Study Title: Cyclic PDT for the Prevention of Actinic Keratosis and Non Melanoma Skin Cancer in Solid Organ Transplant Recipients

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IND Sponsor	Not Applicable (N/A)
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Commercial Agent(s) Supplier	DUSA Pharmaceuticals, Inc. 25 Upton Dr. Wilmington, MA 01887 626-771-7471
Protocol Version(s) and Date(s)	Version 4.0 – 10/12/2017

Investigator Agreement

I have read, understand and will adhere to the protocol as written, that any changes to the protocol will be approved by the sponsor or sponsor-investigator and the IRB, except changes to eliminate an immediate hazard to study subjects.

I agree to conduct this study in accordance with the current International Conference on Harmonization (ICH) guidance, the Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, FDA regulations, local IRB and legal requirements.

_____ _____

Signature Date (MM/DD/YY)

_____

Name of Principal Investigator

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1. INTRODUCTION / SYNOPSIS

This is a pilot, phase 2, prospective, comparative study to evaluate the safety and efficacy of the combination of Levulan® Kerastick® for Topical Solution and blue light illumination using the BLU-U® Blue Light Photodynamic Therapy Illuminator (Levulan-PDT).

The study hypothesis is that post solid organ transplantation patients, highly susceptible to non-melanoma skin cancer, can be treated safely and effectively through clinical cyclic application of PDT, lessening morbidity and possible mortality for this immunosuppressed patient population.

1.1 Phase

Phase 2.

1.2 Indication

Subjects who are 3 to 24 months post solid organ transplantation.

1.3 Endpoints

- The primary endpoint will be the total number of AK/NMSC in the treatment areas compared to the control areas.
- Time to occurrence to first AK/NMSC compared to the control areas.
- Changes in karyometry from baseline in the treatment and non treatment fields.
- Changes on the sun damage scale compared to the control areas.
- Mean pain score between the treatment field locations.

1.4 Patient Population

Adults (age 18 and older) who have recently undergone a solid organ transplant and have a stable graft function. Subjects should be at risk for developing AK/NMSC due to their transplant related immunosuppression and their history of photo damage skin and/or precancerous lesions.

2. STUDY DESIGN

2.1 Phase

This is a pilot, phase 2, prospective, comparative study. Each subject will undergo split-side face and dorsal forearm/hand PDT treatment at: Day 1 (initial treatment), Day 30 (1 month after initial treatment), Day 180 (6 months after initial treatment), 1 year after initial treatment, and every 6 months thereafter for 2 additional years.

2.2 Number of centers

One; the University of Arizona Cancer Center (Phoenix, AZ)

2.3 Number of subjects

We estimate a total of 16 to 20 subjects would be enrolled in this study.

2.4 The subject participation time period

Each subject would receive treatment at the beginning of the study Day 1 (Initial treatment), Day 30 after initial treatment, Day 180 after initial treatment, 1 Year after initial treatment and every 6 months thereafter for 2 additional years. The total subject participation time period from the first to last visit will be approximately 37 months. Treatment visits are based on the Day 1 treatment visit date to the 3 year treatment visit.

3. OBJECTIVES

3.1 Primary Objective

- To examine the safety and efficacy of cyclic Levulan-PDT on primary prevention of AKs/NMSC in recently transplanted solid organ recipients.

3.2 Secondary Objectives

- To investigate pain control with Levulan-PDT in SOTR.

4. BACKGROUND AND RATIONALE

4.1 Disease/Condition

Photodynamic therapy (PDT) is a field-based therapy with well-documented clinical efficacy in the treatment of non-melanoma skin cancer (NMSC) and its precursor lesions, i.e., actinic keratosis (AK) and Bowen's disease (BD) [1-3]. There are three major components of PDT: a photosensitizer (PS), a light source, and oxygen. Individually each component is not toxic, but combined they initiate a photochemical reaction which generates singlet oxygen. In turn, this reactive oxygen species can rapidly cause significant toxicity leading to cell death [4].

4.2 Investigational Intervention

There are two types of PSs employed in PDT, systemic and topical [5]. In dermatology, PDT is primarily delivered through the use of the topical PS 5-aminolevulinic acid (ALA) or its methylated ester, methyl aminolevulinate (MAL). Only ALA is currently available in the USA and FDA approved, while MAL is used in Europe and Canada. Both ALA and MAL are precursors in the heme biosynthesis and act as prodrugs in the skin, and get converted into photoactivatable porphyrins, including protoporphyrin IX (PpIX) [1]. The excitability of these molecules coupled with their tumor-localizing properties underscores their utility as PS agents [6]. Importantly, none of the clinically approved PDs accumulate in cell nuclei, limiting their carcinogenic potential [4].

In terms of light sources, there are two types: lasers and non-laser. Non-laser light sources include light-emitting diode (LED) arrays and blue light fluorescent tubes which are widely commercially available for PDT. Only blue light is currently FDA approved for use with PDT.

4.3 Preclinical Experience

PDT in Organ Transplant Recipients (OTR)

Clinical applications for the use of PDT that have shown successful outcomes include actinic keratosis (AK), Bowen's disease (BD), and basal cell carcinoma (BCC). OTRs are at significant risk for the development of NMSC. They have between a 65- and 200-fold increased risk for the development of squamous cell carcinoma (SCC) and a 10-fold increased risk of developing BCC compared to the general population [7-10]. These patients are also at increased risk for the development of precancerous lesions including AK and BD, with AKs demonstrating a greater propensity toward malignant transformation into invasive SCC [9, 11]. Overall, NMSC and its precursor lesions tend to be more numerous, diffusely located, recurrent, and aggressive in OTRs compared to immunocompetent patients [12-17]. Not surprisingly, cutaneous malignancy is therefore the leading cause of morbidity and mortality in this immunosuppressed patient population. Given this significant disease burden, a great deal of interest has focused on the treatment and prevention of NMSC in OTRs. As a convenient and economical field-based therapy capable of treating large areas or multiple lesions simultaneously with excellent cosmetic outcomes, the use PDT has been explored as both a primary modality for and in prevention of NMSC, and its precursors, in the OTR population.

Prevention of NMSC and Precursors

The multiplicity and widespread involvement of NMSC and precursor lesions seen in OTRs have spawned a great deal of interest in exploring the effectiveness of PDT for prevention of premalignant and malignant lesions in OTRs. Preclinical studies have substantiated this interest, with PDT demonstrating a significant preventative effect in UV-related photocarcinogenesis when delivered to accepted murine models for both SCC and BCC development [18-21].

4.4 Clinical Experience

Wulf and colleagues showed in their intra patient randomized study, a single session of MAL-PDT was delivered to 27 renal transplant patients with AKs and other skin lesions and subsequently compared to an untreated contralateral control area of similar size. Overall, the average time to occurrence for new lesions was significantly longer in the treated areas with a larger percentage of these areas remaining lesion-free after 12 months compared to untreated [22]. A similar, proof-of-concept, study examining the use of PDT in cancer prevention was also conducted in immunocompetent patients by Apalla and colleagues. Utilizing a split-face, placebo- controlled study evaluating a PDT field treatment of facial AKs, they were also able to show a significant delay in the appearance of new AK lesions in PDT-treated regions after 6 months [23, 24].

Continued use of PDT for prevention of NMSC and precursors in OTR has been documented with some success in small case series and randomized trials with varied protocols. De Graaf and colleagues were the first to examine the effect of PDT on the development of new SCCs with a large randomized intra patient controlled trial. In this study, 1–2 sessions of blue light ALA-PDT were given to a randomly selected forearm and hand of 40 OTRs, and SCC occurrence was subsequently compared to the contralateral untreated forearm and hand [25]. After 1 year of follow-up, there was a trend in favor of PDT reducing the occurrence of SCC; however, no significant difference was observed at 2 years. No debulking of lesions was performed prior to PDT. In a similarly structured study, Wennberg et al. delivered two sessions of MAL-PDT with red light over 2 weeks at study inception with single treatment follow-ups at 3, 9, and 15 months to 81 OTRs [26]. At 3 months, MAL-PDT was shown to significantly reduce the occurrence of new skin lesions, primarily AKs; however, the significance of this effect was again lost at 27 months follow-up.

Most recently, Willey and colleagues treated 12 OTRs with cyclic ALA-PDT every 4–8 weeks for 2 years [27]. They found a 79% decrease in new SCC/BD at 12 months and a 95% decrease compared to baseline at 24 months. Of note, baseline occurrence in this study was defined as the number of SCCs developed during the previous 12–24 months prior to initiation of cyclic PDT.

Togsverd-Bo et al [28] found that repeated PDT sessions in renal transplant patients could serve as primary prevention for skin dysplasia. In their randomized controlled trial, 15 patients with clinically normal skin received PDT red light at inclusion and at 6 month intervals. PDT significantly delayed the onset of AK compared to untreated areas. They observed AK in 63% of patients in untreated skin compared to 28% in PDT treated skin at 3 years.

These findings are further supported by molecular studies, which mirror the clinical response, showing that PDT can reverse or reduce field cancerization but that one single dose is not sufficient to achieve these results [29,30]. For example, Bagazgoitia and colleagues have shown that two or more treatments of PDT can

delay the appearance of AKs, reduce histological features of actinic damage, and decrease expression of early markers of carcinogenesis such as K1-67 and p53 [29]. Sun-damaged skin has a higher baseline expression level of p53 than non-sun-damaged skin, and p53 and p53 family members may be important mediators of cell death signaling in photodynamic therapy of cancer [32]. This again underscores the need for repeated PDT sessions with vigilant follow-up when using this field therapy for cancer prevention. In addition, karyometric analysis has been used successfully to detect nuclear changes from sun-damaged skin to actinic keratosis to squamous cell carcinoma, and to provide sensitive, quantitative method to assess the efficacy of prevention interventions [33-36].

Associated Risks

Pain is by far the most common, and limiting, adverse event associated with PDT. Pain most often occurs early during illumination. Standard methods to decrease pain include the use of fans and the use of non-contact cold air skin cooling device during treatment. Given the larger size, number, and involvement of lesions, pain is often significantly greater in the OTR population, especially in field cancerization areas such as the head and scalp [10, 31]. Several, well-studied, pain-relieving techniques are available to complement the delivery of PDT including use of cooling fans, intra lesional anesthetics, nerve blocks, transcutaneous electrical nerve stimulation, and modified irradiance treatment. In addition, if the cooling alone is not sufficient and pain is moderate to severe (VAS>6-7), very brief interruption in illumination can be done. Daylight PDT has also been reported to have little to no treatment related pain.

SORT are especially at risk of developing multiple, aggressive or metastatic SCC, with an associated high morbidity and mortality rate. Prevention studies have typically looked at the effect of PDT in patients who had already developed many skin cancers and who may have undergone transplantation years prior to intervention. The current protocol involves early prevention of SCC development with field therapy in high risk patients who have only recently been transplanted. The proposed intervention would be an essential benefit that could be implemented in the early overall management of these patients, and may contribute to an improved long term quality of life.

5. INVESTIGATIONAL INTERVENTION

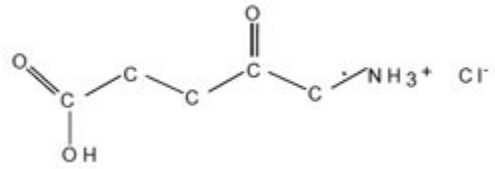
5.1 Investigational Intervention

The investigational intervention consists of a topical solution (Levulan® Kerastick®) and blue light illumination using the BLU-U® Blue Light Photodynamic Therapy Illuminator (Levulan-PDT). Levulan-PDT is indicated for the treatment of minimally to moderately thick actinic keratosis of the face or scalp.

5.1.1 Levulan® Kerastick® for Topical Solution

Levulan® Kerastick® for Topical Solution is a porphyrin precursor, containing 20% aminolevulinic acid hydrochloride (ALA HCl) by weight in a plastic applicator device.

ALA HCl is a white to off-white, odorless crystalline solid that is very soluble in water, slightly soluble in methanol and ethanol, and practically insoluble in chloroform, hexane and mineral oil. The chemical name for ALA HCl is 5-amino-4-oxopentanoic acid hydrochloride (MW = 167.59). The structural formula is represented below:



The Levulan® Kerastick® for Topical Solution applicator consists of a plastic tube (containing two sealed glass ampules) and an applicator tip. One ampule contains 1.5 mL of solution vehicle comprising alcohol USP (ethanol content = 48% v/v), water, laureth-4, isopropyl alcohol, and polyethylene glycol. The other ampule contains 354 mg of ALA HCl as a dry solid. The applicator tube is enclosed in a protective cardboard sleeve and cap. The 20% topical solution is prepared just prior to the time of use by breaking the ampules and mixing the contents by shaking the Levulan® Kerastick® for Topical Solution applicator.

5.1.2 BLU-U Blue Light Photodynamic Therapy

The BLU-U Blue Light Photodynamic Therapy Illuminator (Dusa Pharmaceuticals, Inc.) produces a photodynamic response with 20% ALA at 10 J/cm^2 for 1000 seconds. BLU-U peak absorption wavelength occurs at 417±5 nm and the maximum absorption peak for porphyrins occurs at 410 nm.

5.2 Investigational intervention supply

The Levulan® Kerastick® for Topical Solution is a single-unit dosage form, supplied in packs of 6. Levulan® Kerastick® for Topical Solution will be supplied by the manufacturer (Dusa Pharmaceuticals, Inc) specifically for the purpose of this study.

5.3 Investigational Intervention Accountability

Levulan® Kerastick® will be supplied directly to the Principal Investigator, Dr. Zeitouni, at the UACC dermatology clinic for use in this study. The principal investigator will be responsible for ordering Levulan® Kerastick® from the manufacturer, assuring proper storage of the medication, maintaining appropriate inventory and other necessary records, and assuring safe disposal of the medication. Levulan Kerastick (Active ingredient 5-ALA) is a nonhazardous medication and does not have special handling or disposal requirements. The only role of the pharmacy will be to receive the medication upon delivery and provide it to the principal investigator. The receipt of shipment, dispensing and return or destruction records will be tracked using the Investigational Agent Accountability Record or other applicable and similar record.

5.4 Storage

The Levulan® Kerastick® for Topical Solution will be stored between 20°-25 °C (68°-77 °F); excursions permitted to 15°-30 °C (59°-86 °F). The Levulan® Kerastick® for Topical Solution will be stored in the clinical trial office medication storage at UACC Phoenix.

5.5 Preparation

Preparation and application of Levulan-PDT solution will be conducted according to the intervention package insert:
http://www.dusapharma.com/levulan-product-information.html

The BLU-U® Blue Light Photodynamic Therapy Illuminator will be used according to the manufacturer Operating Manual: http://www.dusapharma.com/assets/files/blu-u-manuals/MAN-1211AW-EN%20Rev%20G.pdf

5.6 Handling

The Levulan® Kerastick® for Topical Solution should be used immediately following preparation (dissolution). Application must be completed within 2 hours of preparation. An applicator that has been prepared must be discarded 2 hours after mixing (dissolving) and, if needed, use a new Levulan® Kerastick® for Topical Solution.

6. SUBJECT ELIGIBILITY

Investigators will maintain an electronic subject log (in the UACC OnCore system) of all potential (i.e. consented) study subjects, which will include demographics, informed consent, eligibility, treatment assignment, on treatment, off treatment, follow up, and off study dates.

6.1 Inclusion Criteria

a. Males or females, at least 18 years of age.

b. Received solid organ transplant (kidney or other).

c. 3-24 months post-transplant (any number of transplant).

d. Time interval of at least 6 days duration where complications such as rejection episodes, viral infections, surgical interventions and therapies with mono or polyclonal antibodies are ruled out by the transplant team.

e. No prior history of NMSC in the treatment fields.

f. No AK/Bowen's disease in the treatment fields within the last 3 months.

g. Moderate to severe sun damage.

h. Be willing to forego other interventions in the treatment fields than the ones approved by the investigator that would interfere with the protocol or evaluation of the study medication.

6.2 Exclusion Criteria

a. Patients with Fitzpatrick's scale skin type IV-VI (see appendix 4).

b. Cutaneous photosensitivity to wavelengths of 400-450 nm, porphyria or known allergies to porphyrins.

c. Known sensitivity to any of the components of the Levulan® Kerastick® for Topical Solution.

d. Prior use of topical or systemic therapies that might interfere with the evaluation of the study medication during the study, within a 3 month washout period from the time of the screening visit.

e. Unable to return for follow-up visits and tests.

f. Any condition or situation which in the Investigator's opinion may put the subject at significant risk, could confound the study results, or could interfere significantly with the subject's participation in the study.

6.3 Enrollment

All subjects who complete the screening period of the study will be registered and assigned a unique sequential subject identification number. This number will be used to identify the subject throughout the clinical study and will be used on all applicable study documentation related to that subject. The subject identification number will remain constant throughout the study.

The written informed consent document(s) must be signed and personally dated by the subject or by the subject's legally authorized representative, and completed to a fully executed informed consent document and processed per the institution standard operating procedures.

Before subjects may be entered into the study, a copy of the written institutional review board (IRB) approval of the protocol, informed consent form (ICF), and all other applicable subject information and/or recruitment material must be on file at the institution.

7. STUDY PLAN

7.1 Intervention Regimen

Levulan® Kerastick® for Topical Solution will be applied to a designated area for 1 hour without occlusion prior to illumination with blue light using the standard FDA approved treatment time for the BLU-U device of 16 minutes 40 seconds. Each subject will be randomized to undergo treatment to one side face and one dorsal forearm/hand treatment, while the other side will serve as untreated control. Treatments will be conducted at the beginning of study Day 1 (Initial Treatment), Day 30 after the initial treatment (± 3 days), Day 180 after initial treatment (± 30 days), 1 year after the initial treatment (± 30 days), and every 6 months (± 30 days) thereafter for 2 additional years.

7.2 Pre-medications

Pretreatment will consist of cleaning the skin with 70% isopropyl alcohol and using 3 M prep tape to prepare treatment area prior to Levulan® Kerastick® for Topical Solution application.

7.3 Rescue Medications

Not Applicable

7.4 Excluded medications/treatments

No formal studies of drug interactions with Levulan® Kerastick® for Topical Solution with other drugs have been conducted. During controlled clinical studies, there were no drug-specific interactions noted. However, it is possible that concomitant use of other systemic photosensitizing agents such as griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulfonamides and tetracyclines may increase the photosensitizing effects of Levulan-PDT. Subjects using other photosensitizing agents will be asked to forgo other interventions in the treatment fields while participating in this study.

8. REQUIRMENTS FOR TREATMENT

8.1 Standard intervention

Levulan® Kerastick® for Topical Solution will be applied to the designated area for 1 hour without occlusion prior to illumination with blue light using the BLU-U for 16 minutes 40 seconds (FDA approved treatment time). Each subject will undergo treatment on one side face and dorsal forearm and hand treatment, while the other side will serve as an untreated control. Treatments will be conducted at the beginning of study Day 1 (Initial Treatment), Day 30 after the initial treatment (± 3 days), Day 180 after initial treatment (± 30 days), 1 year after the initial treatment (± 30 days), and every 6 months (± 30 days) thereafter for 2 additional years. Focal treatment procedures such as liquid nitrogen, excisional surgery, electrodessication and curettage or Mohs surgery,

for precancerous or skin cancers in intervention sites or control sites, will be performed as necessary.

8.2 Dose Intervention modification

Not Applicable.

8.3 IP intervention delays

Treatment delays up to 30 days due to grade 3 AEs or higher, patient health concerns, or long distance travel issues to treating facility may be allowed according to the discretion of the treating physician. Reason for treatment delays should be documented. Treatment delays will not be counted towards the next treatment time-point (all subsequent treatment schedules will not be interrupted or changed due to a delay).

8.4 Definition of a Dose Limiting Toxicity (DLT)

Not Applicable.

9. STUDY PROCEDURES

9.1 Screening

Potential subjects will enter the screening period of the study after a completely executed informed consent has been obtained. Please see schema section 26.

9.2 Registration/Randomization

All regulatory requirements must be in place prior to subject registrations.

UACC subject identification numbers will begin with 100 and will be assigned sequentially.

9.3 On Intervention

Please refer to study schema in section 26 of this protocol for procedures while subjects are on treatment.

9.4 End of Intervention

Subjects will have their last PDT treatment at visit 9 which will be considered off treatment when the visit is completed.

9.5 Follow up

There are no specific “Follow up” visits other than the Off Study (or End of Study) follow-up visit. Please refer to section 9.7 for more details.

9.6 Early Treatment Termination

Early treatment termination visits/procedures will be conducted when the subject decides to withdraw from the study or the PI deems it necessary to end the treatment. Procedures that will be completed during the early termination visit are outlined in the Schema table Section 26.

9.7 Off Study

Subjects will be considered off study when all planned treatment and follow-up visits have been completed, unless death or withdrawal of consent to continue participation occurs. The end of study visit will be conducted per the schema in section 26.

10. PHARMACOKINETIC STUDIES

10.1 Collection

One skin biopsy with a 4-mm punch will be taken from each forearm (treatment and non treatment sites) prior to the first session and another skin biopsy with a 4-mm punch will be taken at the end of all the sessions at 3 years, on each forearm of all patients for a total of 4 biopsies per patient. Gelfoam or 1-2 sutures will be used to close the biopsy site.

10.2 Processing

All skin biopsy specimens will be sent and processed at the University of Arizona Cancer Center in Tucson, in Dr. David Alberts laboratory..Karyometry analysis will be done at Dr. Alberts laboratory for all specimens. Karyometric measures of nuclear abnormalities scores will be recorded for statistical analysis.

10.3 Storage

Specimens and slides will be kept in a slide portfolio, properly labelled and stored in Dr. David Alberts lab.

10.4 Destruction

Not Applicable

11. DATA AND SAFETY MONITORING PLAN

Data and Safety Monitoring Plan: Medium

Medium risk studies are intended to include all trials involving therapeutic intervention(s), which are **not** designated as high risk per NCI, do not meet the criteria of medium plus IND risk, and **do not require an IND (i.e. IND exempt).**

11.1 Identification of the DSMB obligated for oversight responsibilities

The Arizona Cancer Center Data and Safety Monitoring Board (DSMB) will provide ongoing oversight for this trial.

11.2 Identification of the entity obligated for routine monitoring duties

Routine monitoring will be provided by the Quality Assurance/Quality Control (QA/QC) Program to ensure that the investigation is conducted according to protocol design and regulatory requirements. All processes, subject information and study data will be recorded in the study regulatory binder(s) and in OnCore, which will be available to the monitoring staff.

11.3 Monitoring progress and data review process

Routine monitoring of subject data will be conducted at least annually.

The first routine monitoring visit will include at a minimum:

- Informed consent – 100% of cases enrolled;
- Subject eligibility - 50% of cases, up to two subjects;
- Data review - 50% of cases, up to two subjects.

All subsequent monitoring visits will consist of randomly selected subject cases based on current enrollment and include continuing review of previously selected cases, as applicable.

A monitoring visit report and follow-up letter will be completed approximately two weeks after the routine monitoring visit; a copy will be maintained in the study file. A query/finding form or an electronic record will also be completed by the monitor to request additional source documentation, clarification, information or corrections to the CRF and/or regulatory records. The Clinical Research Coordinator or other applicable staff responsible for the study will be given a copy of this form, or will be notified of the electronic record for resolution of queries/findings. The query/finding form will be maintained with a copy of the visit report for follow-up at the next monitoring visit. Electronic records will be available in the institution database or provided by the QA/QC Program staff.

The Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in the Case Report Form (CRF). Source documentation supporting the study data should indicate the subject's participation in the trial and should document the dates and details of study procedures, adverse events, and patient status.

Case report forms, which include the inclusion/exclusion criteria form*,* adverse event forms and serious adverse event forms *[other forms, depending on study] will* be completed via the institution database. All subject forms and study files will be stored in a secure area limited to authorized staff.

11.4 Process to implement study closure when significant risks or benefits are identified

The PI will be advised of all study related AEs and will determine if the study should be closed due to significant AEs and risks.

11.5 Description of adverse events and reporting procedures

ADVERSE EVENTS: An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Any and all adverse events will be recorded on the UACC adverse events record form and reviewed by the Principal Investigator.

All adverse events will be classified using either the MedDRA term or NCI Common CTCAE version 4.02 and will address:

- Grade
- Relationship to study drug (not related, unlikely, possible, probable, definitely)
- Causality other than study drug (disease related, concomitant medication related, intercurrent illness, other)
- Date of onset, date of resolution
- Frequency of event (single, intermittent, continuous)
- Event outcome (resolved, ongoing, death)
- Action taken (none, held, dose reduced, discontinued, medication given)

SERIOUS ADVERSE EVENTS: An SAE is any untoward medical occurrence that at any dose:

1) Results in death;
2) Is life-threatening;
3) Requires in-patient hospitalization or prolongation of an existing hospital stay;
4) Results in disability persistent or significant disability/incapacity, or:
5) Is a congenital anomaly/birth defect.

Note: A SAE may also be an important medical event, in the view of the investigator that requires medical or surgical intervention to prevent one of the outcomes listed above.

All serious adverse events, regardless of attribution, and any deaths will be reported within 24 hours of notification of the event to the sponsor and DSMB Coordinator. All serious adverse events, regardless of attribution, and any deaths will be reported within 5 days of notification of the event to the University of Arizona Human Subjects Protection Program.

All serious adverse events will be processed by the DSMB Coordinator monthly for initial trend analysis and fully reviewed by the DSMB every six months. The DSMB coordinator will review the SAE reporting process to confirm reporting requirements are met.

11.6 Plan for assuring data accuracy and protocol compliance

Routine study activity and safety information will be reported to the DSMB every six months, or more frequently if requested. These reports will include:

- Study activity, cumulative and for the period under review;
- Safety (narrative description on non-serious and serious adverse events, protocol pre-determined early stopping rules for safety or treatment-emergent adverse events);
- Predetermined protocol early stopping rules for efficacy/futility;
- Status of study in relationship to stopping rules;
- Current dose level of study agent;
- Routine monitoring and protocol compliance (describe the monitoring process and identify the status of the monitoring);
- Comments;
- Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies.

Data, safety and study progress will be reported to:
- Human Subjects Protection Program (IRB) at least annually;
- Sponsor (if applicable) at least every six months.

11.7 Identification of the sponsor or funding agency, as applicable

The PI will immediately notify; in writing, the funding agency, if applicable, any action resulting in a temporary or permanent suspension of the study. A copy of this correspondence will also be forwarded to the DSMB and the SRC.

12. ADDITIONAL SAFETY REPORTING REQUIREMENTS

Not Applicable.

13. QUALITY ASSURANCE MEASURES

Per the UACC DSMB Charter, Internal *Ad Hoc* audits may be performed on any UACC clinical trial if identified for audit, the audit will be conducted by an identified audit team per the UACC DSMB Charter. A QA/QC representative will coordinate the audit team functions and a written audit report will be provided to the principal investigator and the DSMB.

14. RECIST CRITERIA

Not Applicable.

15. REMOVAL OF SUBJECTS

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. If this occurs, the investigator, or designee, is to discuss with the subject the safe and appropriate processes for discontinuation from the investigational treatment.

The investigator or designee must document the change in status of the subject's participation in the study and as applicable, the level of follow up that is agreed to by the subject (i.e. agrees to follow up exams, adverse event review, but not to further treatment and/or procedures).

Subject withdrawal of consent for a study indicates that the subject does not wish to receive further protocol required therapies or procedures, and the subject does not wish to, or is unable to continue further study participation. Subject data only up to the time when consent is withdrawn will be included in the analysis of the study.

The study is expected to close after all patients have been treated for 3 years.

16. STATISTICAL CONSIDERATIONS

Characteristics of study subjects will be summarized by appropriate abstract statistics, including frequency, proportion and 95% Clopper-Pearson confidence interval (CI) for the proportion for categorical variables, median, and range for continuous variables.

Evaluable subjects for safety outcome measures will be those who complete any study visits or those who discontinue the study treatments due to adverse events (AE). Evaluable subjects for efficacy outcome measures will be those who complete all study visits. At least 15-16 evaluable subjects for each of these analyses are expected.

Primary efficacy outcome measure will be the difference in the total number of AK/NMSC in the treatment areas compared to the control areas. All unique AK/NMSC

observed during the 3 year study period will be identified and summed in each area. The statistical significance of the difference will be tested using the Wilcoxon Signed-Rank Test.

Secondary safety and efficacy measure: Time to the occurrence of the first AK/NMSC in the control versus treated areas will be estimated using the Kaplan-Meier estimate. Changes in the p53 staining from baseline to end of treatment will be evaluated using McNemar's Test. Mean pain scores (VAS) and photo damage scale global scores of the study population will be compared with each respectively using Wilcoxon Signed-Rank Test.

Sample Size Determination: Safety will be evaluated using a one-sided confidence interval (as the lower bound is not of interest). At least fourteen patients will be evaluable for safety. If none of the patients have an adverse primary safety outcome, the upper bound of a 95% one-sided confidence interval is < 20%.

17. ANALYSIS

17.1 Safety Analysis

The primary safety outcome measures will be estimated with 95% Clopper-Pearson CI: The proportion of evaluable study participants who had a grade 3 or higher AE or any serious adverse event that's determined to be at least possibly or probably related to study treatment, or any AE which is at least possibly or probably related to study treatment that causes permanent study discontinuation. AE's will be documented and kept in the study regulatory binder and in OnCore.

Pain will be assessed on the 10 point Visual Analogue Scale (VAS), as mild (0-3), moderate (4-7) or severe (8-10). Patients will be asked to rate the pain at the beginning, midway point (approximately 8 minutes later), and at the end of each PDT session.

17.2 Efficacy Analysis

Number of AK/NMSC will be counted for each site using the photographs of the treatment and the control areas. AKs will be graded by thickness I-III: I = mild, slightly palpable, II = moderate, easily felt, III= severe, very thick. NMSC, including basal cell carcinoma, Bowen's disease and squamous cell carcinoma, will be diagnosis and confirmed histologically by biopsy.

Photo damage in the treatment and control fields will be assessed by the sun damage scale as: absent, mild, moderate, and severe. The scale includes 4 points: fine wrinkling, coarse wrinkling, abnormal pigmentation and global (0-10). Ratings for epidermal dysplasia will be obtained by immunohistochemistry of p53 staining of skin biopsies in the treatment areas at baseline and after the last treatment.

Time to occurrence of AK/NMSC will be calculated from the first visit to the development of an AK or NMSC in the treatment areas and in the control areas.

17.3 Interim Analysis

No interim analyses is planned.

18. REGULATORY OBLIGATIONS

18.1 Informed Consent

Before a subject's participation in the clinical study, the investigator or identified, trained designee is responsible for obtaining written informed consent from the subject or legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specified procedures, investigational treatment are administered or initiated.

18.2 Institutional Review Board (IRB)

A copy of the protocol, proposed ICF, and all other applicable subject information will be submitted to the IRB for written approval. A copy of the written approval of the protocol and ICF must be on file at the institution before recruitment of subjects into the study.

The investigator is responsible for obtaining IRB approval/renewal at least annually throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be on file at the institution.

The investigator must submit study information to the IRB as required by all applicable guidelines and requirements. The investigator will obtain IRB approval for subsequent protocol amendments, except changes to eliminate an immediate hazard to study subjects. The investigator will notify the IRB of deviations from the protocol or serious adverse events.

19. ADMINISTRATIVE PROCEDURES

19.1 Investigator Responsibilities

The PI will conduct this study in accordance with the current International Conference on Harmonization (ICH) guidance, the Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, FDA regulations, local IRB and legal requirements.

19.2 Data and Safety Monitoring Board Protocol Review

Initial DSMB protocol review will be conducted prior to SRC and IRB submissions.

Any protocol revision or amendment that includes a potential change to any section of data and safety monitoring plan must be reviewed and approved by the DSMB ***prior to*** **the protocol amendment submission to the IRB**.

19.3 Multicenter Trials

Not Applicable

20. SUBJECT CONFIDENTIALITY

The principal investigator will ensure that the subject's confidentiality is maintained in compliance with Federal regulations, the International Conference on Harmonization (ICH), and Good Clinical Practice (GCP) Guidelines.

Oversight entities and/or regulatory authorities will be permitted direct access to review the subject's original medical records, electronic medical records or certified copies for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

21. STUDY DOCUMENTATION AND ARCHIVE

The investigator will maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Delegation of Responsibilities Form.

Source documents, data, and records from which the subject's CRF data are obtained include, but are not limited to, hospital records, clinical/office/research charts, laboratory and pharmacy records, radiographs, and correspondence. Source data will include information necessary for the reconstruction and evaluation of the trial. CRF data from the Phoenix site will be either sent to the UACC Tucson QA/QC staff for routine monitoring of the trial, when requested, or monitored utilizing OnCore as the electronic e-CRF. In addition, the Confidentiality Section of the ICF and HIPAA Authorization will list the University of Arizona Cancer Center Tucson main staff and DSMB as entities who may see their records, so patients are aware that their information will be reviewed and disclosed to the University of Arizona Cancer Center Tucson staff for routine monitoring.

The principal investigator or sponsor-investigator is responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation as required per ICH Guidelines. This can be accomplished by the PI, through the site's standard operating procedures and/or the institutions infrastructure.

The investigator will follow ICH Good Clinical Practice Guidelines and the Code of Federal Regulations for records and record retention.

22. DATA

Applicable data specified as required in the protocol will be reported/submitted in the case report form (CRF). Data reported in the case report forms that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. **CRFs will be completed via UACC OnCore electronic system.**

Additional procedures and assessments may be performed as the institution's standard of care; however these data should remain in the medical records and should not be provided as part of the clinical study data unless it pertains to a serious adverse event.

The investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational intervention, or employed as a control in the investigation.

23. PROTOCOL DEVIATIONS

The investigator will conduct the study in conformance with this protocol, generally accepted standards of Good Clinical Practice and all applicable federal, state and local laws, rules, and regulations.

Approvals or waivers for protocol deviations will be obtained from the sponsor-investigator ***prior to*** occurring, except changes to eliminate an immediate hazard to study subjects. If immediate verbal approval is obtained, it will be documented by the research staff obtaining the approval and followed by a written protocol deviation form per the site standard operating procedures. The sponsor or the sponsor-investigator will sign the Protocol Deviation (Waiver) Approval Form or other similar document. The original will be filed in the regulatory binder and a copy will be placed in the subject's research file.

24. ECOG

Not Applicable.

25. COMMON TOXICITY CRITERIA (CTCAE)

The study will utilize the NCI Common Toxicity Criteria for Adverse Events Version 4.02 for toxicity and Serious Adverse Event reporting.
http://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf

26. SCHEMA OR STUDY SCHEDULE

Study Procedures	Screening/ Baseline [A]	On Study Treatment [B]								Early Termin-ation	End of Study [C]
		Day 1	Day 30	Day 180	12 Month	18 Month	24 Month	30 Month	36 Month		
Visits	1	2	3	4	5	6	7	8	9	ET	EOS
Eligibility Verification	x										
Informed Consent	x										
Registration	x										
Medical History [D]	x										
Physical Exam [E]	x										
Concomitant medications	x	x	x	x	x	x	x	x	x		
Levulan-PDT		X	X	X	X	X	X	X	X		
Adverse events		x	x	x	x	x	x	x	x	x	
Punch Biopsy [F]		x							x		
VAS Scale [G]		x	x	x	x	x	x	x	x		
Sun Damage Scale [H]		x	x	x	x	x	x	x	x	x	x
Photographs [I]		x	x	x	x	x	x	x	x	x	x

[A] Screening may be conducted within 28 days before first treatment.

[B] Treatments may be conducted ± 3 days for Day 30 treatment and ± 30 days for Day 180, 1 year, 1.5 year, 2 year, 2.5 year, and 3 year visits respectively. Treatment visits are based on the Initial Day 1 treatment visit.

[C] 3 months (± 30 days) after the last treatment.

[D] Medical history including past medical, meds, allergies, social and HPI will be done.

[E] Physical exam will consist of vital signs (blood pressure & pulse), and a full treatment area skin exam.

[F] Punch biopsies will be used for karyometric analysis between baseline and end of treatment.

[G] For more information about the VAS Scale, please refer to Appendix 1.

[H] For more information about the Sun Damage Scale, please refer to Appendix 2.

[I] For more information about digital photography, please refer to Appendix 3.

27. ABBREVIATIONS

AE	Adverse Event
AK	Actinic Keratosis
ALA	5-Aminolevulinic Acid
BCC	Basal Cell Carcinoma
BD	Bowen's Disease
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
LED	Light-Emitting Diode
Levulan-PDT	Levulan Kerastick and Blue Light Photodynamic Therapy
MAL	Methyl Aminolevulinate
NMSC	Nonmelanoma Skin Cancer
OTR	Organ Transplant Recipient
PDT	Photodynamic Therapy
PpIX	Protoporphyrin IX
PS	Photosensitizer
QA/QC	Quality Assurance/Quality Control
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma

SOTR	Solid Organ Transplant Recipient
SRC	Scientific Review Committee
UACC	University of Arizona Cancer Center
VAS	Visual Analogue Scale

28. REFERENCES

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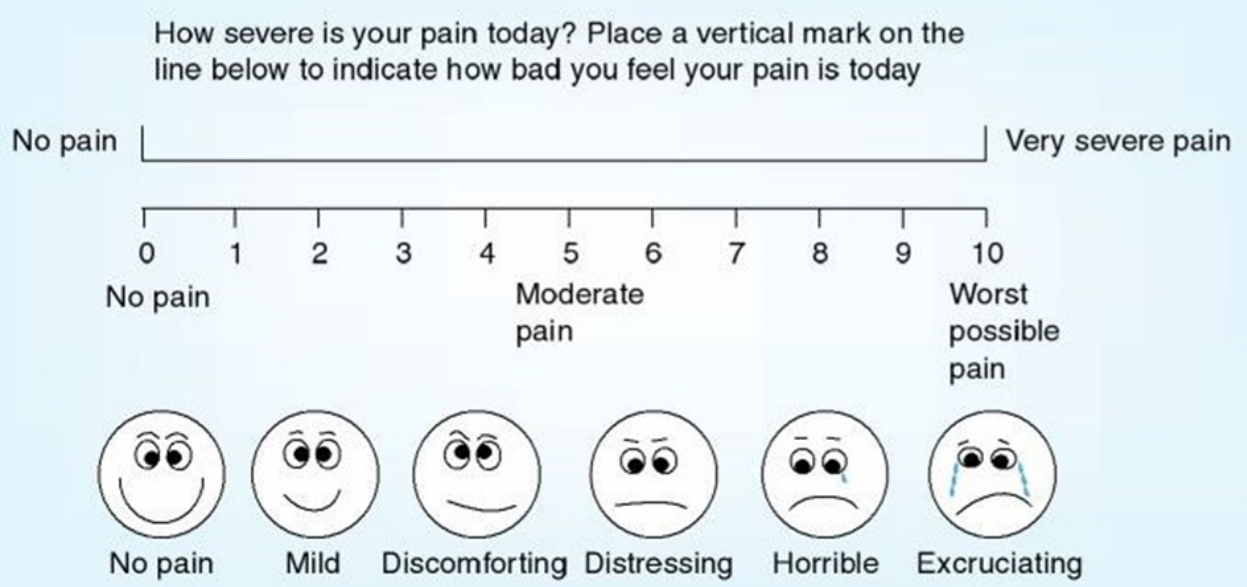
29. APPENDICES

Appendix 1. Visual Analogue Scale (VAS)



Source: Expert Rev Hematol. 2011 Feb; 4(1): 81-93. PMID 21322781.

Appendix 2. Sun Damage Scale

Clinical Sign	Absent	Mild	Moderate	Severe
Fine wrinkling	0	1 2 3	4 5 6	7 8 9
Coarse wrinkling	0	1 2 3	4 5 6	7 8 9
Abnormal pigmentation	0	1 2 3	4 5 6	7 8 9
Global	0	1 2 3	4 5 6	7 8 9

Source: Arch Dermatol. 2011 Jan; 147(1): 31-36. PMID: 21242389.

Appendix 3. Digital Photography

Digital photographs will be taken using a Nikon COOLPIX 4300 digital camera (Nikon, Tokyo, Japan) with standardized methods to ensure consistency. Standardized lighting will be available using overhead lighting and no separate skin illumination. The Anytime Flash setting will be used with maximum aperture (preset between 2.8 and 7.6), and all photographs will be taken on a uniform blue background. Additional settings include image size, 2272 × 1704; image quality, fine; focus, macro close-up automatic single mode; and sensitivity, 100 ISO. The focal length of the COOLPIX lens system is 8 to 24 mm.
Source: Arch Dermatol. 2011 Jan; 147(1): 31-36. PMID: 21242389.

Appendix 4. Fitzparick's Skin Type Scale