 cm VAS ranging from “not at all” to “very severe”. The distance marked in centimeters from “not at all” to “very severe” and the change from baseline (Visit 2/Day 0) will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum) by visit.

2.10.5.Lesion/ulcer surface area

Surface area of the lesions(s)/ulcer will be measured by the Investigator and by photography. Continuous outcomes, separately for those measured by the Investigator and by photography, and changes from baseline (Visit 2/Day 0), will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum) by visit.

The outcomes detailed below will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum) by visit.

- 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.

The outcomes detailed below will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum) by visit, for patients with ulceration at Baseline only.

- 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.

2.10.6.Dermatology Life Quality Index (DLQI)

The DLQI consists of 10 items and covers six sub-scales 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 health related quality of life (HRQL).

Each question is scored on a four-point Likert scale (0-3) where the score of 0 can represent one of three possible scenarios:

- Score of 0 can mean “Not at all”, “Not relevant”, or “Question unanswered”
- Score of 1 means “A little”
- Score of 2 means “A lot”
- Score of 3 means “Very much”

The DLQI is administered starting at Visit 2/Day 0 and at every clinic visit until Month 12. Total and sub-scale specific continuous outcomes, and the change from baseline (Visit 2/Day 0), will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum) by visit.

The six sub-scales include the following items and have the noted maximum score

- Symptoms and feelings includes Questions 1 and 2 with a maximum score of 6
- Daily activities includes Questions 3 and 4 with a maximum score of 6
- Leisure includes Questions 5 and 6 with a maximum score of 6
- Work and school includes Question 7 with a maximum score of 3
- Personal relationships includes Questions 8 and 9 with a maximum score of 6
- Treatment includes Question 10 with a maximum score of 3

2.10.7.Skindex-29

The Skindex-29 includes 29-items with 3 domains: Symptoms, Emotions and Functioning. Each domain is scored from 0 to 100 with higher scores indicating a lower quality of life and a higher impact of the skin disease. Scoring is based on the Skindex-29 documentation and is done as follows:

- Never = 0
- Rarely = 25
- Sometimes = 50
- Often = 75
- All the time = 100

The Skindex-29 is administered starting at Visit 2/Day 0 and at every clinic visit until Month 12. Total and domain specific continuous outcomes, and the change from baseline (Visit 2/Day 0), will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum) by visit

The three domains include the following items

- Emotions includes Questions (10) 3, 6, 9, 12, 13, 15, 21, 23, 26, and 28
- Symptoms includes Questions (7) 1, 7, 10, 16, 19, 24, and 27
- Functioning includes Questions (12) 2, 4, 5, 8, 11, 14, 17, 20, 22, 25, 29, and 30

2.10.8.Variables in Ulcerated Patients

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. Time to complete wound closer will be defined as the difference between the date when wound closure is determined and the date of first dose. Time to closure will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum).

Continuous outcomes for ulcers that do not close will be included in the listing output but will be excluded from the summary table output.

Ulcer volume

Ulcer volume will be assessed using a 3D-imaging system. Data for ulcer volume will be provided to Integrium by an external vendor. Continuous outcome for volume and changes from baseline (Visit 2/Day 0) will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum).

The outcomes detailed below will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum) by visit.

- 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 defined as the difference between the date the new ulceration is reported and the date of first dose administration.

The outcomes detailed below will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum) by visit, separately for patients with ulceration at Baseline only.

- 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.

2.10.9.Biomarkers

Blood collection for biomarker outcomes will occur at Visit 2/Day 0 and Months 1, 3, 6, 9, and 12. Selected serum biomarkers include TNF-α, IFN-γ, IL-1β, IL-6, IL-12, IL-17 and MCP-1. Continuous biomarker outcomes and changes from baseline (Visit 2/Day 0) will be listed and, whenever possible, summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum), separately for all patients and for patients with ulceration at Baseline only.

Additionally, C-peptide levels will be measured to assess whether there is any benefit of PCS499 in maintaining natural insulin production. Continuous C-peptide level outcomes and changes from baseline (Visit 2/Day 0) will be listed and summarized by descriptive statistics (n, mean, median, standard deviation, minimum and maximum), for all patients and separately for patients with ulceration at Baseline only.

2.11. Interim Analyses

No interim analyses are planned.

2.12. Other Analyses

No other analyses are planned.

2.13. Sample Size and Power Considerations

This study is not powered for statistical significance. No sample size calculations were performed.

2.14. Handling Missing Data

Listings will be provided for all data. Descriptive statistics will be provided for all planned visits as provided on the Case Report Forms (CRFs). No imputations for missing data will be used in calculations.

Visit windows will not be used in this study. Likewise, unscheduled visits will not be reassigned a visit number based on the visit date.

Dates related to the medications will be imputed using the rules below in an effort to categorize them properly into the summary tables.

Imputing partial or missing start dates:

- If the year is unknown, then the start date will not be imputed. The date will remain missing.
- If the month is unknown, impute the month as January.
- If the day is unknown, impute the day as '01'.

Impute partial or missing stop dates:

- If the year is unknown, then the stop date will not be imputed. The date will remain missing.
- If the month is unknown, impute the month as December.
- If the day is unknown, impute the day to be the last day of the month.

If an imputed stop date is greater than the date of study completion/discontinuation date of the study, then the imputed stop date will be set equal to the date of completion/discontinuation date.

The imputed dates will be stored in the analysis datasets along with the original dates as recorded by the sites.

2.15. Computer Systems and Packages Used for Statistical Analyses

SAS® version 9.4 on the Microsoft Server 2008 R2 64-bit platform will be used for all analyses. All computations will be performed using SAS®. The exact form of the various algorithms will be the SAS® defaults. The output from any SAS® procedure will be used in the tables using SAS® macros.

3. Data Listing Shells

3.1. Data Listings Table of Contents

The following post-text listings will be generated.

Listing Number	Listing Title
16.2.1	Patient Completion / Discontinuation
16.2.2	Protocol Deviations
16.2.3	Population Definitions
16.2.4.1	Demographics and Baseline Characteristics
16.2.4.2	Patient Eligibility and Informed Consent
16.2.4.3	Medical/Surgical/Procedural History
16.2.4.4	Necrobiosis Lipoidica History
16.2.4.5.1	Reference Lesion History
16.2.4.5.2	Reference Ulcer History
16.2.4.6	Non-drug Treatment History
16.2.4.7	Prior and Concomitant Medications
16.2.4.9	Safety Check In
16.2.5	Treatment Compliance
16.2.6.1.1	Reference Lesion Measurement Results
16.2.6.1.2	Reference Ulcer Measurement Results
16.2.6.1.3	Additional Lesion and Ulcer Reporting Results
16.2.6.2.1	Investigator Global Assessment: Necrobiosis Lipoidica Reference Lesion (IGA:NL) Results
16.2.6.2.2	Color and Ulcer Scale Reference Lesion (NLCUS) Results
16.2.6.2.3	Global Assessment Results
16.2.6.3.1	Dermatology Life Quality Index Results
16.2.6.3.2	Skindex-29 - Dermatology Survey Results
16.2.6.4	Biomarkers
16.2.6.5	Reference Lesion and Ulcer Photography
16.2.7.1	Adverse Events
16.2.7.2	Adverse Events Leading to Discontinuation of Study
16.2.7.3	Serious Adverse Events

Listing Number	Listing Title
16.2.8.1	Safety Laboratory Results - Hematology
16.2.8.2	Safety Laboratory Results - Chemistry
16.2.8.3	Safety Laboratory Results - Urinalysis
16.2.8.4	Safety Laboratory Results - Infectious Serology
16.2.9.1	Vital Sign Results
16.2.9.2	Physical Examination Results
16.2.9.3	Electrocardiogram Results

3.2. Data Listings

All patients and all data will be presented in the listings. The listings will be sorted by patient number. All listings will contain the patient number and the treatment.

There are currently 34 listings that are planned to be generated. The 34 listings are broken down as follows: 18 Standard Unique, 0 Standard Repeat 16 Non-Standard Unique and 0 Non-Standard Repeat.

4. Summary Table and Figure Shells

4.1. Post-text Table of Contents

The following post-text tables will be generated.

Table Number	Table Title
14.1.1.1	Summary of Patient Disposition – Modified Intention-to-Treat Population
14.1.1.2	Summary of Patient Disposition – Safety Population
14.1.1.3	Summary of Patient Disposition – Per Protocol Population
14.1.2.1	Summary of Demographics and Baseline Characteristics – Modified Intention-to-Treat Population
14.1.2.2	Summary of Demographics and Baseline Characteristics – Safety Population
14.1.2.3	Summary of Demographics and Baseline Characteristics – Per Protocol Population
14.1.3.1	Summary of Medical/Surgical/Procedural History – Safety Population
14.1.3.2	Necrobiosis Lipoidica History – Safety Population
14.1.3.3	Necrobiosis Lipoidica Reference Lesion and Ulcer History – Safety Population
14.1.4.1	Summary of Prior Medications – Safety Population
14.1.4.2	Summary of Concomitant Medications – Safety Population
14.1.5.1	Summary of Treatment Compliance – Modified Intention-to-Treat Population
14.1.5.2	Summary of Treatment Compliance – Safety Population
14.1.5.3	Summary of Treatment Compliance – Per Protocol Population
14.2.01.1.1	Summary of Reference Ulcer Measurement Results – Modified Intention-to-Treat Population
14.2.01.1.2	Summary of Reference Lesion Measurement Results – Modified Intention-to-Treat Population
14.2.01.2	Summary of Reference Lesion and Ulcer Measurement Results – Per Protocol Population
14.2.02.1	Summary of Reference Ulcer Measurement Results -External Data – Modified Intention-to-Treat Population
14.2.02.2	Summary of Reference Ulcer Measurement Results -External Data – Per Protocol Population
14.2.03.1	Summary of Variables in Ulcerated Patients – Modified Intention-to-Treat Population
14.2.03.2	Summary of Variables in Ulcerated Patients – Per Protocol Population

Table Number	Table Title
14.2.04.1	Summary of Reference Lesion Measurement Results - External Data – Modified Intention-to-Treat Population
14.2.04.2	Summary of Reference Lesion Measurement Results -External Data – Per Protocol Population
14.2.05.1	Summary of Investigator Global Assessment: Necrobiosis Lipoidica Reference Lesion (IGA:NL) Results – Modified Intention-to-Treat Population
14.2.05.2	Summary of Investigator Global Assessment: Necrobiosis Lipoidica Reference Lesion (IGA:NL) Results – Per Protocol Population
14.2.06.1	Summary of Color and Ulcer Scale Reference Lesion (NLCUS) Results – Modified Intention-to-Treat Population
14.2.06.2	Summary of Color and Ulcer Scale Reference Lesion (NLCUS) Results – Per Protocol Population
14.2.07.1	Summary of Global Assessment Results – Modified Intention-to-Treat Population
14.2.07.2	Summary of Global Assessment Results – Per Protocol Population
14.2.08.1	Summary of Dermatology Life Quality Index Results – Modified Intention-to-Treat Population
14.2.08.2	Summary of Dermatology Life Quality Index Results – Per Protocol Population
14.2.09.1	Summary of Skindex-29 - Dermatology Survey Results – Modified Intention-to-Treat Population
14.2.09.2	Summary of Skindex-29 - Dermatology Survey Results – Per Protocol Population
14.2.10	Summary of Biomarker Results – Biomarker Population
14.3.1.1	Overall Summary of Adverse Events – Safety Population
14.3.1.2	Summary of Treatment Emergent Adverse Events by Body System and Preferred Term – Safety Population
14.3.1.3	Summary of Treatment Emergent Adverse Events by Body System, Preferred Term and Severity – Safety Population
14.3.1.4	Summary of Treatment Emergent Adverse Events by Body System, Preferred Term and Relationship to Study Medication – Safety Population
14.3.1.5	Summary of Adverse Events Leading to Study Discontinuation – Safety Population
14.3.1.6	Summary of Serious Adverse Events – Safety Population
14.3.5.1	Summary of Laboratory Results - Hematology – Safety Population
14.3.5.2	Summary of Laboratory Results - Chemistry – Safety Population

Table Number	Table Title
14.3.5.3	Summary of Laboratory Results - Urinalysis – Safety Population
14.3.6.1	Summary of Vital Signs Results – Safety Population
14.3.6.2	Summary of Electrocardiogram Results – Safety Population

4.2. Summary Tables

There are currently 45 tables that are planned to be generated. The 45 tables are broken down as follows: 16 Standard Unique, 4 Standard Repeat, 15 Non-Standard Unique and 10 Non-Standard Repeat.

4.3. Post-text Figures Tables of Contents

There are no figures planned for this study.

4.4. Table Shells

The table shells can be found in a separate file. The following number of decimal places will be used when presenting summary statistics:

- N to 0 decimal places
- Minimum and maximum to the same number of decimal places as recorded in the raw data.
- Means and medians, and confidence intervals to 1 more decimal place than is recorded in the raw data. Standard deviations to 2 more decimal places than is recorded in the raw data.
- Percentages to 1 decimal place.

The precision may be changed for individual endpoints as needed.