CLINICAL RESEARCH PROTOCOL

DRUG:	HyBryte™ (0.25% hypericin ointment)
STUDY NUMBER(S):	HPN-CTCL-02
PROTOCOL(S) TITLE:	Phase 2a Study of Systemic PK and Serial ECG Determinations Following 8 Weeks of HyBryte Treatment
IND NUMBER:	[redacted]
SPONSOR:	Soligenix, Inc.
ORIGINAL PROTOCOL DATE:	20 January 2022
VERSION NUMBER:	Amendment 1
VERSION DATE:	22 April 2022

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HPN-CTCL-02

PHASE 2A STUDY OF SYSTEMIC PK AND SERIAL ECG DETERMINATIONS FOLLOWING 8 WEEKS OF HYBRYTE TREATMENT

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to HyBryte™ are the confidential and proprietary information of Soligenix, Inc., and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Soligenix.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Conference on Harmonization guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Soligenix, Inc. or specified designees. I will discuss the material with them to ensure that they are fully informed about HyBryte and the study.

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

STUDY SYNOPSIS

Name of Sponsor/Company: Soligenix, Inc.		(For National Authority Use only)
Name of Finished Product HyBryte™		
Name of Active Ingredient Hypericin (0.25% ointment)		

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

Investigators: Brian Poligone, MD; potentially one additional TBD Investigator

Study Centre(s): Rochester Skin Lymphoma Center; 1 other site TBD

Publication (reference): N/A

Study Period (years): 0.4 year **Date of First Enrollment:** 02 May 2022 **Date of Last Completed:** 31 October 2022	**Phase of Development:** Phase 2a

Objectives: The primary objectives of this study are to assess:

- the systemic blood levels of hypericin during 8 weeks of standard HyBryte photodynamic therapy; and
- any ECG changes during 8 weeks of standard HyBryte photodynamic therapy.

Methodology: This will be an open label trial. Subjects with CTCL (stage IB or IIA) with lesions of ≥10% of body surface area will be enrolled and receive topical HyBryte applied to all accessible lesions twice per week followed by visible light treatment 18-24 hours later starting at 5 J/cm^2 and titrated up at each visit until there is evidence of mild erythema of the treated lesions following the light session (Grade 1 erythema on the Erythema Score). At baseline and at the end of weeks 4, 6, 8, and 10, serum for Hypericin levels will be obtained and 12-lead ECG's will be performed at baseline (prior to drug application), at Week 4, Session 2 (immediately before and 2 hours after completion of the light session), at Week 6, Session 2 (immediately before the light session), Week 8, Session 2 Light Session visit (immediately before and 2 hours after completion of the light session), and Week 10/End of Study visit. Routine safety laboratories (hematology, clinical chemistries) will be analyzed at baseline, at the Week 8 Session 2 Light Session visit, and 2 weeks after completion of therapy (Week 10/End of Study). AE's will be recorded throughout the study.

Number of patients (planned): Approximately 6 subjects will be recruited

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Diagnosis and main criteria for inclusion:

Inclusion Criteria:

In order to be enrolled into the trial, subjects must meet ***all*** of the criteria below:

1. ≥18 years of age
2. Active treatment-accessible CTCL lesions covering ≥ 10% of their body surface area
3. Subjects must have a clinical diagnosis of cutaneous T-cell lymphoma (CTCL, mycosis fungoides), Stage IB or Stage IIA
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

Exclusion Criteria:

In order to be enrolled into the trial, subjects ***cannot*** have any of the following criteria:

1. History of allergy or hypersensitivity to any of the components of HyBryte
2. Pregnancy or mothers who are breast-feeding
3. Males and females not willing to use effective contraception
4. Subjects with history of sun hypersensitivity or photosensitive dermatoses (e.g., porphyria, systemic lupus erythematosus (SLE), Sjogren's syndrome, etc.)
5. Subjects whose condition is spontaneously improving
6. Subjects receiving topical steroids or other topical treatments (e.g., nitrogen mustard) on index lesions for CTCL within 2 weeks of enrollment
7. Subjects receiving systemic steroids, psoralen ultraviolet A (UVA) radiation therapy (PUVA), narrow band ultraviolet B (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 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 enrollment

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Name of Active Ingredient Hypericin (0.25% ointment)		

11. Subject has any condition that, in the judgment of the PI, is likely to interfere with participation in the study

12. Subjects receiving drugs known to cause photosensitization within 2 weeks of starting HyBryte therapy unless they have not had evidence of photosensitization after receiving a stable dose of the medication for a minimum of 4 weeks

Test product, dose and mode of administration: HyBryte (0.25% hypericin ointment) applied in a thin film on all lesions avoiding treatment of healthy skin (weight of drug actually used will be measured by weighing the drug jar at the time of each light treatment by study personnel and estimating the amount applied by changes in jar weight) and covered with opaque covering. The light panel for use in this study is the Daavlin 7 Series Phototherapy Device using visible light lamps (510K clearance K212510). The drug will be activated 18-24 hours after application starting at 5 J/cm^2 of visible light metered by duration of exposure and titrated up at each visit until a mild erythema (Grade I Erythema Score) in the treated lesions is seen following the light session.

Duration of treatment: Subjects will apply HyBryte to all accessible lesions followed 18-24 hours later by visible light treatment twice per week using the Daavlin 7 Series Phototherapy Device. Treatments will continue twice per week (at least 2 calendar days apart) for a total of 8 weeks of treatment (16 actual treatments). Subjects will have serum hypericin levels obtained at baseline (prior to drug application) and at weeks 4 (immediately before and 2 hours after light session), 6 (immediately before light session), and 8 (immediately before drug application, immediately before and 2 hours after light session). Subjects will have ECGs obtained at baseline (prior to drug application) and at weeks 4 (immediately before and 2 hours after light session), 6 (immediately before light session), and 8 (immediately before and 2 hours after light session). Subjects will return as outpatients 2 weeks after the final drug application (Week 10/End of Study) for safety laboratory assessments, PK samples, ECG, lesion evaluations and collection of adverse events.

Reference therapy, dose and mode of administration: Not applicable as there is no reference therapy in this uncontrolled study.

Criteria for evaluation:

Primary Objectives:

This is an exploratory study to assess the systemic exposure to hypericin following topical application of HyBryte. Given the relatively small sample size, no formal efficacy assessments will be performed.

Safety:

The safety variables evaluated are: Serial ECG's, clinical hematology assessments, clinical chemistry assessments, vital signs, and the collection of adverse/serious adverse events.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BCNU	Carmustine
bid	Twice Daily
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CONMED	Concomitant Medication
CRF	Case Report Form
CTCL	Cutaneous T-cell Lymphoma
ECG	Electrocardiogram
GCP	Good Clinical Practice
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICD	Immunogenic Cell Death
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board

Kg	Kilogram
L	Liters
LN	Lymph Node
MF	Mycosis Fungoides
Mg	Milligram
Min	Minute
mmHg	Millimeters Mercury
mSWAT	Modified Severity Weighted Assessment Tool
NB-UVB	Narrow Band UVB
PI	Principal Investigator
PK	Pharmacokinetic
Po	Per Os (By Mouth), Orally
PUVA	Psoralen Ultraviolet A Radiation Therapy
ROS	Reactive Oxygen Species
SAE	Serious Adverse Event
SLE	Systemic Lupus Erythematosus
SOP	Standard Operating Procedure
SS	Sézary Syndrome
ULN	Upper Limit of Normal
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B
WHO	World Health Organization

INTRODUCTION AND RATIONALE

1.1 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 HyBryte. Please refer to the Investigator's Brochure (IB) for additional details and information.

1.1.1 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 LN 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). Response to skin directed therapies is often slow with peak response seen only after 6-18 months of therapy.

1.1.2 Hypericin

Hypericin is a natural compound found in the stems and petals of plants of the genus *Hypericum* (15-17). HyBryte™ is chemically synthesized hypericin formulated for topical application and not extracted from plants.

Hypericin is an effective virucidal agent that directly inactivates a broad range of viruses, including retroviruses (18-23), both as a stand-alone drug (24, 25) and after photoactivation (22, 26-29). Based on these promising *in vitro* virucidal effects, the compound was clinically evaluated for its utility in the management of human immunodeficiency virus (HIV) (30) and hepatitis C infections (31). However, no convincing evidence of clinical effectiveness as an antiviral was observed in these studies up to toxicity-limited doses, which were exclusively phototoxicity related.

In addition to its antiviral activity, hypericin has been shown in animal models to accumulate selectively in cancer cells up to a ratio of 12:1 cancer to healthy cells (32, 33). Again, hypericin appears to have tumoricidal effects both as a stand-alone drug (34-37) and after activation with visible light (15, 38-45). A clinical trial of parenteral synthetic hypericin for the treatment of brain gliomas found the drug to be safe and 10 of the 41 treated patients were considered treatment responders (46).

Although the information from these parenteral clinical trials is not directly applicable to the evaluation of the topical formulation of synthetic hypericin (HyBryte), the systemic doses of the drug were safe and at blood levels many magnitudes higher than expected following topical administration.

The dose-limiting toxicity in the systemic hypericin clinical trials was phototoxicity. The existence of this photoactivity, however, forms a basis for considering hypericin as an agent in topical phototherapy. *In vitro* studies with T-cells showed that hypericin could inhibit induced proliferation and near complete apoptosis in malignant CTCL T-cells with substantially less effects on normal T-cells similarly treated (47) and induced the inhibition of cell proliferation in adult T-cell leukemia cell lines with minimal effect on peripheral blood CD4+ T lymphocytes (48).

In general, it appears that the primary mechanism of the light-activated hypericin is through a Type II photoreaction. Hypericin localizes in the perinuclear region within the endoplasmic reticulum and Golgi apparatus (50, 51). When activated with visible light in

the 500-650 nm range (exact activation wavelengths dependent on the solute used), the molecule is converted into a high energy state that transfers the energy to free oxygen creating high energy, singlet oxygen, $^1O_2$. This, in turn, leads to a sequence of photochemical and photobiological processes generating highly reactive oxygen species (ROS), which activate the caspase signaling cascade leading to apoptosis via the mitochondrial pathway. Hypericin additionally interacts with a variety of cytosolic proteins and lipoproteins. ROS generation also leads to cell necrosis, a cell death pathway that may augment its anti-tumor effects through a process of immunogenic cell death (ICD) that activates the immune system against the tumor (52).

A Phase 2 clinical trial demonstrated a statistically significant reduction in both CTCL and psoriatic lesions after 6 weeks of treatment with HyBryte and treatment was well tolerated (49).

A Phase 3 trial with a short, 6-week course of HyBryte therapy demonstrated a statistically significant improvement of lesion response as compared to the blinded placebo rate as well as further improvement afforded by an additional 6-week cycle of open label drug use. At the end of the initial treatment period, there was a statistically significant improvement in the response rate among the HyBryte group compared to the placebo group ($p=0.0416$) and this rate dramatically improved with more prolonged treatment with increased response rates of 40% with 12 weeks of therapy ($p<0.0001$) and 49% with 18 weeks of therapy ($p<0.0001$). This benefit was similar in patch lesions as well as with the thicker, more difficult to treat plaque lesions. Treatment response was durable and more durable with extended treatment. HyBryte treatment was well tolerated, with a low rate of adverse events (AE). The most prevalent AEs were related to skin reactions and application site pain and irritation. The rate of skin/application site reactions was significantly lower than has been reported for other skin-directed therapies.

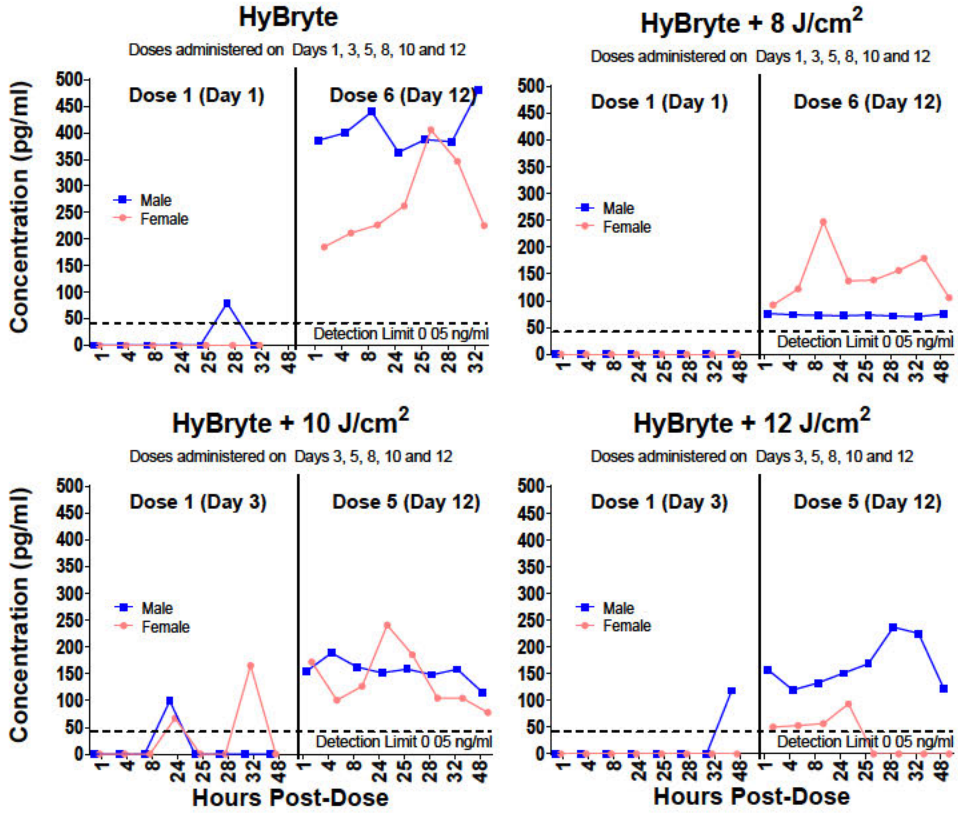
1.2 Pharmacokinetics

Hypericin was initially developed for the systemic treatment of enveloped viral infections including HIV and hepatitis C virus (HCV) and gliomas. Following dosing with either intravenous (iv) or oral (po) routes, the only consistently reported AEs were caused by phototoxicity, the biologic effect that is being exploited and tightly regulated in the topical treatment of CTCL. Minimal blood levels of hypericin were expected to result from low dose topical application of the drug. During the Phase 3 trial, serum blood levels of systemic hypericin were assessed at the end of the third cycle of therapy (after 5-6 weeks of continuous therapy on multiple lesions). Specific serum blood samples were taken approximately 24 hours after the application of the drug, the time when the maximal skin effects were seen. ***Systemic hypericin was not detected in the blood***, indicating levels were <5 ng/mL (lower limit of detection of the bioanalytical method). This study is designed to expand the information about the systemic absorption of hypericin after topical application. Since the systemic levels of hypericin following topical administration were expected to be orders of magnitude lower than that following iv or po administration in which there was no evidence of electrocardiogram (ECG)

changes, minimal ECG monitoring of CTCL patients has been done. Subsequent to completion of the Phase 3 study, the hypericin blood assay was modified to be more sensitive with a detection level of 0.05 ng/mL. Using this improved assay, hypericin levels were measured in a minipig pilot study in which healthy animals were dosed with hypericin every 2 days and treated with ointment only or varying amounts of light treatment. The results of the study are shown in Figure 1.

Figure 1: Hypericin Blood Levels in Minipigs

Each line represents a single animal. Healthy male and female Göttingen mini-pigs received HyBryte applied to 10% BSA every second day. Most animals were below detection limit on Day 1. After 6 doses, healthy animals receiving no light treatment had less than 0.5 ng/ml hypericin in their blood stream, while healthy animals receiving 6 treatments HyBryte + 8 J/cm^2 light treatment 24 hours after drug application and occlusion, had less than 0.3 ng/mL hypericin. Similarly, animals receiving 5 treatments of HyBryte and 10 or 12 J/cm^2 light treatment had less than 0.3 ng/mL hypericin.



As seen, all hypericin levels were low and well below the lower limit of detection of the original assay. While systemic hypericin levels were barely detectable (LLOQ <0.05 ng/mL) after the first administration, this appeared to increase after 5 or 6 doses, with the highest detectable levels seen in animals receiving ointment only with no light sessions. Since very low levels were seen, it was determined that a small study of patients with

CTCL would provide more information about the PK of the topical drug over time (using the more sensitive assay) and allow contemporaneous assessment of ECG readings.

1.3 Systemic Hypericin Pharmacokinetics

The PK and safety margin afforded by topical application of HyBryte is best understood in the context of PK results obtained in studies of well tolerated ***systemic*** hypericin (po or iv administration) as shown in Table 1. With blood levels uniformly determined to be <5 ng/ml after continuous hypericin use in the Phase 3 study, comparison to the well-tolerated po and iv dosing suggest a safety margin 6-1280 fold.

Table 1: PK of Systemically Administered Synthetic Hypericin

Patients	Route	Dose mg/kg	Cmax ng/mL	$t_{½}$ α hrs	$t_{½}$ β hrs	AUC ng-hr/mL
Healthy	po- fasting	1.25	1,180	3.23	39.7	42,950
		2.00	2,120	5.96	68.8	63,310
	po- feeding	1.25	1,010	5.64	42.4	36,350
		2.00	1,420	8.48	83.7	63,990
	iv	0.25	4,200	2.50	24.2	41,900
		0.375	6,400	3.3	40.2	66,600
HIV[1]	po	0.05	31.3	20.2	NR	522
		0.10	72.9	21.0	NR	1,455
HCV[2]	po	0.05	30.6	36.1	NR	930
		0.10	64.9	33.8	NR	3,100

[1] HIV = human immunodeficiency virus patients
[2] HCV = hepatitis C virus patients

1.4 Clinical Adverse Event Profile

The reported MedRA coded AE in ≥3% of patients in any treatment group from the Phase 3 Clinical Trial are shown in Table 2.

Table 2: Adverse Events by System Organ Class and Preferred Term Reported in ≥3% of Patients in Any Treatment Group

System Organ Class	Cycle 1		Cycle 2	Cycle 3	HyBryte	
Preferred Term	HyBryte (N=116) n (%)	Placebo (N=50) n (%)	HyBryte (N=155) n (%)	HyBryte (N=110) n (%)	Overall (N=161) n (%)	Overall (N=166) n (%)
#Patients ≥1 TEAE	56 (48.3)	27 (54.0)	66 (42.6)	49 (44.5)	108 (67.1)	116 (69.9)

System Organ Class Preferred Term	Cycle 1 HyBryte (N=116) n (%)	Cycle 1 Placebo (N=50) n (%)	Cycle 2 HyBryte (N=155) n (%)	Cycle 3 HyBryte (N=110) n (%)	HyBryte Overall (N=161) n (%)	Overall (N=166) n (%)
Skin and subcutaneous tissue disorders	19 (16.4)	5 (10.0)	21 (13.5)	19 (17.3)	48 (29.8)	53 (31.9)
Pruritus	6 (5.2)	2 (4.0)	2 (1.3)	5 (4.5)	12 (7.5)	14 (8.4)
Erythema	3 (2.6)	0	3 (1.9)	1 (0.9)	7 (4.3)	7 (4.2)
Infections and infestations	20 (17.2)	10 (20.0)	19 (12.3)	16 (14.5)	43 (26.7)	51 (30.7)
Upper respiratory tract infection	8 (6.9)	4 (8.0)	2 (1.3)	2 (1.8)	12 (7.5)	16 (9.6)
Viral upper respiratory tract infection	4 (3.4)	0	4 (2.6)	4 (3.6)	11 (6.8)	11 (6.6)
Sinusitis	1 (0.9)	0	3 (1.9)	3 (2.7)	7 (4.3)	7 (4.2)
Urinary tract infection	1 (0.9)	2 (4.0)	3 (1.9)	0	4 (2.5)	6 (3.6)
Influenza	0	2 (4.0)	1 (0.6)	2 (1.8)	3 (1.9)	5 (3.0)
General disorders and administration site conditions	22 (19.0)	5 (10.0)	18 (11.6)	12 (10.9)	38 (23.6)	42 (25.3)
Application site pain	8 (6.9)	2 (4.0)	5 (3.2)	6 (5.5)	16 (9.9)	17 (10.2)
Application site pruritus	5 (4.3)	1 (2.0)	5 (3.2)	0	9 (5.6)	9 (5.4)
Fatigue	3 (2.6)	1 (2.0)	3 (1.9)	2 (1.8)	8 (5.0)	9 (5.4)
Application site paresthesia	6 (5.2)	0	2 (1.3)	2 (1.8)	7 (4.3)	7 (4.2)
Pain	3 (2.6)	0	2 (1.3)	0	5 (3.1)	5 (3.0)
Gastrointestinal disorders	11 (9.5)	6 (12.0)	7 (4.5)	7 (6.4)	20 (12.4)	24 (14.5)
Nausea	3 (2.6)	1 (2.0)	2 (1.3)	2 (1.8)	7 (4.3)	8 (4.8)
Diarrhea	4 (3.4)	0	3 (1.9)	0	6 (3.7)	6 (3.6)
Nervous system disorders	9 (7.8)	4 (8.0)	6 (3.9)	5 (4.5)	18 (11.2)	22 (13.3)
Headache	5 (4.3)	3 (6.0)	5 (3.2)	2 (1.8)	10 (6.2)	13 (7.8)
Dizziness	3 (2.6)	1 (2.0)	1 (0.6)	2 (1.8)	6 (3.7)	7 (4.2)
Respiratory, thoracic and mediastinal disorders	9 (7.8)	1 (2.0)	5 (3.2)	5 (4.5)	17 (10.6)	17 (10.2)

System Organ Class Preferred Term	Cycle 1 HyBryte (N=116) n (%)	Cycle 1 Placebo (N=50) n (%)	Cycle 2 HyBryte (N=155) n (%)	Cycle 3 HyBryte (N=110) n (%)	HyBryte Overall (N=161) n (%)	Overall (N=166) n (%)
Injury, poisoning and procedural complications	6 (5.2)	2 (4.0)	4 (2.6)	5 (4.5)	14 (8.7)	16 (9.6)
Musculoskeletal and connective tissue disorders	3 (2.6)	3 (6.0)	6 (3.9)	4 (3.6)	11 (6.8)	14 (8.4)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	1 (2.0)	3 (1.9)	2 (1.8)	5 (3.1)	6 (3.6)
Eye disorders	3 (2.6)	0	2 (1.3)	0	5 (3.1)	5 (3.0)
Vascular disorders	2 (1.7)	1 (2.0)	1 (0.6)	1 (0.9)	4 (2.5)	5 (3.0)

= Number; TEAE = treatment-emergent adverse event,
Note: TEAE was defined as an AE that was new or worsened in severity after the first dose of study drug and within 1 month following last evaluation visit. At each summary level (SOC, PT), a patient was counted only once or each AE he/she experienced within that level. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.

1.4.1 Dosing Regimen

HyBryte ointment will be applied to all accessible CTCL lesions by the patients following training by the site staff. Care will be taken to minimize application to other skin areas, and cover the treated area with opaque bandaging/clothing. The lesions will then be exposed to visible light using the Daavlin Series 7 Phototherapy Device with visible light lamps (FDA 510K approval K212510) 18-24 hours later starting at 5 J/cm^2 and titrated up until the treated lesions exhibit a mild erythema following the light session. Drug application/light session will be done twice a week (at least 2 calendar days apart) for 8 weeks. The light treatment will be performed at least 2 calendar days apart each week. Light treatment is not permitted on consecutive days.

2 STUDY OBJECTIVES

2.1 Primary

Assess any ECG changes during standard HyBryte photodynamic therapy.

Assess the systemic blood levels of hypericin during standard HyBryte photodynamic therapy.

2.2 Secondary

Assess the safety of HyBryte photodynamic therapy.

3 STUDY ENDPOINTS

This is an exploratory study to confirm the low-level systemic exposure to hypericin and the associated potential for any ECG changes. Given the small size of the study and its open label design, no formal efficacy assessments will be performed.

3.1 Primary

The primary endpoints for the study are:

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

a. Baseline prior to drug application

b. Week 4, Session 2 obtained immediately before and 2 hours after the light session

c. Week 6, Session 2 obtained immediately before the light session

d. Week 8, Session 2 Light Session visit obtained immediately before and 2 hours after the light session

e. Week 10 follow-up visit

Serial measurements of serum hypericin levels obtained at:

f. Baseline prior to drug application

g. Week 4, Session 2 obtained immediately before and 2 hours after the light session

h. Week 6, Session 2 obtained immediately before the light session

i. Week 8, Session 2 Drug Application visit immediately prior to the drug application

j. Week 8, Session 2 Light Session visit obtained immediately before and 2 hours after the light session

k. Week 10/End of Study during the follow-up visit

These levels will be correlated with amount of drug applied by the patient estimated by weighing the drug jars at each light session.

3.2 Secondary

Routine safety laboratory investigations and vitals will be obtained at baseline prior to drug application, at Week 8, Session 2 Light Session visit prior to light therapy and 2 weeks after the completion of therapy (Week 10 follow-up visit/End of Study).

4 STUDY PLAN

4.1 Study Design

This study is an observational, Phase 2a trial. Patients will receive treatments twice a week consisting of drug application followed 18-24 hours later with a light session (using Daavlin Series 7 Phototherapy Device with visible light lamps) for 8 weeks (up to 16 total treatments). The light treatment will be performed at least 2 calendar days apart each week. Light treatment is not permitted on consecutive days. Blood samples for evaluation of serum hypericin concentration will be obtained at baseline, Week 4, Week 6, Week 8, and 2 weeks after the last light session (Week 10/End of Study), and ECGs will be obtained at baseline, Week 4, Week 6, Week 8, and the Week 10 follow-up visit. Safety laboratory tests and vital signs will be obtained at baseline, at the end of treatment (Week 8), and at the end of the 2-week follow-up period (Week 10/End of Study).

4.2 Schedule of Assessments

Subjects will be screened within 28 days of enrollment. Detailed timing of the assessments is shown in Table 3.

Table 3: Schedule of Assessments

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

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

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

5 POPULATION

5.1 Number of Subjects

Approximately 6 subjects will be enrolled.

5.2 Selection of Subjects

5.2.1 Inclusion Criteria

In order to be enrolled into the trial, subjects must meet ***all*** of the criteria below:

1. ≥18 years of age
2. Active treatment-accessible CTCL lesions covering ≥ 10% of their body surface area
3. Subjects must have a clinical diagnosis of cutaneous T-cell lymphoma (CTCL, mycosis fungoides), Stage IB or Stage IIA
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

5.2.2 Exclusion Criteria

In order to be enrolled into the trial, subjects ***cannot*** have any of the following criteria:

1. History of allergy or hypersensitivity to any of the components of HyBryte
2. Pregnancy or mothers who are breast-feeding
3. Males and females not willing to use effective contraception
4. Subjects with history of sun hypersensitivity or photosensitive dermatoses (e.g., porphyria, systemic lupus erythematosus (SLE), Sjogren's syndrome, etc.)
5. Subjects whose condition is spontaneously improving
6. Subjects receiving topical steroids or other topical treatments (e.g., nitrogen mustard) on index lesions for CTCL within 2 weeks of enrollment

7. Subjects receiving systemic steroids, psoralen ultraviolet A (UVA) radiation therapy (PUVA), narrow band ultraviolet B (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 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 enrollment

11. Subject has any condition that, in the judgment of the principal investigator (PI), is likely to interfere with participation in the study

12. Subjects receiving drugs known to cause photosensitization within 2 weeks of starting HyBryte therapy unless they have not had evidence of photosensitization after receiving a stable dose of the medication for a minimum of 4 weeks

5.3 Study Procedures by Time Point

5.3.1 Screening Visit

The screening visit must be done within 28 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

Vital Signs

Serum HCG pregnancy test (women of childbearing age only)

5.3.2 Baseline

After enrollment but prior to application of HyBryte the following assessments will be performed:

Interval medical history from screening obtained

Complete Physical Examination

Vitals taken (heart rate, respiratory rate, and sitting blood pressure)

Hematology panel drawn

Clinical chemistry panel drawn

Pregnancy test results reviewed

Three lesions that are representative of the patient's disease and are discrete with defined borders, will be chosen as the index lesions, and classified as patch or plaque lesions

Charting of all CTCL lesions on the "Body Lesion Diagram" form (Appendix II) locating and numbering each of the index lesion

Each of the index lesions will have a CAILS score assessed and recorded

The mSWAT score will be assessed and recorded

5 mL of blood obtained and processed for serum hypericin levels

12-lead ECG obtained including QT interval measurements

The patient will complete the Skindex-29 (Appendix III) and VAS_{itch} forms and the data transcribed into the eCRF

A jar of ointment will be issued and the weight of the jar prior to dispensation will be recorded

Only after all of the above have been completed, patients will be instructed on proper drug application and demonstrate proficiency in drug application and all accessible lesions will be treated with study drug

The weight of the jar after drug application will be recorded

5.3.3 Week 1, Session 1; Week 1, Session 2; Week 2 Session 1; Week 2, Session 2; Week 3, Session 1; Week 3, Session 2; Week 4, Session 1

18-24 hours after drug application, the patient will return to clinic for their light session using the Daavlin 7 Series Phototherapy Device with visible light lamps. At that visit the following will be performed:

The patient will complete an VAS_{itch} form and the data transcribed into the eCRF.

Adequate application of the drug will be verified by a pink staining on visual inspection of lesions.

Each patient will bring in their jar of study drug to the clinic. The jar will be weighed by clinic staff in order to estimate the amount of drug applied.

5-10 minutes ***before*** the light session, lesions will be graded using the Erythema Grading Score.

During the first session, 5 J/cm^2 of light will be administered. Subsequent light sessions will deliver light doses based on the Erythema Grading Score after the previous light treatment. If the Erythema score was <1, the next light dose should be increased as deemed appropriate by the PI. If the Erythema score is 1, the subsequent dose should be held at the same dose. If the score is >1, the next dose should be lowered.

The patient will undergo the light treatment (may require repositioning to assure that all lesions are being treated).

5-10 minutes ***after*** completion of the light session, lesions will be graded using the Erythema Grading Score. If the score is <1, the light dose should be increased in the next light session. If the Erythema score is 1, the subsequent dose should be held at the same dose. If the score is >1, the next dose may be lowered by at least 1 J/cm^2.

Patients will be asked about any AEs experienced since the last light session and these will be recorded in the eCRF. Information on all unresolved, previously reported AEs will be obtained.

5.3.4 Week 4, Session 2

18-24 hours prior to the scheduled light session, the patient will be instructed to apply study drug to all accessible lesions. At that visit the following will be performed:

The patients will complete an VAS_{itch} form and the data transcribed into the eCRF.

Prior to the light session, 5 mL of blood obtained and processed for serum hypericin levels.

Prior to the light session, a 12-lead ECG obtained including QT interval measurements.

Adequate application of the drug will be verified by a pink staining on visual inspection of lesions.

Each patient will bring in their jar of study drug to the clinic. The jar will be weighed by clinic staff in order to estimate the amount of drug applied.

5-10 minutes ***before*** the light session, lesions will be graded using the Erythema Grading Score.

Patients will undergo the light treatment (may require repositioning to assure that all lesions are being treated).

5-10 minutes ***after*** completion of the light session, lesions will be graded using the Erythema Grading Score. If the score is <1, the next light dose should be increased. If the Erythema score is 1, the subsequent dose should be held at the same dose. If the score is >1, the next dose should be lowered by at least 1 J/cm^2.

2 hours ***after*** completion of the light session, 5 mL of blood obtained for serum hypericin levels.

2 hours ***after*** completion of the light session, 12-lead ECG obtained including QT interval measurements.

Patients will be asked about any AEs experienced since the last light session and these will be recorded in the eCRF. Information on all unresolved, previously reported AEs will be obtained.

5.3.5 Week 5, Session 1; Week 5, Session 2; Week 6, Session 1

18-24 hours prior to the scheduled light session, the patient will be instructed to apply study drug to all accessible lesions. At that visit the following will be performed:

The patients will complete an VAS_{itch} form and the data transcribed into the eCRF.

Adequate application of the drug will be verified by a pink staining on visual inspection of lesions.

Each patient will bring in their jar of study drug to the clinic. The jar will be weighed by clinic staff in order to estimate the amount of drug applied.

5-10 minutes ***before*** the light session, lesions will be graded using the Erythema Grading Score.

The light duration for the session to deliver the target dose of light determined by the Erythema Score of the previous treatment response of light will be calculated.

Patients will undergo the light treatment (may require repositioning to assure that all lesions are being treated).

5-10 minutes ***after*** completion of the light session, lesions will be graded using the Erythema Grading Score. If the score is <1, the next light dose should be increased. If the Erythema score is 1, the subsequent dose should be held at the same dose. If the score is >1, the next dose should be lowered by at least 1 J/cm^2.

Patients will be asked about any AEs experienced since the last light session and these will be recorded in the eCRF. Information on all unresolved, previously reported AEs will be obtained.

5.3.6 Week 6, Session 2

18-24 hours prior to the scheduled light session, the patient will be instructed to apply study drug to all accessible lesions. At that visit the following will be performed:

The patients will complete an VAS_{itch} form and the data transcribed into the eCRF.

Prior to the light session, 5 mL of blood obtained and processed for serum hypericin levels.

Prior to the light session, a 12-lead ECG obtained including QT interval measurements.

Adequate application of the drug will be verified by a pink staining on visual inspection of lesions.

Each patient will bring in their jar of study drug to the clinic. The jar will be weighed by clinic staff in order to estimate the amount of drug applied.

5-10 minutes ***before*** the light session, lesions will be graded using the Erythema Grading Score.

The light duration for the session to deliver the target dose of light determined by the Erythema Score of the previous treatment response of light will be calculated.

Patients will undergo the light treatment (may require repositioning to assure that all lesions are being treated).

5-10 minutes ***after*** completion of the light session, lesions will be graded using the Erythema Grading Score. If the score is <1, the next light dose should be increased. If the Erythema score is 1, the subsequent dose should be held at the same dose. If the score is >1, the next dose should be lowered by at least 1 J/cm^2.

Patients will be asked about any AEs experienced since the last light session and these will be recorded in the eCRF. Information on all unresolved, previously reported AEs will be obtained.

5.3.7 Week 7, Session 1; Week 7, Session 2; Week 8, Session 1

18-24 hours prior to the scheduled light session, the patient will be instructed to apply study drug to all accessible lesions. At that visit the following will be performed:

The patients will complete an VAS_{itch} form and the data transcribed into the eCRF.

Adequate application of the drug will be verified by a pink staining on visual inspection of lesions.

Each patient will bring in their jar of study drug to the clinic. The jar will be weighed by clinic staff in order to estimate the amount of drug applied.

5-10 minutes ***before*** the light session, lesions will be graded using the Erythema Grading Score.

Patients will undergo the light treatment (may require repositioning to assure that all lesions are being treated).

5-10 minutes ***after*** completion of the light session, lesions will be graded using the Erythema Grading Score. If the score is <1, the next light dose should be increased. If the Erythema score is 1, the subsequent dose should be held at the same dose. If the score is >1, the next dose should be lowered by at least 1 J/cm^2.

Patients will be asked about any AEs experienced since the last light session and these will be recorded in the eCRF. Information on all unresolved, previously reported AEs will be obtained.

5.3.8 Week 8, Session 2 Drug Application Visit

Patients will be asked to attend the clinic for the last drug application. At that visit, the following will be performed:

5 mL of blood obtained and processed for serum hypericin levels.

The drug will be applied by the patient under supervision of the site personnel.

The weight of the drug container will be weighed prior and after application of the drug.

Patients will be asked about any AEs experienced since the last light session and these will be recorded in the eCRF. Information on all unresolved, previously reported AEs will be obtained.

5.3.9 Week 8, Session 2 Light Session Visit

18-24 hours after application of study drug, patients will return to the clinic for their final light session. At that visit, the following will be performed:

The patients will complete an VAS_{itch} and Skindex-29 (Appendix III) forms and the data transcribed into the eCRF.

Adequate application of the drug will be verified by a pink staining on visual inspection of lesions.

Prior to the light session, 5 mL of blood obtained and processed for serum hypericin levels.

Prior to the light session, a 12-lead ECG obtained including QT interval measurements.

Prior to the light session, vitals will be taken (heart rate, respiratory rate, and sitting blood pressure).

Prior to the light session, a hematology panel will be drawn.

Prior to the light session, a clinical chemistry panel will be drawn.

5-10 minutes ***before*** the light session, lesions will be graded using the Erythema Grading Score.

The light duration for the session to deliver the target dose of light determined by the Erythema Score of the previous treatment response of light will be calculated.

Patients will undergo the light treatment (may require repositioning to assure that all lesions are being treated).

5-10 minutes ***after*** completion of the light session, lesions will be graded using the Erythema Grading Score.

2 hours ***after*** completion of the light session, 5 mL of blood obtained and processed for serum hypericin levels.

2 hours ***after*** completion of the light session, a 12-lead ECG obtained including QT interval measurements.

Patients will be asked about any AEs experienced since the last light session and these will be recorded in the eCRF. Information on all unresolved, previously reported AEs will be obtained.

5.3.10 Week 10, Follow-up visit/End of Study

During the last visit of the study, expected to occur 2 weeks following the final light treatment, the following assessments will be performed:

The patient will complete the VAS_{itch} form and the data transcribed into the eCRF.

Vitals taken (heart rate, respiratory rate, and sitting blood pressure).

Hematology panel drawn.

Clinical chemistry panel drawn.

5 mL of blood obtained and processed for serum hypericin levels.

CAILS scores for the 3 index lesions will be measured and recorded.

The mSWAT and PGA scores will be assessed and recorded.

A 12-lead ECG obtained including QT interval measurements.

Patients will be asked about any AEs experienced since the last light session and these will be recorded in the eCRF. Information on all unresolved, previously reported AEs will be obtained.

5.4 Premature Discontinuation

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 study may be replaced up to a total of 8 subjects provided that both the PI and the Soligenix Medical Monitor agree that the reasons for withdrawal do not suggest a change in the risk assessment of the HyBryte therapy.

6 DESCRIPTION OF STUDY PROCEDURES

Subjects will have the following procedures performed.

6.1 Light Session

The amount of visible light to be delivered will start at 5 J/cm^2 and be titrated up until either the patient experiences a mild (Erythema Grade 1) response to the light treatment 5-10 minutes post-treatment or a dose of 25 J/cm^2 is reached, whichever occurs first. The

duration of light treatment is dictated by the light treatment table listed below (Table 4). Depending on the distribution of the patient's lesions, more than one position for light treatments may be necessary.

Table 4: Duration of Light Exposure Required for Given Light Doses

Light Dose (J/cm^2)	Duration (Min: Sec)
5	10:49
6	12:59
7	15:09
8	17:19
9	19:29
10	21:39
11	23:49
12	25:58
13	28:08
14	30:18
15	32:28
16	34:38
17	36:48
18	38:58
19	41:08
20	43:17
21	45:27
22	47:37
23	49:47
24	51:57
25	54:07

6.2 Electrocardiogram (ECG)

12-lead ECGs, including QT interval measurement, will be done at baseline (prior to drug application), Week 4, Session 2 (immediately prior to and 2 hours after the light session), Week 6, Session 2 (immediately prior to the light session), Week 8, Session 2 Light Session Visit (immediately prior to and 2 hours after the light session), and at the Week 10 Follow-up visit. ECG will be interpreted by site personnel trained in the evaluation of ECGs for any interval changes.

6.3 Hypericin Blood Levels

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

- Baseline, prior to drug application
- Week 4 Session 2, prior to light session
- Week 4 Session 2, 2 hours after completion of the light session
- Week 6 Session 2, prior to the light session
- Week 8 Session 2 Drug Application visit, prior to drug application
- Week 8 Session 2 Light Session visit, 2 hours after completion of the light session
- Week 10/End of Study follow-up visit

Blood samples will be collected with K_2EDTA tubes and mixed (inverting top to bottom) at least 5 times after collection. Tubes will be placed on wet ice pending transfer to labeled 2 mL amber vials or tubes and then frozen (temperature ≤ -60 °C). The times that samples are collected and frozen must be noted.

Blood will be processed and shipped to the central laboratory as detailed in the "HPN-CTCL-02 Laboratory Manual For Pharmacokinetic Sample Collection". Samples will be shipped on dry ice to:

6.4 Clinical Laboratory Tests

6.4.1 Hematology Tests

The hematology panel will be performed on blood obtained at baseline, Week 8, Session 2 Light Session visit prior to the light session, and Week 10/End of Study. The panel will consist of the following tests:

Red blood cell count (RBC)

Hematocrit

Hemoglobin

Mean corpuscular volume (MCV)

Mean corpuscular hemoglobin (MCH)

Mean corpuscular hemoglobin concentration (MCHC)

Platelet count

White blood cell count (WBC)

Percent and absolute neutrophil count

Percent and absolute lymphocyte count

Percent and absolute monocyte count

Percent and absolute eosinophil count

Percent and absolute basophil count

6.4.2 Clinical Chemistry Laboratory Tests

The clinical chemistry panel will be performed on blood obtained at baseline, Week 8, Session 2 Light Session visit prior to the light session and during the Week 10/End of Study follow-up visit. The panel will consist of the following tests:

Serum sodium

Serum potassium

Serum chloride

Serum bicarbonate (CO_2)

Alanine aminotransferase (ALT)

Aspartate aminotransferase (AST)

Total bilirubin

Total protein

Serum creatinine

Blood urea nitrogen (BUN)

Alkaline phosphatase

6.5 Vital Signs

Vital signs will be obtained by site personnel at baseline, Week 8, Session 2 Light Session visit prior to the light session and during the Week 10/End of Study follow-up visit. Vital signs obtained will consist of:

- Resting Blood Pressure
- Heart Rate
- Respiratory Rate

6.6 Quality of Life Assessments

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

6.7 VAS Itch Assessment

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

6.8 Composite Assessment of Index Lesions Severity (CAILS) Score

The CAILS score will be assessed for the prospectively identified representative lesions at baseline and at the Week 10/End of Study visit. CAILS score will be calculated by assessing the erythema (Table 5), scaling (Table 6), plaque elevation (Table 7) and involved surface area (Table 8) for each of the index lesions. Each of the assessments and the total score for each evaluated lesion will be recorded in the case report form (CRF). The total CAILS score will be calculated by adding the scores of all evaluated lesions together.

Table 5: Erythema Subscore of the modified CAILS Score

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

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

Table 6: Scaling Subscore of the modified CAILS Score

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

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

Table 7: Plaque Elevation Subscore of the modified CAILS Score

Score	Description
0	0 mm: No evidence of plaque above normal skin level
1	Mild elevation
2	Moderate elevation
3	Marked elevation

Table 8: Surface Area Subscore of the modified CAILS Score

Longest diameter and the longest diameter perpendicular to this diameter of each index lesion will measured to the nearest millimeter. The lesion area will be the product of these two diameters	
Score	**Area**
0	0 cm^2
1	>0 and ≤4 cm^2
2	>4 and ≤10 cm^2
3	>10 and ≤16 cm^2
4	>16 and ≤25 cm^2
5	>25 and ≤35 cm^2
6	>35 and ≤45 cm^2
7	>45 and ≤55 cm^2
8	>55 and ≤70 cm^2
9	>70 and ≤90 cm^2
10	>90 and ≤110 cm^2
11	>110 and ≤130 cm^2
12	>130 and ≤155 cm^2
13	>155 and ≤180 cm^2
14	>180 and ≤210 cm^2
15	>210 and ≤240 cm^2
16	>240 and ≤270 cm^2
17	>270 and ≤300 cm^2
18	>300 cm^2

6.9 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 9. This assessment is designed to consider ***all cutaneous lesions***, including both index and non-index lesions. PGA score will be assessed at Week 10/End of Study.

Table 9: 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%

6.10 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 BSA. The types of lesions are weighted by the lesion characteristic (patch, plaque, or tumor) as shown in Table 10. The mSWAT score will be assessed at baseline and at Week 10/End of Study.

Table 10: 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%			

Body Region	% BSA[1] in Body Region	Assessment of Involvement in Patient's Skin		
		Patch[2]	Plaque[3]	Tumor[4]
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.

6.11 Erythema Scoring

Approximately 5-10 minutes before and after the completion of light therapy, treated lesions will be graded for erythema with the worst, best, and "average" scores recorded. The reaction will be graded using the definitions in Table 11.

Table 11: 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

7 STUDY DRUG MANAGEMENT

7.1 Description

HyBryte is synthetic hypericin formulated as a 0.25% hypericin (2.5 mg/gram) ointment. The ointment is lavender/purple.

7.1.1 Study Drug Packaging and Labeling

HyBryte will be supplied in plastic screw-top jars containing 25 grams of 0.25% hypericin (2.5 mg/gram). Jars will be labeled with the study number (HPN-CTCL-02), HyBryte™ (0.25% Hypericin) and the warning "Caution: New Drug-Limited by U.S. Federal Law to Investigational Use."

7.3 Administration

After adequate patient training, patients will apply HyBryte ointment to all accessible CTCL lesions, applied to cover a thin layer of drug 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. Personnel applying the drug should wear disposable gloves and wash their hands after applying the study ointment. If the medicine gets on healthy skin, it should be washed-off with soap and water. Patients will bring their drug jars to the clinic at each light treatment and site personnel will weigh the jars to estimate the amount of drug applied.

7.4 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 until distributed to patients. 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.

Patients will be instructed to store the drug in their refrigerator.

7.5 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.

7.6 Prohibited Concomitant Medication

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.

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

Topical steroids (including 1% hydrocortisone cream or ointment)

Other topicals (nitrogen mustard, carmustine/BCNU, retinoids, imiquimod)

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

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

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

Radiation therapy (localized or total skin)

Patients taking medication to cause photosensitization must be discontinued for at least 2 weeks prior to initiating HyBryte or have been on a stable dose of such drugs without any evidence of photosensitivity for a period of no less than 4 weeks. A list of the most common photosensitizing agents are as follows:

- Antibiotics: tetracyclines (doxycycline, tetracycline), fluoroquinolones (ciprofloxacin, ofloxacin levofloxacin), sulfonamides
- Nonsteroidal anti-inflammatories: ibuprofen and ketoprofen
- Diuretics: furosemide and hydrochlorothiazide
- Retinoids: isotretinoin and acitretin
- Hypoglycemics: sulfonylureas (glipizide, glyburide)
- PDT pro-photosensitizers: 5-aminolevulininc acid, methyl-5-aminolevulininc acid, verteporfin, Photofrin
- Neuroleptic drugs: phenothiazines (chlorpromazine, fluphenazine, perazine, perphenazine, thioridazine), thioxanthenes (chlorprothixene, thiothixene)
- Sunscreens: para-aminobenzoic acid (PABA), cinnamates, benzophenones, salicylates
- Fragrances: musk ambrette, 6-methylcoumarin
- Others: 5-FU, amiodarone

7.7 Compliance

Containers will be weighed before each light session. Any study drug discarded (eg, wiped off healthy skin, dropped or otherwise discarded) will be recorded.

8 ADVERSE EVENTS

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.

8.1 Definitions

8.1.1 Adverse Event (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.

8.1.2 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).

8.1.3 Potentially Serious AE

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.

8.2 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.

8.3 Severity of Adverse Event

A clinical determination of the intensity of an AE should be done for all reported AEs. The severity assessment for AEs 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.

8.4 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 CRF. 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.

9 SERIOUS ADVERSE EVENT

9.1 Definition of Serious Adverse Event

An SAE is any event that meets any of the following criteria:

Death

Life-threatening

Inpatient hospitalization or prolongation of existing hospitalization

Persistent or significant disability/incapacity

Congenital anomaly/birth defect in the offspring of a subject who received HyBryte

Other: 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 may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:

a. Intensive treatment in an emergency room or at home for allergic bronchospasm

b. Blood dyscrasias or convulsions that do not result in inpatient hospitalization

c. Development of drug dependency or drug abuse

Definition of Terms

Life threatening: An AE is life threatening if the subject was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient

setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

9.2 Reporting 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 EVENT REPORTING OR MEDICAL QUESTIONS THE MEDICAL MONITOR SHOULD BE CONTACTED:

Richard Straube, MD
Senior Vice President & Chief Medical Officer,
Study Medical Monitor
[redacted]

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
Medical Director
[redacted]

10 STATISTICS

10.1 General Procedures

This is an observational study. No analyses for efficacy will be performed.

10.2 Analysis of Safety

Listings of findings per patient will be provided. Average and median results for laboratory findings, vital signs, ECG findings and PK outcomes will be provided. Any significant outliers (>2x the standard deviation) will be highlighted. Listings of AEs within 48 hours of ointment application will be tabulated. Any serious or related AEs determined within 14 days of last drug application will be tabulated, in addition to any medications received during the 10-week period.

10.3 Interim Analysis

No interim analysis is planned.

11 ETHICS AND RESPONSIBILITIES

11.1 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 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.

11.2 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.

11.3 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.

11.4 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 enrollment code/subject number only. Authorized representatives 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.

11.5 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.

12 RECORDS MANAGEMENT

12.1 Source Documentation

Copies of CRFs 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 CRFs 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.

13 AUDITING AND MONITORING

13.1 Study Monitoring

It is the responsibility of the PI and site personnel to assure that the data recorded in the CRFs 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.

13.1.1 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 adequately 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.

13.1.2 Site Initiation Visit

Once all required trial 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.

13.1.3 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

CRFs 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 CRFs 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.

13.1.4 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 CRFs 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.

13.2 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).

14 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Soligenix, Inc. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. Soligenix, Inc., will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or Soligenix, Inc., the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

15 STUDY REPORT

Soligenix, Inc., is responsible for providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

16 STUDY DISCONTINUATION

Both Soligenix, Inc., and the Principal Investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, Soligenix, Inc. or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Principal Investigator will inform the IRB/IEC of the same. In terminating the study, Soligenix, Inc. and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

17 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Soligenix, Inc. However, authorized regulatory officials, IRB/IEC personnel, Soligenix, Inc. and its authorized representatives are allowed full access to the records.

Identification of subjects and CRFs shall be by initials, screening and treatment numbers only. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

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19 APPENDICES

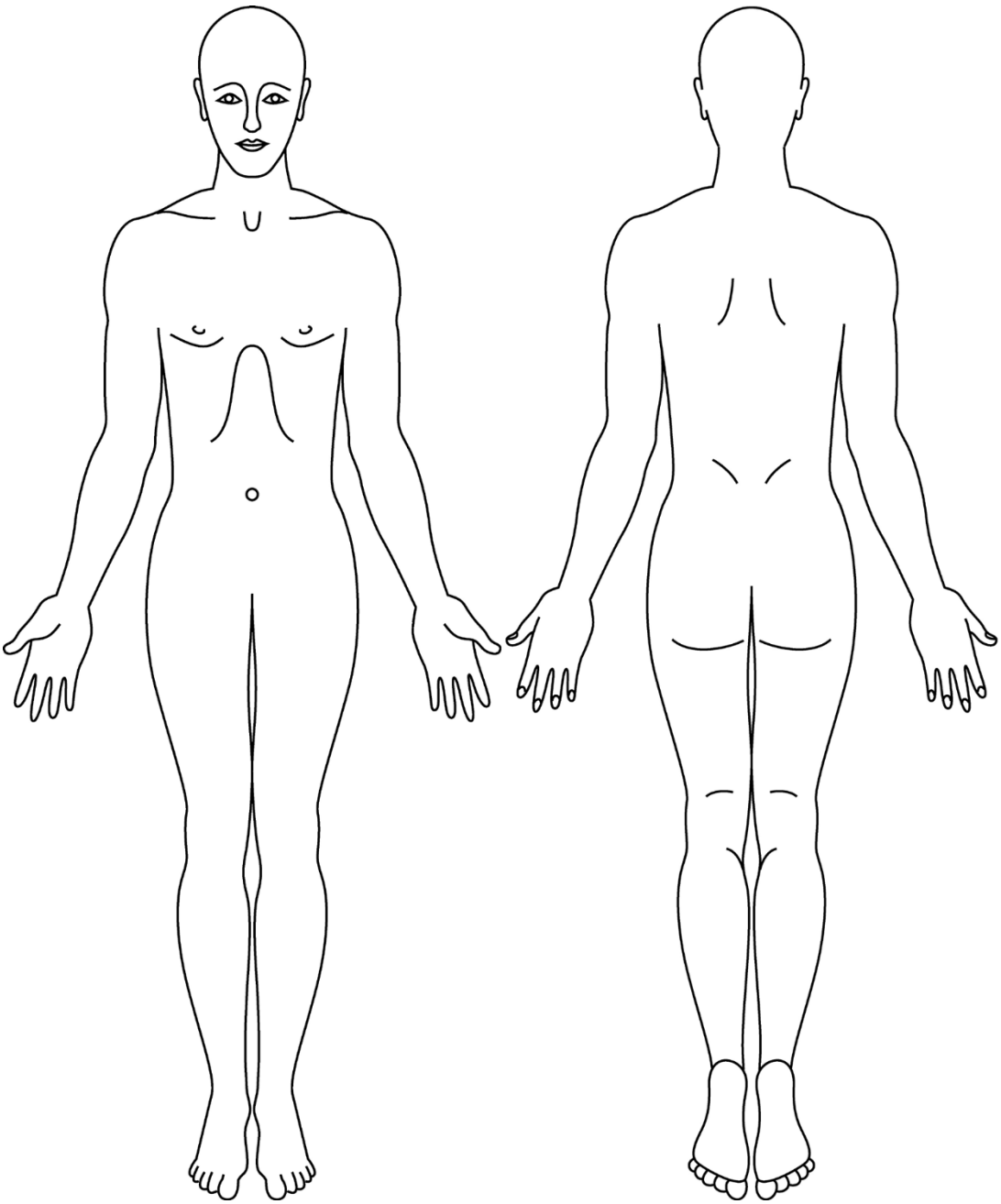
19.1 APPENDIX I – Names of Study Personnel

Sponsor:	Soligenix, Inc. Christopher Pullion, DO Medical Director 29 Emmons Drive; Suite B-10 Princeton, NJ 08540 [redacted]
Medical Monitor:	Richard Straube, MD Senior Vice President, Chief Medical Officer 29 Emmons Drive; Suite B-10 Princeton, NJ 08540 [redacted]

19.2 APPENDIX II – Body Lesion Diagram

BODY LESION DIAGRAM: SOLIGENIX / HyBryte

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



19.3 APPENDIX III – Skindex-29 Assessment

Skindex29
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These questions concern your feelings over the past 4 weeks about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

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

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

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

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