CLINICAL RESEARCH PROTOCOL

DRUG:	HyBryte™ (0.25% hypericin ointment)
STUDY NUMBER(S):	HPN-CTCL-04
PROTOCOL(S) TITLE:	Pilot Study of HyBryte™ (synthetic hypericin) versus Valchlor® (mechlorethamine) in the Treatment of CTCL
IND NUMBER:	[redacted]
SPONSOR:	Soligenix, Inc.
ORIGINAL PROTOCOL DATE:	02 August 2023
VERSION NUMBER:	Amendment 2
VERSION DATE:	05 March 2024

NCT06149247

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: Pilot Study of HyBryte™ (synthetic hypericin) versus Valchlor® (mechlorethamine) in the Treatment of CTCL

Study No: HPN-CTCL-04

Original Protocol Date: 02 August 2023

Protocol Version No: Amendment 2

Protocol Version Date: 05 March 2024

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Name and Title	Approval	Signature	Date
[redacted]	☒ Yes ☐ No (select one)	[redacted]	
[redacted]	☒ Yes ☐ No (select one)	[redacted]	
[redacted]	☒ Yes ☐ No (select one)	[redacted]	
[redacted]	☒ Yes ☐ No (select one)	[redacted]	

HPN-CTCL-04

Pilot Study of HyBryte™ (synthetic hypericin) versus Valchlor® (mechlorethamine) in the Treatment of CTCL

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: Pilot Study of HyBryte™ (synthetic hypericin) versus Valchlor® (mechlorethamine) in the Treatment of CTCL

Investigators: Brian Poligone, MD

Study Centre(s): Rochester Skin Lymphoma Center

Publication (reference): N/A

Study Period (years): 0.5 year **Date of First Enrollment:** January 2024 **Planned Date of Last Completed:** May 2024	**Phase of Development:** Phase 2

Objectives: The objectives of this study are to:

- Obtain experience with tactical issues of conducting an open-label study of HyBryte versus Valchlor
- Obtain preliminary comparative assessment of safety and efficacy of Valchlor versus HyBryte following 12 weeks of treatment
- Obtain data on the impact of timing on the ease of measuring mCAILS (modified Composite Assessment of Index Lesion Severity) during treatment of CTCL patients receiving HyBryte therapy

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

Methodology: This will be an open-label trial enrolling patients with CTCL (stage IA, IB, or IIA) randomized to receive topical HyBryte or topical Valchlor for 12 weeks.

Patients randomized to HyBryte will apply the drug to all accessible lesions twice per week followed by visible light treatment 21 (±3) hours later starting at 6 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) and dropping the light dose if there is Grade 2 erythema. Should the patient have Grade ≥3, treatment will be suspended for 1 week and treatment may be restarted at a 1 J/cm^2 lower than the last well-tolerated light dose.

Patients randomized to Valchlor will receive commercially available drug applied as per the package insert.

Three to 5 prospectively identified index lesions will be evaluated for mCAILS assessment and the lesions chosen will be representative of the patient's overall disease and, if the patient has both patch and plaque lesions, the index lesions should include each type in the approximate same percentage as their total lesions.

Patients will be treated for a total of 12 weeks, with follow-up visits at Week 13, Week 14, and Week 16/End of Study. Every three weeks, patients will come to the clinic for an assessment visit (ie, at Week 3, Week 6, Week 9, and Week 12). At these evaluation visits, a cumulative mCAILS, modified Severity-Weighted Assessment Tool (mSWAT), Physician Global Assessment (PGA), Skin Adverse Event Questionnaire (SAEQ) will be completed, and Scoring Dermatitis (SCORD) collected.

For HyBryte patients, these assessments will be done immediately prior to light treatment at the second light treatment visit of the evaluation week (ie, Weeks 3, 6, 9, 12).

Follow-up assessments will be conducted at Week 13 (1-week post-treatment), Week 14 (2 weeks post-treatment), and Week 16/End of Study (4 weeks post-treatment) and will also include mCAILS, mSWAT, PGA, SAEQ, and SCORD assessments.

Physical examinations and safety labs (hematology and chemistry) will be analyzed at Baseline, at the Week 12 assessment visit, and 4 weeks after completion of therapy (Week 16/End of Study). AE's will be recorded throughout the study. Vital signs will be collected at Baseline and Weeks 3, 6, 9, 12, 13, 14 and 16.

Number of patients (planned): Approximately 10 subjects will be randomized 1:1 (HyBryte: Valchlor)

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

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. Minimum of 3 active treatment-accessible CTCL lesions
3. Subjects must have a clinical diagnosis of cutaneous T-cell lymphoma (CTCL, mycosis fungoides), Stage IA, 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 severe allergic reaction to any of the components of HyBryte or mechlorethamine (Valchlor)
2. Pregnancy or mothers who are breast-feeding
3. All women of childbearing potential (WOCBP) and males with female partners who are WOCBP not willing to use effective contraception (see section 5.3, Exclusion Criteria; Exclusion Criterion #3 for more details)
4. Subjects with history of sun hypersensitivity or photosensitive dermatoses (eg, porphyria, systemic lupus erythematosus (SLE), Sjogren's syndrome, etc.)
5. Subjects whose condition is spontaneously improving
6. Subjects receiving Valchlor in the preceding 2 months
7. Subjects receiving topical steroids or other topical treatments (eg, Targretin gel) on treatment accessible lesions for CTCL within 2 weeks of enrollment
8. 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
9. Subjects who have received electron beam irradiation within 3 months of enrollment
10. Subjects with a history of significant systemic immunosuppression
11. Subjects taking other investigational drugs or drugs of abuse within 30 days of enrollment
12. Subject has any condition that, in the judgment of the PI, is likely to interfere with participation in the study
13. 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

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Name of Finished Product HyBryte™		
Name of Active Ingredient Hypericin (0.25% ointment)		

Test product, dose and mode of administration: HyBryte (0.25% hypericin) will be applied in a thin film on all lesions avoiding treatment of healthy skin. The drug will be activated 21 ± 3 hours after application starting at 6 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 and dropping the light dose if there is Grade 2 erythema. Should the patient have Grade ≥3, treatment will be suspended for 1 week and treatment may be restarted at a 1 J/cm^2 lower than the last well-tolerated light dose.

Valchlor will be administered in accordance with the FDA-approved package insert.

Duration of treatment: Subjects will be randomized to 12 weeks of treatment with either HyBryte or Valchlor in a 1:1 ratio. Subjects randomized to HyBryte will apply HyBryte to all accessible lesions followed 21 (±3) 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 12 weeks of treatment (24 actual treatments). Patients randomized to Valchlor will receive treatment for 12 weeks with Valchlor following the directions in the FDA-approved package insert.

Patients will come to the clinic for an assessment visit at Baseline, Week 3, Week 6, Week 9, and Week 12. Patients will have mCAILS scores collected on their 3 to 5 index lesions, an mSWAT score, PGA, SAEQ, and a SCORD score collected.

For patients randomized to HyBryte, the assessments will be conducted immediately prior to light treatment at the second light treatment visit of the evaluation week (ie, Weeks 3, 6, 9, 12) immediately prior to the corresponding light treatment.

Patients will return to the clinic for follow-up visits and have assessments (SCORD, mCAILS, mSWAT, PGA, SAEQ, and SCORD) at Week 13, Week 14, and Week 16/End of Study.

Safety laboratory assessments and physical exams will be done at Baseline, the Week 12 assessment visit, and the Week 16/End of Study visit. Vital signs will be collected at Baseline and Weeks 3, 6, 9, 12, 13, 14 and 16. Adverse events will be collected throughout the study.

Reference therapy, dose and mode of administration: Valchlor treatment in accordance with prescribing information in package insert.

Criteria for evaluation:

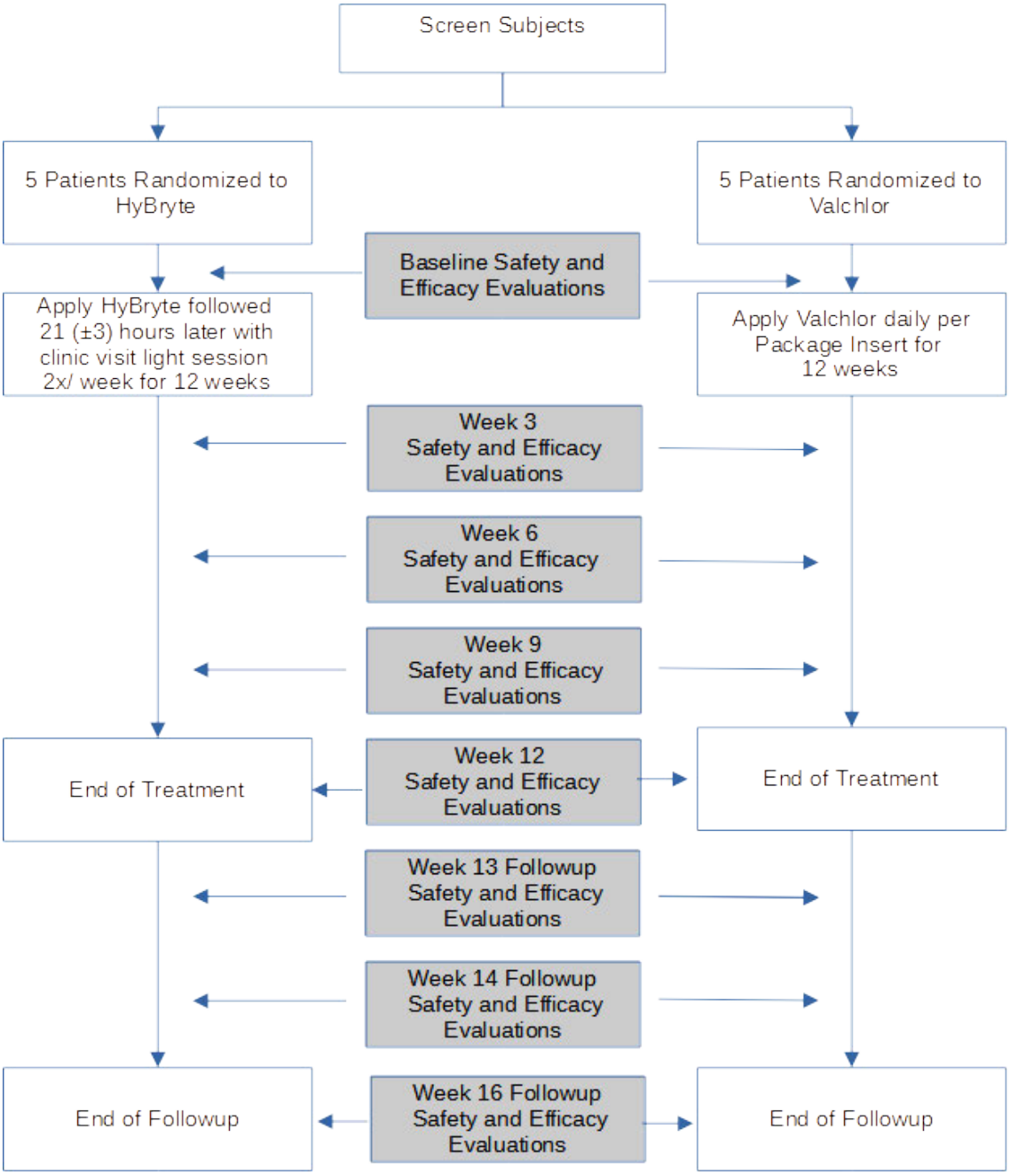
Efficacy:

This is a pilot study to obtain preliminary comparative assessments of safety and efficacy and determine the practical issues likely to arise in a larger clinical study comparing HyBryte to Valchlor. No formal efficacy statistics will be performed. Results will be presented as tables and listings.

Safety:

The safety variables evaluated are: SAEQ, SCORD score, clinical hematology assessments, clinical chemistry assessments, physical examinations, vital signs, and the collection of adverse/serious adverse events.

STUDY SCHEMATIC



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AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATL	Adult T-cell Leukemia
BCNU	Carmustine
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CRF	Case Report Form
CTCL	Cutaneous T-cell Lymphoma
ER	Endoplasmic Reticulum
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HTLV-1	Human T-cell Leukemic Virus Type I
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System

Iv	Intravenous
mCAILS	Modified Composite Assessment of Index Lesion Severity
MF	Mycosis Fungoides
Min	Minute
mSWAT	Modified Severity-Weighted Assessment Tool
NB-UVB	Narrow Band UVB
NDA	New Drug Application
PDT	Photodynamic Therapy
PGA	Physician Global Assessment
PHA	Phytohemagglutinin Antigen
PI	Principal Investigator
Po	Per Os (By Mouth), Orally
PUVA	Psoralen Ultraviolet A Radiation Therapy
ROS	Reactive Oxygen Species
SAE	Serious Adverse Event
SAEQ	Skin Adverse Event Questionnaire
SCORD	SCORing Dermatitis score
SLE	Systemic Lupus Erythematosus
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
UV	Ultraviolet
UVA	Ultraviolet A

UVB	Ultraviolet B
VAS	Visual Analog Scale
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1 INTRODUCTION AND RATIONALE

1.1 Background

HyBryte™ (0.25% hypericin) is a chemically synthesized hypericin formulated for topical use only for the treatment of early-stage Cutaneous T-cell Lymphoma (CTCL) and is intended to be administered only in conjunction with a schedule of controlled doses of visible light. Hypericin is a photodynamic radical generator that has been shown to have anti-cancer effects in the dark with substantially more effects after activation by light in the 500 to 650 nm wavelength range. More complete information on hypericin is available in the Investigator Brochure.

1.2 Study Rationale

The Phase 3 trial, HPN-CTCL-01, demonstrated that HyBryte in combination with visible light activation given 2× per week for 6 weeks statistically significantly increased the number of patients with a ≥50% improvement in their treated lesions when compared to a concurrent placebo group (Kim 2022). Among those that continued HyBryte treatment for an additional 6 or 12 weeks, a significant and substantial improvement in their response rates was seen. Similar safety and efficacy findings were seen in 9 patients enrolled in HPN-CTCL-02 that treated patients for 8 weeks (NCT05380635).

This study is a pilot study to obtain preliminary comparative assessments of the efficacy and safety of Valchlor compared to HyBryte as well explore the practical issues involved with an open-label HyBryte/ active control group design in early-stage CTCL.

1.2.1 Pharmacokinetics

Hypericin was initially developed for the systemic treatment of enveloped viral infections including human immunodeficiency virus (HIV) (Gulick 1999), hepatitis C virus (HCV) (Jacobson 2001) and glioma (Couldwell 2011). Following dosing with either intravenous (iv) or oral (po) routes, the only consistently reported adverse events 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 to 6 weeks of continuous therapy on multiple lesions). 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 circulating levels were <5 ng/mL (lower limit of detection of the bioanalytical method).

A subsequent clinical study of 9 patients (HPN-CTCL-02) utilized a modified assay. Hypericin concentration in K_2EDTA whole blood samples collected before and after light

activation at Weeks 4, 6 and 8 showed an average blood concentration of 0.13 ng/mL and achieved steady state by Week 4, as determined with a validated assay with a detection limit of 0.05 ng/mL. Patients within the study had a range of disease involvement (11 to 65% BSA) and average dose application (maximum 1.7 to 10.3 g HyBryte per topical application). Maximum obtained circulating blood concentration was not well-correlated with either extent of disease or maximum average applied dose indicating that systemic concentration was likely driven by variability in skin permeability. There was no discernible role of gender or race on the measured systemic concentration. No patient had a blood level >0.5 ng/mL at any timepoint. Blood levels were below detection limit for 7/9 patients by the end of study visit (2 weeks after cessation of dosing), with the remaining 2 patients recording blood concentrations of 0.06 and 0.10 ng/mL.

In comparison, hypericin levels following oral or iv administration of the drug in viral and cancer trials were up to 10,000-fold higher and the major and dose limiting restriction was photosensitization - the biologic effect being exploited in this CTCL treatment.

1.2.2 Preclinical Pharmacology

The pharmacology of hypericin has been extensively studied in the literature. Given its unique and highly conjugated structure, hypericin is both extremely chemically stable and easily photoactivated (with visible light in the yellow/red spectrum; 500 to 650 nm). While hypericin has been found to have some biological activities in the absence of light, it is between 10- and 100-fold more potent via photoactivated mechanisms, assuming the presence of oxygen. Photoactivation of hypericin contributes to the formation of singlet oxygen and reactive oxygen species (ROS), increasing oxidative stress on the cell (Dąbrowski 2017). Downstream of this oxidative stress, a number of intracellular pathways may be activated, depending on the specific characteristics of the cell. Generally speaking, the oxidative stress can drive apoptosis (at lower light/dose concentrations) and necrosis (at higher light/dose concentrations). Malignant cells are generally more sensitive to this oxidative stress condition.

Hypericin is highly lipophilic, sparingly soluble in aqueous settings, and carries a single negative charge at the pHs relevant to the biological milieu. Because of these characteristics, hypericin is rapidly absorbed into the cellular membrane and then redistributed within the cell across all lipoprotein organelles including the Golgi apparatus, endoplasmic reticulum (ER), and lysosomes (de Andrade 2021).

In the in vivo setting, hypericin has been found to be tumoritropic, favoring absorption into tumor cells over normal cells. In addition to its increased absorption into tumor cells and potentially other cells lacking E-cadherin, hypericin also has significant necrotic avidity. Indeed, hypericin has been explored as both a photodiagnostic agent (eg, for bladder cancer) and as a radiotherapy (via the use of radioiodinated hypericin).

The primary mode of biological activity relates to the photoactivation of hypericin, forming singlet and triplet hypericin and, upon interaction with oxygen and other intracellular species, generating ROS and driving apoptosis via the mitochondrial pathway. The degree of phototoxicity elicited by hypericin is related to its concentration, subcellular localization and light intensity (Jendzelovska 2016). The permeability, presence of oxygen and specific intramolecular pathways of the targeted cell will also impact outcomes. Generally, low doses of phototoxicity are associated with apoptosis while higher doses can also result in necrosis (de Andrade 2021).

Observations in the laboratory of Dr. Alain Rook at the University of Pennsylvania have demonstrated a significant antiproliferative effect of synthetic hypericin on activated normal human lymphoid cells upon exposure of the synthetic hypericin-treated cells to visible light (Fox 1998). At concentrations of synthetic hypericin ranging between 0.1 and 0.5 μM, a 20-minute exposure of normal lymphoid cells to fluorescent light resulted in complete inhibition of proliferative responses to the potent mitogens phytohemagglutinin antigen (PHA) and concanavalin A (Con A). Similarly, malignant T-cells purified from the blood of patients with Sézary syndrome or the leukemic phase of CTCL displayed markedly inhibited growth rates in response to T-cell growth factors when treated with 0.3 μM of synthetic hypericin and 20-minute exposure to fluorescent light. While the precise mechanism of inhibition of proliferation is unclear, it appears that synthetic hypericin has the capacity to induce a high rate of apoptotic death in both normal and malignant lymphoid cells. The implications of these findings for the use of topical synthetic hypericin to treat CTCL, which is characterized by malignant lymphocytic infiltrates in the skin, are significant and serve as the mechanistic basis for the use of HyBryte in CTCL.

Selective apoptosis has also been generated for T-cells infected with human T-cell leukemic virus type I (HTLV-1), known to be the primary etiologic agent for adult T-cell leukemia (ATL). In contrast, primary T-cells were shown to be resistant to apoptosis at similar concentrations and exposure to light between 520 and 750 nm at 11.28 J/cm^2. Cell death was partially driven by caspase dependent apoptosis, as demonstrated by the increased concentration of cleaved caspase-3, 7 and 9. Similarly, hypericin photodynamic therapy (PDT) was also associated with inhibition of cell cycle progression (arresting ATL cells in G2/M phase) and with inhibition of viral genes (Xu 2019).

Hypericin has been assessed for skin pre-malignancies and malignancies. Topical hypericin PDT for actinic keratosis was assessed in a model in which skin tumors were induced in mice by chronic UV irradiation, and antitumor activity of topical hypericin (0.1%) kept under occlusion for 24 hours prior to light exposure (587-589 nm, 40 J/cm^2) was evaluated by measurement of lesion diameter (Boiy 2011). Hypericin fluorescence accumulated in the stratum corneum prior to irradiation, with greater accumulation in skin that was previously irradiated with UV light to encourage tumor formation and skin with overt lesions. Hypericin PDT groups demonstrated 44% total lesion clearance 3

weeks after a single treatment. In addition, hypericin PDT drove the replacement of atypical actinic keratosis cells with normal keratinocytes.

1.2.3 Potential for Drug-Drug Interactions

No significant drug-drug interactions are expected due to increased expression or decreased activity of cytochrome P450 enzymes after topical application of HyBryte.

There are reported interactions between hypericin and cytochrome P450 proteins at micromolar dose levels (Silva 2016). It is unlikely that significant cytochrome P450 inhibition would occur with the proposed topical application given the very low systemic concentration of hypericin after topical applications.

1.2.4 Clinical Adverse Event Profile

The best information on safety comes from the HPN-CTCL-01 Phase 3 study. Treatment Emergent Adverse Events (TEAEs) occurring in at least 3% of patients are shown in Table 1, below. In this trial, patients were randomized 2: 1 as HyBryte: placebo and their 3 index lesions were treated 2×/week. In Cycle 1, patients received 6 weeks of treatment with either placebo or HyBryte and in Cycle 2, all patients received 6 weeks of treatment of their index lesions with HyBryte. An optional Cycle 3 was offered that treated all of the patient's lesions for 6 weeks with HyBryte.

Table 1: TEAEs by System Organ Class and Preferred Term, Total Incidence ≥3%: Safety Population

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 (%)	Total (N=161) n (%)	Total (N=166) n (%)
#Patients ≥1 TEAE	56 (48.3)	27 (54.0)	66 (42.6)	49 (44.5)	108 (67.1)	116 (69.9)
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)

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 (%)	Total (N=161) n (%)	Total (N=166) n (%)
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 paraesthesia	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)

n = 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. A patient was counted only once for each AE he/she experienced. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.
Note: The majority of the AEs shown were mild, required no intervention or treatment and did not interfere with continued use or light therapy and participation in the study. Study drop-out rate during the treatment cycles was 1.2% due to AEs.

1.2.5 Potential Risk to Fetal Development

Although the available animal data suggest that the risk to pregnancy is low, available human data are insufficient to inform the drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Topically applied HyBryte is minimally systemically absorbed and maternal use is not expected to result in fetal exposure to the drug. Nonetheless, it is recommended pregnancy be avoided while taking HyBryte and treatments be discontinued immediately if the patient becomes pregnant.

In a rat developmental toxicity study, hypericin was evaluated for maternal and embryo/fetal toxicity and teratogenic potential when orally administered to pregnant rats during the period of organogenesis. There was no evidence of an effect on *in utero* growth, survival, or development at any dose level. It is also not known whether HyBryte can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HyBryte and any potential adverse effects on the breastfed child from HyBryte or from the underlying maternal CTCL. It is recommended that breastfeeding be discontinued during HyBryte therapy.

2 STUDY OBJECTIVES

Objectives: The objectives of this study are to:

- Obtain experience with tactical issues of conducting an open-label study of HyBryte versus Valchlor
- Obtain preliminary comparative assessment of safety and efficacy of Valchlor versus HyBryte following 12 weeks of treatment
- Obtain data on the impact of timing on the ease of measuring mCAILS (modified Composite Assessment of Index Lesion Severity) during treatment of CTCL patients receiving HyBryte therapy

3 STUDY ENDPOINTS

Efficacy:

This is a pilot study to obtain preliminary comparative assessments of safety and efficacy and determine the practical issues likely to arise in a larger clinical study comparing HyBryte to Valchlor. No formal efficacy statistics will be performed. Results will be presented as tables and listings. Efficacy assessments are:

- mCAILS score on 3 to 5 prospectively identified index lesions
- Modified Severity-Weighted Assessment Tool (mSWAT) score
- Physician Global Assessment (PGA)

Safety:

The safety variables evaluated are:

- Skin Adverse Event Questionnaire (SAEQ)
- SCORing Dermatitis (SCORD) score
- Changes in clinical hematology results
- Changes in clinical chemistry assessments
- Changes in physical examinations
- Changes in vital signs
- Collection of adverse/serious adverse events

4 STUDY PLAN

4.1 Study Design

This is a randomized, pilot study assessing outcomes of patients receiving HyBryte compared to Valchlor in patients with stage IA, IB, and IIA CTCL. Subjects will be randomized to 12 weeks of treatment with either HyBryte or Valchlor in a 1:1 ratio. Subjects randomized to HyBryte will apply HyBryte to all accessible lesions followed 21 (±3) 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 12 weeks of treatment (24 actual treatments). Patients randomized to Valchlor will receive treatment for 12 weeks with Valchlor following the directions in the FDA-approved package insert.

Patients will come to the clinic for an assessment visit at Baseline, Week 3, Week 6, Week 9, and Week 12. Patients will have mCAILS scores collected on their 3 to 5 index lesions, an mSWAT score, PGA, SAEQ completed, and a SCORD score collected.

For patients randomized to HyBryte, the assessments will be conducted immediately prior to light treatment at the second light treatment visit of the evaluation week (ie, Week 3, 6, 9, 12) immediately prior to the corresponding light treatment.

Patients will return to the clinic for follow-up visits and have assessments (mCAILS, mSWAT, PGA, SAEQ, and SCORD) at Week 13, Week 14, and Week 16/End of Study.

Safety laboratory assessments and physical exams will be done at Baseline, the Week 12 assessment visit, and the Week 16/End of Study visit. Vital signs will be collected at Baseline and Weeks 3, 6, 9, 12, 13, 14 and 16. Adverse events will be collected throughout the study.

4.2 Schedule of Assessments

Patients randomized to receive HyBryte will have assessments and treatment as shown in Table 2.

Table 2: HyBryte Patients: Schedule of Assessments

Activity	Screen	Base-line	Week														
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	16
Clinic visit	X	X	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	X	X	X
Drug Treatment[a]		X	X	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX			
Informed consent	X																
Entry criteria	X	X															
Medical history	X	X															
Serum HCG (females only)	X	X												X			
Identify index lesions		X															
Interim medical history/AEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy assessments[b]		X			X			X			X			X	X	X	X
Safety assessments[c]		X			X			X			X			X	X	X	X
Vital signs		X			X			X			X			X	X	X	X
Physical Exam		X												X			X
Labs[d]		X												X			X

[a] Patients will apply HyBryte and come in to clinic 21 ± 3 hours later for light treatments. applications will be done at home twice per week at least 2 calendar days apart except for the second treatment in Weeks 3, 6, 9, and 12 when application should occur following the assessment visit either in the clinic or at home. Patients will have erythema assessment and a dermatologic grading of treated areas before and 10-30 minutes after completion of the light treatment.

[b] Efficacy assessments are: mCAILS, mSWAT, PGA

[c] Safety Assessments are: SAEQ, SCORD, and collection of AEs

[d] Labs are: Clinical hematology panel, Clinical Chemistry panel

Patients randomized to receive Valchlor will be treated as per the Package Insert and will apply a thin film of Valchlor on lesions daily. The Schedule of Assessments for this arm of the study is shown in Table 3.

Table 3: Valchlor Patients: Schedule of Assessments

Activity	Screen	Base-line	Week						
			3	6	9	12	13	14	16
Clinic visit	X	X	X	X	X	X	X	X	X
Informed consent	X								
Entry criteria	X	X							
Medical history	X	X							
Serum HCG (females only)	X	X				X			
Identify index lesions		X							
Interim medical history/AEs			X	X	X	X	X	X	X
Efficacy assessments[a]		X	X	X	X	X	X	X	X
Safety assessments[b]		X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X
Physical Exam		X				X			X
Labs[c]		X				X			X

[a] Efficacy assessments are: mCAILS, mSWAT, PGA

[b] Safety Assessments are: SAEQ, SCORD, and collection of AEs

[c] Labs are: Clinical hematology panel, Clinical Chemistry panel

5 POPULATION

5.1 Number of Subjects

Approximately 10 patients will be randomized 1:1 into the HyBryte: Valchlor arms.

5.2 Inclusion Criteria

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

1. ≥18 years of age
2. Minimum of 3 active treatment-accessible CTCL lesions
3. Subjects must have a clinical diagnosis of cutaneous T-cell lymphoma (CTCL, mycosis fungoides), Stage IA, 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

5.3 Exclusion Criteria

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

1. History of severe allergic reaction to any of the components of HyBryte or mechlorethamine (Valchlor)
2. Pregnancy or mothers who are breast-feeding
3. All women of childbearing potential (WOCBP) and males with female partners who are WOCBP not willing to use effective contraception
    a. Women are considered to be WOCBP following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy and bilateral oophorectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. Effective contraception methods for WOCBP should be started prior to randomization and continued for a minimum of 35 days following completion of study drug administration.

b. Acceptable contraceptive methods for WOCBP are those that achieve a failure rate of less than 1% per year and include:

   i. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

      (1) Oral

      (2) Intravaginal

      (3) Transdermal

   ii. Progestogen-only hormonal contraception associated with inhibition of ovulation:

      (1) Oral

      (2) Injectable

      (3) Implantable

   iii. Intrauterine device (IUD)

   iv. Intrauterine hormone-releasing system (IUS)

   v. Bilateral tubal occlusion

   vi. Vasectomised partner

   vii. Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments

c. Male subjects should use condoms during treatment and for 98 days following the last study drug administration period.

4. Subjects with history of sun hypersensitivity or photosensitive dermatoses (eg, porphyria, systemic lupus erythematosus (SLE), Sjogren's syndrome, etc.)

5. Subjects whose condition is spontaneously improving

6. Subjects receiving Valchlor (or any topical compound containing Mechlorethamine) in the preceding 2 months

7. Subjects receiving topical steroids or other topical treatments (eg, targretin gel) on treatment accessible lesions for CTCL within 2 weeks of enrollment

8. 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

9. Subjects who have received electron beam irradiation within 3 months of enrollment

10. Subjects with a history of significant systemic immunosuppression

11. Subjects taking other investigational drugs or drugs of abuse within 30 days of enrollment

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

13. 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

6 STUDY CONDUCT

6.1 General Instructions

This is a pilot, randomized, open-label, active comparator, US, single-center trial in which patients will be randomized to receive HyBryte or Valchlor in a 1:1 randomization. Patients will be treated for 12 weeks and follow-up visits will be conducted 1, 2, and 4 weeks after completion of the treatment phase of the trial.

Patients randomized to HyBryte will have HyBryte applied twice weekly and an opaque covering applied for 21 (±3) hours followed by the administration of visible light encompassing wavelengths of 500 to 650 nm. The light will be administered with a precisely calibrated device with a light dose starting at 6 J/cm^2 twice weekly that is titrated up according to the physician's discretion on subsequent sessions, limited by occurrence of Grade 2 erythema or greater but targeting a mild, Grade 1 reaction immediately following the light treatment. All of the patient's lesions that are readily available for exposure to the visible light source will be treated.

Patients randomized to Valchlor will apply a thin film of Valchlor gel once daily to affected areas of the skin and the dosing will follow the instructions for use in the package insert.

Prior to randomization, each patient will have at least 3 and up to 5 index lesions identified. These lesions should be representative of the patient's treated lesions and, if the patient has both plaque and patch lesions, include approximately the same distribution as the patient's other lesions.

6.2 Study Procedures by Time Point

6.2.1 Screening

Patients will be screened up to 30 days prior to randomization. At the screening visit the following will be done:

- Signed, Informed Consent Form obtained
- Inclusion/exclusion criteria reviewed
- Complete medical history completed
- Women of child-bearing potential will have a serum pregnancy test obtained

6.2.2 Baseline

At the Baseline visit, the following will be done prior to randomization:

- Confirmation that the patient meets all inclusion/exclusion criteria
- History of any medical changes obtained
- Women of child-bearing potential will have a serum pregnancy test obtained unless the screening test was obtained 7 days or less
- Physical exam
- Vital signs obtained
- Blood for the hematology panel obtained
- Blood for the clinical chemistry panel obtained
- Three to five 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" (APPENDIX III – Body Lesion Diagram) locating and numbering each of the index lesions
- Each index lesion will have an mCAILS score assessed and recorded
- The mSWAT score will be assessed and recorded
- The SAEQ score will be collected and recorded
- The SCORD score will be collected and recorded

Once all of these assessments are completed, the patient will be randomized into one of the two treatment arms, to receive HyBryte or Valchlor as the study drug. Patients who are randomized into the HyBryte treatment arm will follow the assessments outlined in Section 6.2.3. Patients who are randomized into the Valchlor treatment arm will follow the assessments outlined in Section 6.2.4.

6.2.3 HyBryte Patients

Patients who are randomized into the HyBryte treatment arm will be given a jar of ointment at the Baseline visit. They will be instructed on proper drug application and demonstrate proficiency in drug application and all accessible lesions will be treated with study drug.

6.2.3.1 Standard light treatment clinic visits

Patients randomized to HyBryte will have HyBryte applied twice weekly and an opaque covering applied for 21 (±3) hours followed by the administration of visible light encompassing wavelengths of 500 to 650 nm. The light will be administered with a precisely calibrated device with a light dose starting at 6 J/cm^2 twice weekly that is titrated up according to the physician's discretion on subsequent sessions. Treatment will target a post-light treatment Erythema score of 1. The light dose will be reduced, maintained or treatment administrations may be suspended if a Grade 2 or greater erythema is present. Additional assessments of treated lesions and surrounding areas will include:

- Erythema
- Pain
- Pruritus
- Edema
- Hyperpigmentation
- Hypopigmentation
- Rash
- Vesiculation

Each dermatological assessment will be graded according to Table 4. All of the patient's lesions that are readily available for exposure to the visible light source will be treated.

Table 4: Dermatologic Assessment Grading

Toxicity Grade:	Severity
Grade 0	No apparent reaction
Grade I	Mild
Grade II	Moderate
Grade III	Severe
Grade IV	Life-threatening

At each visit, the following assessments will be conducted:

- Interval medical history obtained

- Any AEs documented
- Adequate application of the drug will be verified by a pink staining on visual inspection of lesions prior to administration of light
- Delivery of light session, the time of treatment calculated by the target dose (starting at 6 J/cm² and titrated up at the Investigator's discretion to a dose that generates an Erythema score >1 at the treated lesions or 25 J/cm^2, whichever occurs first)
- A dermatologic assessment of treated lesions will be performed immediately before and 10 to 30 minutes following completion of the light session.

6.2.3.2 Week 3 Session 6, Week 6 Session 12, and Week 9 Session 18

6.2.3.2.1 Light Treatment Day

The patient will return to the clinic 21 (±3) hours after study drug is applied and the following assessments will be conducted ***prior to*** light treatment:

- Each index lesion will have an mCAILS score assessed and recorded
- The mSWAT score will be assessed and recorded
- The PGA score will be assessed and recorded
- The SAEQ score will be collected and recorded
- The SCORD score will be collected and recorded

Once the assessments are completed, the standard light treatment procedures will be conducted, as follows:

- Interval medical history obtained
- Any AEs documented
- Adequate application of the drug will be verified by a pink staining on visual inspection of lesions
- Delivery of light session, the time of treatment calculated by the target dose
- A dermatologic assessment of treated lesions will be performed immediately before and 10 to 30 minutes following completion of the light session. This includes assessment of treated lesions and surrounding areas for:
    - Erythema

- Pain
- Pruritus
- Edema
- Hyperpigmentation
- Hypopigmentation
- Rash
- Vesiculation

6.2.3.3 Week 12 Session 24

6.2.3.3.1 Light Treatment Day

The patient will return to the clinic 21 (±3) hours after study drug is applied and the following assessments and procedures will be conducted ***prior to*** light treatment:

- Each index lesion will have an mCAILS score assessed and recorded
- The mSWAT score will be assessed and recorded
- The PGA score will be assessed and recorded
- The SAEQ score will be collected and recorded
- The SCORD score will be collected and recorded
- Physical Exam
- Vital Signs obtained
- Blood for the hematology panel obtained
- Blood for the clinical chemistry panel obtained

Once the assessments are completed, the standard light treatment procedures will be conducted, as follows:

- Interval medical history obtained
- Any AEs documented

- Adequate application of the drug will be verified by a pink staining on visual inspection of lesions
- Delivery of light session, the time of treatment calculated by the target dose
- A dermatologic assessment of treated lesions will be performed immediately before and 10 to 30 minutes following completion of the light session. This includes assessment of treated lesions and surrounding areas for:
    - Erythema
    - Pain
    - Pruritus
    - Edema
    - Hyperpigmentation
    - Hypopigmentation
    - Rash
    - Vesiculation

6.2.3.4 Follow-Up Visits (Week 13, 14, and 16)

Patients will return to the clinic during Weeks 13, 14, and 16 (End of Study) for follow-up assessment. At each follow-up visit, the following will be conducted:

- Interval medical history obtained
- Any AEs documented
- Each index lesion will have an mCAILS score assessed and recorded
- The mSWAT score will be assessed and recorded
- The PGA score will be assessed and recorded
- The SAEQ score will be collected and recorded
- The SCORD score will be collected and recorded
- Vital signs obtained

In addition to the assessments above, the following will be done at the Week 16 Follow-Up/End of Study visit:

- Physical Exam
- Vital Signs obtained
- Blood for the hematology panel obtained
- Blood for the clinical chemistry panel obtained

6.2.4 Valchlor Patients

Patients who are randomized into the Valchlor treatment arm will be given a tube of gel at the Baseline visit. They will be instructed on proper drug application according to the instructions on the package insert.

6.2.4.1 Week 3, Week 6, and Week 9

Patients will be instructed to come to the clinic during Weeks 3, 6, and 9.

At the clinic, the following assessments will take place ***before*** Valchlor is applied:

- Interval medical history obtained
- Any AEs documented
- Each index lesion will have an mCAILS score assessed and recorded
- The mSWAT score will be assessed and recorded
- The PGA score will be assessed and recorded
- The SAEQ score will be collected and recorded
- The SCORD score will be collected and recorded
- Vital signs obtained

Once these assessments have been completed, the patient will apply study drug at the clinic.

6.2.4.2 Week 12

Patients will come in to the clinic at Week 12, and the following assessments and procedures will be completed ***before*** Valchlor is applied:

- Interval medical history obtained
- Any AEs documented
- Each index lesion will have an mCAILS score assessed and recorded
- The mSWAT score will be assessed and recorded
- The PGA score will be assessed and recorded
- The SAEQ score will be collected and recorded
- The SCORD score will be collected and recorded
- Physical Exam
- Vital Signs obtained
- Blood for the hematology panel obtained
- Blood for the clinical chemistry panel obtained

Once these assessments and procedures have been completed, the patient will apply study drug at the clinic.

6.2.4.3 Follow-Up Visits (Week 13, 14, and 16)

Patients will return to the clinic during Weeks 13, 14, and 16 (End of Study) for follow-up assessment. At each follow-up visit, the following will be conducted:

- Interval medical history obtained
- Any AEs documented
- Each index lesion will have an mCAILS score assessed and recorded
- The mSWAT score will be assessed and recorded
- The PGA score will be assessed and recorded
- The SAEQ score will be collected and recorded
- The SCORD score will be collected and recorded
- Vital signs obtained

In addition to the assessments above, the following will be done at the Week 16 Follow-Up/End of Study visit:

- Physical Exam
- Vital Signs obtained
- Blood for the hematology panel obtained
- Blood for the clinical chemistry panel obtained

6.3 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.

7 DESCRIPTION OF STUDY PROCEDURES

7.1 Efficacy Assessments

7.1.1 Modified Composite Assessment of Index Lesion Severity (mCAILS)

mCAILS score will be calculated by assessing the erythema, scaling, plaque elevation and involved surface area using the grading scale shown in Table 5, Table 6, Table 7, and 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 mCAILS score will be calculated by adding the scores of all evaluated lesions together.

Table 5: 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

* 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: Composite Assessment of Index Lesion Severity – 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

* 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: Composite Assessment of Index Lesion Severity – Plaque Elevation

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

Table 8: Composite Assessment of Index Lesion Severity – Surface Area

Score	Area[a]
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

[a] 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

7.1.2 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 9. It will be noted in the CRF if any lesions included in the mSWAT table will not be treated.

Table 9: 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.

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

Table 10: 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 Safety Assessments

7.2.1 Dermatologic Assessment Grading

For patients randomized to the HyBryte treatment arm, immediately prior to and approximately 10 to 30 minutes after the completion of light therapy, treated lesions and surrounding areas will be graded for erythema, pain, pruritus, edema, hyperpigmentation, hypopigmentation, rash, and vesiculation, with the average score recorded. The reaction will be graded using the definitions in Table 4.

7.2.2 SCORD Scoring

The Scoring Atopic Dermatitis (SCORAD) tool is well established in Dermatology to provide a numeric assessment of the degree and severity of dermatitis in atopic dermatitis. Recently, this tool was modified to assess the severity of dermatitis in CTCL patients undergoing mechlorethamine treatment (Alexander-Savino 2022). This score is calculated as:

- the percent of CTCL lesion showing dermatitis
- the severity of the dermatitis on a 3-point scale (0-none, 1-mild, 2-moderate, 3-severe) for redness, oozing/crusting, scratch marks, skin thickening, and dryness
- the patient's self-reported assessment of itch

The scoring form for SCORD is attached in Appendix 20.2 APPENDIX II – SCORD Calculation Worksheet on page 69.

7.2.3 Patient Reported SAEQ Score

The Skin Adverse Event Questionnaire is a series of patient self-reported assessments of application site events over the last 24 hours recorded in a visual analog scale (VAS) format and reported as a score of 0 to 10 as shown in Appendix 20.4 Appendix IV - Skin Adverse Event Questionnaire. The number of application sites experiencing these symptoms will be noted. Symptoms specifically queried are:

- Rash
- Tenderness
- Pain
- Burning
- Swelling
- Redness
- Blistering
- Change in color

7.3 Clinical Laboratory Tests

7.3.1 Hematology

The hematology panel will be performed at the Central Laboratory. 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

7.3.2 Clinical Chemistry Laboratory Tests

The clinical chemistry panel will be performed at the Central Laboratory. The panel will consist of the following tests:

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

7.4 Vital Signs

Vital signs obtained will consist of:

- Resting Blood Pressure
- Heart Rate
- Respiratory Rate

8 STUDY DRUG MANAGEMENT

8.1 HyBryte

8.1.1 Formulation

HyBryte will be supplied in plastic screw-top jars containing 25 grams of 0.25% hypericin ointment (2.5 mg/gram). Jars are stored at room temperature.

8.1.2 Storage

HyBryte can be kept at room temperature (23 to 27°C, 73 to 81°F). HyBryte should be mixed with an applicator (eg, tongue depressor) prior to application.

8.1.3 Packaging and Shipment

HyBryte will be supplied in plastic screw-top jars containing 25 grams of 0.25% hypericin ointment (2.5 mg/gram). Jars will be labeled with the study number (HPN-CTCL-04), a jar identification number, the designation “Topical HyBryte (0.25% hypericin)”, and the warning “Caution: New Drug-Limited by U.S. Federal Law to Investigational Use."

8.1.4 Dose and Administration

Patients randomized to the HyBryte treatment arm will be instructed to mix and apply the study drug to cover the entire surface of each lesion in a thin layer. 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.

8.2 Valchlor

Commercially available Valchlor will be used as the active comparator in this trial. Valchlor will not be provided by Soligenix and will be obtained by the site. All information below is extracted from the approved Valchlor package insert which should be followed for all storage, handling and administrations instructions. If there are discrepancies between this protocol and the approved Valchlor package insert, the package insert should prevail and be followed by the site (this will not be considered a protocol deviation)

8.2.1 Formulation

The active ingredient in Valchlor is mechlorethamine. Each tube of Valchlor contains 60 g of 0.016% w/w mechlorethamine clear gel (equivalent to 0.02% mechlorethamine HCl).

8.2.2 Storage

Prior to dispensing, store in the freezer at -13°F to 5°F (-25°C to -15°C). Advise patients that refrigerated storage is required once dispensed.

8.2.3 Packaging and Shipment

Valchlor is supplied in 60 g tubes of 0.016% w/w mechlorethamine as a clear gel.

8.2.4 Dose and Administration

Apply a thin film of Valchlor gel once daily to affected areas of the skin.

Stop treatment with Valchlor for any grade of skin ulceration, blistering, or moderately-severe or severe dermatitis (ie, marked skin redness with edema). Upon improvement, treatment with Valchlor can be restarted at a reduced frequency of once every 3 days. If reintroduction of treatment is tolerated for at least one week, the frequency of application can be increased to every other day for at least one week and then to once daily application if tolerated.

Valchlor is a cytotoxic drug. Follow applicable special handling and disposal procedures. Patients must wash hands thoroughly with soap and water after handling or applying Valchlor. Caregivers must wear disposable nitrile gloves when applying Valchlor to patients and wash hands thoroughly with soap and water after removal of gloves. If there is accidental skin exposure to Valchlor, caregivers must immediately wash exposed areas thoroughly with soap and water for at least 15 minutes and remove contaminated clothing.

Patients or caregivers should follow these instructions when applying Valchlor:

- Apply immediately or within 30 minutes after removal from the refrigerator. Return Valchlor to the refrigerator immediately after each use.

- Apply to completely dry skin at least 4 hours before or 30 minutes after showering or washing. Allow treated areas to dry for 5 to 10 minutes after application before covering with clothing.

- Emollients (moisturizers) may be applied to the treated areas 2 hours before or 2 hours after application.

- Do not use occlusive dressings on areas of the skin where Valchlor was applied.
- Avoid fire, flame, and smoking until Valchlor has dried.

8.3 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.

8.4 Prohibited Concomitant Therapy

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. A detailed history of prior CTCL treatments will be collected.

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

- Topical steroids (including 1% hydrocortisone cream or ointment)

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:

- 5-fluorouracil
- Vinblastine

- Dacarbazine
- ALA or 5-aminolevulinic acid
- Methyl-5-aminolevulinic acid
- Investigational drugs
- Drugs of abuse
- Agents known to cause photosensitization

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

The following drugs are **not allowed within 2 months** of enrollment.

- Topical nitrogen mustard
- Valchlor

8.5 Compliance

Patients will be trained in the proper application of HyBryte and Valchlor. Application of HyBryte will be documented by site personnel by noting pink staining on lesions indicating application of the drug. Valchlor compliance will be determined by patient reports.

9 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.

9.1 Definitions

9.1.1 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.

9.1.2 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).

9.1.3 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.

9.2 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.

9.3 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.

9.4 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. If photographic evidence is available and relevant, it may be recorded. 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.

10 SERIOUS ADVERSE EVENT

10.1 Definition of Serious Adverse Event

A 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 study drug
- 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:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias or convulsions that do not result in inpatient hospitalization
    - Development of drug dependency or drug abuse

10.2 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; ie, 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 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.

10.3 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 emailed 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 (ie, 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
[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]

10.4 Overdose

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved HyBryte or Valchlor) must be communicated to Soligenix, Inc within 24 hours and be fully documented as an SAE. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

11 STATISTICS

11.1 General Procedures

This is a randomized, pilot study assessing outcomes of patients receiving HyBryte compared to Valchlor in patients with stage IA, IB, and IIA CTCL. Subjects will be randomized to 12 weeks of treatment with either HyBryte or Valchlor in a 1:1 ratio. Additionally, the practical issues likely to arise in a larger clinical study comparing HyBryte to Valchlor will be identified. No formal efficacy statistics will be performed. Results will be presented as tables that include group means, standard deviations, medians, maximum, and minimum values for continuous variables and counts and percentages for dichotomous variables as well as individual patient listings.

12 ETHICS AND RESPONSIBILITIES

12.1 Good Clinical Practice

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

12.2 Institutional Review Board/Independent Ethics Committee

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 enrollment 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.

12.3 Informed Consent

The Investigator will ensure that the subject or a legally authorized representative of the subject is 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.

12.4 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 (eg, FDA) may require direct access to parts of the trial site records relevant to the study, including subjects' medical history for data verification purposes.

12.5 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 (eg, patent, licensing agreement) and financial (eg, 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 questions 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, eg, 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.

13 RECORDS MANAGEMENT

13.1 Source Documentation

Original source documents include all 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 which are used to support the data recorded CRFs of each subject. When possible, all data should be documented in an original source document and copied into the CRF.

13.2 Study Files and Record Retention

Copies of CRFs should be retained by sites along with all original source documents (eg, 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.

14 AUDITING AND MONITORING

14.1 Study Monitoring

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

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.

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 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.

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 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.

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 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.

14.2 Audits and Inspections

Health Authorities (eg, 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 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Soligenix. 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 will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or Soligenix, 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.

16 STUDY REPORT AND PUBLICATIONS

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

Soligenix's publication policy is discussed in the investigator's Clinical Research Agreement.

17 STUDY DISCONTINUATION

Both Soligenix and the Principal Investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, Soligenix 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 and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

18 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. However, authorized regulatory officials, IRB/IEC personnel, Soligenix 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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20 APPENDICES

20.1 APPENDIX I – Names of Study Personnel

Sponsor: Soligenix, Inc.
29 Emmons Drive
Princeton, NJ 08540

Medical Monitors: Richard Straube, MD
29 Emmons Drive
Princeton, NJ 08540
[redacted]

Christopher Pullion, DO
29 Emmons Drive
Princeton, NJ 08540

20.2 APPENDIX II – SCORD Calculation Worksheet

The following form will be used to calculate a severity of dermatitis score for treated lesions.

SCORING DERMATITIS (SCORD) SCALE

A. Percentage of lesions with dermatitis score (enter % of involved treated lesions)
Score _____ %

Range 0 = no dermatitis in treated lesions to 100 = all treated lesions are entirely involved with dermatitis

A score can range from 0 to 100

B. Lesion severity score (circle average score of affected lesions for each finding)

a.	Redness	0- None	1- Mild	2- Moderate 3- Severe
b.	Oozing/crusting	0- None	1- Mild	2- Moderate 3- Severe
c.	Scratch marks	0- None	1- Mild	2- Moderate 3- Severe
d.	Skin thickening	0- None	1- Mild	2- Moderate 3- Severe
e.	Dryness	0- None	1- Mild	2- Moderate 3- Severe

B score is the sum of the 5 sub-scores and can range from 0 to 18

C. Patient self-reported current itch measured on a 0 to 10 scale marking itch intensity on a visual analog scale. The scale will be 10 cm long and the score is the centimeter from 0 to the patient's slash.

No itch Worst imaginable itch
|_____|

0 10

C score is the number of centimeters from 0 and can range from 0 to 10

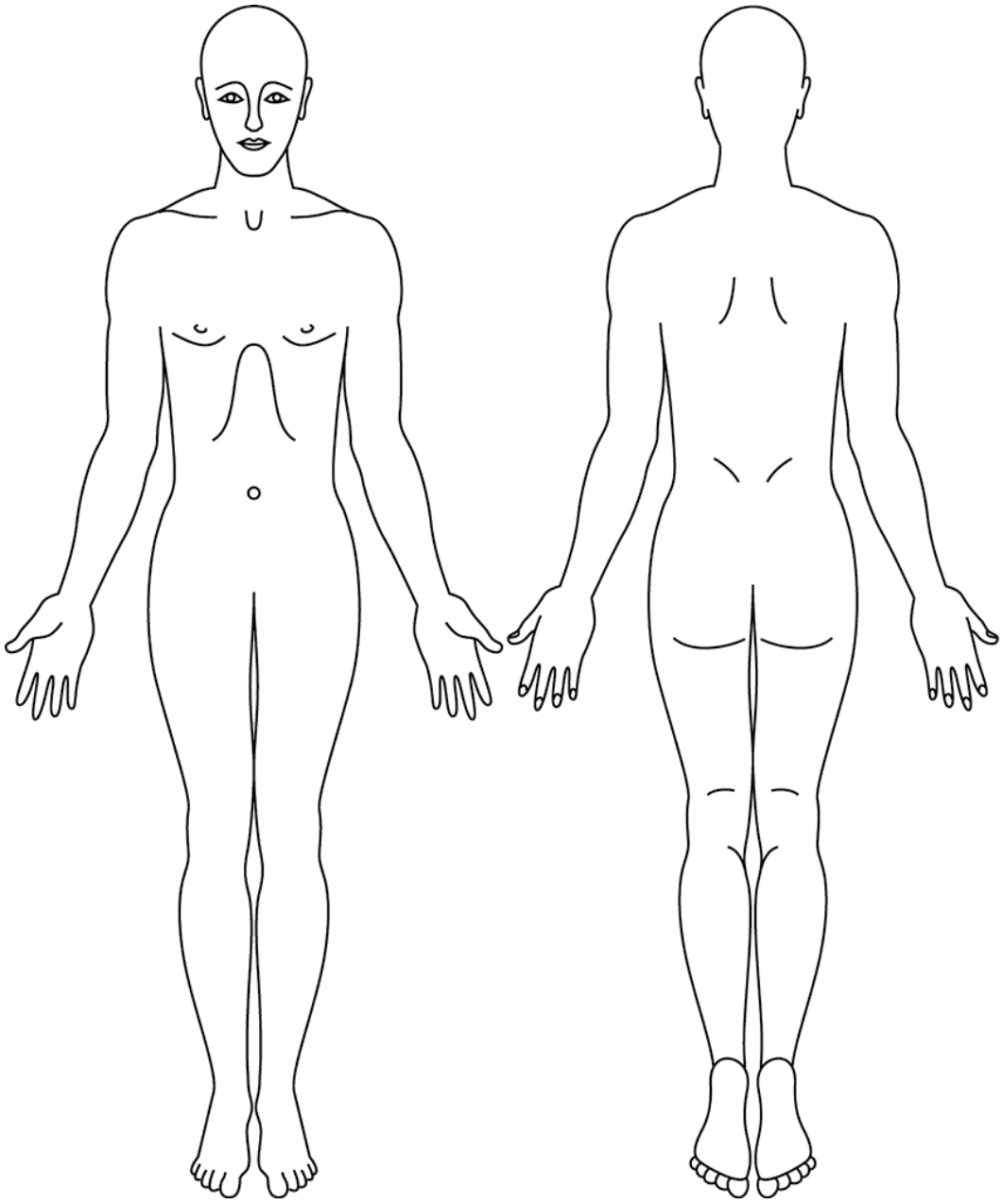
Total SCORD score is calculated by adding the score for each of the subscores (A, B, and C) weighted as follows:

Calculation of SCORD score = (A/5 +7B/2 +C)

20.3 APPENDIX III – Body Lesion Diagram

BODY LESION DIAGRAM

Please identify the index lesions' location (Ex. 1, 2 or 3) in the diagram below.



20.4 Appendix IV - Skin Adverse Event Questionnaire

Patient Number: _____ Date:__ __ / __ __ / 202 ___

Over the last 24 hours, please rate the degree of discomfort you have had at areas that have been treated with your drug. Place a vertical mark on each line corresponding the worst area that has been treated for each of the symptoms you have had.

1. Rash:

None |_____| Worst imaginable

2. Tenderness

None |_____| Worst imaginable

3. Pain

None |_____| Worst imaginable

4. Burning

None |_____| Worst imaginable

5. Swelling

None |_____| Worst imaginable

6. Redness

None |_____| Worst imaginable

7. Blistering

None |_____| Worst imaginable

8. Change in color

None |_____| Worst imaginable

20.5 APPENDIX V – Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles

for

Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly

Helsinki, Finland, June 1964

and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

GENERAL PRINCIPLES

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

RISKS, BURDENS AND BENEFITS

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

VULNERABLE GROUPS AND INDIVIDUALS

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

RESEARCH ETHICS COMMITTEES

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must

not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

PRIVACY AND CONFIDENTIALITY

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

INFORMED CONSENT

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

USE OF PLACEBO

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

POST-TRIAL PROVISIONS

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.