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

Sponsor:

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US IND Number: [redacted]

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CONFIDENTIALITY STATEMENT

PROCEDURES IN CASE OF EMERGENCY

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2. SYNOPSIS

Name of Sponsor/Company:
Soligenix, Inc.

Name of Investigational Product:
SGX301

Name of Active Ingredient:
Synthetic hypericin

Title of Study:
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

Study Center(s): 35 active sites

Principal Investigator: [redacted]

Studied Period (years):	**Phase of development:**
Date first patient enrolled: December 14, 2015 Estimated date last patient enrolled: December 2019	3

Objectives:

Primary:

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 8-week 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 ~107 Cycle 1 SGX301 patients) and to extend the data on the response rate of SGX301 in untreated lesions (the~53 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.

Secondary:

Secondary objectives will include the following:

- [redacted]
- To evaluate the ability of topical SGX301 and visible light in patients with patch/plaque phase CTCL to induce Complete Response each cycle.
- 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.

- To evaluate the duration of Partial and/or Complete Response in the index lesions induced by topical SGX301 and visible light in patients with patch/plaque phase CTCL.
- [redacted]
- Assess the safety of topical SGX301 and visible light in patients with patch/plaque phase CTCL.
- To evaluate the ability of the two 6 week courses of SGX301 and visible light (Cycle 2 patients who also received active drug in 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 16-week Evaluation Visit when compared to patients receiving placebo and visible light.

Methodology:

Approximately 180 subjects with CTCL will be enrolled into this Phase 3, placebo-controlled, double blind, multicenter study in order to assure 160 evaluable patients will complete the trial. The study will evaluate the efficacy and safety of SGX301 ointment at a concentration of 0.25% synthetic hypericin, applied twice weekly for six weeks, under opaque covering for 18-24 hours followed by the administration of visible light up to a dose of 12 Joules/cm^2 twice weekly for each of three 6-week cycles. Three index lesions in each patient will be identified and indexed for treatment and evaluation prior to randomization.

In the first 6-week treatment period (Cycle 1), each patient's 3 index lesions will be treated with either SGX301 ointment (~107 patients) or placebo (~53 patients). The treatment response will be assessed after a 2-week rest period (at Week 8) in order to permit any light induced erythema to subside. This first cycle is the primary efficacy period for this study.

Following the assessment visit at the end of Cycle 1, all patients will have their index lesions that have NOT achieved a complete response following Cycle 1 therapy treated for a 6-week treatment period with SGX301 in Cycle 2. The treatment assessments for this treatment cycle will be done at Week 16 following a 2-week rest period to permit any light induced erythema to subside.

Following the Cycle 2 evaluation, all patients will be given the opportunity to enter an open-label treatment (Cycle 3) in which all lesions (index and non-index) selected by the patient and physician will be treated for an additional 6 weeks with SGX301 ointment. Evaluation of safety and efficacy during the open label cycle will take place at Week 24 following a 2-week rest period to permit any light induced erythema to subside.

Long-term outcome in all patients will be evaluated 6 months after their last evaluation visit (12 months (48 weeks) for those participating in Cycle 3 and 10 months (40 weeks) for those only participating in Cycles 1 and 2).

Number of Patients (planned):

Approximately 180 patients will be enrolled to assure enrollment of 160 evaluable patients.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

Patients must meet all of the following criteria in order to be eligible for enrollment:

- ≥18 years of age.
- Subjects must have a clinical diagnosis of cutaneous T-cell lymphoma (CTCL, mycosis fungoides), Stage IA, Stage IB, or Stage IIA.
- Subjects with a minimum of three (3) evaluable, discrete lesions.
- Subjects willing to follow the clinical protocol and voluntarily give their written informed consent.
- Female subjects not pregnant or nursing and willing to undergo a pregnancy test within 30 days prior to treatment initiation.
- Subjects must be willing to refrain from sunbathing for the duration of the study.

Exclusion Criteria

Patients with any of the following criteria are **NOT** eligible for enrollment:

- History of sun hypersensitivity and photosensitive dermatoses including porphyria, systemic lupus erythematosus, Sjögren's syndrome, xeroderma pigmentosum, polymorphous light eruptions, or radiation therapy within 30 days of enrolling.
- History of allergy or hypersensitivity to any of the components of SGX301.
- Pregnancy or mothers who are breast-feeding.
- Males and females not willing to use effective contraception.
- Unhealed sunburn.
- Subjects receiving topical steroids or other topical treatments (e.g., nitrogen mustard) on index lesions for CTCL within 2 weeks.
- Subjects receiving systemic steroids, psoralen UVA radiation therapy (PUVA), narrow band UVB light therapy (NB-UVB) or carmustine (BCNU) or other systemic therapies for CTCL within 3 weeks of enrollment.
- Subjects who have received electron beam irradiation within the potential treatment field within 3 months of enrollment.
- Subjects with a history of significant systemic immunosuppression.
- Subjects taking other investigational drugs or drugs of abuse within 30 days of entry into this study.
- Subjects whose condition is spontaneously improving.
- Subjects with tumor stage or erythrodermic CTCL (stages IIB-IV).
- Subject has any condition that, in the judgment of the principal investigator (PI), is likely to interfere with participation in the study.
- Prior participation in the current study.

Investigational Product, Dosage and Mode of Administration:

SGX301 will be supplied in plastic screw-top jars containing 25 grams of SGX301 (0.25% synthetic hypericin, 2.5 mg/gram). Ointment will be applied twice weekly and covered using opaque bandaging approved/provided by Soligenix for a period of 18 to 24 hours prior to light treatment. Light treatments will be given using a bank of 12 cool white visible fluorescent bulbs for a period calculated using dosimeter readings and tables to determine the duration of therapy (approximately 1 minute/Joule with the initial dose of 5 Joules/cm^2) and the patient's position marked to assure consistent positioning

through the initial 2 Cycles of the trial. Light treatments will be administered twice weekly separated by 3-4 calendar days (±1 day). The light dose may be increased by 1 Joule/cm^2 until symptoms or signs of mild phototoxicity appear when the dose will be either maintained or reduced by 1 Joule if phototoxicity is pronounced (skin erythema of greater than Grade I) or to a maximum light dose of 12 Joules/cm^2.

Duration of Treatment:

Patients will undergo 3 treatment cycles each comprised of a 6-week treatment period and a 2-week rest period. During the first cycle, patients will be randomized (2:1) to receive either SGX301 or placebo and 3 prospectively indentified index lesions will be treated. In Cycle 2, all patients will have their index lesions that have NOT achieved a complete response following Cycle 1 therapy treated with SGX301. In Cycle 3, all patients will have all lesions chosen by the physician and patient treated with SGX301.

Reference Therapy, Dosage and Mode of Administration:

Placebo will consist of the identical ointment vehicle (USP Hydrophilic Ointment) without the addition of synthetic hypericin and color matched to the active drug. The administration of the placebo ointment and subsequent visible light treatment will be identical to the active drug. Placebo will be used only during Cycle 1 of the study.

Criteria for Evaluation:

Efficacy:

The primary efficacy will be assessed on the percent of patients in each of the 2 treatment groups achieving a Partial or Complete Response (yes/no) of the treated lesions defined as a ≥50%reduction in the total CAILS score for the 3 index lesions at the Cycle 1 evaluation visit (Week 8) compared to the total CAILS score at baseline.

Secondary analyses will include the following comparisons for Cycle 1:

- The number of index lesions with a Partial or Complete Response defined as a ≥50%reduction in the CAILS score for that lesion at the Cycle 1 evaluation visit (Week 8) compared to its CAILS score at baseline.
- Percent of patients achieving a Complete Response (yes/no) of the treated lesions defined as a CAILS score of 0 at the Cycle 1 evaluation visit (Week 8).

[redacted]

[redacted]

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 2 cycles of SGX301 unless a lesion achieved a complete response following Cycle 1 therapy) and patients in the placebo treatment group during Cycle 1 (whose index lesions will have been treated with 1 cycle of SGX301 unless a lesion achieved a complete response following Cycle 1 therapy):

- Percent of patients achieving a Partial or Complete Response (yes/no) of the treated lesions 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).
- The number of index lesions with a Partial or Complete Response defined as a ≥50%reduction in the CAILS score for that lesion at the Cycle 2 evaluation visit (Week 16) compared to its CAILS score at the start of Cycle 2 (Week 8).

[redacted]

- The percent of patients who completed Cycle 2 and received active drug in Cycle 1 who achieved a Partial or Complete Response (yes/no) of the treated lesions defined as a ≥50% reduction in the total CAILS score for the 3 index lesions compared to the percent of patients who received placebo in Cycle 1 and achieved a Partial or Complete Response (yes/no) of the treated lesions defined as a ≥50% reduction in the total CAILS score for the 3 index lesions

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]

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

- [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]
- [redacted]
- [redacted]
- [redacted]

Safety:

Safety will be assessed by the number and types of adverse events reported and changes from baseline values of routine laboratory test results, vital signs, and physical examination.

Statistical Methods:

The primary population for evaluation is the ITT (Intent-to-treat) 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. In addition, a PP (per-protocol) population will be identified and analyzed. The PP population is comprised of all subjects completing the first 6-week cycle of treatment and who have been in full compliance with the clinical protocol (e.g., no sunbathing, no concomitant medication that are restricted, etc.). The safety population is the same as the ITT population but categorized by drug actually administered. In general, descriptive statistics for continuous variables will include the number of patients, mean, standard deviation, median, minimum, and maximum. For categorical data, frequency counts and percentages will be presented. Except where explicitly indicated, data will be pooled across study sites. Unless otherwise specified, all statistical analyses will be based on two-tailed evaluations with the threshold for statistical significance level set at ≤0.05.

The primary endpoint for the study is a comparison of the percent of each treatment group achieving a treatment response of the treated lesions (either a Partial or Complete Response defined as a ≥50% reduction in the CAILS score [CAILS ratio ≤50%]) at the 8-week evaluation. The groups will be compared using a chi-squared test.

Chi-squared testing will be completed with regards to the relative frequency of patients with a treatment response of the treated lesions (Complete or Partial Response), biopsy-confirmed Complete Response of the treated lesions, Complete Response of the treated lesions, the number of lesions with a treatment response, and the number of lesions with a Complete Response. The change in CAILS assessment will be compared and analyzed using logistic regression with the ordered categorical response as the dependent variable and treatment as the independent variable in the first two cycles. CAILS score is a continuous variable and will be analyzed for Cycles 1 and 2 using Analysis of Variance (ANOVA) with treatment as an independent variable. Duration of response will be categorized as a semi-continuous variable and analyzed using repeated measures ANOVA with treatment, lesion and patient as independent variables. Time to progression will be evaluated using the standard Kaplan-Meier analysis. Complete details of analyses and relative order of importance of each

analysis are delineated in the Statistical Analysis Plan.

Interim Analysis:

The Data Monitoring Committee (DMC) will conduct one (1) interim analysis when approximately 60% (n = 80) of the total subjects have completed the Cycle 1 Week 8 evaluation (i.e., the primary endpoint evaluation). Soligenix, Inc., participating clinical investigators, and any personnel involved in trial conduct will remain blinded to study treatment. The primary efficacy endpoint and the key safety endpoints will be analyzed. A sample size recalculation may be performed after examining the assumptions. 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 $\alpha = 0.001$ for the interim analysis and a 2 sided significance level of $\alpha = 0.049$ for the final analysis. Specific guidelines concerning recommendations for resizing the study, including terminating the study early for reasons of safety or overwhelming efficacy, are outlined in the DMC charter. The Interim analysis was performed and the DMC recommended that enrollment continue to 160 evaluable patients.

Final Analysis:

Upon completion of enrollment, the study database is to be locked, released, and analyzed in two parts, the first being an analysis of data through Cycle 1 Week 8, and the second final analysis of all data through long-term follow-up.

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

3.1. Table of Contents

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations and specialist terms

Abbreviation or specialist term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANOVA	Analysis of Variance
BCNU	Bis-chloroethylnitrosourea (Carmustine)
BSA	Body Surface Area
BUN	Blood urea nitrogen
BVDV	Bovine diarrhea virus
CAILS	Composite Assessment of Index Lesion Severity
CD#	Cluster of differentiation #
CFR	Code of Federal Regulations
CLL	Chronic lymphocytic leukemia
CO_2	Carbon dioxide
CR	Complete response
CTCL	Cutaneous T-cell Lymphoma
DCF	Deoxycoformycin
DMC	Data Monitoring Committee
ECP	Extracorporeal Photopheresis
eCRF	Electronic Case Report Form
FDA	United States Food and Drug Administration
FV	Friend Leukemia Virus
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCV	Hepatitis C Virus
HCG	Human chorionic gonadotropin
HCL	Hairy cell leukemia
HIV	Human Immunodeficiency Virus

Abbreviation or specialist term	Explanation
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDB	Investigator's Drug Brochure
IFN	Interferon
IFN-α	Interferon-alpha
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent-to-Treat population
J	Joules
LN	Lymph Nodes
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MF	Mycosis Fungoides
MPD	Minimum Phototoxic Dose
mSWAT	Modified Severity Weighted Assessment Tool
NB-UVB	Narrow band Ultraviolet-B light radiation
NDA	New Drug Application
PDT	Photodynamic Therapy
PGA	Physician Global Assessment
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per-protocol Population
PUVA	Psoralen Ultraviolet-A treatment
RBC	Red blood cell
SAE	Serious adverse event
SS	Sézary Syndrome
USP	United States Pharmacopeia
UV	Ultraviolet
UVA	Ultraviolet-A light radiation

Abbreviation or specialist term	Explanation
UVB	Ultraviolet-B light radiation
WBC	White blood cell

5. INTRODUCTION

5.1. Background Introduction

This section contains a brief description of the rationale and available information concerning the chemistry, non-clinical pharmacology and toxicology, pharmacokinetics (PK), and previous clinical experience with SGX301. Please refer to the Investigator's Drug Brochure (IDB) for additional details and information.

5.1.1 Natural History and Treatment of Cutaneous T-cell Lymphoma

Cutaneous T-cell lymphoma (CTCL), of which the most common early stages are also known as mycosis fungoides (MF), is the most common type of T-cell lymphoma. CTCL affects approximately 25,000 to 50,000 individuals in the US [1]. MF most commonly presents with skin involvement only, manifested as scaly, erythematous patches. As MF progresses, patients develop thicker skin lesions (plaques), skin tumors, lymph node (LN) involvement, blood involvement (Sézary syndrome), and visceral organ involvement. A few patients will present with more advanced stages of CTCL requiring systemic therapy from the time of diagnosis [2]. Advanced disease with diffuse LN and visceral organ involvement is usually associated with a poorer response rate to standard therapies and the patient's survival can often be measured in months [3]. A sub-group of CTCL patients present with extensive skin involvement (generalized erythroderma) and circulating malignant cerebriform T-cells that is commonly designated Sézary syndrome (SS) [4, 5].

MF has substantial morbidity and potential mortality. Mortality is related to stage of disease [6]. Median survival for stage T1 (cutaneous patches or plaques <10% body surface area (BSA)) or T2 (patches or plaques >10% BSA) exceeds 12 years; T1 or T2 patients with lymph node or blood involvement and T3 (one or more cutaneous tumors) or T4 patients (erythroderma) have a 5 year median survival; those with visceral involvement or lymph node effacement by tumor have only a 2.5 year median survival.

The diagnosis of CTCL is confirmed by skin biopsy which characteristically demonstrates the pathognomonic epidermal infiltration (Pautrier's micro-abscesses) of hyperchromatic T-cells that are immunohistochemically positive for the CD4 marker identifying the "helper" T-cell subset and often fail to express CD7 [7, 8]. Blood involvement can be investigated through flow cytometry, Sézary count and/or gene rearrangement studies to determine the presence of a circulating clone [6, 9]. More advanced skin disease produces vertical growth resulting in tumors or ulcers and is frequently associated with regional LN involvement that can be detected via physical examination and radiological imaging.

Treatment of MF involves skin directed therapies, biologic response modifying therapies aimed at promoting a host response to tumor, radiation therapy (directed at individual tumors or total body electron beam irradiation), and in some instances multi-agent chemotherapeutic modalities. Most patients have received short courses of topical corticosteroids prior to the diagnosis of MF [10]. The malignancy-specific topical treatments include mechlorethamine [11-13] (nitrogen

mustard or Mustargen®) administered in a tap water solution or as an ointment, and carmustine (BCNU) [14]. Both treatments have significant response rates in early stage MF disease, but have virtually no effect on extra cutaneous disease or the circulating malignant T-cells in SS patients [13].

Most currently used MF treatments are not approved by the United States Food and Drug Administration (FDA) and must still be considered investigational agents [15, 16]. Oral 5- or 8-methoxypsoralen (Psoralen) given with ultraviolet A light (PUVA) [17-19] is commonly used in the treatment of plaque stage and cutaneous tumors. The durable efficacy of PUVA is largely limited to patients with early stage disease (Stage IA, IB and IIA). Patients with Stage IIB (tumors plus adenopathy) and Stage III (generalized erythroderma plus adenopathy) have a complete response (CR) rate in less than 50% of cases [19]. The CR rate is not as high as seen in earlier stage patients. The majority of these patients will relapse after PUVA and are eventually refractory to this treatment [18]. A variation of PUVA called extracorporeal photopheresis (ECP) is one of the few systemic treatments currently approved by the FDA for the treatment of CTCL patients (the others being Bexarotene and Denileukin Diftitox, discussed below). With ECP, the peripheral blood of a patient is diverted through a leukophoresis machine (the ECP circuit) and exposed to UVA wavelength light in the presence of Psoralen. In addition to the direct destruction of the malignant T-cells, an immune response toward other non-UVA exposed malignant T-cells has been postulated [17]. Photopheresis has demonstrated efficacy not only for MF patients but, in particular, is also effective in the treatment of SS patients [19]. Ultraviolet B length light has also been used to treat MF patients. This treatment can be given at home and does not require pretreatment with Psoralen. Although UVB treatment has appreciable response rates in early stage disease [20], it has not gained wide popularity for the treatment of more advanced MF patients.

Patients with advanced cutaneous lesions or disease refractory to topical therapies have received conventional combination chemotherapeutic lymphoma regimens with unimpressive long-term results [21, 22]. Recently, the nucleoside analogs Fludarabine®, deoxycoformycin (DCF) and 2-chlorodeoxy adenosine (2-CDA), which have significant activity in other lymphocytic malignancies such as chronic lymphocytic leukemia (CLL) and hairy cell leukemia (HCL), have been introduced into clinical trials for MF and SS patients [23-26]. Early results suggest activity and additional trials are underway or in the planning stage.

Several biologic agents have been tested in patients with MF or SS [27-35]. Interferon-alpha (IFN-α) treatment has been tested in MF and SS patients in a variety of dosing regimens [16, 27, 28]. The results from these trials have demonstrated great variations in response rates with some suggestion of dose related improvements in sustained efficacy [29]. The toxicities of higher dose and the cumulative toxicities with chronic administration have tempered the early enthusiasm for the promise of IFN-α in MF (29), but IFN-α remains a mainstay of treatment for MF and SS, and may represent one of the most active biological agents for CTCL. Although results from other types of IFNs [31, 32] and biological response modifiers [33, 34] have been less encouraging, several recent reports of efficacy with combined IFN-α and nucleoside chemotherapeutics have led to renewed appraisal of IFN in this setting [35]. Furthermore, recent

observations support the combined use of IFN with photopheresis for the treatment of SS [36, 37].

5.2. Rationale

Hypericin is a known photodynamic agent with potential to treat a variety of inflammatory dermatological diseases associated with lymphocytic infiltrates, including CTCL.

The most commonly used regimen, PUVA light treatment, is a form of photodynamic therapy (PDT) since oxygen consuming photoreactions may be involved in this phototherapy [38]. Similar to other known photosensitizing agents, singlet oxygen is the principal product in the photosensitization of hypericin. In the presence of light irradiation, hypericin excites oxygen to its singlet state and is capable of generating superoxide radicals that can lead to oxidation of tryptophan imidazole groups in proteins and to oxidation of fatty acids in biological systems. Hypericin is maximally activated by light of about 590-650 nm wavelength (i.e., in the yellow region) [39-41]. Hypericin binds to phospholipids such as phosphatidylcholinei of cell membranes and it binds to retroviral particles, probably by associating with the membrane derived lipid envelope (42).

Emerging evidence indicates that hypericin binds to heat shock protein 90 leading to its enhanced ubiquitinylation. This disrupts several critical growth pathways ultimately leading to cell death [42].

Hypericin is reported to be equal in photodynamic potency to other photosensitizing porphyrins, chlorophyll and rose benga1 [43]. Several studies have shown that benign hyperproliferative and hypervascular conditions such as psoriasis can be improved by photosensitization with porphyrins. Selective sensitization of psoriasis using porphyrins has been demonstrated as an effective treatment and may be related to the increased vascularity of psoriatic plaques [44]. Another report using systemic tin-protoporphyrin in combination with long wavelength ultraviolet light suggests amelioration of psoriasis in psoriatic patients [45].

Hypericin has several attributes that make it attractive for investigating its clinical use in skin disorders with potential advantages over phototherapy with PUVA. Hypericin has been shown to be non-mutagenic; it does not intercalate into DNA. Hypericin is maximally activated by visible light at wavelengths produced by fluorescent light that may significantly reduce the side effects associated with UV irradiation and allows for deeper skin penetration. Hypericin has a relatively long half-life (20-24 hours) which allows for repeated light activation with single doses. Hypericin has been demonstrated to be present in skin after systemic administration and it has been shown to be about 20% bioavailable after oral administration. The mechanism of photoreactions (singlet oxygen production) is the same as other phototherapeutic agents that have been shown to be beneficial in the treatment of psoriasis.

A Phase 1 clinical study in healthy subjects determining the photosensitive concentrations of topically-applied hypericin and the minimum phototoxic dose (MPD) of light required to cause photosensitivity was completed [46]. Data derived from this clinical trial indicate that hypericin concentrations of 0.1% and 0.5% in Hydrophilic Ointment USP cause cutaneous photosensitivity when topically applied for 24 hours and activated by visible light. The MPD was found to be

4 Joules/cm^2, whereas 8 Joules/cm^2 was determined to be a very effective light dose yielding brisk phototoxic reactions.

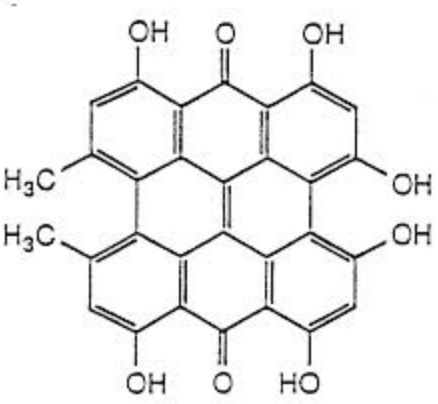
Furthermore, recent research indicates that photoactivated hypericin possesses significant antiproliferative effects on activated normal human lymphoid cells and malignant T-cells purified from the blood of patients with SS, the leukemic phase of CTCL. The mechanism of the antiproliferative activity may be related to the high rate of apoptotic death in these lymphoid cells [47].

The *in vitro* data generated using activated lymphocytes and malignant T-cells led to the initiation of a Phase 2, multicenter, placebo-controlled clinical trial using topical SGX301 followed by light activation to treat early stage patients with CTCL as well as plaque psoriasis. Different skin lesions were treated with one of two different strengths of topical SGX301 or placebo. A total of 12 patients with CTCL were entered. A high rate of clinical response was observed among those lesions treated with the photoactive SGX301, which was statistically significant as compared to lesions treated with placebo [48].

These laboratory data indicating inhibition of cell proliferation and apoptotic death by light-activated SGX301 in lymphoid cells, taken together with the Phase 1 and Phase 2 clinical results demonstrating cutaneous photosensitivity reactions to topically-applied, light-activated SGX301, and clearing of active skin lesions of CTCL patients serve as the basis for conducting the proposed Phase 3 clinical trial in CTCL.

5.3. Chemistry

Hypericin is a natural compound found in stems and petals of plants of the genus *Hypericum*. Within this genus are 8 families and 43 species, including the common St. John's wort plant, *Hypericum perforatum*. The chemical name is 4,5,7,4',5',7' - dimethyl-meso naphthodianthrone, a compound composed of eight conjugated rings containing six hydroxyl groups, two carbonyl and two methyl groups in a symmetric pattern when inverted about a central axis. When dissolved in ethanol solutions it produces a bright f1uorescent compound. Hypericin to be used in this clinical trial is chemically synthesized and not extracted from plants.



5.4. Preclinical Data

5.4.1 Antiviral Activity

Hypericin is an effective virucidal agent that directly inactivates a broad range of viruses and retroviruses. Affected viruses include the murine Friend [40] and Rauscher viruses [49], equine infectious anemia virus [50], murine immunodeficiency virus [39], murine cytomegalovirus (51), influenza [49], vesiculostomatitis virus [51], Sendai [51], herpes [49], and duck hepatitis B virus [52].

In vitro experiments have demonstrated that hypericin inhibits the ability of HIV to establish productive infection in activated mononuclear cells in a concentration dependent manner. In addition, the production of HIV by cells pre-infected by relatively low amounts of HIV was also inhibited to a lesser extent.

Recently, infectious virus titers of bovine diarrhea virus (BVDV) were completely inactivated by hypericin *in vitro* in the presence of light (Prince et al. unpublished). BVDV is a pestivirus that shares close similarities and significant homology with hepatitis C virus (HCV) in the 5' untranslated region sequence, in secondary structures and in the organization of genes encoding the polyprotein [53]. These studies suggest that hypericin may have potential efficacy against HCV. Studies by Tang et al. [49] suggest that lipid enveloped viruses as a group are inactivated by hypericin, whereas non-enveloped viruses such as adenovirus and poliovirus are unaffected. Hypericin appears to become associated with the lipid envelope of the virus and generates singlet oxygen that cross-links viral capsid proteins and prevents virus uncoating during infection [41, 54, 55]. The mechanism of action does not appear to allow for the development of drug resistant mutants *in vitro*.

Several lines of evidence suggest that the antiretroviral activity of hypericin results from its ability to increase rigidity of the retroviral capsid. Capsid rigidity may then inhibit virus infectivity and prevent release of reverse transcriptase enzyme. Interactions with the capsid proteins may also account for electron microscopic evidence that shows a diffused, improperly formed capsid in virions budding from hypericin-treated cells. Apparently, the action of hypericin on the capsid can occur whenever the drug comes in contact with the virus, whether the virus is in solution or infecting or budding from a cell whose membrane contains hypericin.

In vivo studies have demonstrated that hypericin produces complete inhibition of splenomegaly at 10 days in BALB/c mice infected with Friend leukemia virus (FV) when the dose (50 µg/mouse) is administered simultaneously with the viral inoculum. When co-administered with the virus, hypericin inhibited splenomegaly in a dose-dependent fashion across the dosage range from 0.1 ng to 50 µg (per mouse). The degree of inhibition ranges from approximately 20% at 0.1 µg /mouse to 100% at 50 µg/mouse. Assuming a 25 g mouse, these doses would range from 4 µg/kg to 2 mg/kg. At the highest dose, hypericin was also shown to prevent viremia as measured by reverse transcriptase activity in the serum, and spleens of treated animals were free of biologically active FV. When the dose (50 µg/mouse) was administered on the same day, but following inoculation with the virus, FV-induced splenomegaly was only reduced by approximately 70%. In addition to the studies in FV, *in vitro* murine studies have also shown hypericin to be active against radiation leukemia virus and chronic LP-BM5 infection (murine AIDS).

5.4.2 Antiproliferative Effects on Lymphoid Cells

Data from the laboratory of Dr. Alain Rook of the University of Pennsylvania have demonstrated a significant antiproliferative effect of hypericin on activated normal human lymphoid cells when the hypericin-treated cells are exposed to visible light [47]. At concentrations of hypericin ranging between 0.1 and 0.5 µM, a 20-minute exposure of normal lymphoid cells to fluorescent light produced complete inhibition of proliferative responses to the potent mitogens PHA and

Con A. Similarly, malignant T-cells purified from the blood of patients with SS, the leukemic phase of CTCL, had their ability to grow in response to T-cell growth factors markedly inhibited by 0.3 µM of hypericin and 20-minute exposure to fluorescent light. While the precise mechanism of inhibition of proliferation is unclear, it appears that hypericin has the capacity to induce a high rate of apoptotic death in both normal and malignant lymphoid cells [47]. The implications of these findings for the use of topical hypericin to treat CTCL, which is characterized by malignant lymphocytic infiltrates in the skin, are significant, and serve as the basis for the program.

5.4.3 Toxicology

To date, animal toxicology studies have been performed in monkeys following intravenous (IV) administration of hypericin and in rats and monkeys following oral administration.

Following administration of an IV bolus dose of 30 mg/kg to cynomolgus monkeys, pupil dilation, emesis, rhinorrhea, salivation, prostration, ataxia, and tremors were observed. The effects were observed shortly after administration of the dose and were reported to last for 10 to 20 minutes. These effects were prevented or reduced in intensity and frequency by infusing the dose over a 20-minute period. With the exception of a transient increase in SGOT, no other abnormalities were reported in the clinical chemistry parameters. Pathologic evaluations revealed a dose-related reaction at the site of injection, characterized by pleocellular infiltrates, fibrin, or organizing thrombi. At higher doses, the severity progressed to include acanthosis, epidermal necrosis, and vasculitis. Fibrin thrombi were also observed in the lung and myocardium, and were believed to be a result of the reaction at the injection site (platelet counts and coagulation indices were reported to be within normal limits).

Twenty-eight day, repeated-dose oral toxicity studies have been conducted in rats at doses of 20, 40, and 80 mg/kg/day, and in rhesus monkeys at doses of 3, l0, and 30 mg/kg/day (in comparison to placebo). In preclinical animal safety studies, no detectable evidence of systemic toxicity was observed in rats receiving oral doses up to 80 mg/kg/day for 28 days. In cynomolgus monkeys, oral doses of 3 mg/kg/day for 28 days showed no signs of systemic toxicity; however, signs of phototoxicity were observed with 10 and 30 mg/kg/day. In both an Ames test and an *in vitro* cytogenic assay, hypericin has been shown to be non-mutagenic. In the monkey study, skin reactions including bullae, erythema, and scratching were observed in animals receiving 10 and 30 mg/kg/day. This reaction is thought to represent the known phototoxic effects of hypericin. The average plasma concentrations in this study have been reported to be 0.5 µg/mL at 3 mg/kg/day, 3.3 µg/mL at 10 mg/kg/day, and 15 µg/ml at 30 mg/kg/day. No other toxic effects were reported (see IDB).

In addition to systemic toxicity studies described above, a 28-day dermal toxicity study was undertaken in rabbits with hypericin combined with fluorescent light treatment (see IDB). The purpose of this study was to determine the toxicity potential of hypericin administered twice-weekly to the dorsal area of rabbits at doses of 10, 20 and 100 µg/dose in Hydrophilic Ointment USP followed by fluorescent light treatment 24 hours later. A dose-related response was observed in the incidence of erythema, edema and desquamation among animals receiving 10, 20 or 100 µg/dose of hypericin and light treatment compared to animals receiving the placebo

vehicle and light treatment. Atonia was seen only at 20 and 100 µg/dose; fissuring was observed at only 100 µg/dose but eschar formation was not observed in any group. The only finding in the group receiving the placebo vehicle and light treatment was very slight erythema, which was seen intermittently in all animals in this group. The dermal effects observed with hypericin ointment in this group were not severe and seemed to resolve with time.

Dermal application of hypericin had no apparent effects on clinical pathology results. There were test material-related findings upon anatomical pathology examination of the skin. Macroscopically, one of three or two of three animals from the group administered 20 and 100 µg/dose, respectively, had observations in the treated skin. Microscopically, treated skin had epithelial hyperplasia and increase in inflammatory cells. Animals administered 100 µg/dose had the most severe changes and females were more severely affected than males. Minimal hyperplasia and increased inflammatory cells could be attributed to light treatment of sites treated with placebo vehicle alone. Urinary bladder calculi were more common at the higher dose groups especially in males treated with 100 µg/dose. Whether the increase in calculi was a test-material-related effect is uncertain.

5.4.4 Pharmacokinetics

The PK of hypericin following IV bolus administration has been investigated in mice (4.5 mg/m^2), rhesus monkeys (2.5 mg/kg), and cynomolgus monkeys (2 mg/kg). The average elimination half-life was reported to be 36.7 hours in the cynomolgus monkey, 40.3 hours in the mouse, and 55.8 hours in the rhesus monkey.

5.5. Prior Clinical Trials

5.5.1 Systemic Hypericin

To date, six (6) clinical trials have been conducted and/or initiated with orally and intravenously administered hypericin. These trials include:

(1) A bioavailability study in 10 healthy subjects,

(2 & 3) Two trials (ACTG 150 and ACTG 258) sponsored by the National Institute of Allergy and Infectious Disease [redacted]

(4) A dose determining study after daily oral administration for 28 days in HIV-infected patients to determine the maximum tolerated dose (MTD),

(5) A trial for hepatitis C patients to determine the anti-HCV activity after 2 months of oral hypericin, and

(6) A clinical trial for patients with malignant brain gliomas treated for three months with oral hypericin.

A single-dose bioavailability study was conducted in 10 healthy subjects. Five (5) subjects received 1.25 mg/kg orally and 0.25 mg/kg intravenously while the other five (5) subjects received 2.0 mg/kg orally and 0.375 mg/kg intravenously. Each subject received one (1) IV dose,

one (1) oral dose under fasting conditions, and one (1) oral dose following a standard fatty breakfast. The doses were administered in random order, and each dose was separated by a 1-week washout period. Some individuals who received oral hypericin in the first week developed considerable cutaneous discomfort within hours of being exposed to light. A few of these individuals developed this reaction after only a few minutes of sun exposure. After this experience, subjects took appropriate precautions to minimize sunlight exposure and, as a result, experienced less symptomatology.

In ACTG 150, IV hypericin was administered to 27 HIV-infected patients at three (3) dose levels (0.25 mg/kg two times weekly, 0.5 mg/kg two times weekly, and 0.25 mg/kg three times weekly). Dose-limiting toxicity including painful paresthesia, cutaneous discomfort, and erythema due to photosensitization was observed at 0.5 mg/kg twice weekly. Similar symptoms were observed at 0.25 mg/kg twice weekly, but they were milder and generally did not require discontinuation of treatment. No significant changes were observed in hematology or serum chemistry panels for patients treated with hypericin with the exception of one (1) patient who developed abnormal liver function test results following the initial dose and again on re-challenge. Study ACTG 258 was initiated as a concentration-controlled study of escalating oral doses of hypericin in HIV-infected patients. The initial treatment group started at a dosage of 0.5 mg/kg once daily with the objective of producing a trough hypericin concentration in the range of 0.4 to 0.7 µg/mL. After enrolling three (3) subjects into the first dosage level (0.5 mg/kg/day), the study was placed on clinical hold after all three (3) patients developed phototoxic reactions after 6 - 8 days of treatment. The photosensitivity reactions were characterized by erythema, burning sensation and tingling and were most prominent on the face and hands, particularly when exposed to the sun. Symptoms abated after 4 - 5 days. Ibuprofen was reported to provide some benefit.

In addition to these trials, a clinical trial has been undertaken in 27 patients to determine the dose separation between anti-HIV activity and cutaneous photosensitivity. The dose-response study was carried out in HIV-infected patients after daily oral administration of hypericin for 28 days. This trial was conducted at the Vaccine Trial Centre at Mahidol University, Bangkok, Thailand. The oral dose of 0.05 mg/kg was well tolerated and 0.1 mg/kg appears to be the maximum tolerated dose in these HIV infected patients. Bioavailability of hypericin was further determined in this trial. Dose proportionality in terms of trough (C_{min}) and peak (C_{max}) concentrations and area under the serum concentration-time curves was manifested with the 0.05 and 0.10 mg/kg doses. The mean biologic half-life of hypericin in the HIV-infected patients was about 20 hours.

All subjects but one who received the 0.05 mg/kg dose completed 28 days of dosing. Four (4) of eleven (11) who received 0.05 mg/kg dosage complained of mild burning sensation. Two (2) patients who received 0.16 mg/kg were withdrawn from the study due to severe burning sensation; one (1) of these two (2) developed erythema which disappeared within 7 days of stopping the drug. Nine (9) of twelve (12) patients who received 0.10 mg/kg had mild photosensitivity symptoms and five (5) of twelve (12) had mild hyperesthesia on exposure to room temperature water.

Additionally, a clinical trial was undertaken with hypericin in forty-two (42) patients with malignant brain gliomas using oral doses of hypericin (0.05 to 0.50 mg/kg) administered once daily for up to three (3) months. There were ten (10) patients who were deemed "responders" and these patients were continued on drug therapy under 'compassionate use". Of the ten (10) responders, four (4) patients continued on the drug beyond 17.5 months up to 45 months. A summary of the Adverse Events (AE) can be found in the Investigator's Drug Brochure (IDB). Phototoxicity associated with mild urticaria, erythema, itching and redness on face and hands were the majority of symptoms. Heat exhaustion and facial sunburn were definitely associated with hypericin therapy. Elevated LDH, seizure and blood clot to right leg were observed in separate patients and deemed "possibly related to drug".

Another clinical study has been completed in patients infected with hepatitis C virus at 0.05 mg/kg and 0.1 mg/kg for up to two (2) months of daily dosing with hypericin. Twelve (12) subjects consisting of ten (10) men and two (2) women ranging in age from 36 to 66 years were entered into the 0.05 mg/kg dose level; seven (7) subjects consisting of five (5) men and two (2) women ranging in age from 40 to 53 years were entered in the 0.10 mg/kg dose level. At the 0.05 mg/kg dosage level, eight (8) of twelve (12) subjects treated and at the 0.10 mg/kg dosage level, all seven (7) subjects experienced at least one (1) AE which was a photosensitivity reaction. There were four (4) different types of photosensitivity reactions - namely, paresthesias, dermatitis, darkened coloration of exposed skin and pruritic nodules. One (1) subject experienced sleepiness which was deemed "possibly related" to drug therapy.

Serial blood and urine specimens were obtained during the study to monitor the subjects for laboratory abnormalities. For most subjects, laboratory values remained fairly stable over the course of the study. There were no laboratory-related Grade 3 (severe) AEs for either dosage group and no subject had to withdraw because of laboratory abnormalities. Five (5) subjects complained of chronic fatigue. Four (4) subjects (two per dosage group) had intermittent upper quadrant abdominal pain. All but two (2) subjects had mild-to-moderate elevations of serum alanine aminotransferase at baseline (median 70 U/L; range 30 to 158 U/L). There were no significant changes in these values with hypericin dosages.

5.5.2 Topical Hypericin

In a Phase 1 trial of topical SGX301 (synthetic hypericin), 15 healthy subjects had SGX301 applied to the skin in concentrations of 0.02% to 0.5% synthetic hypericin in hydrophilic ointment under occlusion for 2 to 24 hours followed by exposure to 20-watt fluorescent lights yielding a total exposure ranging from 4 to 8 Joules/cm^2. Delayed erythema was observed in one-third of subjects using 0.1% SGX301 under occlusion for 24 hours following exposure to 4 Joules/cm^2 of light, while both immediate and delayed erythema occurred in all subjects with 0.1% SGX301 under occlusion for 24 hours followed by administration of 8 Joules/cm^2 of light. No erythema was observed using 0.02% SGX301.

In a Phase 2 trial of topical SGX301 for CTCL and plaque psoriasis, a total of 12 patients with early stage CTCL and 12 patients with plaque psoriasis had three (3) different lesions treated with either placebo or two (2) different strengths of SGX301 ointment (0.10% and 0.25% synthetic hypericin) followed the next day by exposure to visible light in the form of cool white

fluorescent tubes. Following six (6) weeks of twice-weekly therapy of 12 low dose treated lesions, 5 (41.7%) responded to SGX301 treatment. Of 11 high-dose treated lesions, 6 (54.5%) responded to SGX301 treatment. Of 12 placebo ointment treated lesions, 1 (8.3%) resolved with only placebo treatment, and the difference in response was statistically significant ($p < 0.04$). Among psoriasis patients, 5 of 12 (41.7%) total low dose treated lesions responded to SGX301 treatment; 5 of 12 (41.7%) total high dose treated lesions responded to SGX301 treatment; and 0 of 12 (0%) placebo ointment treated lesions resolved with only placebo treatment, and the difference in response was statistically significant ($p < 0.02$). Findings with both the CTCL patients and psoriasis patients indicate an active treatment effect of SGX301 [48].

The results of this study support the conclusion that:

(a) SGX301 topical phototherapy has a beneficial treatment effect on CTCL and psoriasis, and

(b) The benefit appears to be maximized over a certain concentration-treatment time range.

Importantly, no drug related or potentially drug related AEs were reported for these patients other than mild phototoxicity at the treatment site. This AE rapidly resolved upon lowering the time for light exposure or skipping of an application and light treatment episode.

Based on the safety profile obtained in the Phase 1 trial with topical SGX301 and light treatment coupled with the dose related, statistically significant clinical results in the treatment of CTCL, and the demonstrated safety from the Phase 2 trial, a pivotal Phase 3 trial with topical SGX301 and phototherapy is warranted as described in this protocol to determine clinical efficacy and safety in CTCL patients. The concentration of SGX301 and the dose of light are based upon the results obtained from the Phase 1 trial in normal subjects and from the Phase 2 trial in patients with CTCL.

5.6. Current Trial

This study will evaluate the effect of SGX301 (0.25% synthetic hypericin) associated with fluorescent-light bulb visible light on skin lesions in patients with early mycosis fungoides (CTCL Stages IA, IB, and IIA). This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB), and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

This study will be conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice E6 (ICH-GCP) and the applicable regulatory requirements as specified in the U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46 and 21 CFR including parts 50 and 56 concerning informed consent and IRB regulations in 21 CFR 312).

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary objective

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 in patients (Cycle 1) with patch/plaque phase CTCL to induce a treatment response in the 3 index lesions as defined by 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.

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 and to extend the data on the response rate of SGX301 in untreated lesions.

Cycle 3: In this optional, open-labeled 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.

6.2. Secondary objectives

Secondary objectives will include the following:

[redacted]

To evaluate the ability of topical SGX301 and visible light in patients with patch/plaque phase CTCL to induce a Complete Response (CAILS score of 0) after each cycle.

To evaluate the ability of topical SGX301 and visible light in patients with patch/plaque phase CTCL to induce a treatment response (Complete or Partial Response of ≥50% improvement in CAILS score) after Cycles 2 and 3.

To evaluate the degree of improvement of the index lesions induced by topical SGX301 and visible light in patients with patch/plaque phase CTCL during Cycles 1 and 2.

To evaluate the duration of treatment response in the index lesions induced by course of topical SGX301 and visible light in patients with patch/plaque phase CTCL.

[redacted]

Assess the safety of a 6-week course of topical SGX301 and visible light in patients with patch/plaque phase CTCL.

To evaluate the ability of the two 6 week courses of SGX301 and visible light (Cycle 2 patients who also received active drug in 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 16-week Evaluation Visit when compared to patients receiving placebo and visible light.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan: Description

Approximately 180 subjects will be enrolled into this Phase 3, placebo-controlled, double blind, multicenter study (in order to finish with 160 evaluable patients) to evaluate the efficacy and safety of topical phototherapy with SGX301 (synthetic hypericin) at a concentration of 0.25%. The primary endpoint of this study is the number of patients achieving a treatment response of 3 treated lesions (Partial or Complete Response defined as a ≥50% reduction in the CAILS score summed over the 3 index lesions when the 8-week assessment is compared to the baseline value) after undergoing a 6-week cycle of twice per week study ointment followed 18-24 hours later by fluorescent bulb visible light treatment.

Patients may undergo 3 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 unless a lesion had achieved a CR following Cycle 1 therapy.

Optional Cycle 3: All patients will receive SGX301 treatment of all of their lesions chosen by the physician and patient.

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 Joules/cm^2. The light treatment will be performed 3-4 calendar days apart (±1 day) each week (e.g., Monday/Thursday, Monday/Friday, or Tuesday/Friday).

Prior to randomization, each patient will have 3 lesions identified. These should be discrete lesions and be representative of the patient's lesions that are easily accessible for phototherapy. These lesions 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 the 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 2-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 6 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 synthetic hypericin in 1 gram of SGX301 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 the 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; GE® 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 3 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 3: 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 shall be recorded.

The study overall study design is summarized in Figure 1 and the schedule of procedures is presented in Table 4 through Table 11. These schedules assume a Tuesday/Friday schedule but other day combinations, e.g., a Monday/Thursday or Monday/Friday schedule are acceptable once the Study Staff is comfortable that the patient is capable of reliably applying study ointment and instructed to apply the drug on Sunday.

Figure 1: Study Schema

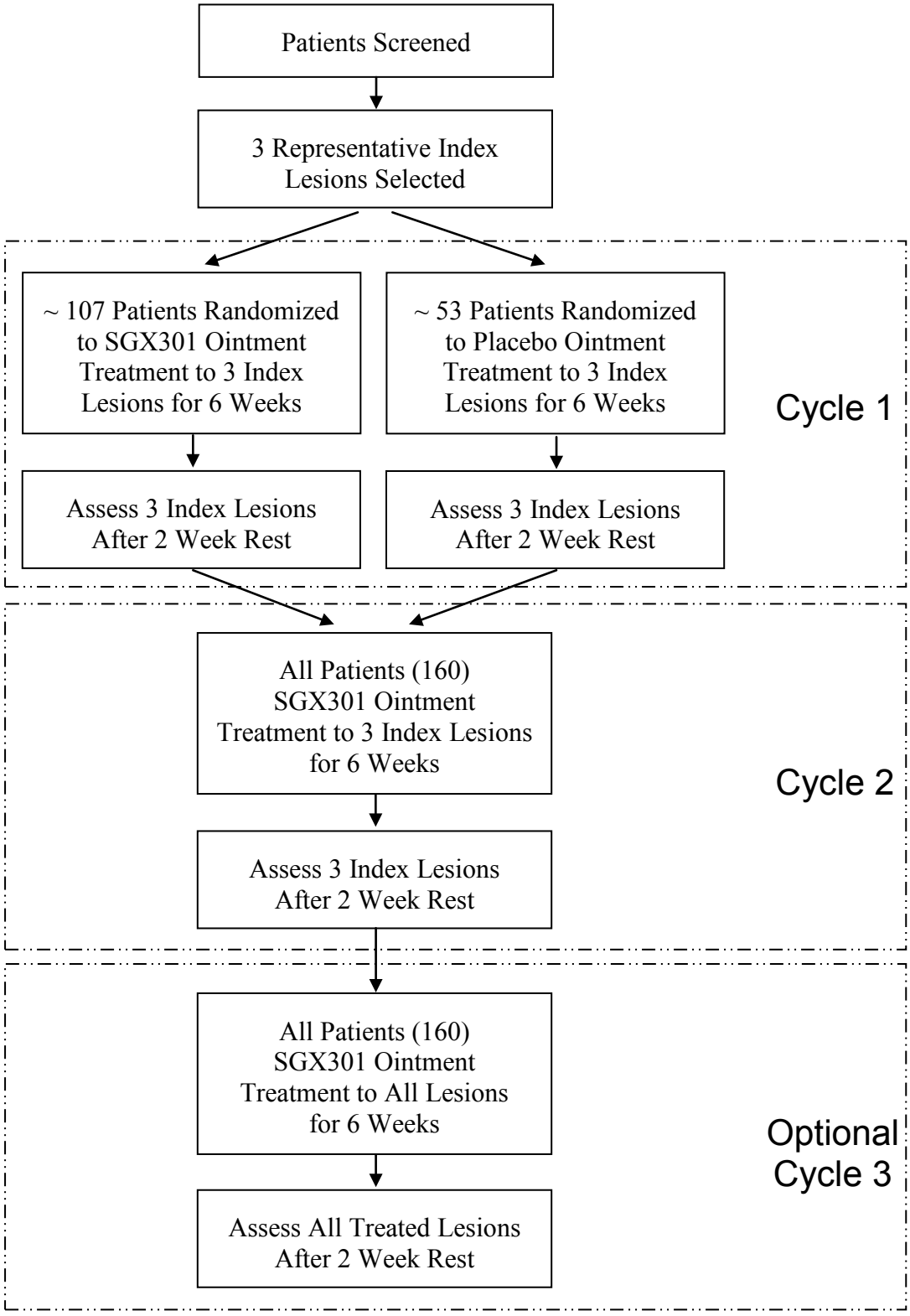


Table 4: Study Assessments: Cycle 1- Week 1 *Randomized Drug to Index Lesions*

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 5: Study Assessments: Cycle 1 - Application and Light Treatment #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
Visual lesion inspection		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 apply appropriately

Table 6: Cycle 1 - Weeks 7 and 8 *Treatment Evaluation*

Evaluation	Week 7 Rest Period	14 (±2) Days After Last Treatment
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 7: Cycle 2 - Light Treatment #13-24 *All Patients 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 only for those lesions that were a complete response after Cycle 1.

Table 8: 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
Distribution of Cycle 3 drug		X

Table 9: Optional Cycle 3 - Week 17 through 22 *All Patients 0.25% SGX301 Ointment to All Treated 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 Cycle 3 (Weeks 21 and 22 and Administration 33 – 36)

Table 10: 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 11: 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
Vital signs	X	X	X	X	X	X
Physical exam	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

7.2. Specific Assessments

7.2.1 Laboratory Assessments

7.2.1.1. Screening Tests

If necessary, a blood sample will be obtained at the screening visit that will occur within 3 weeks of starting the study medication. Laboratory tests will be performed by the local laboratory. Results of these tests must be reviewed prior to starting the patient on study medication.

- Serum pregnancy test (human chorionic gonadotropin [HCG]) for all women

7.2.1.2. Hematology Tests

The hematology panel will be performed at the Central Laboratory on samples collected at Baseline (Day 1), Week 8, Week 16, and Week 24 (provided the patient elects to continue into Cycle 3). 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 immature granulocyte count
- Percent and absolute lymphocyte count
- Percent and absolute monocyte count
- Percent and absolute eosinophil count
- Percent and absolute basophil count

7.2.1.3. Clinical Chemistry Laboratory Tests

The clinical chemistry panel will be performed at the Central Laboratory on samples collected at Baseline (Day 1), Week 8, Week 16, and Week 24 (provided the patient elects to continue into Cycle 3). 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

7.2.1.4. Skin punch 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 for 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 as described in Appendix 18.4. on page 85. The stained and unstained slides will be sent to the Central Pathology Laboratory for grading and further analysis.

7.2.1.5. SGX301 Plasma Concentration Samples

During the course of the Cycle 3 (optional open label), plasma samples shall be obtained in patients within 30 minutes of completing each of the two light treatment sessions during Week 21 and Week 22 (i.e., Treatments 33, 34, 35, and 36) to determine the concentration of SGX301 in the circulation following topical application of SGX301 to all lesions. Samples will be obtained in the initial 25 patients and should all samples have undetectable hypericin levels, as expected, testing on subsequent patients will not be done.

7.2.2 Other Assessments

7.2.2.1. Medical History

Demographic information will be collected at screening and include the following information that will be recorded in the Electronic Case Report Form (eCRF):

- Birth date
- Age (calculated from the date of ICF signature minus the birth date)
- Sex

- Race
- Ethnic group

Complete medical history will be obtained at the screening visit. Details of the diagnosis of CTCL will be collected including:

- Date of diagnosis of CTCL
- Number of relapses
- Treatments received - type, duration, dates
- Date of last relapse
- Date of last therapy
- Staging of CTCL

At each clinical visit, interval medical history will be obtained and recorded.

7.2.2.2. Physical Examination and Visual Lesion Inspection

At screening, the treatment evaluation visits (Weeks 8, 16, and 24), and every month during the 6-month follow-up visits a complete physical examination will be performed and all abnormalities noted in the eCRF with particular attention for evidence of visceral organ involvement of the CTCL. Interval visual lesion inspections will be performed by qualified personnel at each clinic visit to assess all skin lesions that will be charted on a "Body Map" and new lesions noted in the eCRF.

7.2.2.3. Vital Signs

Vital signs will be collected at each clinic visit. BMI will be calculated at baseline only. Vital signs will include the following measurements:

- Heart rate
- Respiratory rate
- Temperature
- Blood pressure (sitting)
- Height (Baseline only)
- Weight

7.2.2.4. Composite Assessment of Index Lesions Severity (CAILS) Score

CAILS score will be calculated by assessing the erythema, scaling, plaque elevation and involved surface area using the grading scale shown in Table 12 for each of the 3 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 - the 3 index lesions for Cycles 1 and 2 and all treated lesions in Cycle 3.

Table 12: 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	
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

Table 12: Composite Assessment of Index Lesion Severity

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

7.2.2.5. 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 13. This assessment is designed to consider ***all cutaneous lesions***, including both index and non-index lesions.

Table 13: Physician's 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%

7.2.2.6. 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 14.

Table 14: 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%			
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.

7.2.2.7. Skin Reaction Safety Grading

Skin reactions will be evaluated before and after each light treatment. Each site of treatment shall be examined and assessed during the visit but at least 5 minutes after completion of the light treatment using the scale in Table 3 on page 32.

7.3. Visit Schedule

7.3.1 Screening

The screening visit must be done within 21 days prior to the start of the Baseline visit. Prior to starting the study medication, the results of all tests must be reviewed to assure that the patient meets all entry criteria. Procedures to be done at this visit are:

- Obtain Informed Consent Form (ICF) signature
- Assessment of entry criteria
- Complete Medical History
- Complete Physical Examination
- Vital Signs
- Laboratory Tests
  - Serum HCG pregnancy test (women only)

7.3.2 Cycle 1

7.3.2.1. Baseline Day

Patient will be seen in the clinic on the first day of treatment. The entry criteria will be reviewed and an interim medical history taken to assure that the patient meets all entry criteria. If the patient qualifies, they will undergo the following procedures:

- The 3 index lesions will be identified, labeled "1", "2", and "3", and their location recorded on the "Index Body Map", see Appendix 18.2. on page 81. Each lesion will be documented as to whether they are patch or plaque.
- A 3 mm punch biopsy will be performed on a representative area of the most representative of the 3 index lesions
- Interim Medical History
- Vital Signs
- Physical Examination
- Lesion Assessment
  - Digital photography of each of the 3 index lesions (overview and close-up) and copies sent to the Central Photography Laboratory [redacted]
  - CAILS scoring of the 3 index lesions
  - PGA assessment
  - mSWAT assessment

- Laboratory Tests
  - Hematology panel
  - Clinical Chemistry panel
- Training on drug application/bandaging
- Application of study ointment
- Application of opaque bandaging
- Distribution of blinded study ointment jars and patient information sheet (see Appendix 18.3. on page 82)

7.3.2.2. Light Treatment #1

Patients will return to the clinic 18-24 hours after the study drug was applied. Patients will undergo the following procedures and the details entered into the eCRF:

- Interim medical history including any AEs
- Visual Lesion Inspection
- Vital Signs
- Safety grading of the lesions
- Radiometer used to determine precise fluorescent light-panel emission output
- Patients are to be positioned so that the lesions are equidistant from the light panel and as close to the front of the light-panel as is comfortable. The duration of treatment is calculated from the dosimetry reading at the position of the treated lesion (see the "Visible Light Treatment Manual" for details and Appendix 18.1. on page 80 for calculation of duration of treatment based on the light output measured at the position of the lesion farthest from the light panel with the supplied light meter). The patient should be positioned as consistently as possible.
- During the clinic visit, but at least 5 minutes after completion of the light treatment therapy, the lesions will again undergo safety grading

7.3.2.3. Application Day 2

If the site personnel determine that additional patient training is needed, patients will return to the clinic 2 calendar days after light Treatment #1. Patients will undergo the following procedures:

- Interim medical history including any AEs
- Vital Signs
- Training on drug application/bandaging
- Application of study ointment

- Application of opaque bandaging

7.3.2.4. Light Treatment #2

Patients will return to the clinic 18-24 hours after the study drug was applied. Patients will undergo the following procedures and the details entered into the eCRF.

- Interim medical history including any AEs
- Visual Lesion Inspection
- Vital Signs
- Safety grading of the lesions
- Patients are to be positioned so that the lesions are equidistant from the light panel and as close to the front of the light-panel as is comfortable. The duration of treatment is calculated from the dosimetry reading at the position of the treated lesion (see the "Visible Light Treatment Manual" for details and Appendix 18.1. on page 80 for calculation of duration of treatment based on the light output measured at the position of the lesion farthest from the light panel with the supplied light meter). The patient should be positioned as consistently as possible.
- During the clinic visit, but at least 5 minutes after completion of the light treatment therapy, the lesions will again undergo safety grading

7.3.2.5. Application Days 3-12

Patients will return to the clinic for study drug application until the Study Staff are comfortable that the patient will consistently and reliably apply the study medication. At that time, they will be instructed to apply the study drug to the index lesions 18-24 hours prior to their scheduled light treatments. They will be instructed to record the time of the self-administration of the ointment. When seen in the clinic, patients will undergo the following procedures and the details entered into the eCRF:

- Interim medical history including any AEs
- Vital Signs
- Training on drug application/bandaging
- Application of study ointment
- Application of opaque bandaging

7.3.2.6. Light Treatments #3-12

Patients will receive their light treatment 18-24 hours after the study drug was applied. At the discretion of the PI, the light dose may be increased by 1 Joule/cm^2 each visit provided the Skin Erythema Toxicity grade is ≤1, or may be held at the same dose. If the Skin Erythema Toxicity grade is >1, the light dose should be reduced by 1 Joule/cm^2 or can be held at the current dose at

the PIs discretion. At each light treatment, patients will undergo the following procedures and the details entered into the eCRF:

- Interim medical history including any AEs
- Visual lesion inspection
- Vital Signs
- Safety grading of the lesions
- Patients are to be positioned so that the lesions are equidistant from the light panel and as close to the front of the light-panel as is comfortable. The duration of treatment is calculated from the dosimetry reading at the position of the treated lesion (see the "Visible Light Treatment Manual" for details and Appendix 18.1. on page 80 for calculation of duration of treatment based on the light output measured at the position of the lesion farthest from the light panel with the supplied light meter). The patient should be positioned as consistently as possible.
- During the clinic visit, but at least 5 minutes after completion of the light treatment therapy, the lesions will again undergo safety grading.

7.3.2.7. Cycle 1 Assessment

The index lesions will be assessed 14±2 days after the last light treatment (Treatment #12). Patients will have the following procedures:

- A 3 mm punch biopsy will be performed from a representative area of the same index lesion that was biopsied at baseline that is at least 1 cm from the original biopsy site.
- Interim Medical History including any AEs
- Vital Signs
- Physical Examination
- Lesion Assessment
  - Digital photography of each of the 3 index lesions (overview and close-up) and copies sent to the Central Photography Laboratory [redacted]
  - CAILS scoring of the 3 index lesions
  - PGA assessment
- Laboratory Tests
  - Hematology panel
  - Clinical Chemistry panel
  - HCG pregnancy test (females only)
- Distribution of unblinded SGX301 ointment jars for Cycle 2

7.3.3 Cycle 2

Lesions that have a complete response at the end of Cycle 1 are <u>NOT</u> treated in Cycle 2.

7.3.3.1. Application Days 13-24

Cycle 2 is to start the week after the Cycle 1 Week 8 visit. Patients will be instructed to apply the study drug to the index lesions 18-24 hours prior to their scheduled light treatments.

7.3.3.2. Light Treatments #13-24

Patients will receive their light treatment 18-24 hours after the study drug is applied. **The light dosage for Cycle 2 will start at 5 Joules/cm^2 regardless of where the patients light dose was at the completion of Cycle 1**. At the discretion of the PI, the light dose may be increased by 1 Joule/cm^2 per visit provided the Skin Erythema Toxicity grade is ≤1 or may be held at the same dose. If the Skin Erythema Toxicity grade is >1, the light dose should be reduced by 1 Joule/cm^2 or can be held at the current dose at the PIs discretion. At each light treatment, patients will undergo the following procedures and the details entered into the eCRF:

- Interim medical history including any AEs
- Visual lesion inspection
- Vital Signs
- Safety grading of the lesions
- Patients are to be positioned so that the lesions are equidistant from the light panel and as close to the front of the light-panel as is comfortable. The duration of treatment is calculated from the dosimetry reading at the position of the treated lesion (see the "Visible Light Treatment Manual" for details and Appendix 18.1. on page 80 for calculation of duration of treatment based on the light output measured at the position of the lesion farthest from the light panel with the supplied light meter). The patient should be positioned as consistently as possible.
- During the clinic visit, but at least 5 minutes after completion of the light treatment therapy, the lesions will again undergo safety grading.
- If patients elect to continue participation into Cycle 3, all treatments applied to the non-index lesions need to be stopped at least 2 weeks prior to the start of Cycle 3.
- At Week 10 (2 weeks into Cycle 2), any index lesion with a complete response at 8 weeks will be scored using the CAILS scale and digital photographs taken. Lesions that have a complete response at the end of Cycle 1 are NOT treated in Cycle 2.

7.3.3.3. Cycle 2 Assessment

The index lesions will be assessed 14±2 days after the last light treatment (Treatment #24). Patients will have the following procedures:

- Interim Medical History including any AEs

- Vital Signs
- Physical Examination
- Lesion Assessment
  - Digital photography of each of the 3 index lesions (overview and close-up) and copies sent to the Central Photography Laboratory [redacted]
  - CAILS scoring of the 3 index lesions
  - PGA assessment
  - mSWAT assessment of the extent of disease
- Laboratory Tests
  - Hematology panel
  - Clinical Chemistry panel
- Distribution of unblinded SGX301 ointment jars for Cycle 3 to patients electing to continue to Cycle 3

7.3.4 Cycle 3

7.3.4.1. Application Days 25-36

Cycle 3 visits will start the week following the Cycle 2 Week 8 visit. Patients will be instructed to apply the study drug to all treated lesions 18-24 hours prior to their scheduled light treatments.

7.3.4.2. Light Treatments #25-36

Patients will receive their light treatment 18-24 hours after the study drug is applied. The starting dose of the light therapy should be the maximum well tolerated dose seen during Cycle 2. At the discretion of the PI, the light dose may be increased by 1 Joule/cm^2 per visit provided the Skin Erythema Toxicity grade is ≤1 or can be held at the current dose at the PIs discretion. If the Skin Erythema Toxicity grade is >1, the light dose should be reduced by 1 Joule/cm^2. At each light treatment, patients will undergo the following procedures and the details entered into the eCRF:

- Interim medical history including any AEs
- Visual lesion inspection
- Vital Signs
- Safety grading of the lesions
- Patients are to be positioned so that the lesions are equidistant from the light panel and as close to the front of the light-panel as is comfortable. The duration of treatment is calculated from the dosimetry reading at the position of the treated lesion (see the "Visible Light Treatment Manual" for details and Appendix 18.1. on page 80 for calculation of duration of treatment based on the light output measured at the position

of the lesion farthest from the light panel with the supplied light meter). The patient should be positioned as consistently as possible.

- During the clinic visit, but at least 5 minutes after completion of the light treatment therapy, the lesions will again undergo safety grading.

7.3.4.3. Cycle 3 Assessment

Lesions will be assessed 14±2 days after the last light treatment (Treatment #36). Patients will have the following procedures:

- Interim Medical History including any AEs
- Vital Signs
- Physical Examination
- Lesion Assessment
  - Digital photography of each of the lesions (overview and close-up) and copies sent to the Central Photography Laboratory [redacted]
  - CAILS scoring of all index lesions
  - PGA assessment
  - mSWAT assessment of the extent of disease
- Laboratory Tests
  - Hematology panel
  - Clinical Chemistry panel
- SGX301 Blood levels
  - Plasma levels of SGX301 will be obtained 30 minutes after the light treatment at each of the 4 treatment session in the last 2 weeks of Cycle 3 (Weeks 21 and 22 during Administration 33 – 36)

7.3.5 Follow-up visits

Patients will be seen in clinic every 4 weeks ±5 days for 6 months after the last assessment (either Cycle 2 or Cycle 3). At each visit the follow procedures will be done:

- Interim Medical History including any AEs
- Vital signs
- Physical Examination
- Lesion Assessment
  - Digital photography of each of the 3 index lesions (overview and close-up) and copies sent to the Central Photography Laboratory [redacted]

- CAILS scoring of the 3 index lesions
- PGA assessment
- mSWAT assessment of the extent of disease
- Identification of the number of new lesions since the last clinic visit

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Patients enrolled into this trial must meet **all** of the following criteria:

1. ≥18 years of age.
2. Subjects must have a clinical diagnosis of cutaneous T-cell lymphoma (CTCL, mycosis fungoides), Stage IA, Stage IB, or Stage IIA.
3. Subjects with a minimum of three (3) evaluable, discrete lesions.
4. Subjects willing to follow the clinical protocol and voluntarily give their written informed consent.
5. Female subjects not pregnant nor nursing and willing to undergo a pregnancy test within 30 days prior to treatment initiation.
6. Subjects must be willing to refrain from sunbathing for the duration of the study.

8.2. Subject Exclusion Criteria

Patient with any of the following criteria **cannot** be enrolled into the trial:

1. History of sun hypersensitivity and photosensitive dermatoses including porphyria, systemic lupus erythematosus, Sjögren's syndrome, xeroderma pigmentosum, polymorphous light eruptions, or radiation therapy within 30 days of enrolling.
2. History of allergy or hypersensitivity to any of the components of SGX301.
3. Pregnancy or mothers who are breast-feeding.
4. Males and females not willing to use effective contraception.
5. Unhealed sunburn.
6. Subjects receiving topical steroids or other topical treatments (e.g., nitrogen mustard) on index lesions for CTCL within 2 weeks.
7. Subjects receiving systemic steroids, psoralen UVA radiation therapy (PUVA), narrow band UVB light therapy (NB-UVB) or carmustine (BCNU) or other systemic therapies for CTCL within 3 weeks of enrollment.
8. Subjects who have received electron beam irradiation within the potential treatment field within 3 months of enrollment.
9. Subjects with a history of significant systemic immunosuppression.
10. Subjects taking other investigational drugs or drugs of abuse within 30 days of entry into this study.

11. Subjects whose condition is spontaneously improving.
12. Subjects with tumor stage or erythrodermic CTCL (stages IIB-IV).
13. Subject has any condition that, in the judgment of the PI, is likely to interfere with participation in the study.
14. Prior participation in the current study.

8.3. Patient Withdrawal Criteria

Patients have the right to withdraw from this trial at any time (as described in the informed consent document) without prejudice to further care. An investigator may withdraw a patient from the study at any time for any of the following reasons:

- The patient withdraws his/her consent or refuses follow-up evaluations.
- The patient is lost to follow-up and will not attend further study visits.
- The investigator determines that further participation would be detrimental to the patient's health or well-being.
- The patient fails to comply with the study requirements so as to cause harm to self or seriously interfere with the validity of the study results.
- The female patient becomes pregnant during the treatment period. In this case, treatment should be halted and the patient followed until the end of the pregnancy. If a child is born, the infant should be followed through at least 6 months of age.
- At the discretion of the site investigator if he/she feels that it is in the best medical interest of the patient.

Patients withdrawn from the study will have as many of the trial assessments completed as the patient permits including blood tests and lesion evaluations.

Patients withdrawn from the trial will not be replaced but it is anticipated that inclusion of 180 patients will provide a minimum of evaluable 160 patients.

8.4. Treatment Interruption in the Event of Phototoxicity

For patients experiencing phototoxicity, defined by an erythema score (Table 3: Skin Phototoxicity Grading on page 32) of Grade 3 or 4, therapy will be discontinued for one week, or until the phototoxic reaction has subsided (Grade 1 or better), followed by resumption of therapy. If the phototoxic reaction has not subsided by two weeks, the patient *may* be removed from the study at the discretion of the investigator.

8.5. Termination of the Study

The study may be terminated early for any of the following reasons:

- The US Food & Drug Administration (FDA) or Data Monitoring Committee (DMC) requests termination of the study.
- It has been determined that the risk level associated with the experimental drug is significant and warrants termination of the study.
- The Sponsor, for reasons other than safety, may terminate the study at any time by written notice of intended termination provided at least thirty (30) days prior to termination.
- The investigator or IRB, for reasons other than safety, may terminate participation of this site in the study by written notice of intended termination provided at least thirty (30) days prior to termination.
- Any other clause described in the individual site Study Agreement (e.g., if Good Clinical Practices or other regulatory procedures are not followed; if enrollment rate is not sufficient to meet study goals).

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

During Cycle 1, patients will be randomized 2:1 to either SGX301 (0.25% synthetic hypericin) ointment or an identically appearing placebo ointment. Patients will apply the ointment twice a week to the **3 index lesions**, minimizing application to other skin areas, and cover the area with opaque bandaging. Training for correct application and bandaging will be given during the first week and continue until the site staff is confident that the patient can and will appropriately administer the drug themselves. The lesions will then be exposed to fluorescent light treatment 18-24 hours later. These procedures will be continued for 6 weeks (12 treatments) and, after a 2-week rest period, the response to treatment will be assessed. It is important to note that the main purpose of covering the lesions is to prevent exposure to light. Therefore, any method of covering the lesions such as bandages, wraps, clothing, etc. is acceptable if it creates an opaque barrier over the treated area and is kept in place until it is time for the light therapy. Soligenix will provide a number of different options for covering the lesions to the sites during start up. Because the body habitus and lesion location is different for each patient, the best method of covering the lesions may differ from patient to patient.

During Cycle 2, all patients will be treated with SGX301. Patients will apply the ointment twice a week to the **index lesions that did NOT achieve a complete response following Cycle 1 therapy**, minimizing application to other skin areas, and cover the area with opaque bandaging. The lesions will then be exposed to fluorescent light treatment 18-24 hours later. These procedures will be continued for 6 weeks (12 treatments) and the response to treatment will be assessed after a 2-week rest period.

During the optional Cycle 3, all patients will be treated with SGX301. Patients will apply the ointment twice a week to **all lesions selected by the physician and patient**, minimizing application to other skin areas, and cover the area with opaque bandaging. The lesions will then be exposed to fluorescent light treatment 18-24 hours later. These procedures will be continued for 6 weeks (12 treatments) and the response to treatment will be assessed after a 2-week rest period.

Patients will be followed every 4 weeks for Weeks 24 to 48 but no study medication given during this period.

9.2. Concomitant Medications

Prior medications, going back 3 weeks from the screening date (systemic and topical), will be collected at the screening visit. Concomitant medications (systemic and topical) will be collected at each clinic visit.

Topical steroids can be applied to any ***non-index*** lesion if they are at least 1 cm away from all index lesions during Cycles 1 and 2. Treatments applied to non-index lesions need to be halted a minimum of 2 weeks prior the start of Cycle 3, if the patient intends to participate in Cycle 3.

The following drugs are **not allowed on index lesions within 2 weeks** of enrollment or during the study:

- Topical steroids (including 1% hydrocortisone cream or ointment) of the 3 index lesions.
- Topical Nitrogen mustard of the 3 index lesions

The following drugs are **not allowed within 3 weeks** of enrollment or during the study:

- Systemic steroids
- Psoralen UVA radiation therapy (PUVA)
- Narrow band-UVB
- Carmustine (BCNU)
- Other systemic therapies for CTCL

The following drugs are **not allowed within 30 days** of enrollment or during the study:

- Investigational drugs
- Drugs of abuse
- Agents known to cause photosensitization
    - The following drugs cannot be given within 30 days of enrollment:
        - 5-fluorouracil
        - Vinblastine
        - Dacarbazine
        - ALA or 5-aminolevulinic acid
        - Methyl-5-aminolevulinic acid
    - The following drugs can only be used if there have been no phototoxic reactions to the stable dose of the drug after a minimum of 14 days of treatment:
        - Quinolone antibiotic
        - Tetracycline
        - Sulfonamide
        - Diphenhydramine
        - Quinine
        - Chloroquine
        - Hydroxychloroquine
        - Amiodarone

- Systemic nifedipine
- Quinidine
- Diltiazem
- Furosemide
- Thiazides
- Sulfonylureas
- Isotretinoin
- Acitretin
- Phenothiazines
- Tricyclic antidepressants

9.3. Treatment Compliance

Patients will be trained in the proper application of the study drug. This initial applications will be done under supervision of study personnel and continue until they are comfortable that the patient can appropriately apply the ointment. Patients will be questioned prior to the light treatment to assure that the drug was applied and it was applied 18-24 hours earlier.

9.4. Randomization and Blinding

For Cycle 1, patients will be randomized 2:1 to SGX301:placebo using a randomization code generated by an independent statistician. Randomization will be performed using an Interactive Web Response System in a double-blind fashion. Both SGX301 and the identically appearing placebo ointments will be packed in the same plastic screw-top jars and labeled identically with a unique jar identification number.

Patients will be stratified at randomization by CTCL Stage (IA, IB, and IIA) and site.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

SGX301 will be supplied in plastic screw-top jars containing 25 grams of 0.25% hypericin (2.5 mg/gram) ointment. Jars are stored at room temperature (15-30°C). Placebo will also be supplied in plastic screw-top jars containing 25 grams of USP Hydrophilic Ointment tinted to the same color as the SGX301 ointment and stored at room temperature.

10.5. Administration

The patient will be instructed to apply study drug ointment to the designated MF lesions twice weekly. SGX301 or an identical placebo ointment will be applied to cover the entire surface of each lesion. However, application to uninvolved skin should be as limited as possible. The amount of ointment used for each application will be dependent upon the amount of lesion surface area. The patient should wear disposable gloves and wash their hands after applying the study ointment. If someone else helps apply the study ointment, they should wear disposable gloves. If the medicine gets on the skin of other people, they will be instructed to wash with soap and water.

10.6. Study Drug Accountability

The PI must ensure that all drug supplies are kept under lock and key with access limited to those authorized by the investigator. The PI must maintain accurate records of the receipt of all study medication shipped by the Sponsor, including date received, lot number, expiration/re-test date, amount received and disposition of all study medication. Current dispensing records will be maintained and include date and amount of medication dispensed, initials of subjects receiving the medication, and any amount of medication not used or returned (or lost) by the subject. All remaining medication not required by regulation to be held by the clinical facility, must be destroyed following all appropriate regulatory guidelines or returned to the Sponsor immediately after the study is completed. Any lost, spilled or missing drug must be documented.

10.7. Study Drug Handling and Disposal

Disposable gloves should be used when applying the drug to skin lesions and after applying the ointment, hands and any areas receiving other unintended ointment should be washed with soap and water.

11. ASSESSMENT OF EFFICACY

11.1. Disease Assessment

11.1.1 Composite Assessment of Index Lesion Severity (CAILS)

The complete CAILS assessment scoring system is presented in Table 12 on page 42. 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 that are scheduled to be treated will be evaluated prior to Cycle 3 (Week 16) and then again at the end of Cycle 3 (Week 24). Each lesion will be scored using criteria shown in Table 12.

The total CAILS score will be calculated by adding the scores of each the evaluated lesion together (the same 3 lesions in Cycles 1 and 2, and all of the lesions at the baseline and end of Cycle 3). The change in CAILS score will be calculated by the ratio of the CAILS score at the end of the cycle to the CAILS score at the beginning of the cycle.

11.1.2 Skin Reaction Safety Grading

Skin reactions will be evaluated before and after each light treatment. Each site of light treatment shall be examined and assessed at least 5 minutes after completion of the light treatment and graded using the scale shown in Table 3 on page 32.

11.1.3 Classification of Treated Skin Lesion Response

Based on the ISCL/USCL/EORTC criteria [56], the clinical categorization will be as given in Table 15 using the CAILS score ratio as the measure of skin response.

Table 15: 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.

11.1.4 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 14 on page 44.

11.1.5 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 13 on page 43. This assessment is designed to consider all cutaneous lesions, including both index and non-index lesions.

11.1.6 Digital Photography

All investigators will be carefully trained prior to enrolling patients so that high quality and uniform digital photographs will be obtained throughout the entire study. At the start of each treatment cycle and at the 8-week evaluation point, overview photographs will be obtained and all treated lesions will be evaluated by close-up digital photography. Prior to Cycle 2 and at Week 16 all treated lesions will be evaluated by overview and close-up digital photography. Prior to Cycle 3 and at Week 8 of Cycle 3, close-up and overview photographs will also be obtained for evaluation of the treatment.

11.1.7 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 for 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 as described in Appendix 18.4. on page 85. 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 16.

Table 16: Grading of Biopsy

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

11.2. Endpoints

11.2.1 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% (≥50% reduction in the CAILS score) of treated lesions.

11.2.2 Secondary Efficacy Endpoints

The secondary endpoints for this trial are given below. The relative priority ranking of these endpoints is provided in the SAP.

11.2.2.1. 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%) for that lesion at the Cycle 1 evaluation visit (Week 8) compared to its CAILS score at baseline.
- Percent of patients achieving a Complete Response of treated lesions (yes/no) defined as a CAILS score of 0 at the Cycle 1 evaluation visit (Week 8).
- The number of index lesions with a Complete Response defined as a CAILS score of 0 for that lesion at the Cycle 1 evaluation visit (Week 8).

[redacted]

[redacted]

11.2.2.2. 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 2 cycles of SGX301) and patients in the placebo treatment group during Cycle 1 (whose index lesions will have been treated with 1 cycle of SGX301):

- Percent of patient 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 the start of Cycle 2 (Week 8).
- The number of index lesions with a Partial or Complete Response defined as a ≥50% reduction in the CAILS score (CAILS ratio ≤50%) for that lesion at the Cycle 2 evaluation visit (Week 16) compared to its CAILS score at the start of Cycle 2 (Week 8).

[redacted]

- The percent of patients who completed Cycle 2 and received active drug in Cycle 1 who achieved a Partial or Complete Response (yes/no) of the treated lesions defined as a ≥50% reduction in the total CAILS score for the 3 index lesions compared to the percent of patients who received placebo in Cycle 1 and achieved a Partial or Complete Response (yes/no) of the treated lesions defined as a ≥50%reduction in the total CAILS score for the 3 index lesions.

11.2.2.3. 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]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- Percent of patient achieving a Partial or Complete Response (yes/no) defined as a ≥50% reduction in the CAILS score (CAILS ratio ≤50%) 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).
- The number of the **3 index lesions** with a Partial or Complete Response defined as a ≥50%reduction in the CAILS score for that lesion at the Cycle 3 evaluation visit (Week 24) compared to its CAILS score at the start of Cycle 3 (Week 16).
- [redacted]
- Examine the relative impact on plaque versus patch responses.

12. ASSESSMENT OF SAFETY

Timely, accurate and complete reporting and analysis of safety information from trials is crucial for the protection of subjects, investigators and the Sponsor, and is mandated by regulatory agencies worldwide. Soligenix has established standard operating procedures (SOPs) in conformity with regulatory requirements to ensure appropriate reporting of safety information. All trials that are the responsibility of Soligenix must be conducted in accordance with the procedures as provided below.

12.1. Definitions

12.1.1 Adverse Experience (AE)

Any noxious or unintended event that occurs in association with the use of an investigational agent in humans***, whether considered related to the investigational agent or not.*** This definition encompasses symptoms or signs reported by the subject or detected by the investigator or other competent observer, as well as medically important deviations from normality in the results of ancillary investigations. If present at time of first dose of study drug, such AEs must be recorded as part of the medical history.

Treatment-Emergent AE: An AE that is new in onset or aggravated in severity or frequency following entry into the study. In addition, any pathological finding on physical examination or diagnostic procedure that is new in occurrence or exacerbated in comparison with the subject's status at study entry is considered a treatment-emergent AE if it requires any medical or surgical intervention whatsoever (including, but not limited to, additional diagnostic procedures or alteration of prescribed therapy).

12.1.2 Serious Adverse Experience (SAE)

Any AE occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening AE
- Prolongation of existing hospitalization or subsequent need for hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medical or surgical intervention to prevent one of the above

12.1.3 Potentially Serious Adverse Experience

Any AE that is sufficiently severe or alarming as to require any form of significant medical intervention. Note: Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical

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

12.2. Relationship to Study Drug

The relationship of an AE to the assigned study drug is assessed using the following definitions:

- **Not Related**: The drug experience is clearly related to other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs.
- **Possibly Related:** The drug experience follows a reasonable sequence from the time of drug administration and/or follows a known response pattern to the study drug, but could have been produced by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs.
- **Related:** The drug experience follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug, and cannot be reasonably explained by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs.

12.3. Severity of Adverse Event

A clinical determination of the intensity of an AE should be done for all reported AEs. The severity assessment for should be completed using the following definitions as guidelines:

- **Mild:** Awareness of sign or symptom, but easily tolerated.
- **Moderate:** Discomfort enough to cause interference with usual activity.
- **Severe:** Incapacitating with inability to work or do usual activity.
- **Not applicable:** In some cases, an AE may be an "all or nothing" finding, which cannot be graded.

12.4. Recording Adverse Events

All AEs, whether judged to be related or not to the study drug, should be recorded in both the medical record and the eCRF. The start and resolution dates, the judgment of the severity of the AE, the judgment of the relationship of the AE to the study drug, the action taken for subsequent dose of study drug, and the outcome should be noted.

12.5. Reporting Adverse Events

12.5.1 Adverse Events

All AEs should be noted in the eCRF within 3 days of being recognized. Any AE that is either a SAE or potential SAE should be handled within the timeframes given in section 12.5.2, below. The resolution date for all recorded AEs should be entered within 3 days of determination that

the AE has resolved. All AEs should be followed to resolution or 30 days after the Cycle 3 evaluation.

12.5.2 Serious Adverse Events

When the investigator, or trained designee, becomes aware that a serious or potentially serious AE (as defined above) has occurred, the site monitor or Medical Monitor must be notified ***immediately*** (and no later than 24 hours after notification) by telephone, regardless of the relationship (or lack thereof) of the AE to study therapy.

All reports of serious or potentially serious AEs must be followed within 24 hours (or sooner at the request of the Soligenix Medical Monitor) by the completion of a serious AE form signed by the investigator. This should be faxed to the site monitor and/or Medical Monitor.

In accordance with Soligenix SOPs and Health Authority regulations, investigators may be notified from time to time of the occurrence of serious, unexpected AEs. If such AEs are associated with the use of the study drug (i.e., there is a reasonable possibility that the AE may have been caused by the drug) and are thus deemed significant new AEs or risks with respect to the drug, the investigator must promptly inform the relevant Institutional Review Board (IRB), in accordance with the ICH Guidance on Good Clinical Practices (E6, April 1996).

FOR ADVERSE EXPERIENCE REPORTING OR MEDICAL QUESTIONS THE MEDICAL MONITOR SHOULD BE CONTACTED:

Richard Straube, MD
Senior Vice President & Chief Medical Officer,
Study Medical Monitor
Phone: (609) 538-8200 x 30
[redacted]
Email: rstraube@soligenix.com

If above contact is not accessible, please call:

Soligenix, Inc., 29 Emmons Drive, Suite B-10, Princeton, NJ 08540
Phone: (609) 538-8200

FOR ADDITIONAL ASSISTANCE:

For additional assistance, please contact your clinical research monitor(s) OR

Christopher Pullion, DO
Lead Clinical Research Associate
Office: (609) 538-8200 x 23
[redacted]
Email: cpullion@soligenix.com

12.6. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) consisting of one Biostatistician (chair) and two clinicians, including at least one Dermatologist with expertise in CTCL will be formed to monitor the safety and conduct of the study on an ongoing basis. Parameters to be evaluated will include AEs (clinical and laboratory), number of dropouts overall, those withdrawals specifically due to worsening of disease, and those withdrawals due to failure to improve in a timely fashion. Data will be reviewed for safety in a semi-blinded fashion with the data presented as treatment A and B. However, the DMC, as part of its charter to evaluate and ensure the safety of subjects participating in the trial, has the authority to unblind the data as appropriate.

The DMC may request any safety data including, but not limited to, SAEs, AEs, and laboratory values. The DMC may also request any efficacy data including, but not limited to the primary and secondary outcomes in order to evaluate benefit to risk. Additionally, the DMC will conduct one (1) interim analysis when approximately 60% (n = 80) of the originally planned total number of evaluable subjects (n = 120) have completed the Cycle 1 Week 8 evaluation (i.e., the primary endpoint evaluation). Soligenix, Inc., participating clinical investigators and any personnel involved in trial conduct will remain blinded to study treatment. The primary efficacy endpoint and the key safety endpoints will be compared between treatments in an unblinded manner as described in the Statistical Section 13.3.4.

13. STATISTICS

All analyses will be based on the ITT population that is defined as all randomized patients with their treatment assignment specified as their randomized treatment. Complete details of analyses and relatively order of importance of each analysis are more fully delineated in the Statistical Analysis Plan.

13.1. Sample Size Calculation

The original sample size planned for this trial was 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. Because the of initial feedback from physicians that 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 was estimated that approximately 135 patients would need to be enrolled to have 120 patients complete Cycle 1.

The sample size is now increased to 180 enrolled patients in order to obtain 160 evaluable patients, following the recommendation of the DMC upon its review of the interim efficacy analysis, which has now been conducted as described in Section 12.6 above and Section 13.3.4 below.

[redacted]

[redacted]

13.3. Statistical Analysis

13.3.1 Primary Endpoint

The primary endpoint for the trial is the relative frequency of a Cycle 1 treatment response (≥50% reduction in CAILS score) between the two treatment groups. Treatment response is a binary variable (yes/no). Logistic regression analysis on treatment response will be performed with treatment as an independent variable. Treatment differences will be considered statistically significant if the two-sided p-value is no higher than 0.05.

13.3.2 Secondary Endpoints

Treatment response at Cycles 2 and 3 are secondary endpoints. Treatment response will be analyzed inferentially at Cycle 2 using logistic regression with treatment as an independent variable. Complete clearing, defined as a CAILS score of 0%, is another secondary endpoint. Complete clearing is a binary variable (yes/no). It will be evaluated at all three treatment cycles. Complete clearing will be analyzed inferentially at Cycles 1 and 2 using logistic regression with treatment as an independent variable. CAILS score is a continuous variable and will be analyzed for Cycles 1 and 2 using ANOVA with treatment as an independent variable. For all analyses at Cycles 1 and 2, treatment is the originally randomized treatment. An additional analysis will be the comparison of treatment response between Week 8 and Week 16 within each treatment group. Logistic regression with cycle and patient as independent variables will be used. Duration of response is another secondary endpoint. Duration of response is a semi-continuous variable and will be analyzed using repeated measures ANOVA with treatment, lesion and patient as independent variables. Additionally time to progression will be evaluated using the standard Kaplan-Meier analysis. The calculations of time to progression and duration of response will be delineated in the Statistical Analysis Plan.

[redacted]

13.3.4 Interim Analysis

Additionally, the DMC will conduct one (1) interim analysis when approximately 60% (n = 80) of the originally planned total number of evaluable subjects (n = 120) have completed the Cycle 1 Week 8 evaluation (i.e., the primary endpoint evaluation). Soligenix, Inc., participating clinical investigators and any personnel involved in trial conduct will remain blinded to study treatment. The primary efficacy endpoint and the key safety endpoints will be compared between treatments in an unblinded manner. At this meeting, the following recommendations may be made based on the primary efficacy endpoint interim analysis:

- Halt the trial for overwhelming efficacy defined as an improvement of primary endpoint success rate for the SGX301 groups compared to the placebo group with a p-value < 0.001; in order to preserve an overall Type I error rate of 0.05 following the interim analysis should the study not be halted, the alpha spending function approach with an O'Brien-Fleming type of stopping rule will be used, resulting in a 2 sided significance level of $\alpha = 0.049$ for the final analysis.
- 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%. Such a sample size increase will not require a penalty to the final significance level [57]. The maximum sample size increase will be 2 times the protocol-specified sample size.
- If the conditional power under the protocol-specified sample size is between 10% and 38%, recommend that the final sample size will remain as is specified in the protocol.

[redacted]

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1. Study Monitoring

It is the responsibility of the PI and site personnel to assure that the data recorded in the Case Report Forms is accurate, complete and can be verified from the medical records.

In accordance with the Guidelines for the Monitoring of Clinical Investigations presented in the ICH Guidance on Good Clinical Practices (E6), Soligenix will select, either directly or through subcontract, qualified individuals to monitor the progress of the study and adherence to protocol by the individual clinical sites.

14.1.1 Pre-study Evaluation

This initial encounter with the site will establish that the site has all of the necessary elements to successfully participate in the proposed protocol including adequate trained staff, adequate free time of the staff, adequate facilities for safe and proper trial conduct, evidence for potential enrollment of suitable patients, adequate research pharmacy support, the presence of an IRB meeting the local and FDA requirements, and a commitment for training of all involved staff on the protocol.

14.1.2 Site Initiation Visit

Once all required trials documents have been processed, the Medical Monitor (or trained designee) will initiate the study after on-site training of the participating staff at the institution. Topics covered will include training on:

- The investigational status of the study drug and the requirements for its accountability.
- Background on the study drug.
- Details of the protocol including patient selection, study drug administration, procedures to be performed, and visit schedules.
- Critical nature of obtaining informed consent in accordance with the Declaration of Helsinki and ICH Guidance on GCPs (E6) before enrolling each subject in the study.
- The obligation to ensure IRB review and approval for the study, including the protocol, amendments, ICF and any advertisements, is obtained prior to its initiation at his/her clinical site, to ensure continuing review of the study by the IRB, and to keep Soligenix informed of such approval and subsequent actions concerning the study.

14.1.3 Monitoring Visits

Soligenix or their trained designee will perform on-site monitoring visits as frequently as it deems necessary. At these visits, the site monitor will compare the data entered into the eCRFs

with the source documents and check for protocol compliance including a record of informed consent, enrollment criteria, all subject assessments, all AEs and all concomitant medications. In addition, study drug and supporting records will be reviewed. Additionally, they assure that all serious, life-threatening or fatal AEs are being reported immediately [and in no case later than twenty-four (24) hours after the event] to the Medical Monitor or designee at Soligenix.

Findings from these reviews will be discussed with the investigator and staff. Completed pages of the eCRFs will be evaluated at each visit. The dates of the monitoring visits will be recorded in a sign-in log that will be kept at the site. The study coordinator and investigator are expected to be available for questions, the source documentation readily available, and a suitable environment provided for review of study-related documents.

14.1.4 Close-out Visit

The clinical research monitor(s) will perform an end of trial visit to ensure that:

- All drug reconciliation forms are accurate and complete.
- All unused study drug is returned to the appropriate location.
- All data issues are resolved and eCRFs are completed and verified.
- The IRB has been notified that the study has been completed.
- The investigator at each site is aware that the study has been completed and no further subjects are enrolled.

14.2. Audits and Inspections

Health Authorities (e.g., FDA), in the person of a trained and properly authorized employee, may request access to all study records, including source documents, for inspection and copying. The investigator will immediately notify Soligenix of any upcoming inspections.

Periodic auditing inspections may also be conducted by a representative of the Quality Assurance Department of Soligenix or its designee(s).

15. ETHICS

15.1. Institutional Review Board

The final study protocol, including the final version of the Subject Information and Consent Forms, must be approved in writing by an Institutional Review Board (IRB) that meets the minimum FDA standards before enrolment of any subject into the study. The PI or their designee is responsible for informing the IRB of any SAE and amendment(s) to the protocol as per regulatory requirements.

15.2. Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles in the Declaration of Helsinki, Good Clinical Practices and applicable regulatory requirements.

15.3. Written Informed Consent

The Investigator will ensure that the subject or a legally authorized representative of the subject are given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. ***The subject's signed and dated informed consent must be obtained before conducting any study specific procedure***. The consent form that is used must meet the requirements as outlined in the ICH Guidance on GCPs (E6) and must be approved by both the reviewing IRB and by Soligenix.

15.4. Subject data protection

The Subject Information and Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality. Subjects in this database will be identified by initials or enrolment code/subject number only. Authorized representative of a regulatory authority (e.g., MCC) may require direct access to parts of the trial site records relevant to the study, including subjects' medical history for data verification purposes.

15.5. Financial Disclosure

The FDA has issued regulations (21 CFR Part 54) that require Sponsors (in this case Soligenix) to submit complete and accurate certification or disclosure statements to certify the absence of certain financial interests of clinical investigators and/or disclose those financial interests, as required, when clinical studies are submitted to the FDA in support of marketing approval of a new drug application (NDA). These regulations are intended to ensure that financial interests and arrangements of clinical investigators, that could affect reliability of data submitted to the FDA in support of marketing approval, are identified and disclosed by the Sponsor.

Clinical investigators shall be asked to disclose proprietary (e.g., patent, licensing agreement) and financial (e.g., stock options, royalty) interests as they pertain to Soligenix, prior to participating in the study. In addition, clinical investigators will be required to consult with Soligenix before acquiring any financial interest in the company and must disclose any change in their proprietary or financial interests if it occurs during the course of the study and for one year following study completion. Clinical Investigator is defined under Title 21 CFR Part 54 as an investigator or sub-investigator listed on the FDA Form 1572 that is directly involved in the treatment or evaluation of research subjects. The requirement for proprietary and financial disclosure also includes any ownership by the spouse or any dependent child of the investigator.

If the FDA determines that the financial interests of any clinical investigator raise serious question about the integrity of the data, the FDA will take any action it deems necessary to ensure the reliability of the data, including:

- Initiating agency audits of the data derived from the clinical investigator in question;
- Requesting that the Sponsor submit further analyses of data, e.g., to evaluate the effect of the clinical investigator's data on overall study outcome;
- Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study; and/or
- Refusing to treat the covered clinical study as providing data that can be the basis for an agency action.

If the Sponsor does not include certification or disclosure, or both, if required, or does not certify that it was not possible to obtain the information, the FDA may refuse to file the NDA.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

16.1.1 Monitoring

In accordance with the Guidelines for the Monitoring of Clinical Investigations presented in the ICH Guidance on Good Clinical Practices (E6), the following will be observed:

Soligenix will select, either directly or through subcontract, qualified individuals to monitor the progress of the study and adherence to protocol by the individual clinical sites.

It is the responsibility of the PI to assure that, at mutually agreed upon times, the clinical monitor has appropriate access to all medical records, study materials, study and regulatory binders, laboratory and radiographic results, study personnel, their time to allow adequate assessment as to the quality, completeness and adherence to all aspects of the protocol.

16.1.2 Audits

Health Authorities (e.g., FDA, etc.), in the person of a trained and properly authorized employee, may request access to all study records, including source documents, for inspection and copying. The investigator will immediately notify Soligenix of any upcoming inspections. Periodic auditing inspections may also be conducted by a representative of the Quality Assurance Department of Soligenix or its designee(s).

16.2. Retention of Records

Copies of eCRFs should be retained by sites along with all original source documents (e.g., informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnoses and dates of therapy prior to and during this study, drug dispensing/disposition records) that support eCRFs of each subject must be retained in the files of the responsible investigator or in hospital records for a minimum of two (2) years following notification by Soligenix that all investigations have been discontinued or that the last approval of a marketing application has been obtained.

If the responsible investigator retires, relocates, or for other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Soligenix must be notified in writing of the name and address of the new custodian.

17. INVESTIGATOR AGREEMENT

I have read the foregoing protocol that includes Amendment 5 and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein, in accordance with local and federal regulations, Good Clinical Practices and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the study drugs and the conduct of the study.

I will use only the informed consent form approved by the Institutional Review Board/Ethics Committee and Soligenix and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board/Ethics Committee responsible for this study.

I further agree that the Health Authorities, Soligenix, or their designee(s) shall have access to any source document from which case report form information may have been generated.

I agree that I and all investigators listed on the FDA Form 1572 shall inform Soligenix of any equity interest in the company prior to and during participation in this trial. I further agree that I and all listed investigators will consult with Soligenix before acquiring any financial interest in the company during the study and for one year after the study's completion.

_____

Investigator's Signature Date

_____

Name of Investigator (Typed or Printed)

18. APPENDICES

Appendix 18.1. Light Treatment Duration Based on Light Meter Reading at the Lesion Position

TREATMENT TIMES BASED ON PRESCRIBED DOSE AND LIGHT OUTPUT

LIGHT METER READING AT LESION POSITION IN W / M^2

DOSE IN Joules/cm^2

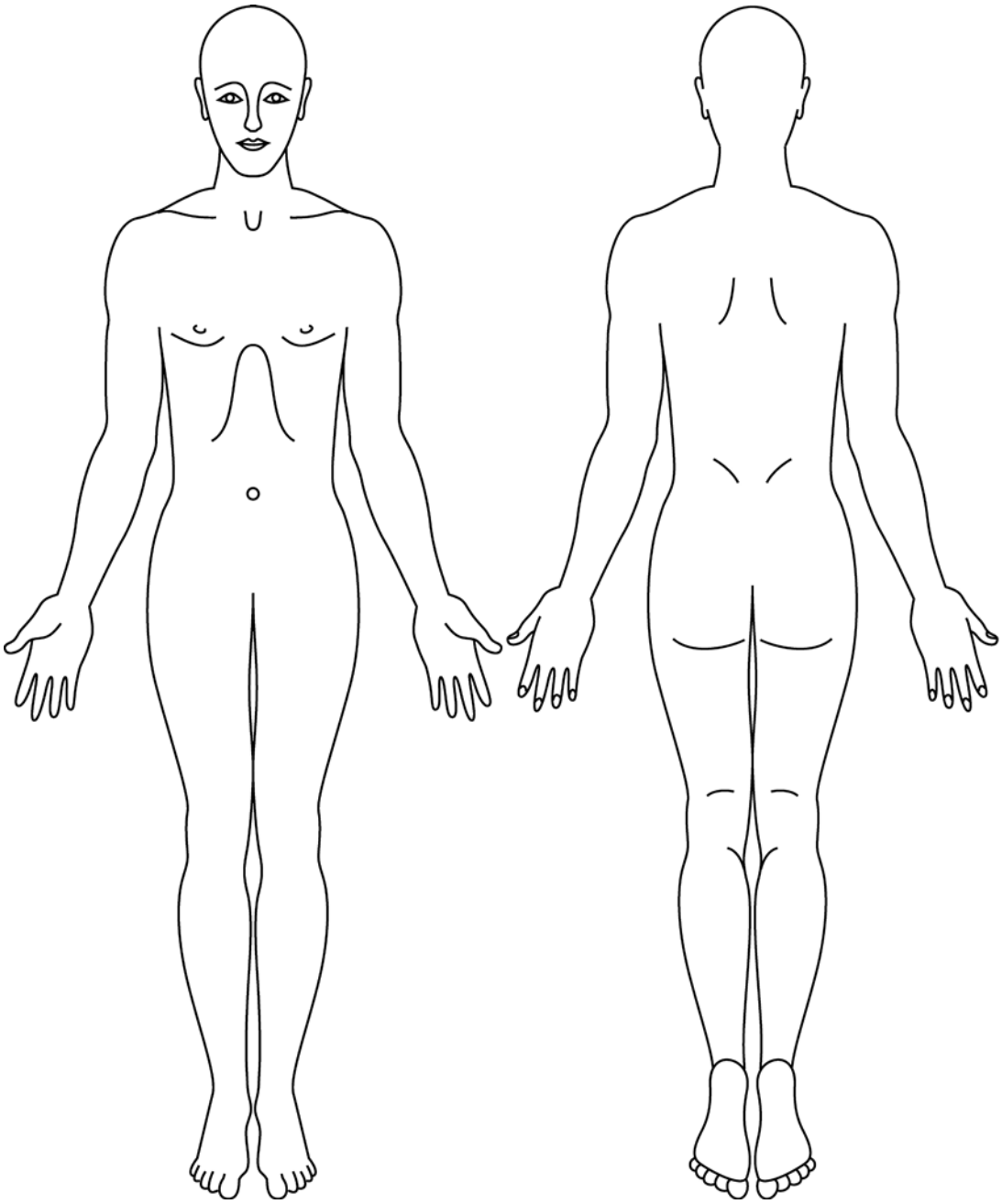
	100	105	110	115	120	125	130	135	140	145	150
5	8:18	7:57	7:36	7:14	6:54	6:39	6:24	6:12	6:00	5:48	5:36
6	10:00	9:33	9:06	8:42	8:18	8:00	7:42	7:24	7:06	6:54	6:42
7	11:42	11:09	10:36	10:09	9:42	9:21	9:00	8:39	8:18	8:03	7:48
8	13:18	12:42	12:06	11:36	11:06	10:39	10:12	9:51	9:30	9:12	8:54
9	15:00	14:18	13:36	13:03	12:30	12:00	11:30	11:06	10:42	10:21	10:00
10	16:42	15:57	15:12	14:33	13:54	13:21	12:48	12:21	11:54	11:30	11:06
11	18:24	17:28	16:40	15:57	15:17	14:40	14:07	13:35	13:06	12:39	12:13
12	20:00	19:03	18:11	17:24	16:40	16:00	15:23	14:49	14:17	13:48	13:20

	155	160	165	170	175	180	185	190	195	200
5	5:24	5:12	5:03	4:54	4:45	4:36	4:30	4:24	4:18	4:12
6	6:27	6:12	6:03	5:54	5:42	5:30	5:21	5:12	5:06	5:00
7	7:33	7:18	7:06	6:54	6:39	6:24	6:15	6:06	5:57	5:48
8	8:36	8:18	8:03	7:48	7:36	7:24	7:12	7:00	6:48	6:36
9	9:42	9:24	9:06	8:48	8:35	8:18	8:03	7:48	7:39	7:30
10	10:45	10:24	10:06	9:48	9:30	9:12	8:57	8:42	8:30	8:18
11	11:50	11:28	11:07	10:47	10:29	10:11	9:55	9:39	9:24	9:10
12	12:55	12:30	12:07	11:46	11:26	11:07	10:49	10:32	10:16	10:00

Appendix 18.2. Lesion Location Map

BODY LESION DIAGRAM: SOLIGENIX / SGX301

Please identify the index lesions location using supplied white reference labels with the appropriate numbering (Ex. 1, 2 or 3) written on them.



Appendix 18.3. Patient Instructions/Treatment Log

FLASH (Fluorescent Light Activated Synthetic Hypericin)

A Phase 3 clinical study for the treatment of Cutaneous T-Cell Lymphoma

Ointment Application Instructions

The night before your hospital visit for light treatment, you will apply the study drug ointment to your skin lesions that were identified as the three index lesions by your doctor. For Cycles 1 and 2, you will only apply the ointment to these 3. For Cycle 3, you will apply the ointment to all lesions. Each time you apply the ointment, write down the date and time of application in the appropriate slot below.

Before applying the study drug ointment to your skin lesions, you or the person helping you should put on disposable gloves. The ointment should be applied thinly and evenly over the entire surface of each lesion. The unaffected skin around the lesion should be avoided as much as possible and any ointment on the unaffected skin should be wiped away. After application, each lesion should be covered with the bandage and tape provided to you by the hospital. This will ensure that the skin lesion is protected from light until your hospital visit and for 24 hours after the light treatment. Make sure that the jar top is tightly closed after using. Finally, after applying the ointment, you or the person helping you should wash their hands with soap and water.

Cycle 1- Week 1, Application 1
Date _____
Time of application _____

Cycle 1- Week 1, Application 2
Date _____
Time of application _____

Cycle 1- Week 2, Application 1
Date _____
Time of application _____

Cycle 1- Week 2, Application 2
Date _____
Time of application _____

Cycle 1- Week 3, Application 1
Date _____
Time of application _____

Cycle 1- Week 3, Application 2
Date _____
Time of application _____

Cycle 1- Week 4, Application 1
Date _____
Time of application _____

Cycle 1- Week 4, Application 2
Date _____
Time of application _____

Cycle 1- Week 5, Application 1
Date _____
Time of application _____

Cycle 1- Week 5, Application 2
Date _____
Time of application _____

Cycle 1- Week 6, Application 1
Date _____
Time of application _____

Cycle 1- Week 6, Application 2
Date _____
Time of application _____

Cycle 2- Week 1, Application 1
Date _____
Time of application _____

Cycle 2- Week 1, Application 2
Date _____
Time of application _____

Cycle 2- Week 2, Application 1
Date _____
Time of application _____

Cycle 2- Week 2, Application 2
Date _____
Time of application _____

Cycle 2- Week 3, Application 1
Date _____
Time of application _____

Cycle 2- Week 3, Application 2
Date _____
Time of application _____

Cycle 2- Week 4, Application 1
Date _____
Time of application _____

Cycle 2- Week 4, Application 2
Date _____
Time of application _____

Cycle 2- Week 5, Application 1
Date _____
Time of application _____

Cycle 2- Week 5, Application 2
Date _____
Time of application _____

Cycle 2- Week 6, Application 1
Date _____
Time of application _____

Cycle 2- Week 6, Application 2
Date _____
Time of application _____

Cycle 3- Week 1, Application 1
Date _____
Time of application _____

Cycle 3- Week 1, Application 2
Date _____
Time of application _____

Cycle 3- Week 2, Application 1
Date _____
Time of application _____

Cycle 3- Week 2, Application 2
Date _____
Time of application _____

Cycle 3- Week 3, Application 1
Date _____
Time of application _____

Cycle 3- Week 3, Application 2
Date _____
Time of application _____

Cycle 3- Week 4, Application 1
Date _____
Time of application _____

Cycle 3- Week 4, Application 2
Date _____
Time of application _____

Cycle 3- Week 5, Application 1
Date _____
Time of application _____

Cycle 3- Week 5, Application 2
Date _____
Time of application _____

Cycle 3- Week 6, Application 1
Date _____
Time of application _____

Cycle 3- Week 6, Application 2
Date _____
Time of application _____

Appendix 18.4. Biopsy Processing

At randomization, one of the three index lesion will be selected for biopsy. At baseline and the Cycle 1 evaluation (Week 8), a 3 mm punch biopsy will be taken from the most representative portion of the lesion. The second biopsy should be obtained at least 1 cm from the original biopsy site. The biopsies should be prepared at the site using their standard procedures. The following guidelines should be followed:

1. The tissue should be formalin fixed and paraffin embedded.
2. The amount of tissue remaining in the paraffin block should be maximized without compromising the quality of the sections. Blocks need not be leveled.
3. A total of 5 slides should be prepared from each biopsy.
4. A minimum of 4 sections should be mounted on each of the slides- sequential sections are acceptable.
5. One (1) of the slides should be stained using the laboratory's standard hematoxylin and eosin staining procedure.
6. The H&E stained slide and the four (4) unstained slides should be handled:
    a. Labeled with:
        i. The patient's ID (site number – patient number)
        ii. Date of biopsy
        iii. Indication as to whether the biopsy is "baseline" or "post-treatment"
    b. The five slides are placed in the shipping slide carrier. The carrier should be labeled as each of the slides:
        i. The patient's ID (site number – patient number)
        ii. Date of biopsy
        iii. Indication as to whether the biopsy is "baseline" or "post-treatment"

Slides should be shipped using the supplied shipping supplies to:

[redacted]

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