Photodynamic Therapy with Levulan® and Blue Light for the Treatment of Actinic Cheilitis

SPONSOR	**Department of Dermatology at Dartmouth-Hitchcock Medical Center**
DRAFT VERSION:	***1.0***
DATE FINAL:	***10.14.14***

1. PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:

M. Shane Chapman, MD

Signature of Principle Investigator	Date
Printed Name of Principle Investigator	

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

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2. STUDY PERSONNEL

Financial Supporter:	Section of Dermatology / DUSA Pharmaceuticals Inc.
Study Location:	Dartmouth Hitchcock Medical Center 18 Old Etna Road Lebanon, NH, 03756 Phone: (603) 625-0151 Fax: (603) 625-6212
Principle Investigator:	Michael Shane Chapman, MD
Sub-Investigators:	Joan Paul, MD, MPH Pamela Gangar, MD

3. PROTOCOL SYNOPSIS

Title	Photodynamic therapy with Levulan® and blue light for the treatment of actinic cheilitis
Protocol Number	1.0
Study Medication	Levulan® Kerastick® containing 20% aminolevulinic acid HCL (ALA) (DUSA Pharmacueticals)
Study Device	BLU-U Blue Light Photodynamic Therapy (PDT) Illuminator Omnilux revive^{2TM}
Study Objectives	To evaluate the safety and efficacy of PDT with blue light and topical Levulan® in the treatment of actinic cheilitis
Study Design	This is a single center, investigator initiated, nonrandomized, open-label, proof of concept study of PDT with blue light and topical Levulan® in the treatment of actinic cheilitis
Inclusion Criteria	• Must be able to understand and voluntarily sign an informed consent form • Must be male or female ≥ 18 years of age at the time of consent • Must be able to adhere to the study visit schedule and other protocol requirements • Must have a diagnosis of actinic cheilitis by histopathological evaluation of biopsy specimen or clinical presentation
Exclusion Criteria	• Inability to provide voluntarily consent or mentally incompetent • No active herpes labialis lesions • Subjects with any condition which places the subject at unacceptable risk if he/she were to participate in the study, or confounds the ability to interpret data from the study • Subjects with any other skin condition that might affect the evaluation of the study disease • Pregnant or breastfeeding female subjects

	• Subjects who have used any investigational medication within one month prior to study entry • Subjects who have been previously exposed to PDT and/or topical Levulan® therapy • Subjects who have used local therapy (e.g. cryotherapy) or topical treatment (e.g. 5% fluorouracil) within three months of study entry • Subjects who have used an oral photosensitizing drug (e.g. Declomycin®) within six months of study entry • Subjects who are currently using photosensitizing agents (e.g. thiazides, tetracyclines, fluoroquinolones, phenothiazines, and sulfonamides) because of the risk of augmented photosensitivity • Subjects who are frequently exposed to ultraviolet radiation (e.g. lifeguards, construction workers, frequent sunbed users, etc.) • Subjects with a history of cutaneous photosensitization, porphyria, hypersensitivity to porphyrins, or photodermatosis • Subjects with a known hypersensitivity to ALA • Subjects who are immunocompromised
Study Procedures	The study will consist of a screening visit, up to three scheduled treatments, and two scheduled office visits. There can be a three-day window period for each scheduled visit in order to accommodate the subject's schedule and unforeseen scheduling conflicts. 1. Visit 1 (Screening): Subjects can be screened for the study up to two weeks before Visit 2 (Baseline). During screening, the study will be reviewed, written informed consent obtained, and eligibility confirmed. If applicable, the washout from prohibited medications or treatments will be determined at this visit.

	2. Visit 2 (Baseline): Following signed, written informed consent and confirmation of eligibility, all subjects will have their lips photographed. Medical history, dermatologic exam, urine pregnancy test (if applicable), review of concomitant medications, clinical evaluations, and tolerability assessments will be performed at this visit. Study medication application to clean skin will be followed by a ninety minute incubation period under occlusion. Subsequently, patients will be exposed to blue light therapy for 16 minutes and 40 seconds. Post-therapy assessments will be performed afterwards, as well as education on appropriate sun protection methods. 3. Visits 3-4: Subjects will return every six weeks for up to two additional treatments. Treatment will be discontinued once the patient has achieved clinical clearance. Tolerability assessments, study medication application, blue light therapy, post-therapy assessments, and photographs will be performed. 4. Visit 5-6 (End of Study): Subjects will return 12 and 24 weeks after the last treatment for clinical evaluations, tolerability assessments, and photographs.
Study Measurements	Primary efficacy will be assessed by the investigator for the following: • Clearance will be estimated clinically as minimal (0%-25%), mild (26%-50%), moderate (51%-75%), good (76%-99%), or complete (100%). • Results will also be evaluated by comparing photographs before and immediately after treatments, and 12 and 24 weeks after the last treatment. Secondary endpoints will include the following: • Subject reported pain during and after blue light illumination using a Visual Analogue Scale (VAS) from 0 (no pain) to 10 (worst pain imaginable).

	• Percent of patients with adverse events. Safety will be assessed by the investigator as follows: • Local Skin Reactions: Assessment of swelling, vesiculation/pustulation, erosion/ulceration, erythema, flaking/scaling, and crusting using a five-point ordinal scale (0: none to 4: severe) will be conducted after each treatment visit. The presence or absence of hyperpigmentation in the treatment area will also be documented after each treatment visit. • Subjects will be asked to rate their pain using a VAS both during and after blue light treatment. • PDT Reactions: Other than those specified under local skin reactions. • Adverse Events: Evaluation of any reported local or systemic events outside the treatment area and other than those specified under local skin reactions.
Study Endpoints	Primary Endpoints: • Clearance will be estimated as a percentage improvement from baseline. Secondary Endpoints: • Tolerability of treatment and tabulation of reported local and systemic adverse events.
Study Duration	24 to 36 weeks
Total Sample Size	20

4.0 SCHEDULE OF ASSESSMENTS

	Treatment Phase				Observational Follow-up Phase	
Visit Number	**1 Screening**	**2 Baseline**	**3**	**4**	**5**	**6 End of Study/ Early Termination Visit**
Week(s)	**-2-0 weeks**	**day 0**	**6 weeks**	**12 weeks**	**24 weeks**	**36 weeks**
Informed Consent	**X**					
Medical History	**X**					
Demographics	**X**					
Inclusion/ Exclusion Criteria	**X**	**X**				
Concomitant Medications	**X**	**X**	**X**	**X**	**X**	**X**
Physical Exam	**X**	**X**				**X**
Treatments		**X**	**X**	**X**		
Physician Efficacy Assessments						
Comparison of photographs		**X**	**X**	**X**	**X**	**X**
Investigator Global Assessment		**X**	**X**	**X**	**X**	**X**
Subject Efficacy Assessments						
Subject Global Assessment of Improvement		**X**	**X**	**X**	**X**	**X**
DLQI		**X**	**X**	**X**	**X**	**X**
Physician Safety Assessments						

	Treatment Phase				Observational Follow-up Phase	
Visit Number	**1 Screening**	**2 Baseline**	**3**	**4**	**5**	**6 End of Study/ Early Termination Visit**
Week(s)	**-2-0 weeks**	**day 0**	**6 weeks**	**12 weeks**	**24 weeks**	**36 weeks**
Swelling, Vesiculation, Erosion, Erythema, Flaking, Crusting		**X**	**X**	**X**	**X**	**X**
Hyperpigmentation		**X**	**X**	**X**	**X**	**X**
Adverse Events		**X**	**X**	**X**	**X**	**X**
Pregnancy Testing[d]	**X**	**X**				**X**
Subject Safety Assessments						
Redness, swelling, and dryness		**X**	**X**	**X**	**X**	**X**
Pain (VAS Scale)		**X**	**X**	**X**	**X**	**X**
Photographs		**X**	**X**	**X**	**X**	**X**

5. INTRODUCTION & RATIONALE

Actinic cheilitis is a common precancerous malformation of the lower lip caused by UV radiation. Conventional therapies, such as cryotherapy, topical 5-fluorouracil, Imiquimod, chemical peels, electrodessication, laser ablation, and vermilionectomy are oftentimes successful in the majority of patients. However, these treatments may be expensive, time-consuming, associated with noncompliance, have a high recurrence rate, require local or general anesthesia, and offer risk of unaesthetic scars. There are also numerous adverse side effects associated with the aforementioned treatments; therefore, alternative treatments for the treatment of actinic cheilitis are essential.

In the literature, several reports have shown photodynamic therapy (PDT) to be efficacious in the treatment of actinic cheilitis. Of note, patients in these case reports/series received therapeutic benefit with relatively few PDT treatments, which were associated with minimal cutaneous side effects.[1-2] PDT is based on the combined use of photosensitizers and photoradiation. Topically applied δ-aminolevulinic acid (ALA) is theorized to be taken up by premalignant cells. Upon irradiation with a light source, photoactivated porphyrins produce singlet oxygen and other potent oxidizers, resulting in cell death.[3] Unfortunately, controlled clinical trials assessing the efficacy of PDT for actinic cheilitis are lacking. As PDT does not appear to have any systemic side effects, if proven efficacious, PDT could be one of the safest treatment options for actinic cheilitis.

6. STUDY OBJECTIVE

To evaluate the safety and efficacy of PDT with blue light and topical Levulan® (aminolevulinic acid) in the treatment of actinic cheilitis.

6.1 HYPOTHESIS

The use of PDT with blue light and topical Levulan treatment will reduce the number of actinic cheilitis lesions.

7. RESEARCH DESIGN & METHODS

This is a single center, investigator initiated, nonrandomized, open-label, proof of concept study of PDT with blue light and topical Levulan® in the treatment of actinic cheilitis.

7.1 SUBJECT RECRUITMENT

Patients with a diagnosis of actinic cheilitis who have been seen at the outpatient dermatology clinic at Dartmouth Hitchcock Medical Center will be contacted by telephone by study coordinator(s), investigator(s), or designee in order to recruit study participants after discussing the study in detail.

7.2 SCREENING & ELIGIBILITY

Male and female subjects ≥ 18 years of age with a diagnosis of actinic cheilitis will be asked to participate in this study after the objectives, methods, and potential hazards of the study have been fully explained, and they have signed the informed consent form. The Principle Investigator will be responsible for keeping a record of all subjects who sign an informed consent form for entry into this study. A total of 20 subjects will be enrolled in this study.

7.2.1 INCLUSION CRITERIA

- Must be able to understand and voluntarily sign an informed consent form
- Must be male or female ≥ 18 years of age at the time of consent
- Must be able to adhere to the study visit schedule and other protocol requirements
- Must have a diagnosis of actinic cheilitis by histopathological evaluation of biopsy specimen or clinical presentation

7.2.2 EXCLUSION CRITERIA

- Inability to provide voluntarily consent or mentally incompetent
- No active herpes labialis lesions
- Subjects with any condition which places the subject at unacceptable risk if he/she were to participate in the study, or confounds the ability to interpret data from the study
- Subjects with any other skin condition that might affect the evaluation of the study disease
- Pregnant or breastfeeding female subjects

- Subjects who have used any investigational medication within one month prior to study entry
- Subjects who have been previously exposed to PDT and/or topical Levulan® therapy
- Subjects who have used local therapy (e.g. cryotherapy) or topical treatment (e.g. 5% fluorouracil) within three months of study entry
- Subjects who have used an oral photosensitizing drug (e.g. Declomycin®) within six months of study entry
- Subjects who are currently using photosensitizing agents (e.g. thiazides, tetracyclines, fluoroquinolones, phenothiazines, and sulfonamides) because of the risk of augmented photosensitivity
- Subjects who are frequently exposed to ultraviolet radiation (e.g. lifeguards, construction workers, frequent sunbed users, etc.)
- Subjects with a history of cutaneous photosensitization, porphyria, hypersensitivity to porphyrins, or photodermatosis
- Subjects with a known hypersensitivity to δ-aminolevulinic acid
- Subjects who are immunocompromised

7.3 VISIT SCHEDULE & ASSESSMENTS

The study will consist of a screening visit, up to three scheduled treatments, and two scheduled office visits. There can be a three-day window period for each scheduled visit in order to accommodate the subject's schedule and unforeseen scheduling conflicts.

1. Visit 1 (Screening): Subjects can be screened for the study up to two weeks before Visit 2 (Baseline). During screening, the study will be reviewed, written informed consent obtained, and eligibility confirmed. If applicable, the washout from prohibited medications or treatments will be determined at this visit.
2. Visit 2 (Baseline): Following signed, written informed consent and confirmation of eligibility, all subjects will have their lips photographed. Medical history, dermatologic exam, urine pregnancy test (if applicable), review of concomitant medications, clinical evaluations, and tolerability assessments will be performed at this visit. Study medication application to clean skin will be followed by a ninety minute incubation period under occlusion. Subsequently, patients will be exposed to blue light therapy for 16 minutes and 40 seconds. Post-therapy

assessments will be performed afterwards, as well as education on appropriate sun protection methods.

3. Visits 3-4: Subjects will return every six weeks for up to two additional treatments. Treatment will be discontinued once the patient has achieved clinical clearance. Tolerability assessments, study medication application, blue light therapy, post-therapy assessments, and photographs will be performed.
4. Visit 5-6 (End of Study): Subjects will return 12 and 24 weeks after the last treatment for clinical evaluations, tolerability assessments, and photographs.

7.4 DURATION OF TREATMENT

After the screening visit, subjects will receive in-office treatments every six weeks for 12 weeks for up to a total of 3 treatments. Treatment will be discontinued once the patient has achieved clinical clearance. Each subject will then be followed for 24 weeks after the last treatment visit. In total, each subject will be part of the study for approximately 36 weeks.

7.5 RISK TO SUBJECTS

PDT often invokes a transient local skin reaction, including increased erythema, edema, and/or scaling. These symptoms typically dissapate after one to two weeks, and are usually well tolerated if strict sun protection and avoidance are heeded; however, certain patients may have a more significant adverse response to PDT, especially if they are taking concomitant photosensitizing drugs (i.e. doxycycline, topical/oral retinoids, etc.). It is therefore of uptmost importance that patients who are currently using photosensitizing agents or frequently exposed to ultraviolet radiiation are exclused from study participation in order to minimize the risk of adverse events.

No patient identifying information will be documented on any of the research materials, except for the informed consent paperwork and the Subject ID Key (see Section 9.1). Only the study investigators and assigned research personel will know the identity of each study subject, but they will not disclose this information unless necessitated by the law. The informed consent paperwork and all of the study research materials (i.e. demographic questionnaires, data collection sheets, etc.) will be held in a secure and

confidential file for at least three years after the conclusion of this study, in accordance with the rules put in place by the IRB.

7.6 DISCONTINUATION OF STUDY TREATMENT

The following events are considered sufficient reasons for considering the discontinuation of a subject from the study:

- An adverse event (AE) that in the judgement of the investigator may cause severe or permanent harm
- Subject withdraws consent
- Subject lost to follow-up
- Death
- Protocol violation

8. TREATMENT & BLUE LIGHT PARAMETERS

8.1 PRE-EXPOSURE SKIN CARE

Subjects will wash their face with CeraVe® Facial Cleanser prior to study treatment. Subsequently, the mixed contents of Kerastick® (see section 8.2) will be applied topically with gloves to the designated target treatment area. After an incubation period of ninety minutes, subjects will wash their face again with CeraVe® Facial Cleanser.

8.2 INVESTIGATIONAL MEDICATION

Kerastick® is the dosage form of Levulan®, which consists of a low-density polyethylene tube with two glass ampules and a sponge applicator tip covered with a protective cardboard sleeve and cap. Each Levulan® Kerastick® applicator contains one ampule containing 354 mg of aminolevulinic acid HCL (ALA) and one ampule of 1.5 mL of vehicle. Upon mixing both ampules, the concentration of ALA becomes 20%.

8.2.1 SUPPLIER

Levulan® Kerastick® will be supplied by DUSA pharmaceuticals, Inc.

8.2.2 RECEIPT & STORAGE OF STUDY DRUG

The Principle Investigator or designee is responsible for taking inventory of each shipment of study drug received. All investigational drug will be stored in a locked, safe area to prevent unauthorized access at the Heater Road clinic at Dartmouth Hitchcock Medical Center. The study drug will be stored as directed on the package insert.

8.2.3 ACCOUNTABILITY

The Principle Investigator or designee is responsible for keeping a record of all investigational drug that is dispensed during the study.

8.2.4 HANDLING & DISPOSAL OF DRUG

Any unused product will be documented, discarded, and need not be returned to DUSA pharmaceuticals, Inc. If any study drug is lost or damaged, its disposition will be documented in the subject's source documents.

8.3 LIGHT TREATMENT

8.3.1 BLUE LIGHT TREATMENT

Blue light will be administered to the lips using the BLU-U® blue light (417 nm) PDT illuminator. The prescribed treatment time will be 16 minutes and 40 seconds, which will result in a total light dose of approximately 10 J/cm^2 delivered at 10 mW/cm^2. Light exposure will be controlled with a timer. The investigator, subject, and anyone else in the light treatment room will wear appropriate protective eyewear at all times.

8.3.2 SUPPLIER

The BLU-U light and Omnilux revive^{2TM} device is available at the dermatology clinic at Dartmouth Hitchcock Medical Center.

8.4 POST-EXPOSURE SKIN CARE

Subjects will be given verbal and written post-treatment instructions to clean treatment sites with warm water and CeraVe® Facial Cleanser®, and to apply topical petrolatum ointment until any weeping or crusting has subsided. Subjects will also apply chapstick with sun protection. All subjects will be instructed to avoid direct sun exposure and to apply a sun block with at least a sun protection factor (SPF) of 30 (Neutrogena® SPF 100) for at least 48 hours after each treatment.

9. CLINICAL ASSESSMENTS

Efficacy and safety assessments during the treatment phase of the study will be done at the intervals specified in Section 4. The same investigator should complete the evaluations for a given subject throughout the study; however, if the assigned investigator is not available, another investigator with overlapping experience with the subject can complete the evaluation.

9.1 DEMOGRAPHIC INFORMATION

After signing the informed consent paperwork, each subject will be given a short questionnaire regarding their personal demographic information (i.e. gender, age, race, ethnicity, highest educational degree, annual income, marital status). Each subject will be assigned a Subject ID number (1-20), which will be documented on each of their study materials.

9.2 PHYSICIAN PERFORMED ASSESSMENTS

9.2.1 EFFICACY ASSESSMENTS

Primary efficacy will be assessed by the investigator for clearance from baseline (Visit 2) to the end of study (Visit 6; week 36). Clearance will be estimated clinically as minimal (0%-25%), mild (26%-50%), moderate (51%-75%), good (76%-99%), or complete (100%). Clinical photographs will also be taken at Visit 2 to 6. Care will be taken to avoid including any identifying landmarks, such as characteristic tattoos, birthmarks, etc.

9.2.2 PRE & POST-TREATMENT SAFETY ASSESSMENTS

A study physician will complete post-treatment assessments based upon visual observation of *swelling, vesiculation/pustulation*, *erosion/ulceration*, *erythema, flaking/scaling,* and *crusting.* The assessment will be based upon the scaling system below:

Swelling	Grade 0: not present Grade 1: slight, lesion specific edema Grade 2: palpable edema extending beyond individual lesions

	Grade 3: confluent or visible edema Grade 4: marked swelling, very easily noticeable from a distance
Vesiculation/Pustulation	Grade 0: not present Grade 1: only vesicles Grade 2: <50% pustules with or without vesicles Grade 3: > 50%, but <75% pustules with or without vesicles Grade 4: >75% pustules with or without vesicles
Erosion/Ulceration	Grade 0: not present Grade 1: lesion specific erosion Grade 2: erosion extending beyond individual lesions Grade 3: erosion >50% Grade 4: black eschar or ulceration
Erythema	Grade 0: not present Grade 1: slightly pink <50% Grade 2: pink or light red >50% Grade 3: red 50-75% Grade 4: severe redness, >75%, very easily noticeable from a distance
Flaking/Scaling	Grade 0: not present Grade 1: isolated scale, specific to lesions Grade 2: scale <50% Grade 3: scale >50%, but <75% Grade 4: scale >75%, very easily noticeable from a distance
Crusting	Grade 0: not present Grade 1: isolated crusting Grade 2: crusting <50% Grade 3: crusting >50% Grade 4: crusting >75%, very easily noticeable from a distance

9.3 PATIENT PERFORMED ASSESSMENTS

Subjective pre-treatment evaluations will be assessed based on the Subjective Global Assessment. Subjects will be instructed to circle their response.

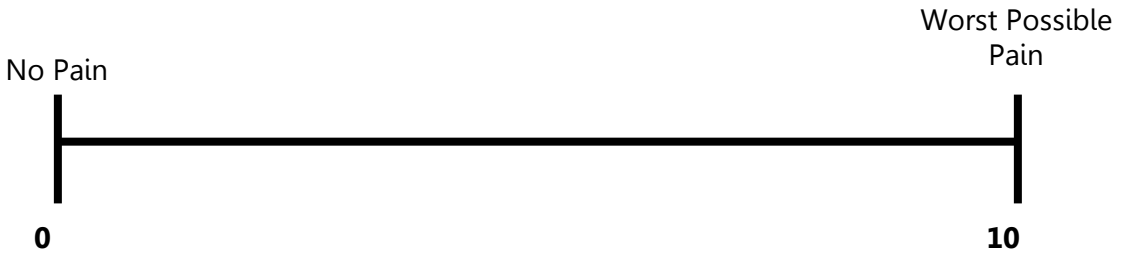
9.3.1 SUBJECT GLOBAL ASSESSMENT

The subject global assessment of improvement will be performed during every visit (except baseline) to assess the subject's impression of their overall improvement as compared to baseline. The subject global assessment scale is defined as follows:

Excellent improvement	My lip lesions are completely (100%) gone, except for possibly some residual color change
Marked improvement	My lip lesions are greatly (~75%) improved
Moderate improvement	My lip lesions are definitely (~50%) improved
Mild improvement	My lip lesions are somewhat (~25%) improved
No improvement	My lip lesions are not (0%) improved

9.3.2 PRE & POST-TREATMENT PAIN ASSESSMENT

Subjects will be asked to describe their pain prior to the application of topical Levulan® and immediately after blue or red light illumination using a Visual Analogue Scale (VAS) from 0 to 10, 0 indicating no pain and 10 indicating the worst possible pain. Pain will be assessed at each treatment visit.



9.3.3 DERMATOLOGY LIFE QUALITY INDEX

Subjects will be asked to complete the Dermatological Life Quality Index (DLQI) at every scheduled visit except for screening. These questionnaires should be completed by the subject before any other procedures or assessments are performed. If the subject is physically unable to complete the questionnaires, study personnel/staff may assist

him/her. Relatives and friends of the subject may not under any circumstances assist the subject with the questionnaire. The subject will initial and date his/her entries in the designated area of the Case Report Form (CRF) for each questionnaire. The CRF will serve as the source documentation for this study. The DLQI questionnaire is as follows:

Dermatological Life Quality Index

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one response for each question.

Question	Response
1. Over the last week, how **itchy, sore, painful, or stinging** has your skin been?	□ 1. Very much □ 2. A lot □ 3. A little □ 4. Not at all
2. Over the last week, how **embarrassed or self-conscious** have you been because of your skin?	□ 1. Very much □ 2. A lot □ 3. A little □ 4. 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**?	□ 1. Very much □ 2. A lot □ 3. A little □ 4. Not at all □ 5. Not relevant
4. Over the last week, how much has your skin influenced the **clothes** you wear?	□ 1. Very much

	□ 2. A lot □ 3. A little □ 4. Not at all □ 5. Not relevant
5. Over the last week, how much has your skin affected any **social or leisure** activities?	□ 1. Very much □ 2. A lot □ 3. A little □ 4. Not at all □ 5. Not relevant
6. Over the last week, how much has your skin made it difficult for you to do any **sport**?	□ 1. Very much □ 2. A lot □ 3. A little □ 4. Not at all □ 5. Not relevant
7. Over the last week, has your skin prevented you from **working or studying**?	□ 1. Yes □ 2. No □ 3. Not relevant
If "No", over the last week how much has your skin been a	□ 1. A lot

problem at **work or studying**?	□ 2.A little □ 3. 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**?	□ 1. Very much □ 2. A lot □ 3. A little □ 4. Not at all □ 5. Not relevant
9. Over the last week, how much has your skin caused any **sexual difficulties**?	□ 1. Very much □ 2. A lot □ 3. A little □ 4. Not at all □ 5. 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?	□ 1. Very much □ 2. A lot □ 3. A little □ 4. Not at all □ 5. Not relevant

9.3.4 TWO-DAY POST-TREATMENT TELEPHONE FOLLOW-UP VISIT

Patients will be asked to rate *redness, swelling*, and *dryness* on the scale below. The scales will be read to the patient over the phone.

Redness	Grade 0: None Grade 1: Minimal redness, only a little noticeable

	Grade 2: Mild redness, easily noticeable and involving less than 1/3 of the face Grade 3: Moderate redness, easily noticeable and involving between 1/3 and 2/3 of the face Grade 4: Severe redness, very easily noticeable from a distance, and involving over 2/3 of the face
Swelling	Grade 0: None Grade 1: Minimal swelling, only a little noticeable Grade 2: Mild swelling, easily noticeable and involving less than1/3 of the face Grade 3: Moderate swelling, easily noticeable and involving between 1/3 and 2/3 of the face Grade 4: Severe swelling, very easily noticeable from a distance, and involving over 2/3 of the face
Dryness of Skin	Grade 0: None Grade 1: Minimal dry skin, only a little noticeable Grade 2: Mild dry skin, easily noticeable and involving less than 1/3 of the face Grade 3: Moderate dry skin, easily noticeable and involving between 1/3 and 2/3 of the face Grade 4: Severe dry skin, very easily noticeable from a distance, and involving over 2/3 of the face

Additionally the subject will be asked the open-ended question, "Have you had any problems since leaving our office after your last appointment?" The study coordinator will then record each subject's response in the appropriate source document.

10. ASSESSMENT OF ADVERSE EVENTS

Safety precautions, such as the use of highly experienced investigators, frequent office visits, and close monitoring of clinical and laboratory findings (pregnancy tests) have been implemented in the protocol and are specified in the Schedule of Assessments (see Section 4). All unexpected physical examination findings will be captured as Adverse Events (AEs) when deemed medically significant by the investigator. Potential events that are anticipated post-treatment include erythema and pain. Other, less frequent potential events associated with any dermatological PDT include bleeding, crusting, numbness, itching, blistering and dryness, all of which tend to be transient.

A qualified physician associated with the study will be available to assess clinical signs and symptoms that may be indicative of an AE. Any clinical sign or symptom that was not present at baseline and are not included in the expected side effect profile of PDT will be recorded as an AE. AEs may be reported spontaneously by the patient or elicited

through open (non-leading) questioning during each visit and up until the end of the period of observation (week 36; Visit 6).

10.1 METHODS & TIMING OF SAFETY ASSESSMENTS

Adverse events (AEs) will be assessed at every visit. Subjects who have an AE will be monitored with relevant clinical assessments and laboratory tests, as determined by the investigator. Every attempt will be made to obtain the resolution dates for ongoing AEs.

Physical exams will be performed as per the Schedule of Assessments. Any clinically significant physical exam abnormalities will be documented as an AE. Pregnancy testing for females of child bearing potential (FCBP) will be done at screening, baseline, and at week 36. The FCBP will consist of a urine pregnancy test for β-hCG with a sensitivity of at least 50 mIU/ml.

10.2 RECORDING & REPORTING OF ADVERSE EVENTS

10.2.1 ADVERSE EVENTS

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. An AE may be a new concurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any medical condition that was present prior to study treatment and remains unchanged or improved should not be recorded as an AE. If there is a worsening of an established medical condition (aside from the expected treatment side effects), this should be considered an AE. Individual signs and symptoms of an AE should be recorded on the AE page of the subject's source documents. All AEs will be recorded by the investigator(s) from the time the informed consent form is signed through the end of the designated follow-up period (week 36; Visit 6).

10.2.2 SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any AE which:

- Results in death
- Is life-threatening (i.e. in the opinion of the investigator, the subject is at immediate risk of death from the AE)

- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject's health or require medical or surgical intervention to prevent one of the other outcomes listed previously. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered to be an SAE are hospitalizations occurring under the following circumstances:

- Hospitalizations planned before entry into the clinical study
- Hospitalizations for elective treatment of a condition unrelated to the studied indication or its treatment
- Hospitalizations that occur on an emergency, outpatient basis and do not result in admission (unless fulfilling the criteria under serious adverse event)
- Hospitalizations that are part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in the condition

If an AE is considered serious, both the AE pages of the CRF and the SAE Report Form must be completed. For each SAE, the investigator will provide information on severity, start and stop dates, relationship to study drug, action taken regarding study treatment, and outcome.

10.2.3 CLASSIFICATION OF SEVERITY

The intensity of all AEs will be graded as *mild, moderate*, or *severe* using the following definitions:

Mild	The adverse event is transient and easily tolerated.
Moderate	The adverse event causes the patient discomfort and interrupts the patient's usual activities.
Severe	The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life-threatening.

10.2.4 CLASSIFICATION OF RELATIONSHIP/CAUSALITY OF AE/SAE TO STUDY DRUG

The investigator must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as *not suspected* or *suspected* as defined below:

Not suspected:	The temporal relationship of the adverse event to study drug administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	The temporal relationship of the adverse event to study drug administration makes **a causal relationship possible,** and other medications, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

10.2.5 REPORT OF ADVERSE EVENTS TO THE INSTITUTIONAL REVIEW BOARD

The Principle Investigator is required to notify the Institutional Review Board (IRB) of a serious adverse events according to institutional policy.

10.2.6 PREGNANCIES

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age) of a female subject or the female partner of a male subject occurring while the

subject is in the study are considered immediately reportable events. Study treatments will be stopped immediately if this occurs.

11. PROTOCOL AMENDMENTS/DEVIATIONS

11.1 PROTOCOL AMENDMENTS

Any amendment to this protocol must be agreed to by the Principle Investigator and reviewed by DUSA Pharmaceuticals, Inc. Written verification of Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval will be obtained before any amendment is implemented. Written signed approval from the IRB/IEC should refer specifically to the investigator, protocol number and title, and mention any applicable amendment numbers. Amendments that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for information purposes.

11.2 PROTOCOL DEVIATIONS

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the aforementioned subject is to continue in the study. The subject's medical records will completely describe and explain the protocol deviation. In addition, the Principle Investigator will notify the IRB/IEC in writing of a protocol deviation. Non-emergency, minor deviations from the protocol will be permitted with approval of the Principal Investigator.

12. QUALITY CONTROL & QUALITY ASSURANCE

12.1 ANALYSES & REPORTING

After all 20 patients have completed the 36-week clinical trial, the Section of Biostatistics and Epidemiology at Dartmouth Medical School will help facilitate data analysis, interpretation, and presentation for future publication.

12.2 INVESTIGATOR RESPONSIBILITIES

The investigator(s) will follow the principles of good clinical practice (GCP) and conduct the study in accordance with the principles of the Declaration of Helsinki.

12.3 AUDITS & INSPECTIONS

The Principle Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of subject participation for audits and inspections by the IRBs/IECs and regulatory authorities (i.e. FDA). The investigator will make every effort to be available for audits and/or inspections.

13. REGULATORY CONSIDERATIONS

13.1 INFORMED CONSENT

Documentation that informed consent occurred prior to a subject's entry into the study and of the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and the person consenting the subject must be maintained in the Principle Investigator's study files. A copy of the informed consent form will be given to the subject.

13.2 STUDY RECORDS REQUIREMENTS

The Principle Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug be retained by the investigator for as long as needed to comply with national regulations (generally two-three years after discontinuing clinical development). The Principle Investigator agrees to adhere to the document/records retention procedures by signing the protocol. The following are examples of pertinent records and documents:

- Copies of CRFs and source documents
- Hospital records
- Clinical and office charts
- Laboratory notes
- Memoranda
- Subject's evaluation checklists
- Pharmacy dispensing records
- Recorded data from automated instruments
- Copies or transcriptions certified after verification as being accurate copies
- Microfiches
- Photographic negatives, microfilm, or magnetic media
- Subject files

- Records kept at the pharmacy, laboratory, and medico-technical departments involved in the clinical study
- Documents regarding subject treatment and study drug accountability
- Original signed informed consent forms

14. REFERENCES

1. Ribeiro, C. F., Souza, F. H. D. M. D., Jordão, J. M., Haendchen, L. C., Mesquita, L., Schmitt, J. V., & Faucz, L. L. (2012). Photodynamic therapy in actinic cheilitis: clinical and anatomopathological evaluation of 19 patients. *Anais brasileiros de dermatologia*, *87*(3), 418-423.

2. Zaiac, M., & Clement, A. (2011). Treatment of actinic cheilitis by photodynamic therapy with 5-aminolevulinic acid and blue light activation. *Journal of drugs in dermatology: JDD*, *10*(11), 1240-1245.

3. Akimoto, M., Maeda, K., Omi, T., Nishimura, T., & Miyakawa, M. (2010). Photodynamic Therapy in the Dermatological Field and Enhanced Cutaneous Absorption of Photosensitizer. *Session 2A7*, 314.

15. ABBREVIATIONS

AE: Adverse Events

ALA: Aminolevulinic Acid

CRF: Case Report Form

DLQI: Dermatological Life Quality Index

FCBP: Females of Child Bearing Potential

GCP: Good Clinical Practice

IEC: Independent Ethics Committee

IRB: Institutional Review Board

PDT: Photodynamic Therapy

SAE: Severe Adverse Events

SPF: Sun Protection Factor

VAS: Visual Analogue Scale