NCT02448381

SGX301, SYNTHETIC HYPERICIN
HPN-CTCL-01

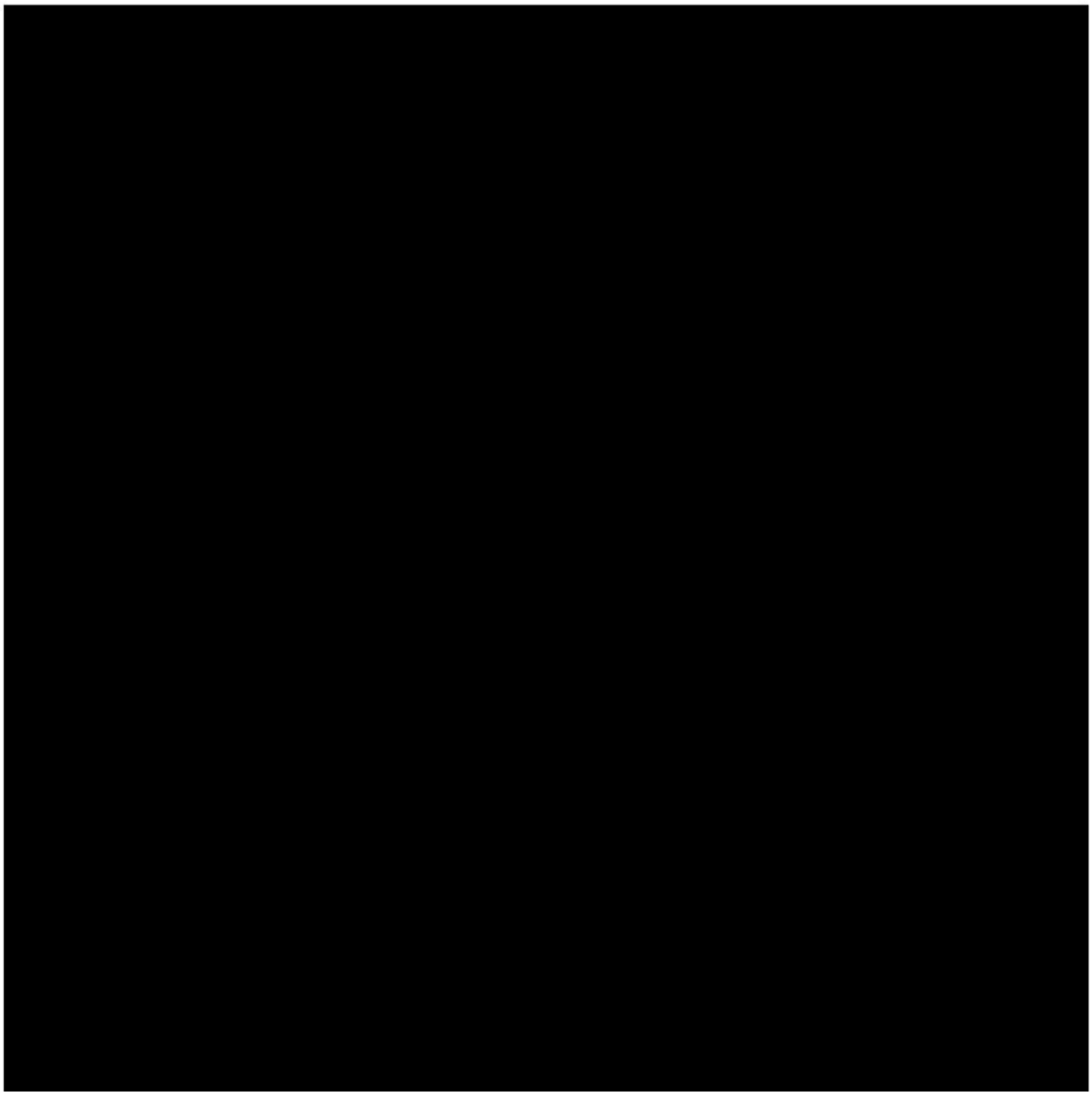
A Phase 3 Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Determine the Efficacy of Topical SGX301 (Synthetic Hypericin) and Fluorescent Bulb-Light Irradiation for the Treatment of Cutaneous T-Cell Lymphoma

STATISTICAL ANALYSIS PLAN

Version: **4.0**
Release Date: **19 May 2020**

Approvals

I have reviewed and accept the information in this document to be a true and accurate representation of the Statistical Analysis Plan for Study HPN-CTCL-01.



Signature Significance

The following significance is lent to the signatures on the *Approvals* page of this document.

Signature	Significance
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.

Table of Contents

List of Figures

List of Tables

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 Disease Severity
CTCL	Cutaneous T-cell Lymphoma
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
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 efficacy and safety as outlined and/or specified in Amendment 5 of the final study protocol dated November 30, 2018. Specifications of tables, figures, and data listings are contained in a separate document (Table shells).

2. STUDY OBJECTIVES

2.1. Primary Objectives

Cycle 1: The primary objective of this Phase 3 study is to evaluate the ability of the initial 6-week course of SGX301 and visible light (Cycle 1) in patients with patch/plaque phase cutaneous T-cell lymphoma (CTCL) to induce a treatment response in 3 index lesions that is defined to be a ≥50% improvement in the Composite Assessment of Index Lesion Severity (CAILS) score from baseline to the Week 8 Evaluation Visit when compared to patients receiving placebo and visible light.

Cycle 2: This cycle is designed to evaluate, as secondary endpoints, the utility of a second course of treatment on index lesions with less than complete response with the initial therapy (the Cycle 1 SGX301 patients) and to extend the data on the response rate of SGX301 in untreated lesions (the Cycle 1 placebo patients).

Cycle 3: In this optional, open-label portion of the study, the objective is to determine the impact of SGX301 treatment on the patient's extent of disease rather than individual lesions.

2.2. Secondary objectives

[redacted]

[redacted]

- To evaluate the ability of topical SGX301 and visible light in patients with patch/plaque phase CTCL to induce Partial and/or Complete Response after Cycles 2 and 3.
- To evaluate the degree of improvement of the index lesions measured by CAILS score induced by topical SGX301 and visible light in patients with patch/plaque phase CTCL during Cycles 1 and 2.

[redacted]

[redacted]

- Assess the safety of topical SGX301 and visible light in patients with patch/plaque phase CTCL.

3. STUDY DESIGN

This is a Phase 3 multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy of topical SGX301 (synthetic hypericin) and fluorescent bulb-light irradiation for the treatment of CTCL.

Approximately 180 subjects will be randomized into this Phase 3, placebo-controlled, double-blind, multicenter study (in order to assure 160 evaluable patients) to evaluate the efficacy and safety of topical phototherapy with SGX301 (synthetic hypericin) at a concentration of 0.25% ointment. Patients will be stratified by site and tumor stage (IA, IB, and IIA) at randomization. Prior to randomization each patient will have 3 discrete lesions judged by the PI to be representative of their disease, and if both plaque and patch lesions are present, at least one of each type will be selected as index lesions that will be treated during Cycle 1 and 2.

Patients may undergo three cycles of therapy:

> ***Cycle 1***: Patients will be randomized 2:1 SGX301: Placebo for treatment of the 3 index lesions selected by the investigator. The results of this cycle will be the basis of the primary efficacy analysis.
>
> ***Cycle 2***: All patients will receive SGX301 treatment of the 3 index lesions.
>
> ***Optional Cycle 3***: All patients will receive SGX301 treatment of up to all of their lesions.

For each cycle, study ointment will be applied twice weekly for 6 weeks and opaque bandage applied for 18-24 hours followed by the administration of visible light up to a dose of 12 Joule/cm^2. The light treatment will be performed 3-4 calendar days (±1 day) apart each week (e.g., Monday/Thursday, Monday/Friday, or Tuesday/Friday).

Prior to randomization, each patient will have three lesions identified. These should be discrete lesions and be representative of the patient's lesions that are easily accessible for phototherapy. These are the lesions that will serve as the index lesions for treatment and evaluation. Cycle 1 patients will receive either SGX301 or placebo ointment applied to their 3 index lesions; in Cycle 2 all patients will have SGX301 applied to their index lesions that did not achieve a CR after Cycle 1 therapy; and in optional Cycle 3, all patients will have SGX301 applied to all of the lesions chosen by the physician and patient. The treatment evaluation for each cycle will be performed after a two week rest period (Week 8, 16 and 24) in order to permit any light induced erythema to subside.

Following evaluation for safety and efficacy at the end of Cycle 2 (Week 16), all patients will be given the opportunity to enter an open-label treatment cycle (Cycle 3) in which all selected lesions (index and non-index) will be treated for an additional six weeks with SGX301 ointment. Evaluation of safety and efficacy during the open-label cycle will take place at Week 24.

All patients will be followed for 6 months following the last assessment visit (Week 48 for those participating in Cycle 3 and Week 40 for those not participating in Cycle 3).

SGX301 will be applied to defined patches or plaques on the skin of subjects at a concentration of 0.25% synthetic hypericin. The amount of synthetic hypericin in each topical application is as

follows: 0.25% = 0.025 mg/cm^2 (2.5 mg SGX301 in 1 gram of ointment). The actual dose will be dependent on the extent of the lesions undergoing treatment.

Study ointment will be applied twice weekly with any excess ointment on healthy skin wiped off and then protected from light for a period of 18-24 hours prior to light treatment. Each application site will be covered by opaque bandaging that has been approved/provided by Soligenix.

Treatment with visible light will be undertaken using the supplied [redacted] fluorescent light panel consisting of a bank of 12 cool white fluorescent bulbs (590-650 nm; [redacted] cool white fluorescent bulbs, 60-watt fluorescent tubes housed in the supplied reflecting bank). Lesions will be positioned as close as practical to the light panel and the duration of light treatment will be calculated from dosimetry measurement based on positioning of the lesion relative to the light source (see visible light treatment manual for details) with the initial dose of 5 Joules/cm^2. The light dose will be administered twice weekly separated by 3-4 calendar days (e.g., Monday/Wednesday, Monday/Thursday, Monday/Friday) and will be assessed using a radiometer to precisely determine the emission of visible light from the bulbs at the position of the lesion farthest from the light panel.

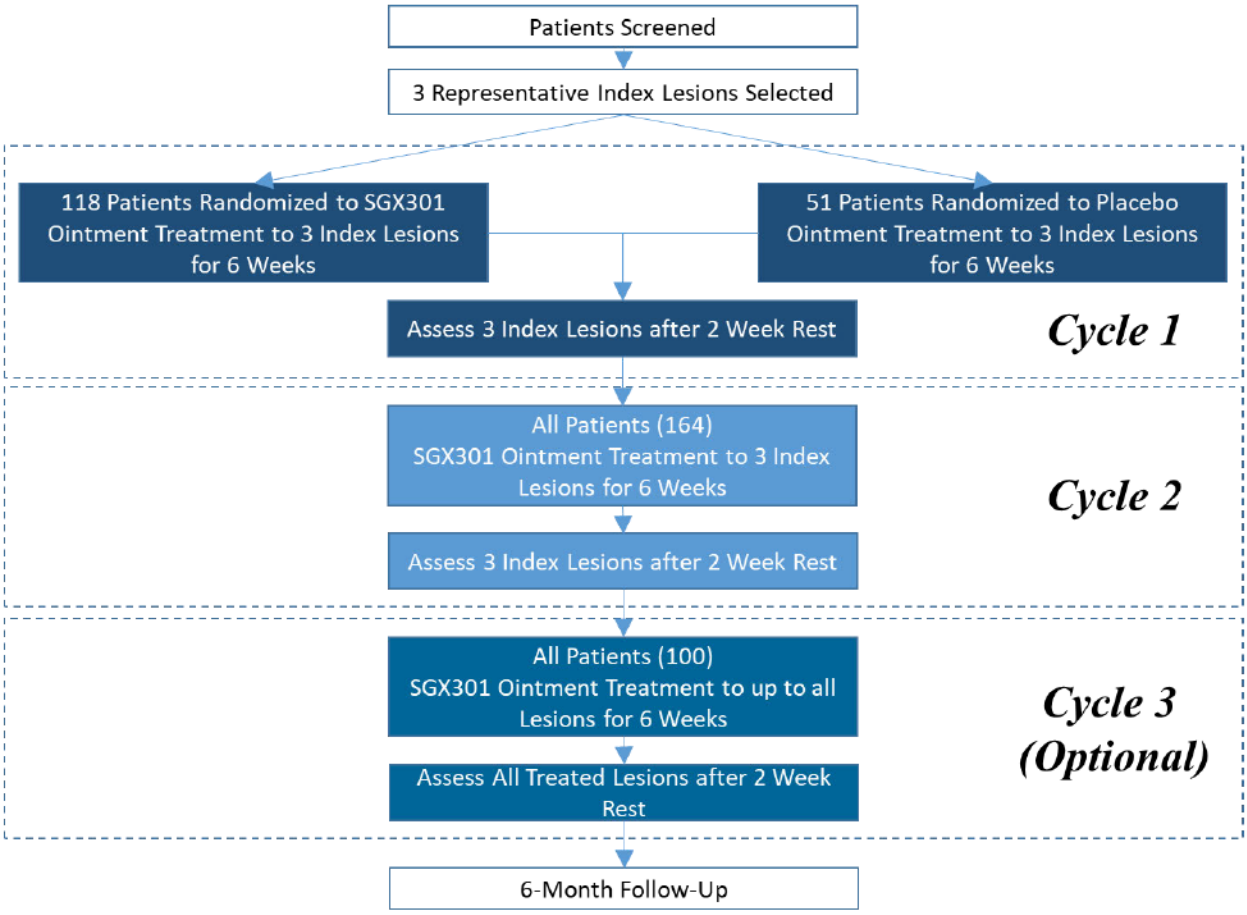
The light dose may be increased by 1 Joule/cm^2 each visit until symptoms or signs of mild phototoxicity appear as defined in Table 1 to a maximum light dose of 12 Joules/cm^2. At that point, the dose can be either maintained or reduced by 1 Joule/cm^2 if phototoxicity is pronounced (skin erythema of > Grade I) until symptoms and signs subside or the dose is at 5 Joules/cm^2.

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

Skin reactions will be evaluated before and after each light treatment. The sites of treatment shall be examined and any changes in erythema, edema, desquamation, and pigmentation shall be recorded. The overall study design is summarized in Figure 1.

Figure 1: Study Schema



4. STUDY ENDPOINTS AND DEFINITION

4.1. Primary Efficacy Endpoint

The primary efficacy endpoint for this trial will be the proportion of patients achieving a treatment response, defined as a CAILS ratio comparing the CAILS score at the end of Cycle 1 (Week 8) assessment divided by the CAILS score at baseline of ≤50% of treated lesions.

4.2. Secondary Efficacy Endpoints

The secondary endpoints for this trial are given below.

4.2.1 Cycle 1 Secondary Endpoints

- The number of index lesions with a Partial or Complete Response defined as a ≥50% reduction in the CAILS score (CAILS ratio ≤50% week 8 score divided by the baseline score) for that lesion at the Cycle 1 evaluation visit (Week 8) compared to its CAILS score at baseline.

4.2.2 Cycle 2 Secondary Endpoints

Secondary analyses from Cycle 2 will include the following comparisons for each of the treatment groups—patients in the SGX301 treatment group during Cycle 1 (whose index lesions will have been treated with two cycles of SGX301) and patients in the placebo treatment group during Cycle 1 (whose index lesions will have been treated with one cycle of SGX301):

- Percent of patient achieving a Partial or Complete Response (yes/no) of treated lesions defined as a ≥50% reduction in the CAILS score (CAILS ratio ≤50%) for the 3 index lesions at the Cycle 2 evaluation visit (Week 16) compared to the total CAILS score at baseline.

[redacted]

- In the placebo group, the above results will be compared to the SGX301 group's results at the end of Cycle 1.

[redacted]

4.2.3 Cycle 3 Secondary Endpoints

Secondary analyses from Cycle 3 will include the following comparisons for each of the treatment groups—the index lesions from patients in the SGX301 treatment group during Cycle 1 (that will have been treated with 3 cycles of SGX301), the index lesions from patients in the placebo treatment group during Cycle 1 (that will have been treated with 2 cycles of SGX301), and all non-index lesions (lesions that will have been treated with 1 cycle of SGX301):

[redacted]

[redacted]

- Percent of patients achieving a partial or complete response (yes/no) defined as a ≥50% reduction in the total CAILS score for the **3 index lesions** at the Cycle 3 evaluation visit (Week 24) compared to the total CAILS score at the start of Cycle 3 (Week 16).

[redacted]

- Examine the relative impact on plaque versus patch responses.

4.3. Safety Endpoints

- Number and percentage of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Changes from baseline of routine laboratory test results
- Changes from baseline in vital signs
- Changes from baseline in physical examinations

4.4. Study Endpoint Definition

4.4.1 Composite Assessment of Lesions Severity (CAILS) Score

All patients will have 3 index lesions identified prior to randomization. These lesions will be assessed at baseline and then at the end of Cycle 1 and Cycle 2 (Weeks 8 and 16). All lesions will be evaluated prior to Cycle 3 (Week 16) and then again at the end of Cycle 3 (Week 24). CAILS score will be calculated by assessing the erythema, scaling, plaque elevation and involved surface area using the grading scale shown in Table 2 for each of the index lesions in Cycle 1 and 2 and for all lesions in Cycle 3. 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 at each time point.

Table 2: 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

Table 2: Composite Assessment of Index Lesion Severity

7	*
8	Very severe: Coarse, very thick scales; all of the lesion covered very rough surface
PLAQUE ELEVATION	
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 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

* Intermediate intervals 1, 3, 5, and 7 are to serve as mid-points between the defined grades 0, 2, 4, 6, and 8

4.4.2 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 3. This assessment is designed to consider all cutaneous lesions, including both index and non-index lesions.

Table 3: 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
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%

4.4.3 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 4.

Table 4: Modified Severity Weighted Assessment Tool (mSWAT)

Body Region	% BSA[1] in Body Region	Assessment of Involvement in Patient's Skin		
		Patch[2]	Plaque[3]	Tumor[4]
Head	7%			
Neck	2%			
Anterior trunk	13%			
Arms	8%			
Forearms	6%			
Hands	5%			
Posterior trunk	13%			
Buttocks	5%			
Thighs	19%			
Legs	14%			

Body Region	% BSA[1] in Body Region	Assessment of Involvement in Patient's Skin		
		Patch[2]	Plaque[3]	Tumor[4]
Feet	7%			
Groin	1%			
Weighting Factor		x1	x2	x4
Subtotal lesion BSA x weighting factor				

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

4.4.4 Skin Reaction Safety Grading

Skin reactions will be evaluated before and after each light treatment. Each site of treatment shall be examined and any changes in erythema, edema, desquamation, and pigmentation shall be recorded, if present. Assessment of erythema will be done at least 5 minutes after completion of the light treatment and graded using the scale in Table 5.

Table 5: 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

4.4.5 Biopsy

Each study participant will have a single index lesion selected for biopsy at study entry. This lesion should be representative of the patient's lesions and the same lesion will be re-biopsied at the conclusion of Cycle 1 to determine the nature of clearing of the malignant infiltrate. Each biopsy should be taken from a representative portion of the lesion and the second biopsy obtained at least 1 cm from the original biopsy site. Each biopsy will consist of a 3 mm punch biopsy that will be formalin-fixed, paraffin embedded, sectioned and stained at the site. The stained and unstained slides will be sent to the Central Pathology Laboratory for grading and further analysis.

All biopsies will be read by a single, study-wide pathologist in a blinded manner. The degree of infiltrate will be characterized at each time period (i.e., at baseline and at the end of Cycle 1) on a 0 to 3+ scale as shown in Table 6.

Table 6: Grading of Biopsy

Grade	Description
3+	Dense lymphocytic infiltrate
2+	Moderate lymphocytic infiltrate
1+	Sparse lymphocytic infiltrate
0	No lymphocytic infiltrate

4.4.6 Duration of Partial and/or Complete Response in the index lesions

The duration of Partial and/or Complete Response in the index lesions is defined as the time of Partial and/or Complete Response in the 3 index lesions (total CAILS ratio 0% to 50%) to next total CAILS ratio greater than 50%. One subject may have multiple durations of partial and/or complete response.

4.4.7 Time to relapse in the index lesions

Time to relapse in the index lesions is defined as the time of first Complete Response (total CAILS ratio 0%) for all 3 index lesions to any disease recurrence in those with Complete Response.

4.4.8 Classification of treated skin lesion response

Based on the ISCL/USCL/EORTC criteria, the clinical categorization will be as given in Table 7 using the CAILS score ratio as the measure of skin response.

Table 7: Clinical Response Definitions

Response	Definition
Complete Response	100% clearing of skin lesions (CAILS ratio 0%)
Partial Response	50-99% clearance of disease (CAILS ratio 1% to 50%) No new ≥ 1 cm diameter tumor defined as a solid or nodular lesion with evidence of depth and/or vertical growth
Stable Disease	25% increase to 50% clearance of skin disease (CAILS ratio of 125% to 49%) No new ≥ 1 cm diameter tumor defined as a solid or nodular lesion with evidence of depth and/or vertical growth
Progressive disease	>25% increase of skin disease (CAILS ratio of >125%) OR 1 or more new ≥ 1 cm diameter tumor defined as a solid or nodular lesion with evidence of depth and/or vertical growth OR loss of partial or complete response defined as an increase of CAILS > sum of the nadir plus 50% of the baseline score
Relapse	Any disease recurrence in those with complete response

Lesions determined to have a Complete Response will not be treated during the next cycle of therapy.

To be categorized as a Partial Response (CAILS Ratio ≤50%), the patient must also have no new clinically abnormal lymph nodes, no cutaneous tumors, and no new pathologically positive lymph node or visceral disease in an area previously documented to be negative in order to maintain the scoring as a Partial Response.

5. STATISTICAL CONSIDERATIONS

5.1. Sample Size Calculation

The sample size used for this trial is based upon the response rates reported from a previous clinical study with the drug. The Phase 2 study of SGX301 (synthetic hypericin) enrolled 12 subjects with mycosis fungoides (Rook et al. *J Am Acad Dermatol* 2010; **63**:984-90). The treatment response rate in the SGX301 group was 58% (7/12) compared to the placebo response rate of 8.3% (1/12). Because of the small numbers, the sample size calculation used the more conservative response rates of 50% for SGX301 and a 20% response rate for placebo. Due to the initial feedback from physicians suggesting enrollment would be substantially enhanced if enrolled patients could be offered a greater than 50% chance of receiving active drug in the trial, a 2:1 randomization SGX301:placebo was elected. Based on the above rates, a 2:1 randomization, a desired significance level with a two-tailed of α=0.05, and a power (1-β) of 92.5%, it was calculated that a sample size of 120 patients (80 patients treated with SGX301and 40 patients treated with placebo) would be required. Based on previous clinical studies in mycosis fungoides, it was assumed that a dropout rate of 11% could be expected in the critical 8-week Cycle 1 treatment period. Therefore, it is estimated that approximately 135 patients will need to be enrolled to have 120 patients complete Cycle 1.

5.2. Analysis Populations

5.2.1 Intent-to-treat (ITT) Population

The primary population for evaluation is the ITT population. The ITT population is defined as all subjects enrolled, treated at least one time, and categorized by the treatment group to which they were randomized. All efficacy endpoints will be summarized and analyzed by the treatment group to which they were randomized.

5.2.2 Per Protocol (PP) Population

The PP population is comprised of all subjects completing the first 6 week cycle of treatment, had a full evaluation of efficacy and safety at the Week 8 clinic visit and who have been in full compliance with the clinical protocol (e.g., no sunbathing, no swimming, no concomitant medications that are restricted, etc.). All efficacy endpoints will be summarized and analyzed using PP population as sensitivity analyses. All efficacy endpoints will be summarized and analyzed by the treatment group to which they were randomized.

5.2.3 Safety Population

The safety population is the same as the ITT population but categorized by drug actually administered. All safety endpoints will be summarized and analyzed by the drug actually administered.

5.3. Methodology and Conventions

All safety endpoints will be analyzed using the safety population. All other endpoints including baseline information and efficacy endpoints will be analyzed using the ITT population. When the actual treatment received by a subject is different from the randomized treatment assigned, the subject will be analyzed per the randomized treatment for the efficacy parameters; while they will be analyzed per actual treatment that was taken for the safety parameters.

Safety and efficacy data will be summarized and presented by treatment group and cycle in summary tables. Continuous variables will be presented by descriptive statistics including n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be tabulated by frequency count and percentage.

Lab results obtained from the central laboratory, rather than local laboratories, will be used for all efficacy and safety analyses. Local laboratory values, if collected in the eCRF's, will be listed only in data listing.

Unless otherwise stated, data will be polled across study sites and all statistical tests will be two-tailed hypothesis tests performed at the 5% level of significance for main effects and all confidence intervals will be two-sided 95% confidence intervals.

All analyses will be performed using SAS® Version 9.1.3 or higher.

5.4. Additional Data Handling Rules and Presentation Specifications

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

- All subject data will be summarized and presented by treatment group (SGX301 and placebo) for Cycle 1. For Cycles 2 and 3, the subject data will be summarized and presented by SGX301 only.

- 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 (TLF) index.

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

- Duration of treatment or days in treatment is calculated as: last dose date – first dose date +1

- Body weight, height and temperatures will be converted using the following formula:
  - kg = lb/2.2
  - cm = 2.54 x in
  - °C = (5/9) x (°F – 32)

- 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 '<.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.

- For all efficacy endpoints with percentage, 95% confidence intervals (CI) will be provided using the normal approximation approach.

- All patients with missing efficacy data at the end of Cycle 1 will be treated as treatment failures for all Cycle 1 analyses. Patients with efficacy data at Cycle 1 but missing data at Cycle 2 for treatment response rate for complete clearing rate will be treated as treatment failures for all Cycle 2 analyses. If a lesion had a complete response (CAILS score of 0) during Cycle 1, it will be censored for Cycle 2 and not considered "missing".

- For the time to relapse analysis missing data will be handled using the standard Kaplan-Meier procedure. If there are no more evaluations after the missing data observation, the patient is censored at the previous evaluation. If there are subsequent evaluations, then the missing data point is ignored.

5.5. Subject Disposition

The following subject data will be summarized and presented by treatment group (SGX301 and placebo):

- Number of subjects screened and randomized (using the screened subject population) for both the ITT and PP populations.
- Number and percentage of subjects in each analysis set by treatment group (categorized by the treatment group to which they were randomized) in both the ITT and PP populations and reasons for excluding patients from the PP population.

- Number and percentage of subjects who completed and prematurely discontinued from investigational period, by study cycles, by reason for discontinuation, and by treatment group for all randomized subjects.
- All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment will be described in the clinical study report
- All subjects who prematurely discontinued during the treatment period will be listed by discontinuation reason for the randomized population.
- The number of light sessions completed for each cycle in both the ITT and PP populations.

5.6. Demographics and Other Baseline Characteristics

Demographic data will be summarized descriptively by treatment arm for the ITT and PP populations. Demographic variables include age, sex, race, ethnic group, baseline weight, and body mass index.

Age will be calculated from the date of birth to the date of the Informed Consent (in years).

Treatment groups will be compared overall for continuous variables using a one-way analysis of variance (ANOVA) and for categorical variables using a chi-square test. P-values for the overall treatment comparison of the three treatment arms will be displayed to evaluate comparability.

Listings of demographic data characteristics will be provided for each patient.

Baseline disease characteristics will be summarized descriptively by treatment arm for ITT and PP populations. Baseline disease characteristics include time from diagnosis to randomization, CAILS evaluation of each index lesion and overall for the three primary evaluation lesions, Physician Global Assessment of extent of disease involvement.

Treatment groups will be compared overall for continuous variables using a one-way analysis of variance (ANOVA) and for categorical variables using a chi-square test. P-values for the overall treatment comparison of the three treatment arms will be displayed to evaluate comparability.

Listings of baseline disease characteristics will be provided for each patient.

5.7. Medical History

Medical history and current conditions will be presented separately for the ITT population. All events 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.

5.8. 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.

Both prior and concomitant medication usage will be summarized by the number and proportion of subjects in each treatment group receiving each drug within each therapeutic class using the safety population. Subjects will only be counted one time in each unique ATC Class and generic name if multiple drugs are used by a subject.

If there is any missing date for the medication, please see Appendix 1 for data handling conventions.

6. INTERIM ANALYSIS

One interim analysis was planned to be performed when monitored Cycle 1 efficacy data is available on approximately 80 evaluable patients. The purpose of this analysis is two-fold: 1) halt the trial if there is overwhelming evidence of superiority of one treatment group (overwhelming efficacy or overwhelming futility) or 2) increase the trial size if the assumption on the placebo rate of "success" is greater or the drug effect has a lower rate of "success" than initially estimated. The trial will only be stopped with fewer than 120 evaluable patients if there is evidence of overwhelming superiority of one treatment arm. In addition to stopping the trial, the DMC will assess the interim data for safety.

An interim study analysis conducted after enrollment of approximately 100 subjects re-sized the study for 90% power based on the actual response rates in the study. A total of approximately 180 subjects were to be randomized to have 160 evaluable patients.

6.1. Assessment of Overwhelming Superiority of One Dose Group

During the unblinded interim analysis, the DMC will assess whether the trial should be halted because of overwhelming efficacy (based on an interim p-value comparing treatments on the primary endpoint rate) of the drug or overwhelming futility (based on conditional power as discussed in Section 6.2). In order to preserve an overall Type I error rate of 0.05, the alpha spending function approach with an O'Brien-Fleming type of stopping rule will be used, with a 2 sided significance level of $\alpha = 0.001$ to reject the null hypothesis of treatment equality at the interim analysis and a 2 sided significance level of $\alpha = 0.049$ to reject the null hypothesis of treatment equality at the final analysis. This is not an exact O'Brien-Fleming rule, but follows the O'Brien-Fleming philosophy of rejecting the null hypothesis at the interim analysis if the treatment difference on the primary endpoint rate at the interim analysis is overwhelmingly large. The 2-sided significance level of $\alpha = 0.001$ is more conservative at the interim analysis than that which would be used using the exact O'Brien-Fleming 2-sided significance level (2-sided 0.012 with 80 evaluable patients at the interim). That is, it is more difficult to reject the null hypothesis at the interim analysis using the 2-sided 0.001 level of significance than it would be using the exact O'Brien-Fleming two-sided significance level at the interim analysis. It is actually desired not to stop the study at the interim stage so that more complete information on safety and on secondary endpoints can be obtained, unless there is such overwhelming efficacy (two-sided $p<0.001$) that it would be potentially unethical not to stop the study at the interim stage. Note that using a two-sided 0.001 level of significance at the interim and a two-sided 0.049 level of significance at the final analysis, the overall Type I error rate is maintained under the null hypothesis at the 2-sided 0.05 level of significance (and is actually slightly less than 0.05), and the overall power is maintained at 90% under the alternative hypothesis.

6.2. Conditional Power Procedure and, If Necessary, Sample Size Re-Estimation

At the interim analysis, the need for increasing the sample size will be evaluated base on the observed rate of success compared to the assumptions of the original sample size calculation. Should these be different, the DMC can make the following non-binding recommendation based on the observed "success" rates in the two treatment arms:

- If the trial is not halted for overwhelming efficacy, inspect the conditional power for achieving a successful trial for the current protocol-specified sample size *under the assumption that the observed interim treatment effect size is the true treatment effect size.* Halt the trial for overwhelming futility, defined as conditional power for achieving success under the protocol-specified sample size being less than 10%.

- If the trial is not halted and the conditional power for a beneficial SGX301 effect under the protocol-specified sample size is between 38% and 90% (the promising zone), recommend an increase of the sample size to maintain conditional power of 90%. As discussed in Mehta and Pocock (2011) [1], such a sample size increase will not require a penalty to the final significance level (the maximum sample size increase will be 2 times the protocol-specified sample size).

The conditional power will be calculated according to Jennison and Turnbull (2000) as indicated below.

$$P_k(\theta) = \Phi\left[\frac{Z_k\sqrt{I_k} - z_{1-\alpha/2}\sqrt{I_K} + \theta(I_K - I_k)}{\sqrt{I_K - I_k}}\right] + \Phi\left[\frac{-Z_k\sqrt{I_k} - z_{1-\alpha/2} - \sqrt{I_K} - \theta(I_K - I_k)}{\sqrt{I_K - I_k}}\right]$$

Where:

θ=the parameter being tested by the hypothesis (that is, the assumed difference in primary endpoint rate between treatment groups).
k= an interim stage at which the conditional power is computed ($k = 1,\ldots, K-1$)
K= the stage at which the study is terminated and the final test computed
Z_k=the test statistic calculated from the observed data that has been collected up to stage k
I_k=the information level at stage k
I_K=the information level at the protocol-planned end of study sample size
$z_{1-\alpha/2}$=the standard normal critical value for the test with a two-sided type I error rate of 0.049

For the test of two proportions with null hypothesis H_0:$P_2 = P_1$, where P_1 and P_2 are the population primary endpoint proportions in groups 1 and 2, respectively, under the alternative hypothesis, these components are computed in Chang (2008) as:

$\theta = P_2 - P_1$ (the expected difference under the alternative hypothesis)

$Z_k = \frac{p_{2k} - p_{1k}}{\sqrt{\bar{p}(1-\bar{p})\left(\frac{1}{n_{1k}} + \frac{1}{n_{2k}}\right)}}$ (the z statistic computed from the observed data)

$I_k = \left[\frac{P(1-P_1)}{n_{1k}} + \frac{P_2(1-P_2)}{n_{2k}}\right]^{-1}$ (the interim information level)

$I_K = \left[\frac{P_1(1-P_1)}{n_1} + \frac{P_2(1-P_2)}{n_2}\right]^{-1}$ (the final information level)

Where

p_{jk} is the sample proportion for group j, estimating P_j at stage k
n_{jk} is the sample size in group j at stage k
n_j is the final sample size in group j
$\bar{p} = \frac{n_{1k}p_{1k} + n_{2k}p_{2k}}{n_{1k} + n_{2k}}$

In this study, K=2. In the calculation of conditional power, I_k and I_K are replaced with their estimates:

$\widehat{I_k} = \left[\frac{p_{1k}(1-p_{1k})}{n_{1k}} + \frac{p_{2k}(1-p_{2k})}{n_{2k}}\right]^{-1}$ (the estimated interim information level)
$\widehat{I_K} = \left[\frac{p_{1k}(1-p_{1k})}{n_1} + \frac{p_{2k}(1-p_{2k})}{n_2}\right]^{-1}$ (the estimated final information level)

7. EFFICACY ANALYSES

Efficacy will be analyzed based on ITT and PP populations.

7.1. Analysis of Primary endpoint

The primary endpoint for the trial is proportion of the treatment response (defined as ≥50% reduction in total CAILS score) between the two treatment groups at the end of Cycle 1. Number and percent of treatment response (yes/no) will be tabulated. Since the interim analysis is performed, in order to control the Type 1 error, 4.9% significance level for the testing hypothesis will be applied to the final primary endpoint testing. A logistic regression analysis on treatment response will be performed with treatment and baseline total CAILS score as independent variables. Treatment difference will be compared using Wald test and considered statistically significant if the two-sided p-value is ≤ 0.049. The odds ratio of treatment response for SGX301 vs. placebo and its 95% confidence interval will be presented.

7.2. Analysis of Secondary endpoints

In order to control the Type 1 error, the following 4 secondary endpoints are arranged in a hierarchical order as following; therefore, a fixed sequence procedure will be used to test these secondary endpoints. In other words, if the primary efficacy endpoint reached the 5% significance level using the Wald test, then the first secondary endpoint will be tested using a 5% significance level. Otherwise, the first secondary endpoint will not be tested. Once the first secondary endpoint reached the statistical significance, the second secondary endpoint will be tested. The rest of secondary endpoints will be tested following this procedure.

[redacted]

1. Percent of patients achieving a Partial or Complete Response of treated lesions (yes/no) defined as a ≥50% reduction in the CAILS score (CAILS ratio ≤50%) for the 3 index lesions at the Cycle 2 evaluation visit (Week 16) compared to the total CAILS score at baseline for patients randomized to SGX301 in Cycle 1 compared to the success rate during Cycle 1 of the placebo treated patients.
2. The number of index lesions with a Partial or Complete Response defined as a ≥50% reduction in the CAILS score (CAILS ratio ≤50% week 8 score divided by the baseline score) for that lesion at the Cycle 1 evaluation visit (Week 8) compared to its CAILS score at baseline comparing the Cycle 1 SGX301 and placebo lesions.

[redacted]

[redacted]

[redacted]

Cycle 2: Secondary analyses from Cycle 2 will include the following comparisons for each of the treatment groups—patients in the SGX301 treatment group during Cycle 1 (whose index lesions will have been treated with two cycles of SGX301) and patients in the placebo treatment group during Cycle 1 (whose index lesions will have been treated with one cycle of SGX301):

- The percent of patients achieving a partial or complete response (yes/no) defined as a ≥50% reduction in the total CAILS score for the 3 index lesions at the Cycle 2 evaluation visit (Week 16) compared to the total CAILS score at the start of Cycle 2 (Week 8) will be tabulated within each of the two treatment groups. [redacted]

[redacted]

[redacted]

Cycle 3: Secondary analyses from Cycle 3 will include the following comparisons for each of the treatment groups - the index lesions from patients in the SGX301 treatment group during Cycle 1 (that will have been treated with three cycles of SGX301), the index lesions from patients in the placebo treatment group during Cycle 1 (that will have been treated with two cycles of SGX301), and all non-index lesions (lesions that will have been treated with one cycle of SGX301):

[redacted]

[redacted]

- The percent of patients achieving a partial or complete response (yes/no) defined as a ≥50% reduction in the total CAILS score for the **3 index lesions** at the Cycle 3 evaluation visit (Week 24) compared to the total CAILS score at the start of Cycle 3 (Week 16) will be tabulated for each of the two treatment groups. Within each treatment group, the percent of patients achieving a partial or complete response will be compared between Week 24 and that for Week 16 using the McNemar test.

[redacted]

[redacted]

8. SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. Safety parameters include adverse events, laboratory parameters, vital signs, ECG parameters, and physical examinations.

8.1. Adverse Events

Summary tables will be provided for all treatment-emergent adverse events (TEAEs) by treatment arm for Cycle 1 and by cycle only for the remaining cycles.

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 report 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.

Descriptive statistics will be used to summarize TEAEs by treatment arm and overall for patients in the ITT population. The following TEAE summaries will be presented:

- Frequency of TEAEs by SOC, high level term, and preferred term
- 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.

If there is any missing date for the AE, please see Appendix 1 for data handling conventions.

8.2. 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 by treatment group 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, immature granulocyte, 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 central 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.

8.3. Vital Signs

Vital signs (systolic and diastolic blood pressures, heart rate, and highest temperature) will be measured at Baseline and at each evaluation 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 by treatment arm, overall total, and evaluation cycle.

Criteria for clinically significant values have been defined as shown in Table 8. For each vital signs 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 values on-therapy will be displayed.

Table 8. Vital Signs Clinically Significant Value

Vital Sign Variable	Absolute Value	
Systolic Blood Pressure	$\geq$ 180 mmHg and increase of $\geq$ 20 mmHg from baseline $\leq$ 90 mmHg and decrease of $\geq$ 20 mmHg from baseline	
Diastolic Blood Pressure	$\geq$ 105 mmHg and increase of $\geq$ 15 mmHg from baseline $\leq$ 50 mmHg and decrease of $\geq$ 15 mmHg from baseline	
Pulse	$\geq$ 120 bpm and increase of $\geq$ 15 bpm from baseline $\leq$ 50 bpm and decrease of $\geq$ 15 bpm from baseline	
Temperature	$\geq$ 38.3 °C and increase of $\geq$ 1.1 °C from baseline	

Listings of all vital signs values will be presented.

8.4. Extent of Exposure

The number of exposures of occlusion and phototherapy for the ITT and PP populations will be summarized by frequency table by treatment arm and cycle for Treatment Cycles 1 and 2. Descriptive statistics will be provided by treatment arm.

APPENDIX 1: DATA HANDLING CONVENTIONS

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.

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.

3. MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to the case where the start 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 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.

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 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 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.

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 9). 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 10.

Table 9: Example for Coding of Special Character Values for Clinical Laboratory Parameters

Lab Test	Possible Lab Results (in SI unit)	Coded Value for Analysis
Chemistry: ALT	< 5	0
Chemistry: AST	< 5	0
Chemistry: Bilirubin, Total	< 2	0
Urinalysis: Glucose	= OR > 55, >= 55, > 0	Positive
	<= 0, Negative	Negative
Urinalysis: Ketones	= OR > 8.0, >=8.0, > 0	Positive
	<= 0, Negative	Negative
Urinalysis: pH	> 8.0, >= 8.0	8.0
	>= 8.5,	8.5
Urinalysis: Protein	= OR > 3.0, >=3.0, > 0	Positive
	<= 0	Negative

Table 10: 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
GGT	U/L		≥3 * ULN
Calcium	mmol/L	<0.8*LLN	>1.2 * ULN
Creatinine	µmol/L		> 1.5x Day 1
Potassium	µmol/L	<0.75*LLN	>1.2 * UNL
Sodium	mmol/L	<0.9*LLN	>1.1 * UNL
Total Bilirubin	µmol/L		>1.5 * UNL
Total Protein	µmol/L	<0.9*LNL	>1.1 * UNL
Urea (BUN)	mmol/L		>1.5X Day 1
HEMATOLOGY			
Neutrophils	10^9/L	≤1	
Platelet Count	10^9/L	≤ 100	≥700
White Blood Cell Count	10^9/L	≤2.5	≥15
LLN: Lower limit of normal, value provided by the laboratory ULN: Upper limit of normal, value provided by the laboratory			

APPENDIX 2: SCHEDULE OF PROCEDURES

Table 11: Study Assessments: Cycle 1 – Week 1 Randomized Drug to Index Lesions

Evaluation	Screening Day -21 to -1	Monday Baseline-Day 1	Tuesday Day 2	Wednesday Day 3	Thursday Day 4	Friday Day 5
Clinic visit	X	X	X		X	X
Entry criteria	X	X				
Informed consent	X					
Medical history	X					
Interim medical history/AEs		X	X		X	X
Vital signs	X	X	X		X	X
Physical exam	X	X				
Visual lesion inspection			X			X
Serum HCG (females only)	X					
Hematology		X				
Chemistry		X				
Identify index lesions		X				
3 mm punch biopsy		X				
CAILS		X				
PGA		X				
mSWAT		X				
Digital photography		X				
Distribute drug		X				
Training on drug application		X			X	
Apply drug/opaque bandage		X			X	
Light Treatment			X			X
Safety grading			Immediately prior and after radiation			Immediately prior and after radiation

Table 12: Study assessments: Cycle 1- Application and Irradiation #3-12 Randomized Drug to Index Lesions

Evaluation	Application Day	Treatment Day
Clinic visit	X[1]	X
Interim medical history/AEs		X
Vital signs		X
Physical exam		X
Apply drug/ opaque bandage	X	
Light Treatment		X
Safety grading		Immediately prior and after radiation

[1] Patient will come to clinic for medication application until study personnel comfortable with their ability to appropriately apply

Table 13: Cycle 1-Weeks 7 and 8 Treatment Evaluation

Evaluation	Application Day	Treatment Day
Clinic visit		X
Interim medical history/AEs		X
Vital signs		X
Physical exam		X
Serum HCG		Females only
Hematology		X
Chemistry		X
3 mm punch biopsy		Same index lesion
CAILS		X
PGA		X
Digital photography		X
Distribute Cycle 2 drug		X

Table 14: Cycle 2- Irradiation Treatment #13-24 All Patients 0.25% SGX301 Ointment to Index Lesions

Evaluation	Application Day	Treatment Day
Clinic visit		X
Vital signs		X
Interim medical history/AEs		X
Visual lesion inspection		X
Apply drug/ opaque bandage	X	
Light treatment		X
Safety grading		Immediately prior and after radiation
CAILS		X[1]
PGA		X[1]
Digital photography		X[1]

[1]Index lesions will be evaluated in Week 10

Table 15: Cycle 2- Assessment

Evaluation	Week 15 Rest Period	14 (±2) Days After Last Treatment
Clinic visit		X
Interim medical history/AEs		X
Vital signs		X
Physical exam		X
Hematology		X
Chemistry		X
CAILS		X
mSWAT		X
PGA		X
Digital photography		X
Distribute Cycle 3 drug		X

Table 16: Optional Cycle 3- Week 17 through 22 All Patients 0.25% SGX301 Ointment to All Lesions

Evaluation	Application Day	Treatment Day
Clinic visit		X
Vital signs		X
Interim medical history/AEs		X
Visual lesion inspection		X
Apply drug/ opaque bandage	X	
Light Treatment		X
PK blood		X[1]
Safety grading		Immediately prior and after radiation

1 During the 4 treatment sessions in last 2 weeks of the cycle (Weeks 21 and 22 and Administration 33 – 36)

Table 17: Cycle 3: Assessment- Cycle 3 Evaluation

Evaluation	Week 23 Rest Period	14 (±2) Days After Last Treatment
Clinic visit		X
Interim medical history/AEs		X
Vital signs		X
Physical exam		X
Hematology		X
Chemistry		X
CAILS		X
mSWAT		X
PGA		X
Digital photography		X

Table 18: Weeks 25-48- Long-term Follow-up

Evaluation	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48
Clinic visit	X	X	X	X	X	X
Interim medical history/AEs	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X
CAILS	X	X	X	X	X	X
mSWAT	X	X	X	X	X	X
PGA	X	X	X	X	X	X
Digital photography	X	X	X	X	X	X
New lesion identification	X	X	X	X	X	X