NCT05380635

HyBryte™ (0.25% hypericin) ointment
HPN-CTCL-02

Phase 2a Study of Systemic PK and Serial ECG Determinations Following 8 Weeks of HyBryte Treatment

STATISTICAL ANALYSIS PLAN

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Signature Significance

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Author	By signing, the author is attesting that the content of the document is complete and accurate.
Reviewer	By signing, the reviewer is attesting that the document's approach and contents are compliant with the study protocol, all appropriate, regulatory requirements, and other significant guidelines. This individual(s) has reviewed the document for accuracy and completeness.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BSA	Body Surface Area
CAILS	Composite Assessment of Index Lesion Severity
CTCL	Cutaneous T-cell Lymphoma
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
ISCL	International Society for Cutaneous Lymphomas
ITT	Intent-to-Treat population
MedDRA	Medical Dictionary of Regulatory Activities
mSWAT	Modified Severity-Weighted Assessment Tool
PGA	Physician Global Assessment
PK	Pharmacokinetic
PP	Per-Protocol Population
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
USCLC	United States Cutaneous Lymphoma Consortium
WHO	World Health Organization Drug Dictionary

INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of safety, pharmacokinetics (PK), and lesion response as outlined and/or specified in Amendment 1 of the final study protocol dated 22 April 2022.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR). The preparation of this SAP has been based on International Conference on Harmonisation (ICH) E3 and E9 guidelines [1, 2]. If the protocol is subsequently amended, this SAP will be amended as well, if warranted. Should the SAP and the protocol be inconsistent with respect to the planned analyses, the language of the SAP prevails.

All data analyses and generation of TFLs will be performed using SAS® version 9.4 or higher. The SAP will be finalized and signed off prior to locking the database and subsequent unblinding of treatment arm assignments.

2. STUDY OBJECTIVES

2.1. Primary Objectives

- Assess any electrocardiogram (ECG) changes during standard HyBryte photodynamic therapy.
- Assess the systemic blood levels of hypericin during standard HyBryte photodynamic therapy.

2.2. Secondary Objectives

- Assess the safety of HyBryte photodynamic therapy
- Describe treatment outcome measures including:
    - Skindex-29 quality of life questionnaire
    - Visual Assessment Scale of itch (VAS_{itch})
    - Composite Assessment of Index Lesion Severity (CAILS) score of the 3 prospectively chosen index lesions
    - Physician Global Assessment (PGA)
    - modified Severity Weighted Assessment Tool (mSWAT)

3. STUDY DESIGN

This study is an interventional, uncontrolled, Phase 2a trial. Patients will receive treatments twice a week consisting of drug application followed 18 to 24 hours later with a light session (using Daavlin Series 7 Phototherapy Device with visible light lamps) for 8 weeks (up to 16 total treatments). The light treatment will be performed at least 2 calendar days apart each week. Light treatment is not permitted on consecutive days.

Blood samples for evaluation of serum hypericin concentration and ECGs will be obtained at Baseline, Week 4, Week 6, Week 8, and at End of Study. Safety laboratory tests and vital signs will be obtained at Baseline, at the end of treatment (Week 8), and at End of Study.

The light dose will be started at 5 J/cm^2 and may be increased each visit until symptoms or signs of mild phototoxicity (see Table 1 for grading scheme) appear in the treated areas or until a maximum light dose of 25 J/cm^2 is reached, whichever occurs first.

Table 1: Skin Phototoxicity Grading

Toxicity Grade: Erythema and/or edema	Severity
Grade 0	No apparent reaction
Grade I	Mild
Grade II	Moderate
Grade III	Severe with edema
Grade IV	Life-threatening with vesiculation

4. STUDY ENDPOINTS AND DEFINITION

This is an exploratory study to confirm the low-level systemic exposure to hypericin and the associated potential for any ECG changes as well as obtaining additional information on patient benefit including, but not limited to, lesion response to HyBryte photodynamic therapy utilizing the Daavlin 7 Series phototherapy device.

4.1. Primary Endpoints

Serial assessments of ECG (including QT interval and QT interval corrected for heart rate using both the Bazett's and Fridericia's formulas) will be obtained at the same timepoints as serum hypericin samples as follows:

- Baseline prior to drug application
- Week 4, Session 2 obtained immediately before and 2 hours after the light session
- Week 6, Session 2 obtained immediately before the light session
- Week 8, Session 2 Light Session visit obtained immediately before and 2 hours after the light session
- End of Study during the follow-up visit

Serial measurements of serum hypericin levels obtained at the following timepoints will be correlated with the cumulative amount of drug applied by the patient estimated by weighing the drug jars at each light session:

- Baseline prior to drug application
- Week 4, Session 2 obtained immediately before and 2 hours after the light session
- Week 6, Session 2 obtained immediately before the light session
- Week 8, Session 2 Drug Application visit immediately prior to the drug application
- Week 8, Session 2 Light Session visit obtained immediately before and 2 hours after the light session
- End of Study during the follow-up visit

4.2. Secondary Endpoints

Routine safety laboratory investigations and vitals will be obtained at Baseline prior to drug application, at Week 8, Session 2 Light Session visit prior to light therapy and 2 weeks after the completion of therapy (End of Study visit).

4.3. Patient Treatment Response Parameters

Given the small sample size in this open-label study, patient treatment response will be summarized as changes in in disease status from Baseline to the end of treatment:

- Skindex-29 quality of life questionnaire
- Visual Assessment Scale of itch (VAS_{itch})
- CAILS score of the 3 prospectively chosen index lesions
- Physician Global Assessment (PGA)
- modified Severity Weighted Assessment Tool (mSWAT)

In addition, the light dose schedules optimized for each patient will be characterized.

4.4. Study Endpoint Definition

4.4.1 Electrocardiograms (ECGs)

12-lead ECGs, including QT interval measurement, will be done at Baseline (prior to drug application), Week 4, Session 2 (immediately prior to and 2 hours after the light session), Week 6, Session 2 (immediately prior to the light session), Week 8, Session 2 Light Session Visit (immediately prior to and 2 hours after the light session), and at the End of Study visit. ECGs will be interpreted by site personnel trained in the evaluation of ECGs for any interval changes.

QT intervals will be measured on each ECG. Heart rate corrected QT intervals will be calculated using the following 2 standard correction equations:

Bazett's Formula:

$$QT_{cB} = QT_m / \text{square root of RR}$$

Where QT_{cB} represents the Bazett's corrected QT interval, QT_m is the measured QT interval, and RR is the time interval between 2 consecutive QRS complexes in seconds.

Fridericia's Formula:

$$QT_{cFri} = QT_m / \text{cube root of RR}$$

Where QT_{cFri} represents the Fridericia's corrected QT interval, QT_m is the measured QT interval, and RR is the time interval between 2 consecutive QRS complexes in seconds.

4.4.2 Hypericin blood levels

Blood samples for pharmacokinetic analysis will be collected at the following timepoints:

- Baseline, prior to drug application

- Week 4 Session 2, prior to light session
- Week 4 Session 2, 2 hours after completion of the light session
- Week 6 Session 2, prior to the light session
- Week 8 Session 2 Drug Application visit, prior to drug application
- Week 8 Session 2 Light Session visit, prior to light session
- Week 8 Session 2 Light Session visit, 2 hours after completion of the light session
- End of Study follow-up visit

Blood samples will be collected with K2EDTA tubes and mixed (inverting top to bottom) at least 5 times after collection. Tubes will be placed on wet ice pending transfer to labeled 2 mL amber vials or tubes and then frozen (temperature ≤-60°C). The times that samples are collected and frozen must be noted. Blood will be processed and shipped to the central laboratory, Syneos Health.

4.4.3 Clinical Laboratory Tests

4.4.3.1. Hematology Tests

The hematology panel will be performed on blood obtained at Baseline, Week 8 Session 2 Light Session visit prior to the light session, and End of Study. The panel will consist of the following tests:

- Red blood cell count (RBC)
- Hematocrit
- Hemoglobin
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Platelet count
- White blood cell count (WBC)
- Percent and absolute neutrophil count
- Percent and absolute lymphocyte count
- Percent and absolute monocyte count
- Percent and absolute eosinophil count
- Percent and absolute basophil count

4.4.3.2. Clinical Chemistry Tests

The clinical chemistry panel will be performed on blood obtained at Baseline, Week 8 Session 2 Light Session visit prior to the light session and during the End of Study follow-up visit. The panel will consist of the following tests:

- Serum sodium
- Serum potassium
- Serum chloride
- Serum bicarbonate (CO_2)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total bilirubin
- Total protein
- Serum creatinine
- Blood urea nitrogen (BUN)
- Alkaline phosphatase

4.4.4 Vital Signs

Vital signs will be obtained by site personnel at Baseline, Week 8 Session 2 Light Session visit prior to the light session and during the End of Study follow-up visit. Vital signs obtained will consist of:

- Resting Blood Pressure
- Heart Rate
- Respiratory Rate

4.4.5 Quality of Life Questionnaire

The Skindex-29, a self-administered survey instrument to measure the effects of skin disease on patients' quality of life will be administered at Baseline and at Week 8 Session 2 Light Session visit. Patients will complete the form on their own and site personnel will review and assure that the form is complete.

Each questionnaire item is answered in a 5-point Likert-type scale and these answers will be transformed into a linear scale of 100 (0 = no effect; 100 = effect experienced all the time) using the following item scores:

Never = 0

Rarely = 25

Sometimes = 50

Often = 75

All the time = 100

The following criteria will be used for interpretation:

- If responses to more than 25% of items are missing overall, the questionnaire will be considered "missing".
- If any domain scale has more than 25% of the responses missing, the score for that domain will be considered "missing".
- Domain scale scores are the average of non-missing items in a given domain scale.
- An item with multiple answers is considered "missing".

Individual questions will be grouped into 3 domains as follows:

Domain	Number of Items	Cluster Items
Emotions	10	3, 6, 9, 12, 13; 15; 21, 23, 26, 28
Symptoms	7	1, 7, 10, 16, 19, 24, 27
Functioning	12	2, 4, 5, 8, 11, 14, 17, 20, 22, 25, 29, 30

For all domains, a higher score is associated with higher impact of disease.

4.4.6 VAS_{itch}

The Visual Analog Score for Itch (VAS_{itch}) is a patient reported outcome measurement of the degree of itchiness that the patient experienced over the preceding 24 hours and is administered at Baseline, each light treatment and the End of Study visit. Patients will be instructed to place a vertical mark on a 10 cm line with a 0 (none) at the right side and a 10 (the worst itch you can imagine) at the left indicating the amount of itch that they have experienced over the preceding day. The score is recorded as the distance in centimeters (to 1 decimal place) between the 0 mark and the vertical line the patient drew.

Patient responses will be categorized as shown in Table 2, with scores rounded to the nearest whole number.

Table 2: VAS_{itch} Grading

VAS_{itch} Score	Category of Itch
0	no pruritus
<3	mild pruritus
3 to <7	moderate pruritus
≥7 to <9	severe pruritus
≥9	very severe pruritus

4.4.7 Composite Assessment of Lesions Severity (CAILS) Score

The CAILS score will be assessed for the 3 prospectively identified representative lesions at Baseline and at the End of Study visit. CAILS score will be calculated by assessing the index lesions for erythema, scaling, plaque elevation and involved surface area using the grading scale shown in Table 3 for each of the index lesions. Each of the assessments and the total score for each evaluated lesion will be recorded in the eCRF. The total CAILS score will be calculated by adding the scores of all evaluated lesions together.

Table 3: Composite Assessment of Index Lesion Severity

ERYTHEMA	
Score	**Description**
0	No evidence of erythema, possible brown hyperpigmentation
1	*
2	Mild: Light red lesion
3	*
4	Moderate: Red lesion
5	*
6	Severe: Very red lesion
7	*
8	Very severe: Extremely red lesion
SCALING	
Score	Description
0	No evidence of scaling on lesion
1	*
2	Mild: Mainly fine scales: lesion partially covered
3	*
4	Moderate: Somewhat coarser scales: lesion partially covered
5	*
6	Severe: Coarse, thick scales; virtually all of the lesion covered; rough surface
7	*
8	Very severe: Coarse, very thick scales; all of the lesion covered very rough surface
PLAQUE ELEVATION	

Table 3: Composite Assessment of Index Lesion Severity

Score	Description
0	0 mm: No evidence of plaque above normal skin level
1	Mild elevation
2	Moderate elevation
3	Marked elevation
SURFACE AREA	**Longest diameter and the longest diameter perpendicular to this diameter of each index lesion will be measured to the nearest millimeter. The lesion area will be the product of these two diameters.**
Score	**Area**
0	0 cm^2
1	>0 and ≤4 cm^2
2	>4 and ≤10 cm^2
3	>10 and ≤16 cm^2
4	>16 and ≤25 cm^2
5	>25 and ≤35 cm^2
6	>35 and ≤45 cm^2
7	>45 and ≤55 cm^2
8	>55 and ≤70 cm^2
9	>70 and ≤90 cm^2
10	>90 and ≤110 cm^2
11	>110 and ≤130 cm^2
12	>130 and ≤155 cm^2
13	>155 and ≤180 cm^2
14	>180 and ≤210 cm^2
15	>210 and ≤240 cm^2
16	>240 and ≤270 cm^2
17	>270 and ≤300 cm^2
18	>300 cm^2

4.4.8 The Physician Global Assessment (PGA)

The PGA represents the investigator's assessment of the overall extent of improvement or worsening of the patient's cutaneous disease compared with baseline as shown in Table 4. This assessment is designed to consider all cutaneous lesions, including both index and non-index lesions. PGA score will be assessed at End of Study.

Table 4: Physician Global Assessment

Grade	Description
0 completely clear	No evidence of disease; 100% improvement
1 almost clear	Very obvious improvement (≥90% to <100%); only traces of disease remain

Grade	Description
2 marked improvement	Significant improvement (≥50 to <90% clear); some evidence of disease remains
3 moderate improvement	Intermediate between marked and mild (≥25% to <50%)
4 slight improvement	≥10% to <25%; significant evidence of disease remains
5 no change	Disease has not changed significantly from baseline (10 to -25%)
6 condition worse	Disease is worse than baseline by ≥25%

4.4.9 Modified Severity Weighted Assessment Tool (mSWAT)

The mSWAT is designed to quantify the disease burden associated with CTCL and is based on an estimate of the percent total area of skin involved based on the body surface area (BSA). The types of lesions are weighted by the lesion characteristic (patch, plaque, or tumor) as shown in Table 5. The mSWAT score will be assessed at Baseline and at End of Study.

Table 5: Modified Severity Weighted Assessment Tool (mSWAT)

Body Region	% BSA [a] in Body Region	Assessment of Involvement in Patient's Skin		
		Patch [b]	Plaque [c]	Tumor [d]
Head	7%			
Neck	2%			
Anterior trunk	13%			
Arms	8%			
Forearms	6%			
Hands	5%			
Posterior trunk	13%			
Buttocks	5%			
Thighs	19%			
Legs	14%			
Feet	7%			
Groin	1%			
Weighting Factor		x1	x2	x4

Body Region	% BSA [a] in Body Region	Assessment of Involvement in Patient's Skin		
		Patch [b]	Plaque [c]	Tumor [d]
Subtotal lesion BSA x weighting factor				

[a] BSA=body surface area
[b] Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present
[c] Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.
[d] Any solid or nodular lesion>1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

4.4.10 Skin Reaction Safety Grading

Approximately 5 to 10 minutes before and after the completion of light therapy, treated lesions will be graded for erythema with the worst, best, and "average" scores recorded. The reaction will be graded using the definitions in Table 6.

Table 6: Phototoxicity/Erythema Score

Toxicity Grade: Erythema and/or edema	Severity
Grade 0	No apparent reaction
Grade I	Mild
Grade II	Moderate
Grade III	Severe with edema
Grade IV	Life-threatening with vesiculation

5. STATISTICAL CONSIDERATIONS

This is an open-label, uncontrolled interventional trial. Data will be summarized as counts for categorical variables and the number, mean, standard deviation, median and ranges will be presented for continuous variables.

5.1. Sample Size Calculation

The sample size used for this trial is arbitrary and not based on power calculations.

5.2. Analysis Populations

The analysis population is the Intent-to-Treat (ITT) population defined as all patients enrolled. All patients enrolled will be reported for all periods in which they have data available.

5.3. Methodology and Conventions

All safety endpoints will be analyzed using all enrolled patients.

Lab results obtained from the local laboratories, will be used for all safety analyses. All analyses will be performed using SAS® Version 9.4 or higher.

5.4. Additional Data Handling Rules and Presentation Specifications

The following general guidelines will apply to all statistical analyses and data presentations:

Baseline is defined as the last available value obtained prior to the first dose of study drug, unless otherwise specified in this SAP.

By default, US conventional units will be used for laboratory value presentations. A set of lab summary tables in International Standard Units (SIU) will also be provided based on tables, listings and figures.

Age is calculated as of date that the informed consent form was signed - age = floor ((date of Informed Consent – birth date+1)/365.25)

All percentages will be rounded to one decimal place and lined up by the decimal place. The percentage will be suppressed when the count is zero.

Any p-values will be rounded to three decimal places and will be presented as ‘<0.001’ if they are less than 0.001 after rounding.

For continuous variables that are recorded as “< X” or “> X”, the value of “X” will be used in the calculation of summary statistics. The original values will be used for the listings.

Decimal points will be presented as follows: N will be presented without decimal, minimum and maximum in same precision as in the database, mean and median in one more decimal than minimum and maximum, and SD in one more decimal than mean and median.

5.5. Demographics and Other Baseline Characteristics

Demographic data will be summarized descriptively and include:

- Age
- Sex
- Race
- Ethnic group

Listings of demographic data characteristics will be provided for each patient and summarized across the study population.

Baseline disease characteristics will be summarized descriptively and will include:

- CTCL Stage (IB, IIA)
- Number of previous CTCL treatments
- Time since original diagnosis to randomization
- Extent of disease (percent body area with lesions)
- Cumulative CAILS score for the 3 index lesions at Baseline
- Baseline VAS_{itch} score
- Baseline mSWAT
- Baseline Skindex-29 QoL score

5.6. Medical History

Medical history and current conditions will be presented and will be coded using the MedDRA (Medical Dictionary of Regulatory Activities, Version 10.1) system organ class (SOC) and preferred term.

The summary tables will include counts of patients in each term. If a patient experiences more than one medical history or current condition event that is coded to the same preferred term, the patient will be counted only once for that preferred term. Similarly, if a patient has more than one medical history or current condition within a SOC, the patient will be counted only once in that SOC.

Listings of medical history and current conditions will be provided.

5.7. Prior and Concomitant Medications

The World Health Organization Drug Dictionary (WHO Drug) will be used to classify prior and concomitant medications by therapeutic class and generic name based on ATC code level 3. Prior medication is defined as any medication taken prior to the first dose of the study medication. Concomitant medication is defined as any medication taken between the day of first dose of the study medication and the day of last study medication date + 14 days.

5.8. Interim Analysis

No Interim Analysis is planned.

6. OUTCOMES

6.1. Electrocardiograms

Changes in ECGs will be assessed by both continuous (analysis of central tendency) and categorical (shift tables) analyses.

6.1.1 Analysis of Central Tendency

The mean and median response at Baseline and at each subsequent timepoint for each parameter will be assessed. Changes in response will be tracked and compared. The clinical meaningfulness of any alterations will be assessed.

Individual changes in each parameter will also be plotted and compared for evidence of trends.

6.1.2 Categorical Analysis

Shift analysis will be conducted, evaluating the number of patients that meet the following criteria:

- Measured QT interval >500 ms
- QTc interval increased from baseline > 60 ms

The number of patients meeting these criteria at each timepoint will be tabulated.

6.2. Hypericin blood concentrations

Hypericin blood calculations will be summarized as the mean, standard deviation and range of blood concentrations for each timepoint. A regression between cumulative drug application and measured blood concentration per visit (average result where samples were collected before and after light collection) will be conducted excluding the End of Study sample, if at least 50% of samples had detectable levels of circulating hypericin.

Changes in blood concentration over time will be described for each individual subject to assess the potential for accumulation.

6.3. Effectiveness Outcomes

Descriptive analyses will include:

- Percent of cumulative CAILS score for index lesion as a proportion of the baseline CAILS score ([cumulative score at End of Study] / [cumulative score at Baseline] * 100). The average, standard deviation and range of the %response at Week 10 will be summarized.
- Mean, standard deviation and range of the PGA score at End of Study.

- Mean, standard deviation and range of the mSWAT score at Baseline and End of Study.
- Mean, standard deviation and range of the change in the mSWAT score (calculated as the mSWAT score at End of Study – mSWAT score at Baseline).
- Mean, standard deviation and range of the Skindex 29 score and its 3 domains (emotions, symptoms, functioning) at Baseline and Week 8.
- Mean, standard deviation and range of the change in Skindex 29 score and its 3 domains.
- Mean, standard deviation and range of the VAS_{itch} score at baseline, each light treatment and the end of study visit.
- Shift analysis of VAS_{itch} categories (none/mild/moderate/severe) over all study timepoints.
- Mean, standard deviation and range for the treatment visit at which the maximum light dose was obtained.
- Mean, standard deviation and range for the maximum light dose that was used.
- Listing of changes of drug used (change in drug jar weight)

7. SAFETY ANALYSES

The safety analysis will be performed in all patients enrolled. Safety parameters include adverse events, laboratory parameters, vital signs, ECG parameters, and physical examinations.

7.1. Adverse Events

Summary tables will be provided for all treatment-emergent adverse events (TEAEs). Treatment-emergent AEs are defined as events whose onsets occur, or severity worsens on or after the date of first dose of study drug. All TEAEs will be included in summaries.

An overview table will contain the number and percentage of patients with any TEAEs, with study drug related TEAEs, serious adverse events (SAEs), with AEs causing death, with related AEs causing death, with related SAEs, with AEs causing study drug discontinuation, and with AEs causing discontinuation from the study.

The TEAE summary tables will include counts of patients. Therefore, if a patient experiences more than one episode of a particular TEAE, the patient will be counted only once for that event. If a patient has more than one AE that is coded to the same preferred term, the patient will be counted only once for that preferred term. Similarly, if a patient has more than one TEAE within a SOC, the patient will be counted only once in that SOC.

All AEs are to be reported from the time of first administration of study drug until study completion or discontinuation. The severity of all AEs is recorded as mild, moderate, or severe. If severity is missing for TEAE, it will be set to severe. If severity is missing for AE at pre-treatment, the severity will be set to mild: if severity change is not reported during the study, then severity of mild is retained for analysis. A treatment-related AE is defined as an AE with relationship to study drug recorded as related or missing in the CRF. All AEs will be coded using the MedDRA (Version 10.1).

The maximum severity of AE is defined as the AE with the worst severity experienced overall during the study, within a SOC, or within a preferred term.

The following TEAE summaries will be presented:

- Frequency of TEAEs by preferred term, sorted by decreasing overall total
- Frequency of TEAEs related to study drug, by SOC and preferred term
- Frequency of TEAEs related to study drug by preferred term, sorted by decreasing overall total
- Frequency of TEAEs by maximum severity, SOC, and preferred term
- Frequency of AEs causing discontinuation from the study drug and study by SOC and preferred term
- Frequency of SAEs by SOC and preferred term
- Frequency of TEAEs with seriousness of fatal by SOC and preferred term.

Listings will be presented to show SAEs, AEs that resulted in early discontinuation from the study or study drug, and AEs with seriousness of fatal. A listing of all reported AEs will also be presented. For each adverse event the following will be specified: the treatment group, MedDRA system organ class, preferred term and adverse event description from the CRF, onset and resolution dates and their respective study days, duration, time of onset, severity, seriousness, AE or current condition number associated with the AE, and relationships to study procedure, the study drug and concomitant medication. The listing will display the outcomes as reported by the investigator.

7.2. Clinical Laboratory Parameters

Descriptive statistics for laboratory values (in US conventional and SI units) and changes from baseline at each assessment time point will be presented for the following laboratory parameters collected in the study including but are not limited to the following:

- Hematology: hemoglobin, hematocrit, RBC count, MCV, MCH, MCHC, WBC count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet counts
- Chemistry: alkaline phosphatase, ALT, AST, bicarbonate, total bilirubin, BUN, chloride, creatinine, potassium, total protein, and sodium.

Laboratory tests values are clinically significant (CS) if they meet either the low or high CS defined by the normal ranges at the site's local laboratory. The number and percentage of subjects with post-Baseline CS values will be tabulated by treatment group. The percentages are to be calculated relative to the number of subjects with available non-CS baseline values and at least one post-Baseline assessment. The numerator is the total number of subjects with at least one post-Baseline CS value. In addition, shift tables will be presented by treatment group and time point. The following three data listings will be presented by subject:

- A listing of lab values for all lab tests at all collected time points.
- A listing of subjects with post-Baseline CS values will be provided including the Baseline and post-Baseline values.
- A listing of all AEs for subjects with CS laboratory values will also be provided.

7.3. Vital Signs

Vital signs (systolic and diastolic blood pressures, heart rate, and respiratory rate) will be measured at Baseline, Week 8, Session 2 Light Session visit prior to the light session and during the End of Study follow-up visit.

For vital signs summaries, the Baseline values will be defined as the assessment obtained at Baseline assessment.

Vital signs data and change from Baseline will be summarized using descriptive statistics.

Criteria for clinically significant values have been defined as shown in Table 7. For each vital sign variable, clinically significant value at Baseline and minimum and maximum clinically significant values during Treatment Cycles will be identified. Shift in number of patients with clinically significant values at baseline to the number of patients with minimum and maximum clinically significant values on-therapy will be displayed.

Table 7: Vital Signs Clinically Significant Values

Vital Sign Variable	Absolute Value
Systolic Blood Pressure	≥180 mmHg and increase of ≥20 mmHg from baseline
	≤90 mmHg and decrease of ≥20 mmHg from baseline
Diastolic Blood Pressure	≥105 mmHg and increase of ≥15 mmHg from baseline
	≤50 mmHg and decrease of ≥15 mmHg from baseline
Pulse	≥120 bpm and increase of ≥15 bpm from baseline
	≤50 bpm and decrease of ≥15 bpm from baseline

Listings of all vital sign values will be presented.

7.4. Extent of Exposure

The number of exposures of drug applications and phototherapy for the study population will be summarized by frequency table. Descriptive statistics will be provided.

8. APPENDIX 1: DATA HANDLING CONVENTIONS

8.1. Missing Severity Assessment for Adverse Events

If severity is missing for an AE started prior to the first study medication, then a severity of "Mild" will be assigned. If the severity is missing for an AE started on or after the first study medication dosing, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summary, while the actual missing values will be presented in data listings.

8.2. Missing Relationship to Study Drug for Adverse Events

If the relationship to the study medication is missing for an AE started after baseline, a causality of "Related" will be assigned. The imputed values for relationship to study medication will be used for incidence summary, while the actual values will be presented in data listings.

8.3. Missing Date Information for Adverse Events

The following imputation rules only apply to the case where the date is incomplete (i.e., partial missing) for adverse events. *Missing day and month*

- If the year is same as the year of first day on study medication, then the day and month of the start date of study medication will be assigned to the missing fields.
- If the year is prior to the year of first day on study medication, then December 31 will be assigned to the missing fields.
- If the year is after the year of first day on study medication, then January 1 will be assigned to the missing fields.

Missing month only

- Treat day as also missing and replace both month and day according to the above procedure.

Missing day only

- If the month and year are same as the year and month of first day on study medication, then the start date of study medication will be assigned to the missing day.
- If the month and year are before the year and month of first day on study medication, then the last day of the month will be assigned to the missing day.
- If the month and year are after the year and month of first day on study medication, then the first day of the month will be assigned to the missing day.

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

8.4. Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (i.e., partial missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a patient, impute the start date first.

- **Incomplete Start Date**

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the first dose date of study medication, then the day and month of the first dose date will be assigned to the missing fields.
- If the year of the incomplete start date is prior to the year of the first dose date of study medication, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the first dose date of study medication, then January 1 will be assigned to the missing fields.

Missing month only

- Treat day as also missing and replace both month and day according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose date of study medication, then the day of the first dose date will be assigned to the missing day.
- If either the year is before the year of the first dose date of study medication or if both years are the same but the month is before the month of the first dose date of study medication, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the first dose date of study medication or if both years are the same but the month is after the month of the first dose date of study medication, then the first day of the month will be assigned to the missing day.

- **Incomplete Stop Date**

The following rules will be applied to impute the missing numerical fields. If the last dose date of study medication is missing, replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

If the year of the incomplete stop date is the same as the year of the last dose date of study medication, then the day and month of the last dose date will be assigned to the missing fields.

- If the year of the incomplete stop date is prior to the year of the last dose date of study medication, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the last dose date of study medication, then January 1 will be assigned to the missing fields.

Missing month only

- Treat day as also missing and replace both month and day according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose date of study medication, then the day of the last dose date will be assigned to the missing day.
- If either the year is before the year of the last dose date of study medication or if both years are the same but the month is before the month of the last dose date of study medication, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the last dose date of study medication or if both years are the same but the month is after the month of the last dose date of study medication, then the first day of the month will be assigned to the missing day.

8.5. Clinical Laboratory Parameters

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table due to, for example, that a character string is reported for a parameter of the numerical type, coded value needs to be appropriately determined and used in the statistical analyses (Table 8). However, the actual values as reported in the database will be presented in data listings.

Categorization of laboratory results into low/normal/high group will be done using the laboratory's scaled lower and upper limits of normal value as present in Table 8 and Table 9.

Table 8: Example for Coding of Special Character Values for Clinical Laboratory Parameters

Lab Test	Reported Lab Results (in SI units)	Coded Value for Analysis
Chemistry: ALT	<5	0

Lab Test	Reported Lab Results (in SI units)	Coded Value for Analysis
Chemistry: AST	<5	0
Chemistry: Bilirubin, Total	<2	0

Table 9: Ranges of Potentially Clinically Significant Lab Values

Parameter	SI Unit	Lower Limit	Higher Limit
CHEMISTRY			
Alanine Aminotransferase (ALT)	U/L		≥3 * ULN
Alkaline Phosphatase	U/L		≥3 * ULN
Aspartate Aminotransferase (AST)	U/L		≥3 * ULN
Bicarbonate	mmol/L		≥3 * ULN
Creatinine	mg/dL		>1.5 * Day 1
Potassium	mmol/L	<0.75*LLN	>1.2 * UNL
Sodium	mmol/L	<0.9*LLN	>1.1 * UNL
Chloride	mmol/L		
Total Bilirubin	mg/dL		>1.5 * UNL
Total Protein	g/dL	<0.9*LLN	>1.1 * UNL
Urea (BUN)	mg/dL		>1.5 * Day 1
HEMATOLOGY			
Red blood cell count (RBC)	$10^6/\mu L$		
Hematocrit	%		
Hemoglobin	g/dL		
Mean corpuscular volume (MCV)	fL		
Mean corpuscular hemoglobin (MCH)	pg		
Mean corpuscular hemoglobin concentration (MCHC)	g/dL		
Neutrophil Percentage	%		

Parameter	SI Unit	Lower Limit	Higher Limit
Neutrophil Count	$10^3/\mu L$	≤1	
Lymphocyte Percentage	%		
Lymphocyte Count	$10^3/\mu L$		
Monocyte Percentage	%		
Monocyte Count	$10^3/\mu L$		
Eosinophil Percentage	%		
Eosinophil Count	$10^3/\mu L$		
Basophil Percentage	%		
Basophil Count	$10^3/\mu L$		
Platelet Count	$10^3/\mu L$	≤100	≥700
White Blood Cell Count	$10^3/\mu L$	≤2.5	≥15

LLN: Lower limit of normal, value provided by the laboratory
ULN: Upper limit of normal, value provided by the laboratory

9. APPENDIX 2: SCHEDULE OF PROCEDURES

Subjects will be screened within 28 days of enrollment. Detailed timing of the assessments is shown in Table 9.

Table 10: Schedule of Assessments

Time point	Blood Hypericin Concentration	ECG[1]	Light Session[2]	CAILS Evaluations	mSWAT	PGA	VAS_{itch}	Skindex-29 QoL	Safety Assessments[3]	AE Collection
Screening[4]										
Baseline[5]	X[6]	X[6]		X[6]	X[6]		X[6]	X[6]	X[6]	
Week 1, Session 1			X				X			X
Week 1, Session 2			X				X			X
Week 2, Session 1			X				X			X
Week 2, Session 2			X				X			X
Week 3, Session 1			X				X			X
Week 3, Session 2			X				X			X
Week 4, Session 1			X				X			X
Week 4, Session 2	X[7]X[8]	X[7]X[8]	X				X			X
Week 5, Session 1			X				X			X
Week 5, Session 2			X				X			X
Week 6, Session 1			X				X			X
Week 6, Session 2	X[7]	X[7]	X				X			X

Time point	Blood Hypericin Concentration	ECG[1]	Light Session[2]	CAILS Evaluations	mSWAT	PGA	VAS_{itch}	Skindex-29 QoL	Safety Assessments[3]	AE Collection
Week 7, Session 1			X				X			X
Week 7, Session 2			X				X			X
Week 8, Session 1			X				X			X
Week 8, Session 2 Drug Application	X[6]									X
Week 8, Session 2 Light Session	X[7]X[8]	X[7]X[8]	X				X	X	X[7]	X
Week 10/End of Study	X	X		X	X	X	X		X	X

[1] ECG will include a standard 12-lead reading with QT interval measurements. Correction for heart rate will be performed electronically using both the Bazett's and Fridericia formulas.
[2] Light Session: Includes application of drug 18-24 hours earlier by the patient and the Erythema Scoring performed 5-10 minutes before and after light therapy
[3] Safety Assessments: consists of vital signs, and hematology and clinical chemistry blood tests
[4] The following assessments will be performed at the Screening visit: Obtain Informed Consent Form (ICF) signature, Assessment of entry criteria, Complete Medical History, Complete Vital Signs, Serum HCG pregnancy test (women of childbearing age only)
[5] Baseline: Includes interval medical history from screening, Complete Physical Examination, review of the results of the serum pregnancy test for eligible female subjects, and charting of index lesions onto the Body Lesion Diagram.
[6] Obtained prior to drug application
[7] Prior to light session
[8] 2 hours after completion of the light session