CLINICAL RESEARCH PROTOCOL

DRUG:	SGX302 (0.25% hypericin)
STUDY NUMBER(S):	HPN-PSR-01
PROTOCOL(S) TITLE:	Phase 2 Study Evaluating SGX302 (Synthetic Hypericin) in the Treatment of Mild-to-Moderate Psoriasis
IND NUMBER:	[redacted]
SPONSOR:	Soligenix, Inc.
ORIGINAL PROTOCOL DATE:	21 April 2022
VERSION NUMBER:	Amendment 4
VERSION DATE:	04 October 2024

NCT05442190

Original: 21 April 2022
Amendment 1: 17 June 2022
Amendment 2: 04 November 2022
Amendment 3: 12 December 2023
Amendment 4: 04 October 2024

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: Phase 2 Study Evaluating SGX302 In the Treatment of Mild-to-Moderate Psoriasis

Study No: HPN-PSR-01

Original Protocol Date: 21 April 2022

Protocol Version No: Amendment 4

Protocol Version Date: 04 October 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
Author: [redacted]	☒ Yes ☐ No (select one)	[redacted]	
Clinical Operations: [redacted]	☒ Yes ☐ No (select one)	[redacted]	
Regulatory Affairs: [redacted]	☒ Yes ☐ No (select one)	[redacted]	
Other: [redacted]	☒ Yes ☐ No (select one)	[redacted]	

Original: 21 April 2022
Amendment 1: 17 June 2022
Amendment 2: 04 November 2022
Amendment 3: 12 December 2023
Amendment 4: 04 October 2024

PHASE 2 STUDY EVALUATING SGX302 IN THE TREATMENT OF MILD-TO-MODERATE PSORIASIS

STUDY NO: HPN-PSR-01

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to SGX302 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, Inc.

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 SGX302 and the study.

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

Original: 21 April 2022
Amendment 1: 17 June 2022
Amendment 2: 04 November 2022
Amendment 3: 12 December 2023
Amendment 4: 04 October 2024

STUDY SYNOPSIS

Name of Sponsor/Company: Soligenix, Inc.		(For National Authority Use only)
Name of Finished Product SGX302		
Name of Active Ingredient Hypericin		

Title of Study: Phase 2 Study Evaluating SGX302 (Synthetic Hypericin) in the Treatment of Mild-to-Moderate Psoriasis

Investigators: Neal Bhatia, MD: up to 2 additional TBD

Study center(s) Therapeutics Clinical Research; up to 2 additional centers TBD

Publication (reference): N/A

Study Period (years):	Estimated 3 Years	**Phase of Development:** Phase 2
Date of First Enrollment:	4Q2022	
Date of Last Completed:	TBD	

Objectives:

Primary:

The primary objective of this two-part Phase 2 study is to evaluate the biologic activity of SGX302 activated with visible light for improving lesions in patients with mild-to-moderate psoriasis.

Secondary:

- Evaluate the profile and time course of changes in disease activity
- Evaluate the sensitivity and ease of use of several currently used instruments to measure disease activity for the purpose of detecting changes in disease status in patients with mild-to-moderate psoriasis targeted for enrollment

Safety:

The safety objective of the trial is to evaluate the safety and tolerability of SGX302 with visible light activation during up to 36 treatments at least 2 calendar days apart in patients with mild-to-moderate plaque psoriasis.

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Name of Active Ingredient Hypericin		

Methodology: The trial consists of two parts: Part A, in which the tolerability of and response to SGX302 (0.25% hypericin) therapy in mild-to-moderate psoriasis will be assessed in an open-label design; Part B, that will be a placebo-controlled, double-blind, randomized design once tolerability and response of the treatment has been assessed. In Part A, up to 15 patients will be assigned open-label SGX302 (0.25% hypericin) at the time of enrollment. 10 patients will receive an ointment formulation of SGX302 and up to 5 patients will receive a gel formulation of SGX302 in Part A. All patients will apply the study drug for a total of 36 treatments at least 2 calendar days apart, targeting an average of 2 treatments per week. Study drug will be activated with visible light 24±6 hours after each drug application. On completion of all treatments, patients will be followed for a 4-week follow-up period in which patients will not receive other psoriasis treatments.

Once the tolerability and response to SGX302 has been established, Part B of the protocol will commence using one of the gel or ointment formulations. In Part B, patients will be randomized to double-blind treatment groups at a ratio 1:1 of active drug to placebo. The differences in treatment response between active drug and placebo will be assessed. All patients will apply the study drug for a total of 36 treatments at least 2 calendar days apart, targeting an average of 2 treatments per week. Study drug will be activated with visible light 24±6 hours after each drug application. On completion of all treatments, patients will be followed for a 4-week follow-up period in which patients will not receive other psoriasis treatments.

In both parts A and B, visible light therapy will be started at 5 J/cm^2, calculated using the supplied visible light devices according to the manufacturer's instructions and titrated up at the Investigator's discretion until patients have a Grade I Erythema Score on their treated lesions following the light treatment or reach a maximum of 40 J/cm^2, whichever occurs first. Active dermatologic assessment of treated lesions for Adverse Events will be done immediately before and 10-30 minutes after each of the light treatments. Patients will be assessed for overall disease status at Baseline and then at Treatment visits 12, 24, 36 and after 4 weeks of follow-up in both Part A and B.

Efficacy assessments will include the 5-point Investigator's Global Assessment (IGA using the mod 2011 scale), Psoriasis Area and Severity Index (PASI; including % change from Baseline and the number of patients achieving a 75%, 90% and 100% improvement from Baseline) to measure disease status and the SkinDex-29, Self-Assessment Simplified Psoriasis Index (saSPI), and the Dermatology Life Quality Index (DLQI) instruments to measure patient reported quality of life (QoL).

Routine safety laboratories (hematology and clinical chemistries), and vital signs will be obtained at Baseline, Treatment 18, Treatment 36, and at the end of the follow-up period. Physical examinations will be performed at Baseline and Treatment 36. Patients in Part A will have an additional assessment of safety laboratories, vital signs and physical exam prior to drug application at Treatment 36. Hypericin blood concentrations and ECGs will be obtained in Part A at Baseline, and Treatments 18, 36 and at the end of the follow-up period. Hypericin blood concentrations and ECGs will be obtained in Part B at Baseline and Treatments 18, 36 and at the end of the follow-up period. Adverse events (AEs) will be recorded throughout the study.

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Name of Active Ingredient Hypericin		
Number of patients (planned): Up to 47 total subjects are planned to be enrolled (Up to 15 in Part A and 32 (16 active and 16 placebo) in Part B). Up to 5 additional patients may be recruited to replace any patient withdrawing from the study prior to treatment completion.		

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

For enrollment, a patient must meet ***all*** of the following criteria:

1. Able to understand and have signed the Informed Consent Form.
2. Men and women between 18 and 75 years old, inclusive.
3. Have a clinical diagnosis of plaque psoriasis (psoriasis vulgaris) of at least 6 months duration that involves the body (trunk and/or limbs) that is amenable to topical treatment and opaque coverage after application.
4. Have a static Investigator Global Assessment (IGA)/ Psoriasis Area and Severity Index (PASI) of disease severity of mild or moderate on the body (trunk and/or limbs) defined by:
    a. **Mild:** mild plaque elevation (0.5 mm); light red coloration; fine scale predominates, or
    b. **Moderate:** moderate plaque elevation (0.75 mm); moderate red coloration; coarse scale predominates.
5. Have lesions involving 2-30% of the body (trunk and/or limbs). For subjects with scalp psoriasis included in the treatment area, the total treatment area on body and scalp must not exceed 30%.

Exclusion Criteria:

For enrollment, a patient must NOT have any of the following:

1. Women who are pregnant, lactating, planning to become pregnant, or women of child-bearing potential who have not successfully been using the same medically acceptable contraceptive methods over the previous 3 months, eg, oral contraceptive agents, intrauterine device (IUD), and barrier method plus spermicide.
2. Use of topical antipsoriatic therapy (including topical retinoids, corticosteroids, or vitamin D analogs) within one week prior to the beginning of the study and willing to not use other psoriasis treatments for 4 weeks following completion of the treatment portion of the study.
3. Received systemic biologic therapy to treat psoriasis (eg, IL-17 inhibitors [eg, secukinumab, Cosentyk®; ixekizumab, Talz®; and broalumab, Siliq®], IL-23 inhibitors [eg, guselkumab, Tremfya®; tidrakizumab, Ilumya® rsiankizumab, Skyrizi®], and JAK inhibitors [eg, Tofacitinib, Xeljanz®]) within 12 weeks prior to the beginning of the study.
4. Received systemic psoriasis therapy (eg, methotrexate, cyclosporine, systemic corticosteroids, retinoids [such as Acitretin]), or biologic immunosuppressives (eg, etanercept, Enbrel®; certolizumab pegol, Cimiza®; adalimumab, Humira®; infliximab, Remicade®) within 4 weeks prior to the beginning of the study.
5. Received phototherapy (including laser) or photodynamic (light activated drug) therapy within 4 weeks prior to the beginning of the study.
6. History of noncompliance to medical regimens or unwilling to comply with the study protocol.
7. Participation in an investigational drug study within 30 days prior to the beginning of the study.
8. Serious or unstable medical or psychological conditions that in the opinion of the Investigator would compromise the subject's safety or successful participation in the study.

Test product, dose and mode of administration:

Patients will apply study drug to all treatment lesions, avoiding application to healthy skin, and covered using opaque coverings (eg, clothes, bandage, etc.). Study drug will be applied for a total of 36 treatments, at least 2 calendar days apart and targeting an average of 2 treatments per week.

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Light treatments will be given using a supplied Daavlin visible light device generating light in the 500-650 nm wavelength (yellow-red spectrum). The patient's position will be marked to assure consistent positioning. Light treatments will be administered 24±6 hours after each study drug application. The light dose may be increased at the Investigator's discretion at each treatment until symptoms or signs of mild erythema at the treated lesions appear or reach a maximum of 40 J/cm^2, whichever occurs first. The dose will be either maintained at that level or reduced if the skin erythema has a score of greater than Grade I.

Initial light treatments will be performed at site visits for at least the first 4 weeks. If the patient has been adequately trained and is comfortable with operating the light device, at the discretion of the site team, the Medical Monitor, and Sponsor, the treatments may be performed at home provided that the use of the device can be regulated and monitored in real time.

Duration of treatment: Patients will be treated for up to a total of 36 occasions. Following completion of their therapy, they will be followed for an additional 4 weeks during which patients will be asked to refrain from any other psoriasis-specific treatments.

Reference therapy, dose and mode of administration:

Part A is open-label and hence has no reference therapy.

In Part B, patients randomized to the placebo treatment group, placebo will be applied to all treatment lesions avoiding treatment of healthy skin and covered using an opaque covering (eg, clothes, bandage, etc.). Placebo will be applied for a total of 36 treatments, at least 2 calendar days apart and targeting an average of 2 treatments per week. Light treatments will be given using a supplied Daavlin visible light device generating light in the 500-650 nm wavelength (yellow-red spectrum). The patient's position will be marked to assure consistent positioning. Light treatments will be administered 24±6 hours after each study drug application. The light dose may be increased at the Investigator's discretion at each treatment until symptoms or signs of mild erythema appear at the treated lesions or reach a maximum of 40 J/cm^2, whichever occurs first. The dose will be either maintained, or reduced if the skin erythema has a score of greater than Grade I.

Initial light treatments will be performed at site visits for at least the first 4 weeks. If the patient has been adequately trained and is comfortable with the operating the light device, at the discretion of the site team, the Medical Monitor, and Sponsor, the treatments may be performed at home provided that the use of the device can be regulated and monitored in real time.

Criteria for evaluation:

Efficacy:

Primary Endpoint:

For each cohort in Part B, the primary endpoint for this trial will be a comparison of the proportion of patients in each group at 18 weeks of treatment that achieve either a 0 or 1 score (clear or almost clear) evaluation using the 5-point Investigator's Global Assessment (IGA) mod 2011 scale.

Secondary Endpoints:

Additional endpoints will be examined for open-label Part A and between the treatment groups in Part B using the following measures:

1. Number of patients achieving a ≥75% improvement in Psoriasis Area and Severity Index (PASI 75);
2. Number of patients achieving a ≥90% improvement in Psoriasis Area and Severity Index (PASI 90);
3. Number of patients achieving a 100% improvement in Psoriasis Area and Severity Index (PASI 100);
4. The mean saSPI score;
5. The mean SkinDex-29 QOL;
6. Proportion of patients with 0, 1, or 2 on the Investigator's Global Assessment (IGA); and
7. The mean score on the Dermatology Life Quality Index (DLQI) instrument.

Safety:

Safety will be assessed by:

1. Active dermatologic assessments will be conducted of all treated lesions and surrounding areas immediately before and 10-30 minutes after each of the light treatments. Assessments will be graded on a scale of 0 (none), 1 (mild), 2 (moderate), 3 (severe), 4 (life threatening). This includes evaluations of erythema, pain, pruritus, edema, hyperpigmentation, hypopigmentation, rash and vesiculation.
2. The number, time course, severity, relatedness, and types of adverse events reported;
3. Changes from Baseline results of standard safety laboratory tests (hematology and clinical chemistry) obtained at Baseline, Treatment 18, Treatment 36 and after 4 weeks of follow-up;
4. Changes from Baseline values in vital signs obtained at Baseline, Treatment 18, Treatment 36, after 4 weeks of follow-up; and
5. Changes in the physical examination obtained at Baseline and Treatment 36.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CRF	Case Report Form
CTCL	Cutaneous T-Cell Lymphoma
DLQI	Dermatology Life Quality Index
DMSO	Dimethyl Sulfoxide
ECG	Electrocardiogram
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICD	Immunogenic Cell Death
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
J	Joule
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
N	Number, Sample Size
PASI	Psoriasis Area and Severity Index
PI	Principal Investigator
PK	Pharmacokinetic
PUVA	Psoralen Plus Ultraviolet A
QoL	Quality of Life
ROS	Reactive Oxygen Species
SAE	Serious Adverse Event
saPSI	Self-Assessment Simplified Psoriasis Score
TEAE	Treatment Emergent Adverse Event
UV	Ultraviolet

1 INTRODUCTION AND RATIONALE

1.1 Background

SGX302 is chemically synthesized hypericin formulated for topical application. Hypericin is a natural compound found in the stems and petals of plants of the genus *Hypericum* and is a powerful photosensitizing agent.

Psoriasis is a chronic, autoimmune skin disease characterized by T-cell mediated inflammation resulting in increased epidermal cell proliferation. It is typically associated with intense T-cell lymphocytic and neutrophilic infiltrates superficially in skin lesions. Psoriasis affects approximately 2% of the total population in the United States. According to the National Institutes of Health, as many as 7.5 million Americans have psoriasis. Currently, there is a need for novel and well-tolerated therapeutics for these lymphocyte-mediated disorders. Combinations of photosensitizing agents and ultraviolet (UV) light are established treatments of psoriasis and CTCL. A commonly used phototherapy regimen includes the use of psoralen plus UVA (PUVA) light treatment. Both CTCL and psoriasis exhibit high clinical response rates to PUVA therapy. However, PUVA appears to exert carcinogenic effects with prolonged treatment resulting in a significant rate of nonmelanoma skin cancers and malignant melanoma. Moreover, the finding that psoralen is mutagenic and intercalates into DNA, coupled with the association of PUVA therapy with skin cancer development, raises the need for safer forms of phototherapy in the treatment of CTCL and psoriasis.

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

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

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

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

In general, it appears that the primary mechanism of the light-activated hypericin is through a Type II photoreaction. Hypericin localizes in the perinuclear region within the endoplasmic reticulum and Golgi apparatus. When activated with visible light in the 500-650 nm range (exact activation wavelengths dependent on the solute used), the molecule is converted into a high energy state that transfers the energy to free oxygen creating high energy, singlet oxygen, $^1O_2$. This, in turn, leads to a sequence of photochemical and photobiological processes generating highly reactive oxygen species (ROS), which activate the caspase signaling cascade leading to apoptosis via the mitochondrial pathway. Hypericin additionally interacts with a variety of cytosolic proteins and lipoproteins. ROS generation also leads to cell necrosis, a cell death pathway that may augment its anti-tumor effects through a process of immunogenic cell death (ICD) that activates the immune system against the tumor.

A Phase 2 clinical trial demonstrated a statistically significant reduction in both CTCL and psoriatic lesions after 6 weeks of treatment with topical hypericin and treatment was well tolerated. In this trial, two different formulations of synthetic hypericin were used in the psoriatic patients, a DMSO/aqueous solution and a formulation in USP ointment. Each patient had 3 lesions treated- one treated with placebo, one lesion treated with low dose hypericin, and one lesion treated with high dose hypericin. Response at 6 weeks in psoriatic patients was defined as a combined lesion score of <50% of Baseline lesion scores for scaling, erythema, and plaque elevation. The results from the 11 patients in this study are shown in Table 1.

Table 1: Response to 6 Weeks of Hypericin Treatment in Psoriasis

		Hypericin Treatment			
Patient	**Formulation**	**Placebo**	**0.05%**	**0.1%**	**0.25%**
CW-006	DMSO	N	–	Y	Y
CW-011	DMSO	N	–	N	N
CW014	DMSO	N	–	Y	Y
CW-015	DMSO	N	–	Y	Y
CW-017	DMSO	N	–	N	Y
P-001	Ointment	N	N	N	–
P-003	Ointment	N	N	N	–
P-004	Ointment	N	N	N	–
P-005	Ointment	N	N	N	–
P-006	Ointment	N	Y	N	–
MDA-002	Ointment	N	–	Y	Y

The conclusion of the authors was that the response rate among the hypericin DMSO treated patients was statistically significant (4/5 responses compared to 0/6 placebo patients, $p \leq 0.02$) while the response rate in the ointment treated group (2/6 responses compared to 0/6 placebo patients) was not statistically significant. It should be noted, however, that only 1 of the 6 ointment treated patients received the highest, 0.25%, strength of hypericin and, therefore, these results may underestimate the utility of the ointment formulation of hypericin in psoriasis.

The utility of the ointment formulation is also supported by the finding in a positive Phase 3 trial of hypericin 0.25% ointment in 166 CTCL patients in which the response rates were similar in both patch lesions as well as with the thicker, more difficult to treat, plaque lesions. It was also clearly shown that more prolonged therapy with hypericin/light session dramatically increased response rates in these CTCL lesions.

In this Phase 3 CTCL trial, the most prevalent AEs related to skin reactions and application site pain and irritation. The rate of skin/application site reactions was significantly lower than has been reported for other skin-directed therapies. The reported MedDRA coded adverse events in ≥3% of patients in any treatment group from the Phase 3 trial are shown in Table 2.

Table 2: Adverse Events by System Organ Class and Preferred Term Reported in ≥3% of Patient in Any Treatment Group in the Phase 3 Study in CTCL patients

System Organ Class	Cycle 1		Cycle 2	Cycle 3	HyBryte	
Preferred Term	HyBryte (N=116) n (%)	Placebo (N=50) n (%)	HyBryte (N=155) n (%)	HyBryte (N=110) n (%)	Overall (N=161) n (%)	Overall (N=166) n (%)
#Patients ≥1 TEAE	56 (48.3)	27 (54.0)	66 (42.6)	49 (44.5)	108 (67.1)	116 (69.9)
Skin and subcutaneous tissue disorders	19 (16.4)	5 (10.0)	21 (13.5)	19 (17.3)	48 (29.8)	53 (31.9)
Pruritus	6 (5.2)	2 (4.0)	2 (1.3)	5 (4.5)	12 (7.5)	14 (8.4)
Erythema	3 (2.6)	0	3 (1.9)	1 (0.9)	7 (4.3)	7 (4.2)
Infections and infestations	20 (17.2)	10 (20.0)	19 (12.3)	16 (14.5)	43 (26.7)	51 (30.7)
Upper respiratory tract infection	8 (6.9)	4 (8.0)	2 (1.3)	2 (1.8)	12 (7.5)	16 (9.6)
Viral upper respiratory tract infection	4 (3.4)	0	4 (2.6)	4 (3.6)	11 (6.8)	11 (6.6)
Sinusitis	1 (0.9)	0	3 (1.9)	3 (2.7)	7 (4.3)	7 (4.2)
Urinary tract infection	1 (0.9)	2 (4.0)	3 (1.9)	0	4 (2.5)	6 (3.6)
Influenza	0	2 (4.0)	1 (0.6)	2 (1.8)	3 (1.9)	5 (3.0)
General disorders and administration site conditions	22 (19.0)	5 (10.0)	18 (11.6)	12 (10.9)	38 (23.6)	42 (25.3)
Application site pain	8 (6.9)	2 (4.0)	5 (3.2)	6 (5.5)	16 (9.9)	17 (10.2)
Application site pruritus	5 (4.3)	1 (2.0)	5 (3.2)	0	9 (5.6)	9 (5.4)
Fatigue	3 (2.6)	1 (2.0)	3 (1.9)	2 (1.8)	8 (5.0)	9 (5.4)
Application site paresthesia	6 (5.2)	0	2 (1.3)	2 (1.8)	7 (4.3)	7 (4.2)
Pain	3 (2.6)	0	2 (1.3)	0	5 (3.1)	5 (3.0)
Gastrointestinal disorders	11 (9.5)	6 (12.0)	7 (4.5)	7 (6.4)	20 (12.4)	24 (14.5)
Nausea	3 (2.6)	1 (2.0)	2 (1.3)	2 (1.8)	7 (4.3)	8 (4.8)
Diarrhea	4 (3.4)	0	3 (1.9)	0	6 (3.7)	6 (3.6)
Nervous system disorders	9 (7.8)	4 (8.0)	6 (3.9)	5 (4.5)	18 (11.2)	22 (13.3)
Headache	5 (4.3)	3 (6.0)	5 (3.2)	2 (1.8)	10 (6.2)	13 (7.8)
Dizziness	3 (2.6)	1 (2.0)	1 (0.6)	2 (1.8)	6 (3.7)	7 (4.2)

System Organ Class Preferred Term	Cycle 1 HyBryte (N=116) n (%)	Cycle 1 Placebo (N=50) n (%)	Cycle 2 HyBryte (N=155) n (%)	Cycle 3 HyBryte (N=110) n (%)	HyBryte Overall (N=161) n (%)	Overall (N=166) n (%)
Respiratory, thoracic and mediastinal disorders	9 (7.8)	1 (2.0)	5 (3.2)	5 (4.5)	17 (10.6)	17 (10.2)
Injury, poisoning and procedural complications	6 (5.2)	2 (4.0)	4 (2.6)	5 (4.5)	14 (8.7)	16 (9.6)
Musculoskeletal and connective tissue disorders	3 (2.6)	3 (6.0)	6 (3.9)	4 (3.6)	11 (6.8)	14 (8.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (2.0)	3 (1.9)	2 (1.8)	5 (3.1)	6 (3.6)
Eye disorders	3 (2.6)	0	2 (1.3)	0	5 (3.1)	5 (3.0)
Vascular disorders	2 (1.7)	1 (2.0)	1 (0.6)	1 (0.9)	4 (2.5)	5 (3.0)

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

A small Phase 2a trial studying systemic PK and serial ECG with hypericin 0.25% ointment in CTCL patients was also conducted. Although this study was not intended to demonstrate efficacy of the drug, the treatment response data strongly substantiates the results of the pivotal phase 3 trial. In this Phase 2a trial, there were only 7 AEs reported from 3 of 9 patients enrolled. All AEs were judged to be “Mild” and 6 of the 7 were judged to be “Not Related” to study drug. The 1 “Related” AE, phototoxicity, was judged to have been “Mild”. This AE profile was very similar to that seen in the Phase 3 trial.

This trial will be conducted in strict compliance with the protocol, GCP guidelines and the applicable FDA requirements.

1.2 Study Rationale

A previous Phase 2 trial of hypericin demonstrated that topical hypericin coupled with light activation approximately 24±6 hours later had a beneficial effect in reducing lesions in patients with stable, mild-to-moderate psoriasis. Data from a large CTCL Phase 3 trial has shown that the use of 0.25% hypericin ointment is safe and effective in treating deep lesions and continues to increase response rates the longer it is used through at least 18

weeks of therapy. This suggests that the current CTCL formulations of hypericin may be effective in reducing the lesions in psoriasis especially if used for more than 6 weeks. Similarly, the criteria used in the initial psoriasis trial were indicative of biologic activity but did not include the measures typically used as endpoints in psoriatic trials. The study also includes an optimized drug product gel formulation which is expected to enhance the patient's ability to accurately apply the medication to affected areas. Therefore, the current trial is designed to assess the ability of topical, 0.25% hypericin ointment and gel formulations in conjunction with visible light activation for up to 36 treatment visits, targeting an average of 2 visits per week to improve lesions in patients with stable mild-to-moderate psoriasis using standard psoriasis endpoints.

2 STUDY OBJECTIVES

2.1 Primary

The primary objective of this two-part Phase 2 study is to evaluate the biologic activity of SGX302 activated with visible light for improving lesions in patients with mild-to-moderate psoriasis.

2.2 Secondary

- Evaluate the profile and time course of changes in disease activity.
- Evaluate the sensitivity and ease of use of several currently used instruments to measure disease activity for the purpose of detecting changes in disease status in patients with mild-to-moderate psoriasis targeted for enrollment.

2.3 Safety

The safety objective of the trial is to evaluate the safety and tolerability of 2 SGX302 formulations with visible light activation during up to 36 treatments at least 2 calendar days apart in patients with mild-to-moderate plaque psoriasis.

3 STUDY ENDPOINTS

3.1 Efficacy

Although efficacy will be assessed in this trial, it is designed as a proof-of-concept trial and is not powered to prove efficacy.

3.1.1 Primary Endpoint

For each cohort in Part B, the primary endpoint for this trial will be a comparison of the proportion of patients in each group at 18 weeks of treatment that achieve either a 0 or 1 score (clear or almost clear) evaluation using the 5-point Investigator's Global Assessment (IGA) mod 2011 scale.

3.1.2 Secondary Endpoints

Additional endpoints will be examined for open-label Part A and between the treatment groups in Part B using the following measures:

1. Number of patients achieving a ≥75% improvement in Psoriasis Area and Severity Index (PASI 75).
2. Number of patients achieving a ≥90% improvement in Psoriasis Area and Severity Index (PASI 90).
3. Number of patients achieving a 100% improvement in Psoriasis Area and Severity Index (PASI 100).
4. Mean score of the saSPI.
5. The mean SkinDex-29 QOL score.
6. Number of patients with 0, 1 or 2 on the Investigator's Global Assessment (IGA).
7. The mean score on the Dermatology Life Quality Index (DLQI) instrument.

3.2 Safety

Safety will be assessed by:

1. Active dermatologic assessments will be conducted of all treated lesions and surrounding area immediately before and 10-30 minutes after each of the light treatments. Assessments will be graded on a scale of 0 (none), 1 (mild), 2 (moderate),

3 (severe), 4 (life threatening). This includes evaluations of erythema, pain, pruritus, edema, hyperpigmentation, hypopigmentation, rash, and vesiculation.

2. The number, time course, severity, relatedness, and types of adverse events reported.

3. Changes from Baseline results of standard safety laboratory tests (hematology and clinical chemistry) obtained at Baseline, Treatment 18, Treatment 36, and after 4 weeks of follow-up.

4. Changes from Baseline values in vital signs obtained at Baseline, Treatment 18, Treatment 36 and after 4 weeks of follow-up.

5. Changes in the physical examination obtained at Baseline and Treatment 36.

4 STUDY PLAN

4.1 Study Design

The trial will consist of two parts.

Part A will be an open-label trial to establish the safety, tolerability and response to SGX302 treatment in this population and evaluate the use of two different formulations of SGX302 (ointment and gel, respectively), in up to 15 patients.

Once safety, tolerability and response has been established to the satisfaction of the Principal Investigator (PI), the Medical Monitor, and the Sponsor, the team will select the formulation (gel or ointment) to include in Part B and Part B will be initiated as a double-blind, placebo-controlled, parallel trial in patients with mild-to-moderate psoriasis comparing the improvement in lesions following 36 treatments with either SGX302 or a color-matched vehicle control. The primary endpoint will be changes from Baseline to Week 18 in the 5-point IGA mod 2011 score. Other measures of improvement will be improvement in several thresholds of the PASI (75%- PASI 75, 90%- PASI 90, and 100%- PASI 100), changes in the SkinDex-29 QoL questionnaire scores, changes in the patient reported saSPI scores, and changes in the DLQI scores.

4.2 Study Schematic

Figure 1: STUDY SCHEMATIC: Part A

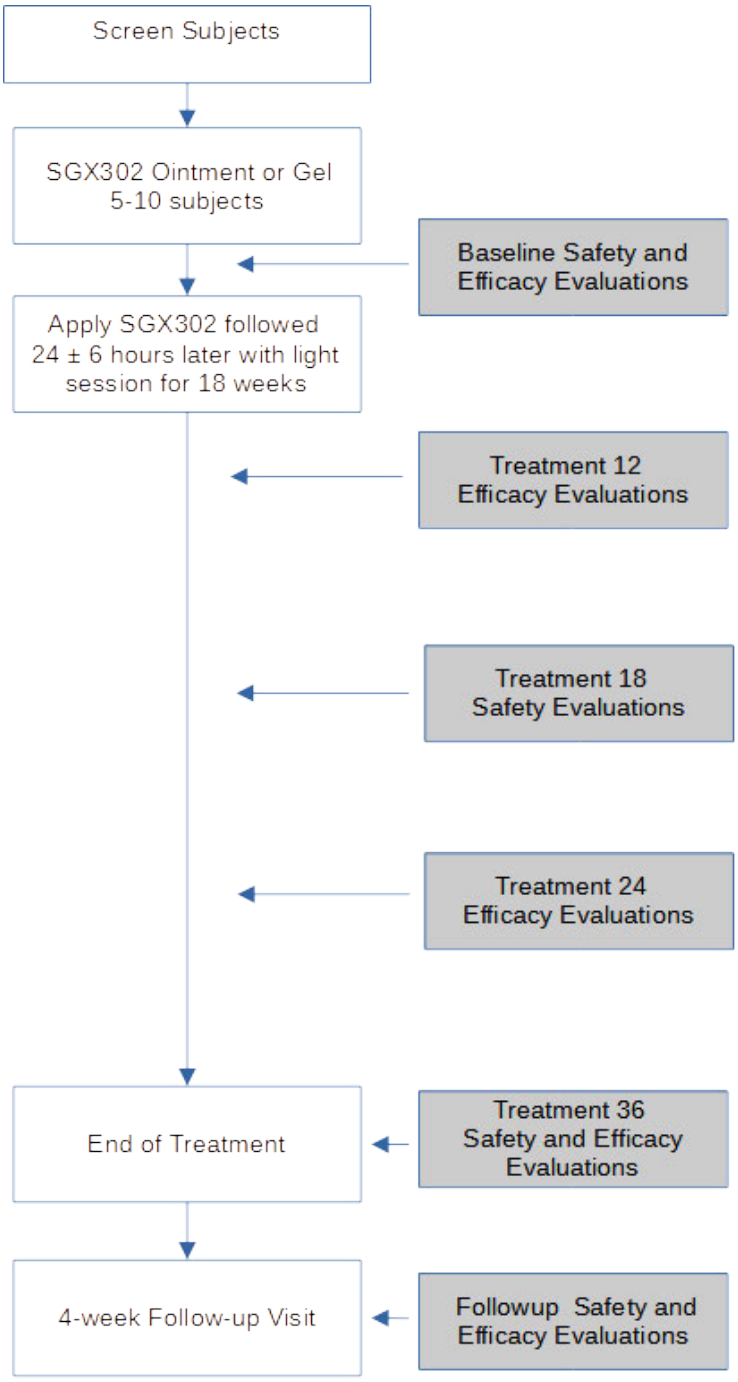
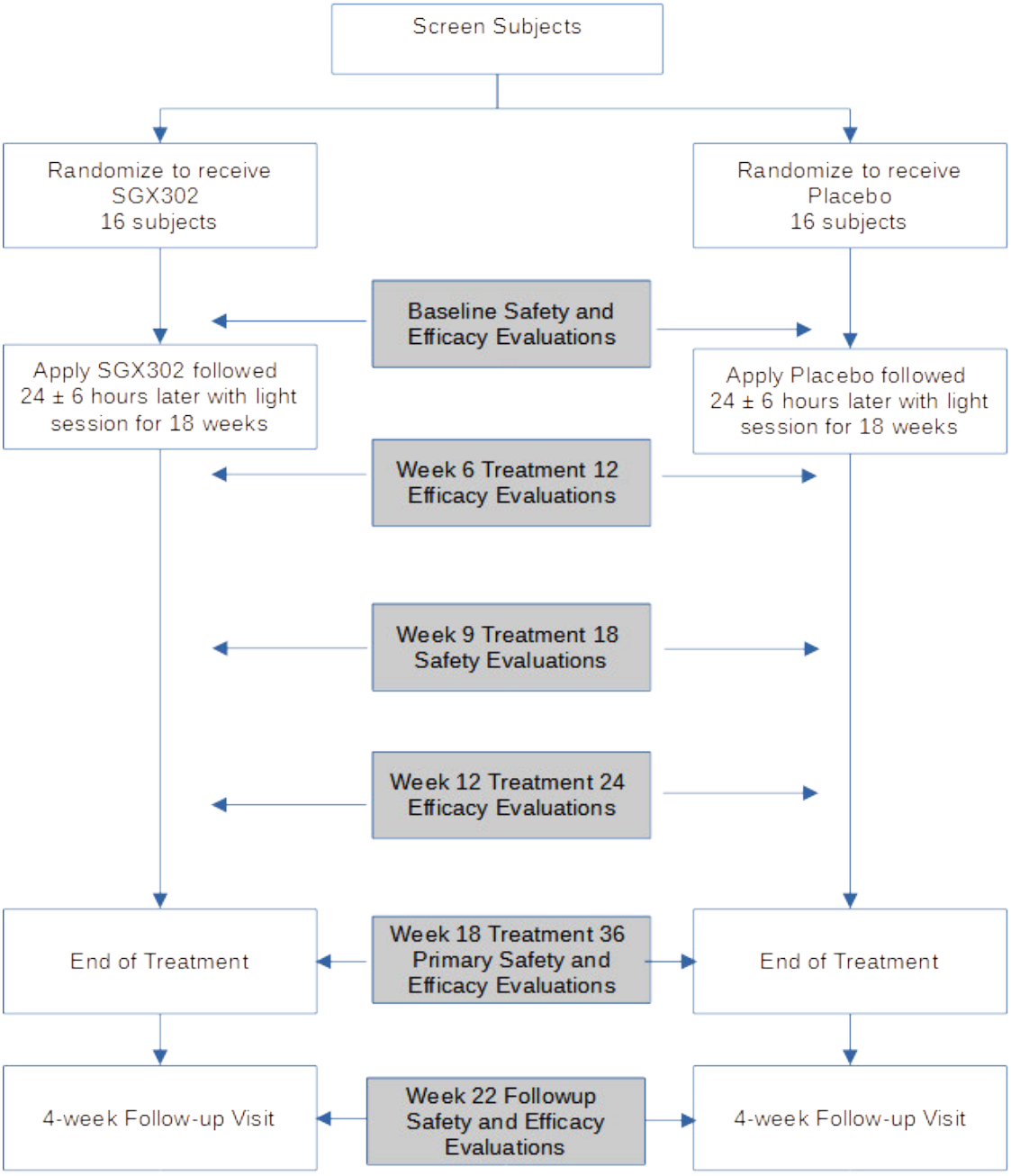


Figure 2: STUDY SCHEMATIC: PART B



4.3 Schedule of Assessments

Schedule of assessments with initial light treatments to be performed at site visits for at least the first 4 weeks. If the patient has been adequately trained and is comfortable with operating the light device, at the discretion of the site team, the Medical Monitor, and Sponsor, the treatments may be performed at home provided that the use of the device can be regulated and monitored in real time. If a patient is treated at home, they must attend the clinic for the Treatment 12, Treatment 18, Treatment 24, Treatment 36 and the 4-week post-treatment follow-up visit.

Table 3: Schedule of Assessments

	ICF[1]	Entry Criteria	Pregnancy Test	Physical Exam	Safety Evaluations[2]	PK and ECG	Efficacy Evaluations[3]	Drug Application	Light Session	Assessment of Treated Lesions[4]	AE[5]
Screening	X	X	X								
Baseline		X	X[7]	X	X	X	X				
Treatment 1								X	X	X	X
Treatments 2-11								P[6]	X	X	X
Treatment 12							X	P[6]	X	X	X
Treatments 13-17								P[6]	X	X	X
Treatment 18					X	X		P[6]	X	X	X
Treatments 19-23								P[6]	X	X	X
Treatment 24							X	P[6]	X	X	X
Treatments 25-35								P[6]	X	X	X
Treatment 36			X	X	X	X	X	P[6]	X	X	X
4-week Follow-up					X	X	X				X

[1] ICF: Signed Informed Consent Form

[2] Safety Evaluations: hematology panel, clinical chemistry panel, and vital signs.
[3] Efficacy Evaluations: IGA using the mod 2011 scale, PASI, SkinDex-29, saSPI, and the DLQI
[4] Assessment of Treated Lesions (and surrounding area): to be obtained immediately before and 10-30 minutes following completion of the light session. Includes assessment of treated lesions for erythema, pain, edema, pruritus, hyperpigmentation, hypopigmentation, rash, and evidence of vesiculation
[5] AE: adverse events
[6] P: patient to apply study drug 24±6 hours prior to the light session
[7] Baseline Pregnancy Test: If the Baseline visit is performed within 7 days of the Screening visit, the Baseline serum pregnancy test is not required

5 POPULATION

5.1 Number of Subjects

Up to 47 subjects are planned to be enrolled (up to 15 [10 ointment formulation and up to 5 gel formulation] in Part A and 32 [16 active and 16 placebo] in Part B). Up to 5 additional patients may be enrolled to replace any patients that dropout prior to completing their 36 treatments.

5.2 Inclusion Criteria:

For enrollment, a patient must meet ***all*** of the following criteria:

1. Able to understand and have signed the Informed Consent Form.

2. Men and women between 18 and 75 years old, inclusive.

3. Have a clinical diagnosis of plaque psoriasis (psoriasis vulgaris) of at least 6-months duration that involves the body (trunk and/or limbs) that is amenable to topical treatment and opaque coverage after application.

4. Have a static Investigator Global Assessment (IGA)/Psoriasis Area and Severity Index (PASI) of disease severity of mild or moderate on the body (trunk and/or limbs) defined by:

   Mild: mild plaque elevation (0.5 mm); light red coloration; fine scale predominates

   Moderate: moderate plaque elevation (0.75 mm); moderate red coloration; coarse scale predominates

5. Have lesions involving 2-30% of the body (trunk and/or limbs). For subjects with scalp psoriasis included in the treatment area, the total treatment area on body and scalp must not exceed 30%.

5.3 Exclusion Criteria:

For enrollment, a patient must NOT have any of the following:

1. Women who are pregnant, lactating, planning to become pregnant, or women of child-bearing potential who have not successfully been using the same medically acceptable contraceptive methods over the previous 3 months, eg, oral contraceptive agents, intrauterine device (IUD), and barrier method plus spermicide.

2. Use of topical anti psoriatic therapy (including topical retinoids, corticosteroids, or vitamin D analogs) within one week prior to the beginning of the study and willing to not use other psoriasis treatments for 4 weeks following completion of the treatment portion of the study.

3. Received systemic biologic therapy to treat psoriasis (eg, IL-17 inhibitors [eg secukinumab, Cosentyk®; ixekizumab, Talz®; and broalumab, Siliq®], IL-23 inhibitors [eg, guselkumab, Tremfya®; tidrakizumab, Ilumya® rsiankizumab, Skyrizi®], and JAK inhibitors [eg, Tofacitinib, Xeljanz®]) within 12 weeks prior to the beginning of the study.

4. Received systemic psoriasis therapy (eg, methotrexate, cyclosporine, systemic corticosteroids, retinoids [such as Acitretin]), or biologic immunosuppressives (eg, etanercept, Enbrel®; certolizumab pegol, Cimiza®; adalimumab, Humira®; infliximab, Remicade®) within 4 weeks prior to the beginning of the study.

5. Received phototherapy (including laser) or photodynamic (light activated drug) therapy within 4 weeks prior to the beginning of the study.

6. History of noncompliance to medical regimens or unwilling to comply with the study protocol.

7. Participation in an investigational drug study within 30 days prior to the beginning of the study.

8. Serious or unstable medical or psychological conditions that in the opinion of the Investigator would compromise the subject's safety or successful participation in the study.

6 STUDY CONDUCT

6.1 General Instructions

The trial consists of two parts:

Part A – up to 36 treatments of open-label SGX302 (either ointment or gel formulation) therapy in up to 15 patients with a four-week follow-up period.

Part B – a randomized, double-blind, placebo-controlled stage enrolling 32 subjects (16 active and 16 placebo with the ability to replace up to 5 dropouts). Patients will undergo 36 study drug (SGX302 or placebo) treatments with a four-week follow-up period.

All patients will apply the study drug at least 2 calendar days apart, targeting an average of 2 treatments per week and will undergo light therapy at the investigational site using a Daavlin-supplied device to activate the drug with visible light 24±6 hours later. Patients will undergo up to 36 study drug treatments and, on completion, will be followed for a 4-week follow-up period in which patients will not receive other psoriasis treatments.

Once Part A is concluded data will be assessed with participating investigators and assuming no unexpected safety concerns are noted, Part B of the protocol will commence using one of the gel or ointment formulations. In Part B, each patient will be randomized to a double-blind treatment group at a ratio of 1:1 of active drug to placebo. Patients with mild-to-moderate plaque psoriasis will receive either SGX302 (0.25% hypericin) or color-matched placebo. All patients will apply the study drug approximately twice per week (at 2-5 calendar days apart) and will activate the drug with visible light 24±6 hours later. Patients will undergo up to 36 treatments and, on completion, will be followed for a 4-week follow-up period in which patients will not receive other psoriasis treatment.

For all patients, visible light therapy will be started at 5 J/cm^2, calculated using the supplied light therapy duration tables and titrated up at the Investigator's discretion until patients have a Grade I Erythema Score following the light treatment at their treated lesions or reach a maximum of 40 J/cm^2, whichever occurs first. Patients will be assessed for disease status at Baseline and then at Treatments 12, 24, 36 and after 4 weeks of follow-up.

Efficacy assessments will include the IGA using the mod 2011 scale and PASI (including % change from Baseline and the number of patients achieving a 75%, 90% and 100% improvement from Baseline) to measure disease status and the SkinDex-29, saSPI, and the DLQI instruments to measure patient reported QoL.

Routine safety laboratories (hematology and clinical chemistries), and vital signs will be obtained at Baseline, Treatments 18, 36 and at the end of the follow-up period. Physical examinations will be performed at Baseline and Treatment 36. Hypericin blood concentrations and ECGs will be obtained in Part A at Baseline, and Treatments 18, 36, and at the end of the follow-up period. Hypericin blood concentrations and ECGs will be

obtained in Part B at Baseline and Treatments 18, 36 and at the end of the follow-up period.

AE's will be recorded throughout the study.

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
- Medical history completed determining eligibility for enrollment
- 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:

- History of any medical changes obtained
- Physical exam
- Confirmation that the patient meets all inclusion/ exclusion criteria
- 12-lead ECG obtained
- 5 mL of blood collected and processed per the Laboratory Manual for measurement of blood hypericin levels
- Blood for the hematology panel obtained
- Blood for the clinical chemistry panel obtained
- Vital signs obtained
- Women of child-bearing potential will have a serum pregnancy test obtained, if the Screening visit was performed more than 7 days prior to the Baseline visit
- IGA form completed; see Section 19.3, page 71
- PASI form completed; see Section 19.4, page 72

- SkinDex-29 form completed; see Section 19.7, page 79
- The patient completes the saSPI; see Section 19.5, page 75
- DLQI form competed; see Section 19.6, page 77

Once the above have been completed:

- Treatment assignment:
  - For Part A, the patient will be assigned open-label SGX302
  - For Part B, patient will be randomized to blinded treatment (SGX302 or placebo)
- Patient will be trained on the application of study drug
- Site personnel will observe the patient applying the drug. Patients will need to be seen in clinic for drug application until the site personnel are comfortable with the patient's ability to properly apply the drug

6.2.3 Standard Visits

Patients will be seen (either in person or through video communication) 24±6 hours after study drug application. At that visit the following will be done:

- Interval medical history obtained
- Any AEs documented
- Adequate drug application verified by observing the pink/purple-staining of all lesions
- Delivery of light session, the time of treatment calculated by the target dose (starting at 5 J/cm^2 and titrated up at the Investigator's discretion to a dose that generates an Erythema score = 1 at the treated lesions or 40 J/cm^2, whichever occurs first); more than one positioning may be necessary to treat all lesions
- A dermatologic assessment of treated lesions will be performed immediately before and 10-30 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

Each assessment will be graded using the criteria in Table 4.

Table 4: Dermatologic Assessment Grading

Toxicity Grade	Severity
Grade 0	No apparent reaction
Grade 1	Mild
Grade 2	Moderate
Grade 3	Severe
Grade 4	Life-threatening

6.2.4 Treatment 12

In addition to the standard visit activities (Section 6.2.3), patients will complete the following additional efficacy assessments at the Treatment 12 visit:

- IGA form completed; see Section 19.3, page 71
- PASI form completed; see Section 19.4, page 72
- SkinDex-29 form completed; see Section 19.7, page 79
- The patient completes the saSPI; see Section 19.5, page 75
- DLQI form competed; see Section 19.6, page 77

6.2.5 Treatment 18

In addition to the standard visit activities (Section 6.2.3), patients will complete the following additional safety assessments at the Treatment 18 visit:

- 12-lead ECG obtained
- 5 mL of blood collected and processed per the Laboratory Manual for measurement of blood hypericin levels
- Blood for the hematology panel obtained
- Blood for the clinical chemistry panel obtained
- Vital signs obtained

6.2.6 Treatment 24

In addition to the standard visit activities (Section 6.2.3), patients will complete the following additional efficacy assessments at the Treatment 24 visit:

- IGA form completed; see Section 19.3, page 71
- PASI form completed; see Section 19.4, page 72
- SkinDex-29 form completed; see Section 19.7, page 79
- The patient completes the saSPI; see Section 19.5, page 75
- DLQI form competed; see Section 19.6, page 77

6.2.7 Treatment 36

In addition to the standard visit activities (Section 6.2.3), patients will complete the following additional safety and efficacy assessments at the Treatment 36 visit:

- IGA form completed; see Section 19.3, page 71
- PASI form completed; see Section 19.4, page 72
- SkinDex-29 form completed; see Section 19.7, page 79
- The patient completes the saSPI; see Section 19.5, page 75

- DLQI form competed; see Section 19.6, page 77
- Physical exam
- 12-lead ECG obtained
- 5 mL of blood collected and processed per the Laboratory Manual for measurement of blood hypericin levels
- Blood for the hematology panel obtained
- Blood for the clinical chemistry panel obtained
- Vital signs obtained
- Women of child-bearing potential will have a serum pregnancy test obtained

6.2.8 4-week Post-Treatment Follow-up Visit

At the 4-week follow-up visit, the following assessments will be completed:

- Interim medical history obtained
- AEs documented
- IGA form completed; see Section 19.3, page 71
- PASI form completed; see Section 19.4, page 72
- SkinDex-29 form completed; see Section 19.7, page 79
- The patient completes the saSPI; see Section 19.5, page 75
- DLQI form competed; see Section 19.6, page 77
- 12-lead ECG obtained
- 5 mL of blood collected and processed per the Laboratory Manual for measurement of blood hypericin levels
- Blood for the hematology panel obtained
- Blood for the clinical chemistry panel obtained

- Vital signs obtained

6.3 Premature Discontinuation

The study will be suspended immediately if any of the following conditions occur:

- Any patient develops a Grade >3 Adverse Event (AE) judged by the Investigator or Medical Monitor to be "Possibly Related", or "Related" to study drug.
- More than half the cohort report similar Grade 2 AEs judged by the Investigator or Medical Monitor to be Possibly Related or Related to study drug.

Following initiation of the suspension, the relevant unblinded, safety data will be presented to a Safety Committee. The Safety Committee will be charged with making a recommendation as to whether the study should be stopped or enrollment re-started. The committee will also have the ability to recommend protocol amendments related to any safety concerns.

The outcome of the meeting and relevant data will be shared with the US Food & Drug Administration. If the committee recommends restarting enrollment into the study, Soligenix will provide ample time for FDA to review the data and clear the study to proceed.

Patients will be withdrawn from the trial if any of the following occur:

- Experience similar Grade ≥2 AEs on 2 separate occasions judged to be "Possibly Related", or "Related" to study drug.
- The Investigator judges that continuation of the treatment is not in the best interest of the patient.

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 Investigator if he/she feels that it is in the best medical interest of the patient.

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

Patients withdrawn from the study may be replaced up to a total of 5 subjects provided that both the Principal Investigator and the Soligenix Medical Monitor agree that the reasons for withdrawal do not suggest a change in the risk assessment of the SGX302 therapy.

7 DESCRIPTION OF STUDY PROCEDURES

Subjects will have the following assessments performed.

7.1 5-point Investigator's Global Assessment (IGA)

This instrument was developed specifically to address the regulatory and psoriasis clinical investigators' input as to a psoriatic endpoint for clinical trials. The specific version used is the 5-point IGA mod 2011 and the form used is attached in the Appendix, Section 19.3 on page 71.

7.2 Psoriasis Area and Severity Index (PASI)

This endpoint has been widely used in psoriasis clinical trials. The specific form used in this trial is attached in the Appendix, Section 19.4 on page 72.

7.3 SkinDex-29

The SkinDex-29 is a validated measure of the effects of skin diseases on quality of life that is suitable for use in research about dermatology patients' experiences of illness and its treatment. The form used in this trial is attached in the Appendix, Section 19.7, page 79.

7.4 Self-Assessment Simplified Psoriasis Index (saSPI)

This instrument was developed as a patient completed measure of the summary impact of psoriasis on a patient's current severity, psychosocial impact, past history and intervention. The form used for this trial is attached in the Appendix, Section 19.5 on page 75.

7.5 Dermatology Life Quality Index (DLQI)

The DLQI was developed as a general quality of life instrument to measure the impact of chronic skin disease on patients. The form used in this trial is attached in the Appendix, Section 19.6 on page 77.

7.6 Electrocardiogram (ECG)

12-lead ECGs, including QT interval measurement, will be done at the following timepoints:

- Baseline
- Treatment 18

- Treatment 36
- 4-week follow-up visit

ECGs will be interpreted by site personnel trained in the evaluation of ECGs for any interval changes.

7.7 Hypericin Blood Levels

Blood samples to measure the blood levels of hypericin will be collected at the following timepoints:

- Baseline
- Treatment 18
- Treatment 36
- 4-week follow-up visit

Blood will be processed and shipped to the central PK laboratory as detailed in the "Laboratory Manual".

7.8 Clinical Laboratory Tests

7.8.1 Hematology Panel Laboratory Tests

The hematology panel will be performed on blood obtained at Baseline, Treatment 18, Treatment 36 and the 4-week follow-up visit. 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

7.8.2 Clinical Chemistry Panel Laboratory Tests

The clinical chemistry panel will be performed on blood obtained at Baseline, Treatment 18, Treatment 36, and the 4-week follow-up visit. The panel will consist of the following tests:

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

7.9 Vital Signs

Vital signs will be obtained by site personnel at Baseline, Treatment 18, Treatment 36, and the 4-week follow-up visit. Vital signs obtained will consist of:

- Resting Blood Pressure
- Heart Rate
- Respiratory Rate

8 STUDY DRUG MANAGEMENT

8.1 Description

[redacted]

8.1.1 Study Drug Packaging and Labeling

[redacted]

8.1.2 Study Drug Storage

Study drug will be stored at room temperature.

8.2 Study Drug Preparation

Ointment will be used directly out of the container and mixed with the supplied application stick. Gel will be used directly out of the tube.

8.3 Administration

After adequate patient training, patients will apply study drug to all accessible psoriatic lesions, applied to cover a thin layer of drug over the entire surface of each lesion. However, application to uninvolved skin should be as limited as possible. The amount of study drug used for each application will be dependent upon the amount of lesion surface area. Personnel applying the drug should wear disposable gloves and wash their hands after applying the study drug. If the medicine gets on healthy skin, it should be washed off with soap and water.

8.4 Study Drug Accountability

The PI must ensure that all drug supplies are kept under lock and key with access limited to those authorized by the Investigator until distributed to patients. The PI must maintain accurate records of the receipt of all study medication shipped by the Sponsor, including date received, lot number, expiration/re-test date, amount received and disposition of all study medication. Current dispensing records will be maintained and include date and

amount of medication dispensed, initials of subjects receiving the medication, and any amount of medication not used or returned (or lost) by the subject. All remaining medication not required by regulation to be held by the clinical facility, must be destroyed following all appropriate regulatory guidelines or returned to the Sponsor immediately after the study is completed. Any lost, spilled or missing drug must be documented.

8.5 Study Drug Handling and Disposal

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

8.6 Prohibited Concomitant Therapy

During the study and 4-week follow-up period, no psoriasis-specific treatments will be allowed.

8.7 Compliance

Adequate application of the study drug will be visually confirmed by noting pink/purple-staining of lesions prior to light sessions.

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

9.2 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.

9.2.1 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).

9.2.2 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.

9.3 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.

9.4 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.

9.5 Recording Adverse Events

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

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 SGX302
- 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; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of 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 SAE 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 (i.e., there is a reasonable possibility that the AE may have been caused by the drug) and are thus deemed significant new AEs or risks with respect to the drug, the investigator must promptly inform the relevant Institutional Review Board (IRB), in accordance with the ICH Guidance on Good Clinical Practices (E6, April 1996).

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



If above contact is not accessible, please call:

Soligenix, Inc., 29 Emmons Drive, Suite B-10, Princeton, NJ 08540

[redacted]

FOR ADDITIONAL ASSISTANCE:

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

[redacted]

10.4 Overdose

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved SGX302) must be communicated to Soligenix, Inc., or a specified designee 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 proof of concept study. It is designed to provide initial estimates of the success rates using current psoriasis endpoints in the SGX302 and placebo treatment groups. Differences in categorical endpoints will be compared using a chi-squared test as well as a logistic regression (initial score and treatment as the independent variables and outcome as the dependent variable) and continuous endpoints will be compared using a student's t-test. The statistical threshold will be a two-sided p of 0.05. No interim analysis is planned. The primary analyses will be calculated in the Intent to Treat population defined as patients having been randomized and receiving at least one drug application/light session. Secondary analyses will examine the effect of the drug treatment in patients completing at least 18 treatments.

11.2 Sample Size

Given the limited information on the utility of SGX302 in psoriasis, the estimated drug effect and placebo rates are uncertain. An arbitrary sample size of 16 patients per group for the controlled part (Part B) of the study was chosen to allow better sample size calculations to be made in subsequent clinical trials with the drug.

The up to 15 patients included in the open-label Part A of the study are expected to provide initial information sufficient to begin characterizing the treatment response in the psoriasis patients and confirm the safety observed in the CTCL programs, informing Part B of the protocol.

11.3 Statistical Methods

11.3.1 Primary Endpoint

The primary endpoint for this trial will be a comparison of the proportion of patients in each treatment group of Part B after approximately 36 treatments that achieve a 0 or 1 score (clear or almost clear) evaluation using the IGA mod 2011 scale. This will be compared using a chi-squared analysis.

11.3.2 Secondary Endpoints:

Additional endpoints will examine outcomes between the treatment groups in each cohort compared using a chi-squared analysis:

1. Number of patients achieving a ≥75% improvement in PASI (PASI 75).

2. Number of patients achieving a ≥90% improvement in PASI (PASI 90).

3. Number of patients achieving a 100% improvement in PASI (PASI 100).

4. Mean score of the saSPI.

5. The mean SkinDex-29 QOL score.

6. Number of patients with an Investigator's Global Assessment (IGA) score of 0, 1, or 2.

7. The mean score on the Dermatology Life Quality Index (DLQI) instrument.

The above endpoints will also be evaluated in the Part B Per Protocol Population defined as patients who met all entry criteria, received a minimum of 28 treatments, did not have more than 10 days between any subsequent treatment, and did not have a "major" protocol deviation.

11.4 Safety

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

11.5 Interim Analysis

No interim analysis is planned.

12 ETHICS AND RESPONSIBILITIES

12.1 Institutional Review Board

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

12.2 Ethical Conduct of the Study

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

12.3 Written Informed Consent

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

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 enrolment code/subject number only. Authorized representative of a regulatory authority (eg, MCC) 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 question about the integrity of the data, the FDA will take any action it deems necessary to ensure the reliability of the data, including:

- Initiating agency audits of the data derived from the clinical investigator in question;
- Requesting that the Sponsor submit further analyses of data, 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

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, and 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 CRFs is accurate, complete and can be verified from the medical records.

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

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

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

14.1.3 Monitoring Visits

Soligenix or their trained designee will perform on-site monitoring visits as frequently as it deems necessary. Remote monitoring visits may also be conducted as per Soligenix SOPs and in compliance with the monitoring plan. 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, Inc. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

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

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

16 STUDY REPORT

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

17 STUDY DISCONTINUATION

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

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, Inc. However, authorized regulatory officials, IRB/IEC personnel, Soligenix, Inc. and its authorized representatives are allowed full access to the records.

Identification of subjects and CRFs shall be by 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.

19 APPENDICES

19.1 Appendix I: Names of Study Personnel

Sponsor:	Soligenix, Inc.
	[redacted]
Medical Monitor:	[redacted]
Central PK Laboratory:	[redacted]

19.2 Appendix II: 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 minimize 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.

19.3 Appendix III: 5-point IGA mod 2011

Score	Short descriptor	Detailed descriptor
0	Clear	No signs of psoriasis; post-inflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominantly fine scaling
3	Moderate	Clear distinguishable to moderate thickening; dull to bright red; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep red coloration; severe/coarse scaling covering almost all lesions

19.4 Appendix IV: Psoriasis Area and Severity Index (PASI)

PASI scores will be calculated as follows:

1. Divide body into four areas: head, arms, trunk to groin, and legs to top of buttocks.
2. Generate an average score for the erythema, thickness, and scale for each of the 4 areas (0 = clear; 1–4 = increasing severity).
3. Sum scores of erythema, thickness, and scale for each area.
4. Generate a percentage for skin covered with psoriasis for each area and convert that to a 0–6 scale:
    a. 0 = 0%
    b. 1= 0 to ≤10%
    c. 2 = 10 to <30%
    d. 3 = 30 to <50%
    e. 4 = 50 to <70%
    f. 5 = 70 to ≤90%
    g. 6 = 90 to100%
5. Only the shaded rows need to be completed by the site. The calculations and final score will be generated by the electronic Case Report Form.
6. Multiply score of item 3 above times item 4 above for each area and multiply that by:
    a. 0.1 for head
    b. 0.2 for arms
    c. 0.3 for trunk
    d. 0.4 for legs
7. Add these scores to get the PASI score.

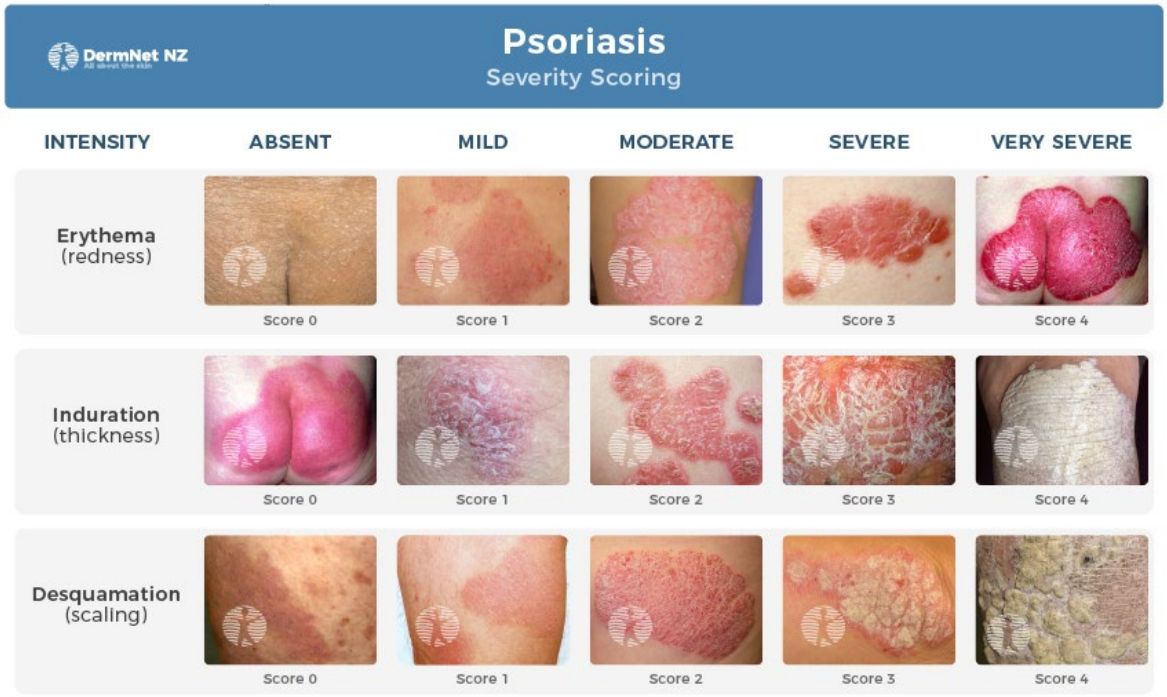
Table 5: PASI Calculation

Row	Element	Head	Upper Extremity	Trunk	Lower Extremity
1	Redness				
2	Thickness				
3	Scale				
4	Sum rows 1-3				
5	Area score[1]				
	Score calculation	Row 4 x row 5 x 0.1	Row 4 x row 5 x 0.2	Row 4 x row 5 x 0.3	Row 4 x row 5 x 0.4
6	Column Score				

[1] Area scoring criteria (score: % involvement)
0: 0 (clear)
1: 0 to <10%
2: 10 to <30%
3: 30 to <50%
4: 50 to <70%
5: 70 to <90%
6: 90 to 100%

The following photographs provide examples of the grading system.

Figure 3: Examples of PASI Severity Grading

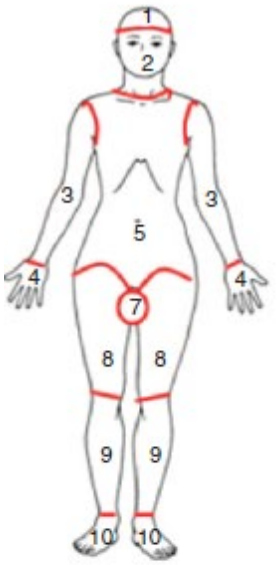


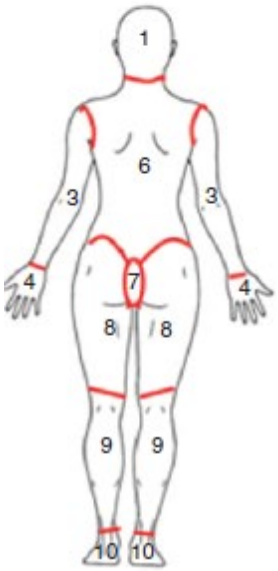
19.5 Appendix VI: Self-Assessment Simplified Psoriasis Index (saSPI)

PART 1: For each of these 10 body areas, please circle the one that best describes your psoriasis today:

0	Clear or so minor that it does not bother me (0)
±	Obvious but still leaving plenty of healthy skin (0.5)
+	Widespread and involving much of the affected areas (1.0)

1	Scalp and hairline	0	±	+
2	Face, neck, and ears	0	±	+
3	Arms and armpits	0	±	+
4	Hands, fingers, and fingernails*	0	±	+
5	Chest and abdomen (stomach)	0	±	+
6	Back and shoulders	0	±	+
7	Genital area and/or anus (back passage)	0	±	+
8	Buttocks and thighs	0	±	+
9	Knees, lower legs, and ankles	0	±	+
10	Feet, toes, and toenails*	0	±	+
*PSORIASIS OF THE NAILS: even if the skin of the hands or feet is unaffected, you can score ± for severe psoriasis of at least 2, and + for 6 or more finger- or toe-nails.		SUM to be done by staff		





PART 2: Please circle whichever of these choices best describes the overall state of your psoriasis today. Your score should reflect the average of all your psoriasis, not just the worst areas.

0	Clear or just slight redness of staining
1	Mild redness or scaling with no more than slight thickening
2	Definite redness, scaling, or thickening
3	Moderately severe with obvious redness, scaling, or thickening

4	Very red and inflamed, very scaly, or very thick
5	Intensely inflamed skin with or without pustules (pus spots)

PART 3: Give one point for each true statement / for each therapy received (whether currently or in the past).	**Points**
About patient's psoriasis	
Patient has had psoriasis for more than 10 years	
Patient has had psoriasis for more than 20 years (additional point)	
Patient has had erythrodermic or generalized pustular psoriasis	
Patient has been admitted to hospital for psoriasis	
About patient's treatment	
Patient has had at least one course of UV treatment or PUVA (psoralen plus UVA)	
Patient has been treated with methotrexate (now or in past)	
Patient has been treated with acitretin or etretinate (now or in past)	
Patient has been treated with another systemic agent for psoriasis (now or in past)	
Patient has been treated with ciclosporin (now or in past)	
Patient has been treated with a "biological" drug (now or in past) Biological drugs include Remicade/infliximab; Enbrel/etanercept; Raptiva/efalizumab; Humira/adalimumab; Stelara/ustekinumab	
Patient has been treated with another systemic agent for psoriasis (now or in past) Name of treatment: _____	

History and interventions score: maximum 10 points | SUM to be done by staff

19.6 Appendix VII: Dermatology Life Quality Index (DLQI)

DERMATOLOGY LIFE QUALITY INDEX FORM

Subject No: _____ Date: ___ ___/ ___ ___/ 2022

The aim of this questionnaire is to measure how much your skin problem has affected your life **OVER THE LAST WEEK**. Please tick (✓) one box for each question.

1	Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2	Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

9	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
10	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐

Please check that you have answered EVERY question
Thank you

19.7 Appendix VIII: SkinDex-29

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

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

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

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

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