Clinical Research Protocol

Tolerability and efficacy of daylight aminolevulinic-acid-photodynamic therapy (ALA-PDT) compared with conventional ALA-PDT for treatment of actinic keratosis on the face or scalp

Protocol Number:	Version 1.0
Version Date:	March 13th, 2017
Investigational Product:	Aminolevulinic acid HCl topical solution 20% (Levulan Kerastick)
IND Number:	
Development Phase:	Not applicable
Sponsor:	Investigator Initiated Protocol
Funding Organization:	Sun Pharmaceutical Industries Ltd
Principal Investigator:	Name: Sarah Arron, MD, PhD Telephone: 415-353-9684 Fax: 415-353-7838 E-mail: Sarah.Arron@ucsf.edu

Approval:

PI Signature (Name and Title) *Date*

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Sun Pharmaceutical Industries Ltd. with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 1.0

Protocol Title: Tolerability and efficacy of daylight aminolevulinic-acid-photodynamic therapy (ALA-PDT) compared with conventional ALA-PDT for treatment of actinic keratosis on the face or scalp

Protocol Date: March 13th, 2017

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Investigator Signature *Date*

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Print Name and Title

Site # _____

Site Name _____

Address _____

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Phone Number _____

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LIST OF ABBREVIATIONS

AE	adverse event
AK	actinic keratosis
ALA	aminolevulinic acid
BLU-U	blue light phototherapy illuminator
CFR	Code of Federal Regulations
CRF	case report form
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCl	Hydrochloride
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LSR	Local skin reaction
PDT	photodynamic therapy
PpIX	protoporphyrin IX
PI	Principal Investigator
SAE	serious adverse event
SCC	squamous cell carcinoma

PROTOCOL SYNOPSIS

TITLE	Tolerability and efficacy of daylight aminolevulinic-acid-photodynamic therapy (ALA-PDT) compared with conventional ALA-PDT for treatment of actinic keratosis on the face or scalp
SPONSOR	Investigator Initiated Protocol
FUNDING ORGANIZATION	Sun Pharmaceutical Industries Ltd
NUMBER OF SITES	1
RATIONALE	Actinic keratoses (AK) are common precancerous skin lesions that arise on sun-damaged skin. Treatment is aimed at preventing progression to cutaneous squamous cell carcinoma (SCC). First-line therapy for clinically apparent lesions includes cryotherapy and curettage; and field therapy options are topical 5-fluorouracil, imiquimod, ingenol mebutate, and photodynamic therapy (PDT). PDT involves the topical application of aminolevulinic acid (ALA), or one of its derivatives, as a photosensitizing agent. In response, rapidly proliferating, dysplastic cells preferentially accumulate protoporphyrin IX (PpIX). When PpIX is activated by blue or red light, singlet oxygen species are produced, resulting in cell death. PDT is beneficial due to its brief treatment course and efficacy in clearing AK. However, its main drawbacks are the adverse effects of pain, burning, pruritus, erythema, crusting, and inflammation associated with treatment. While conventional PDT uses red or blue artificial light to activate a high concentration of accumulated protoporphyrins, daylight PDT uses natural daylight to activate lower levels of protoporphyrins in a continuous manner. Daylight PDT, when compared with conventional PDT, has been associated with significantly less pain while achieving comparable effiacy for the treatment of AK. Daylight PDT is also more cost-effective and reduces the amount of time spent in clinic. Previous randomized studies comparing daylight PDT with conventional PDT have largely used methyl-aminolevulinate as the photosensitizer, have been intra-individual comparative studies, and have been performed in Nordic countries. Because the effective light dose from natural daylight depends on geographic location and seasonal and weather changes, randomized trials in different geographic and environmental conditions are of interest. The proposed randomized clinical trial investigates the tolerability and efficacy of daylight ALA-PDT for the treatment of AK in San Francisco for the first time; subjects will be randomized to various treatment arms, as opposed to previous split-face and intra-individual studies.

STUDY DESIGN	Randomized (1:1:1), single-blind controlled trial with parallel group design
PRIMARY OBJECTIVE	To determine whether daylight PDT affords a reduction in treatment symptoms of pain, burning, and pruritus as measured by 1) symptom level during the treatment period and 2) pain at the end of treatment exposure.
SECONDARY OBJECTIVES	To determine efficacy in clearance of AK at 12 weeks as measured by 1) Reduction in number of AKs and 2) Proportion of patients with partial and complete clearance of AKs. To determine whether daylight PDT affords a reduction in local skin reaction to treatment. To determine whether daylight PDT enables a faster resolution of pain and local skin response during the follow-up period.
NUMBER OF SUBJECTS	30; 10 in each treatment arm
SUBJECT SELECTION CRITERIA	Inclusion Criteria: • Adults at least 18 years old. • Subjects must be able to read, sign, and understand the informed consent • Subjects have at least 4 and no more than 20 clinically typical, visible actinic keratoses in the target treatment area on the face or scalp. • Subject must be willing to forego any other treatments for AK in the treatment area on the face or scalp, during the study period, and for 14 days prior to screening; including cryotherapy, topical 5-fluorouracil, imiquimod, and ingenol mebutate. • Subjects who have previously received PDT must undergo at least an 8-week washout period prior to enrollment in study. • Subject must be willing and able to participate in the study and to comply with all study requirements including concomitant medication and other treatment restrictions, and telephone interview. • If subject is a female of childbearing potential she must have a negative urine pregnancy test result prior to study treatment initiation and must agree to use an approved method of birth control while enrolled in the study. Women who are pregnant, lactating, or planning to become pregnant during the study

	period are excluded from the study. Exclusion Criteria: • Subjects with any dermatologic disease in the treatment area that may be exacerbated by the treatment proposed or that might impair the evaluation of AKs. • Subjects who are currently participating in another clinical study or have completed another clinical study with an investigational drug or device on the study area within 30 days prior to study treatment initiation. • Subjects with any medical condition that, in the opinion of the investigator, makes the patient unsuitable for the trial.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Study medication—Aminolevulinic acid HCl topical solution 20% (Levulan Kerastick) Study device—BLU-U blue light phototherapy illuminator After preparation of the treatment area with acetone, one stick of Levulan (containing 354 mg ALA HCl) will be topically applied to the treatment area (face or scalp). Subjects will be randomized to one of three treatment arms to receive BLU-U exposure and/or daylight exposure. Treatment arms are as follows: **A. Conventional arm:** Acetone preparation, ALA topical application, 1hour incubation, 16 minutes 40 seconds (16:40) BLU-U exposure, application of sunscreen. **B. Combination arm:** Acetone preparation, ALA topical application, 15 minute incubation, 16:40 BLU-U exposure, application of sunscreen, 45 minute daylight exposure. **C. Daylight arm:** Acetone preparation, ALA topical application, 15 minute incubation, application of sunscreen, 1 hour daylight exposure.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 115 days. **Screening:** up to 30 days **Treatment:** 1 day **Follow-up:** 84 days The total duration of the study is expected to be 16 months. Approximately 12 months for subject enrollment and 4 months for treatment and final subject follow-up.

CONCOMMITANT MEDICATIONS	Allowed: Bland topical emollients such as Eucerin, Cetaphil. Prohibited: Any topical prescription medication on the treatment area during the study.
EVALUATIONS	
PRIMARY ENDPOINT	Primary objective is to determine whether daylight PDT affords a reduction in treatment symptoms of pain, stinging/burning, and itching/pruritus. Primary endpoints will be: 1) peak symptom level and composite score during the treatment period 2) symptom level and composite score at the end of treatment exposure.
SECONDARY ENDPOINTS	1) To determine efficacy in clearance of AK at 12 weeks: A. percent reduction in number of AKs from baseline to 12 weeks B. proportion of subjects with complete and partial clearance of AKs as described above 2) To determine whether daylight PDT affords, at end of treatment, a reduction in composite local skin reaction 3) To determine whether daylight PDT has a faster resolution of composite treatment symptoms and local skin response during days 8, 29, and 84.
STATISTICS **Primary Analysis Plan**	Symptom level over time during the treatment period will be graphed for visualization along the three axes of pain, stinging/burning, and itching/pruritus as well as a composite symptom score. Peak symptom level during the treatment period and pain at the end of treatment exposure will be compared between the conventional treatment arm (A), the combination treatment arm B), and the daylight treatment arm (C), with unpaired t-tests. Percent reduction in the number of actinic keratoses and proportions of patients with partial and complete clearance of actinic keratoses will be presented descriptively and visualized as histograms. We will compare the percent reduction in the number of AKs and the proportions of patients with clearance between the conventional treatment arm (A) and the combination treatment arm B), and between the conventional treatment arm (A) and the daylight treatment arm (C), using unpaired t-tests.

	All analyses will be based on the intent-to-treat (ITT) population. In the ITT population, patients will be counted in the treatment group upon randomization, regardless of receiving any dose of study medication. For efficacy analysis, all missing values due to patient early termination from the study will be imputed using last observation carried forward (LOCF) method, as appropriate. For each patient, the Baseline values will be defined as those values recorded at Day 1 prior to dosing. Patients who are lost-to-follow-up after Baseline will be included to the ITT population carrying forward their Baseline values.
Rationale for Number of Subjects	This is a small descriptive study. With ten subjects in each group, we will be powered to detect a 1.25-point difference in pain (pain scale 1-10) with a two-sided alpha of 0.05 and a power of 0.8.

1 BACKGROUND

Photodynamic therapy (PDT) is one field therapy option for the treatment of actinic keratosis (AK). PDT involves the topical application of aminolevulinic acid (ALA), or one of its derivatives, as a photosensitizing agent. In response, rapidly proliferating, dysplastic cells preferentially accumulate protoporphyrin IX (PpIX). When PpIX is activated by blue or red light, singlet oxygen species are produced, resulting in cell death. PDT is beneficial due to its brief treatment course, ease of patient compliance, and efficacy in clearing AK. However, its main drawbacks are the adverse effects of pain, burning, pruritus, erythema, crusting, and inflammation associated with treatment. Daylight PDT, when compared with conventional PDT, has been associated with significantly less pain while achieving comparable efficacy for the treatment of AK in randomized trials from Nordic countries and Australia.[1-2]

1.1 Overview of Clinical and Non-Clinical Studies

Randomized trials, mostly from Nordic countries (Denmark, Norway, Sweden, Finland) [1, 3-10] and one from Australia,[2] have supported the use of daylight PDT for the treatment of AK. One case series from the United States documented the Southern California experience with daylight PDT.[11] PDT has been associated with significantly less pain compared with conventional PDT, while maintaining efficacy comparable to that of conventional PDT for treatment of AK.[1,2,11] Post-treatment cosmesis with daylight PDT has been excellent.[11] The effective dose of sunlight required for AK clearance by daylight PDT is unclear. Effective light dose from natural sunlight has been shown to be highly variable based on geographic location, weather, and time of year.[12-13]

2 STUDY RATIONALE

Actinic keratoses (AK) are common precancerous skin lesions that arise on sun-damaged skin. Treatment is aimed at preventing progression to cutaneous squamous cell carcinoma (SCC). First-line therapy for clinically apparent lesions includes cryotherapy and curettage; and field therapy options are topical 5-fluorouracil, imiquimod, ingenol mebutate, and photodynamic therapy (PDT). PDT involves the topical application of aminolevulinic acid (ALA), or one of its derivatives, as a photosensitizing agent. In response, rapidly proliferating, dysplastic cells preferentially accumulate protoporphyrin IX (PpIX). When PpIX is activated by blue or red light, singlet oxygen species are produced, resulting in cell death. PDT is beneficial due to its brief treatment course and efficacy in clearing AK. However, its main drawbacks are the adverse effects of pain, burning, pruritus, erythema, crusting, and inflammation associated with treatment. While conventional PDT uses red or blue artificial light to activate a high concentration of accumulated protoporphyrins, daylight PDT uses natural daylight to activate lower levels of protoporphyrins in a continuous manner. Daylight PDT, when compared with conventional PDT, has been associated with significantly less pain while achieving comparable efficacy for the treatment of AK. Daylight PDT is also more cost-effective and reduces the amount of time spent in clinic. Previous randomized studies comparing daylight PDT with conventional PDT have largely used methyl-aminolevulinate as the photosensitizer, have been intra-individual comparative studies, and have been performed

in Nordic countries. Because the effective light dose from natural daylight depends on geographic location and seasonal and weather changes, randomized trials in different geographic and environmental conditions are of interest. The proposed randomized clinical trial investigates the tolerability and efficacy of daylight ALA-PDT for the treatment of AK in San Francisco for the first time; subjects will be randomized to various treatment arms, as opposed to previous split-face and intra-individual studies.

2.1 Risk / Benefit Assessment

The risks of aminolevulinic acid HCl are primarily local site reactions such as pain, erythema, burning, pruritus, and crusting. These typically begin on day 1 of treatment. Adverse reactions reported in >10% of patients treated with aminolevulinic acid were erythema, crusted skin, desquamation, burning, stinging, hyperpigmentation, hypopigmentation, pruritus, skin erosion. In 1-10% of treated patients, edema, dysesthesia, local flare, urticaria, localized vesiculation, drug eruption, dermal ulcer, scabbing, excoriation, oozing, hemorrhage, localized tenderness, or local pain were reported. As mucous membrane irritation and ocular injury are risks of treatment, the eyes and mucous membranes will be avoided. During artificial light treatment, the subject, health care personnel, and all present will wear appropriate eye protection; all will be counseled to avoid looking directly at the light source. Due to photosensitization associated with treatment, patients will be advised to avoid sunlight and prolonged or intense light that is not part of the treatment regimen for 40 hours.

Photodynamic therapy with ALA has accepted benefits for the treatment of AK which outweigh the risks. Other field treatments require a longer duration of therapy and require patient compliance at home. Participants in this study will benefit from ALA-PDT, either illuminated by daylight or artificial blue light via BLU-U blue light phototherapy illuminator.

3 STUDY OBJECTIVES

3.1 Primary Objective

To determine whether daylight PDT affords a reduction in treatment symptoms of pain, stinging/burning, and itching/pruritus.

3.2 Secondary Objectives

The secondary objects are (1) to determine efficacy in clearance of AK at 12 weeks; (2) to determine whether daylight PDT affords a reduction in local skin reaction to treatment; (3) to determine whether daylight PDT has a faster resolution of treatment symptoms and local skin response during the follow-up period.

4 STUDY DESIGN

4.1 Study Overview

This is a randomized (1:1:1) controlled trial with parallel group design. Thirty adult subjects are planned; with 10 subjects in each of three treatment arms.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

The following medications and devices will be used:

(1) Aminolevulinic acid HCl topical solution 20% (Levulan Kerastick)

(2) BLU-U blue light phototherapy illuminator

Three treatment arms to be compared are as follows:

A. Conventional arm: Acetone preparation, ALA topical application, 1hour incubation, 16:40 BLU-U exposure, application of sunscreen.

B. Combination arm: Acetone preparation, ALA topical application, 15 minute incubation, 16:40 BLU-U exposure, application of sunscreen, 45 minute daylight exposure.

C. Daylight arm: Acetone preparation, ALA topical application, 15 minute incubation, application of sunscreen, 1 hour daylight exposure.

Total duration of subject participation will be up to 115 days. Total duration of the study is expected to be 16 months.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be (1) symptom level during the treatment period and (2) pain at the end of treatment exposure.

With these endpoints, we will be able to determine whether daylight PDT offers a reduction in treatment symptoms of pain, burning, and pruritus.

5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are efficacy, local skin reaction to treatment, and symptoms and local skin response during follow-up period.

1) Efficacy in clearance of AK at 12 weeks:

   A. percent reduction in number of AKs from baseline to 12 weeks

   B. proportion of subjects with complete and partial clearance of AKs as described above.

2) To determine whether daylight PDT affords, at end of treatment, a reduction in composite local skin reaction

3) To determine whether daylight PDT has a faster resolution of composite treatment symptoms and local skin response during days 8, 29, and 84.

5.3 Safety Evaluations

Evaluations include: adverse event reporting and physician evaluation. Adverse event reporting and physician evaluation will occur at every visit, if applicable. Telephone interview will occur on days 3, 15, and early termination (if applicable). Physical examination will occur at Screening, days 8, 29, 84, and early termination (if applicable).

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a diagnosis of AK who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

• Adults at least 18 years old.

• Subjects must be able to read, sign, and understand the informed consent

• Subjects have at least 4 and no more than 20 clinically typical, visible actinic keratoses in the target treatment area on the face or scalp.

• Subject must be willing to forego any other treatments for AK in the treatment area on the face or scalp, during the study period, and for 14 days prior to enrollment; including cryotherapy, topical 5-fluorouracil, imiquimod, and ingenol mebutate.

• Subjects who have previously received PDT must undergo at least an 8-week washout period prior to enrollment in study.

• Subject must be willing and able to participate in the study and to comply with all study requirements including concomitant medication and other treatment restrictions, and telephone interview.

• If subject is a female of childbearing potential she must have a negative urine pregnancy test result prior to study treatment initiation and must agree to use an approved method of birth control while enrolled in the study. Women who are pregnant, lactating, or planning to become pregnant during the study period are excluded from the study.

6.3 Exclusion Criteria

• Subjects with any dermatologic disease in the treatment area that may be exacerbated by the treatment proposed or that might impair the evaluation of AKs.

• Subjects who are currently participating in another clinical study or have completed another clinical study with an investigational drug or device on the study area within 30 days prior to study treatment initiation.

• Subjects with any medical condition that in the opinion of the investigator, makes the patient unsuitable for the trial.

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

Bland topical emollients such as Eucerin and Cetaphil are allowed.

7.2 Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation: any topical prescription medication on the treatment area during the study.

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Thirty eligible patients will be randomly assigned to one of three treatment arms (Conventional Arm, Combination Arm, Daylight Arm) in a 1:1:1 ratio using a SAS-based computer-generated randomization scheme developed by the study data management provider. The investigator or designee will complete a randomization worksheet prior to Visit 1.

8.2 Blinding

This is a single-blinded study, as the subject cannot be blinded to treatment. AK counts, local skin reaction, and ALA application will be performed by the blinded investigator. History, concomitant medications, randomization, light exposure, symptom assessment, and Skindex-16 will be administered by the unblinded study coordinator.

8.3 Formulation of Test and Control Products

8.3.1 Formulation of Test Product

The active study product is Aminolevulinic acid HCl topical solution 20% (Levulan Kerastick), developed by Sun Pharmaceutical Industries Ltd for topical administration in the management of minimally to moderately-thick AK of the face or scalp. Levulan Kerastick consists of a plastic tube containing two sealed glass ampules and a dry applicator tip. One ampule contains 354 mg ALA HCl as a dry solid, and the other ampule holds 1.5 mL of solution vehicle containing alcohol USP (ethanol content = 48% v/v), water, laureth-4, isopropyl alcohol, and polyethylene glycol. Levulan Kerastick 20% topical solution is obtained by breaking both ampules and shaking the plastic tube to mix contents.

8.3.2 Formulation of Control Product

Not applicable.

8.3.3 Packaging and Labeling

Aminolevulinic acid HCl topical solution 20% (Levulan Kerastick) is supplied in packages of six single-use plastic tubes with applicator tips. Each plastic tube contains one ampule of 354 mg ALA HCl as a dry solid and one ampule of 1.5 mL of solution vehicle.

Each carton (kit) of ALA HCl topical solution 20% will be labeled with the required FDA warning statement, the protocol number, the name of the investigator, patient number, name of sponsor, and directions for use and storage. Each tube will be labeled with the expiration date.

8.4 Supply of Study Drug at the Site

Sun Pharmaceutical Industries Ltd will ship ALA HCl topical solution 20% (Levulan Kerastick) to the investigational site. The initial Levulan Kerastick shipment will be shipped after site activation (i.e., all required regulatory documentation has been received by Sun Pharmaceutical Industries Ltd and a contract has been executed.) Subsequent Levulan Kerastick shipments will be made after site request for resupply.

8.4.1 Dosage/Dosage Regimen

Aminolevulinic acid HCl topical solution 20% (Levulan Kerastick) will be applied topically once by a healthcare provider on the day of treatment. One Levulan Kerastick will be applied to the treatment area on the face or scalp. Care will be taken to avoid the eyes and mouth.

Treatment arms are as follows:

A. Conventional arm: Acetone preparation, ALA topical application, 1 hour incubation, 16:40 BLU-U exposure, application of sunscreen.

B. Combination arm: Acetone preparation, ALA topical application, 15 minute incubation, 16:40 BLU-U exposure, application of sunscreen, 45 minute daylight exposure.

C. Daylight arm: Acetone preparation, ALA topical application, 15 minute incubation, application of sunscreen, 1 hour daylight exposure.

Due to photosensitivity, subjects should avoid sunlight, tanning beds, and any prolonged or intense light exposure for 40 hours after application of ALA HCl, outside of the assigned treatment regimen. Subjects should not wash or clean their faces until all steps of treatment have been completed.

8.4.2 Dispensing

The investigator or other training study staff will dispense ALA HCl 20% topical solution to be used by the study provider on treatment day. Medication will not be dispensed to the subjects for home use.

8.4.3 Administration Instructions

Aminolevulinate acid HCl 20% topical solution (Levulan Kerastick) will be applied topically once by the study provider. After acetone preparation of the treatment area,

Levulan Kerastick will be applied to the subject's affected areas within the treatment area. The treatment area will be either the face or scalp; the site will be determined at Screening. Prior to Levulan treatment, any hypertrophic AKs in the treatment area will be scraped with a curette by the study provider to remove thick scale.

The study provider will prepare and administer Levulan Kerastick in the following manner:

1. Hold Levulan Kerastick so the applicator cap is pointing up.
2. Crush bottom ampule containing solution vehicle by applying finger pressure to marked location on the cardboard sleeve.
3. Crush the top ampule containing the ALA HCl powder by applying finger pressure to marked location on the cardboard sleeve. To ensure both ampules are crushed, continue crushing the applicator downward
4. Holding the Levulan Kerastick between the thumb and forefinger, pointing the applicator cap away from the face, shake the Levulan Kerastick gently for at least 30 seconds to mix ALA HCl and solution vehicle. Do not press on end cap while shaking.
5. Apply contents of one Levulan Kerastick using applicator tip to all affected areas within treatment area. Mouth, periorbital area, and all mucosal surfaces will be avoided.

Depending on the assigned treatment arm, patients will receive 16 minutes, 40 seconds of artificial blue light on the treatment area via BLU-U blue light phototherapy illuminator and/or daylight exposure for the assigned duration. Light exposure will be provided by the unblinded study provider.

8.4.4 Storage

Study drug should be stored by the study site at controlled room temperature, 15 to 30ºC (59-86ºF). If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below this range, this should be reported to the designee and captured as a deviation.

8.5 Study Drug Accountability

An accurate and current accounting of the dispensing of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff.

The number of study drug dispensed for each subject will be recorded on the Investigational Drug Accountability Record.

8.6 Measures of Treatment Compliance

Not applicable.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline/Screening and at Study Days 1 (may be combined with screening), 8, 29, 84, and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Screening.

9.1.4 Physical Examination

A complete physical examination will be performed by either the investigator or a subinvestigator who is a physician at Screening. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.5 Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed after resting for 5 minutes at Screening and at day 1.

9.1.6 Actinic keratosis (AK) count

An AK count will be performed to count the lesions in the treatment area. AK count will be performed at Screening and at days 1, 8, 29, and 84.

9.1.7 Local Skin Reaction (LSR)

Local skin reaction based on known response to PDT (Levulan package insert) will be graded by visual assessment on a custom 4 point scale where 0=none, 1=mild, 2=moderate, 3=severe. Each of the following four reactions will be graded: erythema, vesiculation/postulation, crusting/scabbing/erosion, and edema/swelling. A composite

score will be calculated (range 0-16). LSR assessment will be performed at days 1, 8, 29, and 84.

9.1.8 Symptom assessment

The patient symptom assessment will measure three axes: pain, stinging/burning, and itching/pruritus. Each of these three will be scored by patient report on a numeric scale (0= none, 10= worst possible). Each symptom will be scored and a composite score will be calculated (range 0-30). All subjects will have symptom assessments at 15, 30, 45, 60, and 75 minutes (Table 2). These times allow equivalent assessments relative to medication application regardless of treatment protocol.

A Universal Pain Assessment Tool demonstrating the numeric scale, verbal descriptor scale, and activity tolerance scale will be provided to assist patients in selecting their pain level (Appendix IV).

9.1.9 Skindex-16

Skindex-16 is used to measure quality of life in patients with skin diseases. The Skindex-16 will be administered on Days 1, 3, 8, 15, 29, 84, and early termination (if applicable).

9.1.10 Photography

The investigator or trained study staff will photograph the subject's treatment area on Day 1, Day 8, Day 29, Day 84, and at early termination (if applicable). Prior to photographing the treatment area, study staff will (1) photograph a subject identification card including: subject's initials, subject number, visit day and date; and (2) place a light-balanced sticker in the treatment area.

9.1.11 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9.2 Clinical Laboratory Measurements

9.2.1 Pregnancy Test

A urine pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study.

10 EVALUATIONS BY VISIT

All study visits will have a window +/- 3 days.

10.1 Visit 1 (Screening, Day -29 to 1)

1. Review the study with the subject (or subject's legal representative) and obtain written informed consent and HIPAA authorization.
2. Assign the subject a unique screening number.

3. Record demographics data.
4. Record medical history, including a history of actinic keratosis, diagnosis date, and prior AK treatments.
5. Record concomitant medications.
6. Perform a complete physical examination.
7. Perform and record vital signs.
8. Perform urine pregnancy test in female subjects of childbearing age.
9. Obtain informed consent.
10. Photography of treatment area.
11. Schedule subject for visit 2 in 0-29 days.

10.2 Visit 2 (Day 1, may be combined with Screening)

Unblinded investigator:

1. Randomization to treatment arms (1:1:1). Investigator will use sequential envelopes with randomly prefilled treatment arms. Envelopes will be filled in batches of three (nine patients) to ensure even allocation between arms during the course of treatment.
2. Perform and record vital signs.
3. Concomitant medications and Adverse Events review.

Blinded investigator:

4. Perform abbreviated physical examination.
5. Perform an AK count
6. Perform a pre-treatment local skin response assessment
7. Curette any hypertrophic AK
8. Application of ALA

Unblinded investigator:

9. Monitor ALA incubation duration depending on treatment arm
10. Light exposure (BLU-U and/or sunlight, depending on treatment arm)
11. Symptom assessment. All subjects will have symptom assessments at 15, 30, 45, 60, and 75 minutes (Table 2).
12. Skindex-16
13. Record any Adverse Events.
14. Photography of treatment area.

Blinded investigator:

15. Perform a post-treatment local skin response assessment

10.3 Visit 3 (Day 3, telephone)

1. Record any Adverse Events
2. Symptom assessment
3. Skindex-16

10.4 Visit 4 (Day 8)

Unblinded investigator:

1. Record changes to concomitant medications.
2. Record any Adverse Events
3. Symptom assessment
4. Record Skindex-16
5. Photography of treatment area.

Blinded investigator:

6. Perform abbreviated physical examination.
7. Perform AK count
8. Record LSR

10.5 Visit 5 (Day 15, telephone)

1. Record any Adverse Events
2. Symptom assessment
3. Skindex-16

10.6 Visit 6 (Day 29)

Unblinded investigator:

1. Record changes to concomitant medications.
2. Record any Adverse Events.
3. Symptom assessment
4. Skindex-16
5. Photography of treatment area.

Blinded investigator:

6. Perform abbreviated physical examination
7. Perform an AK count (blinded investigator)
8. Perform a local skin response assessment (blinded investigator)

10.7 Visit 7 (Day 84)

Unblinded investigator:

1. Record changes to concomitant medications.
2. Record any Adverse Events.
3. Symptom assessment
4. Skindex-16
5. Photography of treatment area.

Blinded investigator:

6. Perform abbreviated physical examination
7. Perform an AK count (blinded investigator)
8. Perform a local skin response assessment (blinded investigator)

10.8 Early Withdrawal Visit

Unblinded investigator:

1. Record changes to concomitant medications.
2. Perform complete physical examination.
3. Record any Adverse Events.
4. Symptom assessment
5. Record Skindex-16
6. Photography of treatment area.

Blinded investigator:

7. Perform AK count
8. Record LSR

11 ADVERSE EVENTS REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the event is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse event as it occurred. This does not refer to an event that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.

Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Events (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse event
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Event Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF IRB Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB), the site investigator will report SAEs to the IRB.

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject or the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

Subject withdrawal of consent (or assent)

Subject is not compliant with study procedures

Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment

Protocol violation requiring discontinuation of study treatment

Lost to follow-up

Sponsor request for early termination of study

Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to Section 10 for early termination procedures.

12.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject or the investigator , or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Visit 7) should have an early discontinuation visit. Refer to Section 10 for early termination procedures. Subjects who withdraw should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

12.3 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced.

Subjects who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary

endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

Failure to meet inclusion/exclusion criteria

Use of a prohibited concomitant medication

Failure of compliance with treatment regimen as described for assigned treatment arm

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the Investigator. A copy of the form will be filed in the site's regulatory binder.

14 DATA SAFETY MONITORING

Due to the scope of this study, there will be no formal Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC). This is an open-label, single-center study for an FDA-approved medication, and the investigator will have access to all study data.

15 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

15.1 Data Sets Analyzed

All eligible patients who are enrolled in the study and receive at least one dose of the study drug (the Safety Population) and who have had at least one post-baseline safety evaluation will be included in the safety analysis.

15.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized by dose level: race, gender, age, height and weight.

15.3 Analysis of Primary Endpoint

This is a small descriptive study, with the primary tolerability endpoints: 1) peak symptom level and composite score during the treatment period and 2) symptom level and composite score at the end of treatment exposure.

Symptom level over time during the treatment period will be graphed for visualization along the three axes of pain, stinging/burning, and itching/pruritus as well as a composite symptom score. Peak symptom level during the treatment period and pain at the end of treatment exposure will be compared between the conventional treatment arm (A), the combination treatment arm B), and the daylight treatment arm (C), with unpaired t-tests.

15.4 Analysis of Secondary Endpoints

Efficacy and tolerability data will be summarized by each secondary endpoint.

Symptom level over time during the treatment period will be graphed for visualization along the three axes of pain, stinging/burning, and itching/pruritus as well as a composite symptom score. Peak symptom level during the treatment period and pain at the end of treatment exposure will be compared between the conventional treatment arm (A), the combination treatment arm B), and the daylight treatment arm (C), with unpaired t-tests.

Percent reduction in the number of actinic keratoses and proportions of patients with partial and complete clearance of actinic keratoses will be presented descriptively and visualized as histograms. We will compare the percent reduction in the number of AKs and the proportions of patients with clearance between the conventional treatment arm (A) and the combination treatment arm B), and between the conventional treatment arm (A) and the daylight treatment arm (C), using unpaired t-tests.

All analyses will be based on the intent-to-treat (ITT) population. In the ITT population, patients will be counted in the treatment group upon randomization, regardless of receiving any dose of study medication. For efficacy analysis, all missing values due to patient early termination from the study will be imputed using last observation carried forward (LOCF) method, as appropriate. For each patient, the Baseline values will be defined as those values recorded at Day 1 prior to dosing. Patients who are lost-to-follow-up after Baseline will be included to the ITT population carrying forward their Baseline values.

15.5 Interim Analysis

Not applicable.

15.6 Sample Size and Randomization

This is a small descriptive study. With ten subjects in each group, we will be powered to detect a 1.25-point difference in pain (pain scale 1-10) with a two-sided alpha of 0.05 and a power of 0.8.

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific Case Report Form (eCRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected, but will be identified by a site number, subject number and initials.

If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

16.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

16.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

16.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

16.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued.

16.6 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.1 Protocol Amendments

Any amendment to the protocol will be written by the investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

17.2 Institutional Review Boards

The protocol and consent form will be reviewed and approved by the IRB prior to study initiation. Serious adverse events regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRBs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRBs unconditional approval statement will be transmitted by the Investigator to Sun Pharmaceutical Industries Ltd, prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the

patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse events occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and submit to the IRB. The consent form generated by the Investigator must be acceptable and be approved by the IRB. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

17.4 Publications

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

17.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

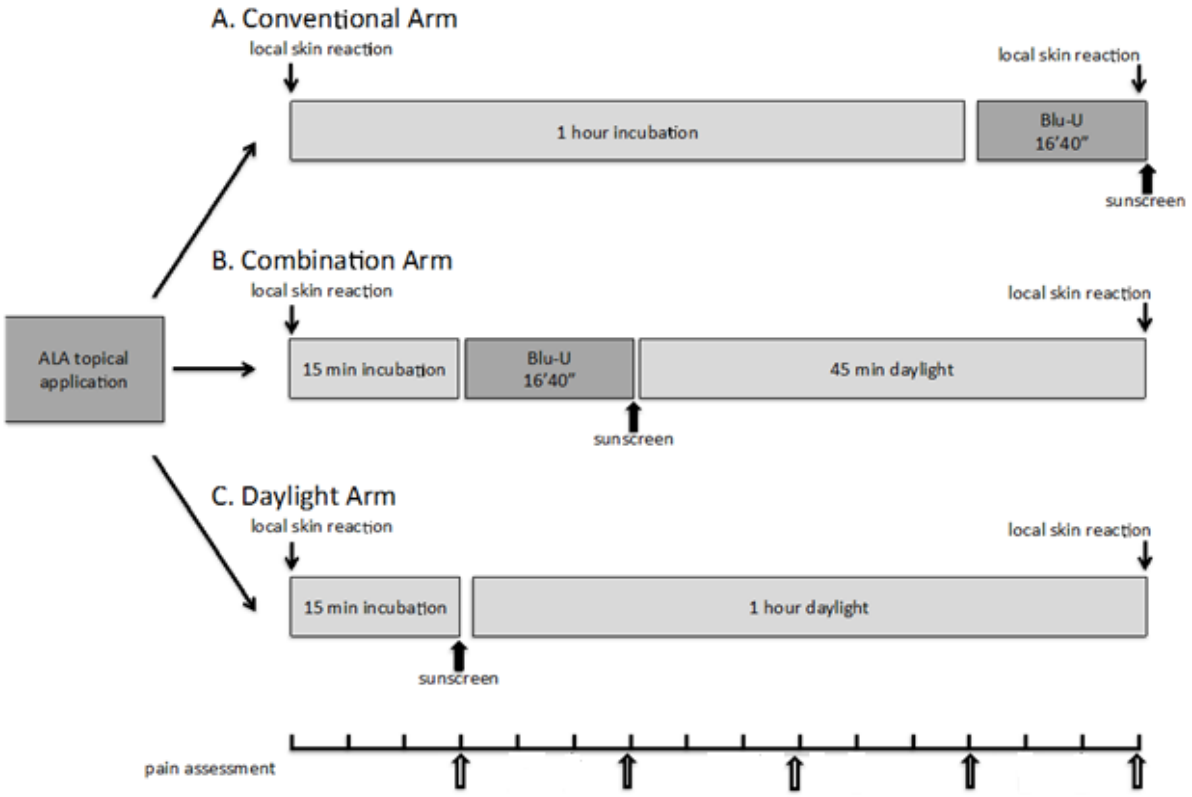
1. Conduct the study in accordance with the protocol, except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.

5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee.
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX I. SCHEDULE OF STUDY VISITS

	Screening (Day -29 to Day 1)	Day 1 (may be combined with screening)	Day 3 (telephone)	Day 8	Day 15 (telephone)	Day 29	Day 84
Informed consent	X						
Medical history	X						
Concomitant medications	X	X		X		X	X
Adverse events		X	X	X	X	X	X
Urine Pregnancy test (if applicable)	X						
Randomization		X					
ALA-PDT		X					
AK count	X	X		X		X	X
AE assessment		X	X	X	X	X	X
Local Skin Reaction		X (pre and post)		X		X	X
Symptom Assessment		X	X	X	X	X	X
Skindex-16		X	X	X	X	X	X
Photography		X		X		X	X

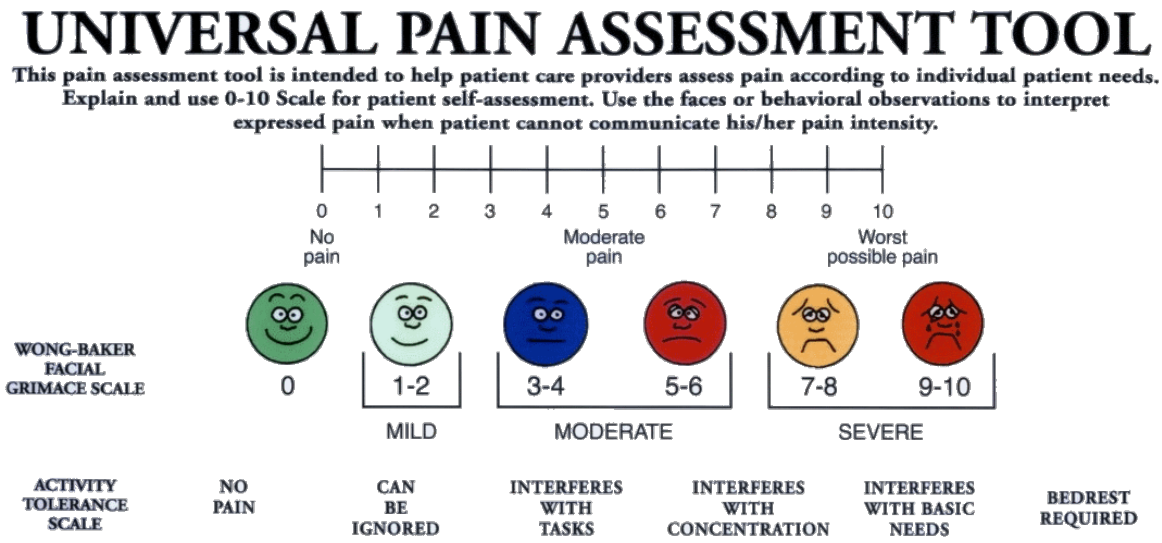
APPENDIX II. TREATMENT PROTOCOL



APPENDIX III. TIMING OF SYMPTOM ASSESSMENTS

Min	Symptom Assessment	Conventional Arm	Combination Arm	Daylight Arm
0		Begin 1 hour Incubation	Begin 15 minute incubation	Begin 15 minute incubation
5		Incubation	Incubation	Incubation
10		Incubation	Incubation	Incubation
15	X	Incubation	Sunscreen, BLU-U Exposure: 16m 40s	Sunscreen, Daylight Exposure: 60m
20		Incubation	BLU-U	Daylight
25		Incubation	BLU-U	Daylight
30	X	Incubation	End BLU-U, Begin Daylight Exposure: 60m	Daylight
35		Incubation	Daylight	Daylight
40		Incubation	Daylight	Daylight
45	X	Incubation	Daylight	Daylight
50		Incubation	Daylight	Daylight
55		Incubation	Daylight	Daylight
60	X	BLU-U Exposure: 16m 40s	Daylight	Daylight
65		BLU-U	Daylight	Daylight
70		BLU-U	Daylight	Daylight
75	X	End BLU-U, Sunscreen	End Daylight	End Daylight

APPENDIX IV. UNIVERSAL PAIN ASSESSMENT TOOL



APPENDIX V. LOCAL SKIN RESPONSE ASSESSMENT

Grade	0	1	2	3	4
Erythema	Not present	Slightly pink <50%	Pink or light red >50%	Red, restricted to treatment area	Red extending outside treatment area
Flaking/Scaling	Not present	Isolated scale, specific to lesions	Scale <50%	Scale >50%	Scaling extending outside treatment area
Crusting	Not present	Isolated crusting, specific to lesions	Crusting <50%	Crusting >50%	Crusting extending outside treatment area
Swelling	Not present	Slight, lesion specific edema	Palpable edema extending beyond individual lesions	Confluent and/or visible edema	Marked swelling extending outside treatment area
Vesiculation/Pustulation	Not present	Vesicles only	Transudate or pustules, with or without vesicles, <50%	Transudate or pustules, with or without vesicles, >50%	Transudate or pustules, with or without vesicles, extending outside treatment area
Erosion/Ulceration	Not present	Lesion specific erosion	Erosion extending beyond individual lesions	Erosion >50%	Black eschar or ulceration

APPENDIX VI. SKINDEX-16

During the past week, how often have you been bothered by:		Never Bothered ↓			●			Always Bothered ↓
1.	Your skin condition **itching**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2.	Your skin condition **burning** or **stinging**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3.	Your skin condition **hurting**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4.	Your skin condition **being irritated**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5.	The **persistence / reoccurrence** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6.	**Worry** about your skin condition (For example: that it will spread, get worse, scar, be unpredictable, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7.	The **appearance** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8.	**Frustration** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9.	**Embarrassment** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10.	**Being annoyed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11.	**Feeling depressed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12.	The effects of your skin condition on your **interactions with others** (For example: interactions with family, friends, close relationships, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13.	The effects of your skin condition on your **desire to be with people**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14.	Your skin condition making it hard to **show affection**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15.	The effects of your skin condition on your **daily activities**.	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16.	Your skin condition making it hard to **work or do what you enjoy**	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Have you answered every item? Yes ☐ No ☐

APPENDIX VII. REFERENCES

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