1) Protocol Title

Pilot study for the use of photodynamic therapy in the treatment of seborrheic dermatitis.

2) Author of Protocol

UC Davis Researchers:
Principal Investigator: Nasim Fazel, MD, DDS, Department of Dermatology
Co- Principal Investigator: Raja Sivamani, MD, MS, Department of Dermatology

3) IRB Review History

The IRB reviewed the protocol and requested that the FDA determines whether an IND is needed or exempt.

4) Objectives

a) To determine the efficacy of photodynamic therapy (PDT) in the treatment of seborrheic dermatitis.

b) To determine how PDT alters the skin microbiome in subjects with seborrheic dermatitis before and after treatment.

c) To determine how PDT alters sebum secretion rates in subjects with seborrheic dermatitis before and after treatment.

We hypothesize that PDT will be efficacious in the treatment of seborrheic dermatitis.

5) Background

Seborrheic dermatitis is a common chronic inflammatory disorder with a prevalence estimated at 3-5% [1, 2]. Although the exact pathophysiology is unclear, seborrheic dermatitis is more prevalent in indviduals that are more heavily colonized with the *Malassezia spp* fungal organism, those with more residual sebum (for example in neuropathic patients such as in Parkinson's disease), and in those with higher sebum production, which leads to more lipid byproduct build up [2]. Current topical treatments include the use of topical antifungals, topical steroids, and topical calcineurin inhibitors [3, 4]. The success of topical treatments requires long-term use and depends on the compliance of the patient. Furthermore, these treatments can expose patients to potential side effects such as atrophy, thinning of the skin and telangiectasias in response to topical steroids. Therefore, alternative therapies that provide long-term control are needed.

This pilot project investigates the use of PDT may be useful in the treatment of seborrheic dermatitis based on the following: 1) The *Malassezia spp* is capable of forming biofilms [5], 2) PDT has been shown to be effective against *Malassezia spp* [6, 7], 3) PDT can break up bioflims of both bacterial and fungal origin [8], and 4)

benzoyl peroxide, a prooxidant treatment similar to PDT, has been shown to be effective in the treatment of seborrheic dermatitis [9].

6) Inclusion and Exclusion Criteria

Healthy subjects 18 years or older with seborrheic dermatitis of the face will be included.

Subjects who are taking systemic corticosteroids (at doses of prednisone greater than or equal to 5 mg daily) or antibiotics (PO, IM or IV) will have to undergo a 4 week "wash-out" period before participating in the study. Subjects who are using topical anti-fungals, steroids, antibiotics, permethrin, or calcineurin inhibitors will have to wait 2-weeks before enrolling. Washout will only occur if subject signs this consent form and the prescribing physician advises for a washout following consultation. Women who have started new birth control regimens within the last two months will have to wait until two months after the start of their regimen.

Recruited subjects will be permitted to use bland emollients, but they will instructed to refrain from using topical emollients such as PromiseSeb® which have been clinically studied for the treatment of seborrheic dermatitis. The exclusion criteria will also include the presence of other untreated inflammatory conditions (such as lupus, atopic dermatitis, or psoriasis) or untreated malignancies on the face (including skin cancers such as basal cell carcinoma, squamous cell carcinoma and melanoma).

Any subjects with known or suspected hypersensitivity to any constituent of the study medication or a history of photosensitivity due to conditions such as lupus erythematosus and porphyria will be excluded. Subjects who have had photodynamic therapy (PDT) to the face for any reason within the past year will be excluded as well.
Adults unable to consent, individuals under the age of 18, pregnant or breastfeeding women and prisoners will be excluded from the study.

7) Study-Wide Number of Subjects

12

8) Study-Wide Recruitment Methods

Patients will be recruited from the outpatient dermatology clinics in the department of Dermatology at UC Davis. We also recruit participants who live within a 100 mile radius of the dermatology clinics in Sacramento. They will be reassured that their participation or non- participation in the study will not affect the level of clinical care received.
Recruitment flyers are attached.

9) Compensation to the Subjects

At the end of visit two, the patient will be paid $40 for completing visits one and two. If the patient does not follow up for visit 2, they will receive no compensation. At the end of visit three, the patient will be paid an additional $20 for completing

visit three. We will make the payments using gift cards.

10) Study Timelines

The research subject will require 4 visits that are spaced 2-10 weeks apart as outlined in the attached protocol. Each visit will take a total of 1.5 hours. We estimate that each subject will participate for a total of 3-4.5 months from initiation of enrollment to completion of the study.

11) Study Endpoints

The primary endpoint of the study is recruitment of a sufficient number of patients (12) who complete two treatments of photodynamic therapy to the face with grading of the severity of seborrheic dermatitis before each treatment and after each follow-up period.

The secondary endpoints for the study are obtaining swabs for microbiome analysis and facial sebum production rates before each treatment and after each follow-up period.

12) Procedures Involved

Duration of seborrheic dermatitis, previous treatments for seborrheic dermatitis and patient response to the treatments will be recorded. Facial photography will be done for grading the Seborrhea Area and Severity Index Face (SASI-F). All seborrheic dermatitis patients will be graded using the SASI-F [3]. This score is a composite score as follows: the area index, also known as the relative area of facial involvement, is denoted as a fraction of 1 with the normal hairline defining the boundaries of the face. Erythema and scale are separately scored on a 5-point scale using the definitions used to conduct Psoriasis Area and Severity Index scoring (ie, 0 = none, 1 = slight, 2 = moderate, 3 = striking, and 4 = exceptionally striking). The scores for erythema and scale are then summed and multiplied by the relative area of facial involvement ratio. The maximal score is 8 whereas no involvement would have a score of 0. The inclusion criteria will be similar to the previous trial that used the SASI-F in their analysis [3]. This study will consist of subjects with an erythema score of at least one with the presence of at an area index of 5% or more.

This study will be a single blinded, randomized, intra-individual comparison study consisting of a total of 12 subjects. Patients will be randomized by utilizing an online randomizer. A power analysis is not truly applicable because this is a pilot study that utilizes a potential treatment for seborrheic dermatitis that has not been previously investigated. We plan to recruit up to 12 patients. The treatment will consist of split-face comparisons of no application of aminolevulinic acid (ALA) vs ALA application to either half of the face. Prior to ALA application, the face will be swabbed for microbiome analysis. A schematic for the split-face study is shown in Figure 1. After the ALA application, the subjects will incubate with the ALA on their face per the standard PDT protocol used at UC Davis Dermatology clinic for facial PDT treatments. The side of the face being treated will remain the same during all treatments. The investigator applying the ALA to the patient will be aware of which side is receiving treatment and which side is not, but the patient will be blinded. For the placebo, Demo Levulan Kerastick, which contains no active ingredient and is enclosed in same cardboard sleeve and cap, will be applied to the other side of the face to mimic the surface of the ALA application stick.

After the ALA incubation is completed, the subjects will be exposed to a treatment dose of blue light from a Blu-U unit per UC Davis Dermatology clinic protocol for PDT treatments.
Calibrated facial pictures will be used for blind grading utilizing the SASI-F scoring system.

A flow diagram of the protocol is shown in Figure 2. The topical ALA used for this study will be Levulan® Kerasticks (DUSA Pharmaceuticals, Inc.). Facial sebum production rate will be measured with SebuMeter®. The swabbing for the microbiome will be performed as non-invasive swabbing from the face that will not cause the patient any pain or discomfort. For the blue light treatment, the total light dose to the face will be consistent with the currently used standard facial exposure PDT protocols at UC Davis.

After the third visit, patients have the option of being seen in the regular dermatology clinics. Based on the disease severity, a treatment modality will then be selected and administered for the untreated side of the face.

The Levulan Kerasticks and Demo Levulan Kerasticks are stored at the Investigational Drug Services (IDS), a Division of the Pharmacy Departmen at the University of California, Davis. IDS dispenses the Kerasticks upon the investigators' request.

13) Data and Specimen Banking

N/A

14) Data Management

This study will be a single blinded, randomized, intra-individual comparison study consisting of a total of 12 subjects. A power analysis is not truly applicable because this is a pilot study that utilizes a potential treatment for seborrheic dermatitis that has not been previously investigated. We plan to recruit up to 12 patients.

SASI-F scores and the SebuMeter® measurements will be compared within the treatment group and an intra-individual comparison will be performed by paired statistical testing such as the paired t-test. A p-value of 0.05 or less will be considered significant. All of the assessors will be blinded to the treatment groups. The primary endpoint will be complete clearance of the seborrheic dermatitis as an intra-individual comparison and statistically analyzed with a two-sided paired t-test. All participants will be included in the study on an intent-to-treat basis.

15) Provisions to Monitor the Data to Ensure the Safety of Subjects

The subjects will be monitored clinically during the treatment for any evidence of side effects such as pain or blisters. All of the treatments are done with topical ALA, which is an FDA approved drug.

No regular blood draws or labs will be necessary. No systemic effects are anticipated because all of the treatments are localized topical applications.

However, the patient will be given a contact number on the consent forms in case there are any treatment related adverse effects such as erythema, blisters, pain, or secondary infection. Any side effects will be noted in a secure document. Secondary infections will be treated with appropriate antibiotics and local inflammation will be treated with topical steroids as necessary.

16) Withdrawal of Subjects

Subjects may be withdrawn without their consent if they acquire any medical issues during the study period which require the use of any other topical medications, oral or parenteral steroids, oral or parenteral antibiotics. They may also be withdrawn if they are found to have any abnormal sensitivity/allergy to the ALA.

If a subject is to be withdrawn without their consent, they will be contacted and the reason(s) for their withdrawal will be explained in full. No further data will be collected from the subject.

17) Risks to Subjects

There is a low chance for any physical, psychological, social or legal injury from participation in the study. The patient will be warned of the standard risks of treatment with topical ALA including erythema, pain, blisters, increased temporary photosensitivity for 24 hours after treatments, and risk for hyper- and hypopigmentation.

These potential adverse events will be localized and can be adequately managed and controlled with wound care and topical antibiotics, if the subject were to develop a secondary infection at the treatment sites. It is also possible, although unlikely, that the subject may develop contact dermatitis after exposure to the topical ALA. This can be adequately managed with topical steroids and topical antibiotics, if necessary.

18) Potential Benefits to Subjects

The individual subject may benefit from the treatment, but this cannot be guaranteed since this study aims to explore the efficacy of PDT in the setting of seborrheic dermatitis. The greater community of patients with seborrheic dermatitis would benefit as this study would provide more insight into the efficacy of PDT for the treatment of seborrheic dermatitis.

Given that half of the subjects' face will receive the standard PDT treatment, as per the dermatology clinic protocol for actinic keratoses on the face, there is the possibility that the treatments will concurrently treat their actinic keratoses.

19) Vulnerable Populations

N/A

20) Multi-Site Research

N/A

21) Community-Based Participatory Research

N/A

22) Sharing of Results with Subjects

N/A

23) Setting

The subjects will be recruited from the patients that attend the dermatology clinics at the UC Davis Dermatology clinic.

Research activities will be conducted at the UC Davis Dermatology Department (3301 C Street, Suite 1300/1400).

24) Resources Available

The Dermatology department and clinic at UC Davis is available for use and the support staff within the department should be sufficient to conduct the study.
The personnel involved in this study, their qualifications and their roles are as follows:

Nasim Fazel, MD, DDS, MAS: Clinical Associate Professor, Principal Investigator.

-Experienced dermatologist with expertise in both seborrheic dermatitis and PDT.

-Role: Study design, grading of treatment site, involved in PDT procedure, patient recruitment, facial photography, specimen collection, and data analysis.

Raja Sivamani, MD, MS: Assistant Professor of Dermatology, Co-Principal Investigator.

- Experienced in the use of PDT.

-Role: Study design, patient recruitment, involved in PDT procedure, facial photography, specimen collection, grading of treatment site, and data analysis

Research assistants: Undergraduate students, medical students and junior specialist.

- Role: Patient recruitment, blue light exposure, facial photography, specimen collection, organization of data

Coordinators:

- Role: Patient recruitment, blue light exposure, facial photography, grading of treatment site, specimen collection, data analysis

Seborrheic dermatitis is one of the most common conditions encountered in dermatology and among our patients. Therefore, we will have a sufficient recruitment pool to meet our required number of subjects.

Photodynamic therapy is frequently used at the Dermatology clinic and we do not expect significant adverse effects. However, the patient will be asked to contact the dermatology attending on-call in the event that there is an adverse effect.

To ensure that all assisting personnel are aware of the research protocols, we will have a pre-recruitment meeting followed by regularly scheduled meetings to discuss duty expectations, the protocol, study progress, and any changes as needed.

25) Prior Approvals

N/A

26) Recruitment Methods

We will recruit from the patients that attend the outpatient dermatology clinic at UC Davis using flyers with contact numbers of the research team. We also use UC Davis Study Pages website. Patients will be assured that their clinical care will not be affected by their participation or non- participation in the study.

Recruitment flyers are attached.

27) Local Number of Subjects

A total of 12 subjects will be recruited.

28) Confidentiality

This study is not a multicenter study. All of the data will be stored in secured data files in a password-protected computer within a locked room. All of the subjects will be coded with the codes listed in a separate password protected file. All paper files of the subjects will be stored in a locked cabinet within a locked room. Dr. Fazel, Dr. Sivamani, and the research coordinator will have access to the paper files and password protected data files.

Subjects' images may be used for educational purposes, publications and/or presentations at conferences, and scientific meetings. Pictures will be used without using any identifying information or features. We will follow the institutional policy for the use of recorded material for educational purposes and/or presentations at

conferences, scientific meetings etc... that is outside of the research: http://intranet.ucdmc.ucdavis.edu/policies/hospital_policies_and_procedures/consents_legal_documents/1426.shtml

29) Provisions to Protect the Privacy Interests of Subjects

To protect subjects' privacy interests, data and/or specimens will be labeled with a code that the research team can link to personal identifying information when acquired. The code sheet will be secured and kept separate from the dataset. Only authorized research personnel will have access to this information. All paper records containing study data will be stored in a study binder. This study binder will be securely stored in a locked cabinet, in a locked office, in the UC Davis Department of Dermatology at 3301 C St, Suite 1400, Sacramento, CA 95816. Any study-related electronic information will be kept in a password-protected computer database. Only the PI, study staff, IRB and other authorized/designated governing bodies and individuals will be allowed to access these study-related documents. All HIPAA, IRB, State, and Federal policies and guidelines will be followed to ensure patient confidentiality.

Patient photographs taken during this study will be handled according to the UC Davis Dermatology clinic protocol, which is as follows. Photographs will be taken with the clinic's cameras (which never leave the clinic), uploaded to the patient's electronic medical record, and deleted from the camera.

Interviews with patients will be conducted in a private clinic room. The participant may choose not to answer any or all of the questions during the interview, or they may stop the interview at any time, if they are uncomfortable or unsure about the study.

30) Compensation for Research-Related Injury

If the patient is injured as a result of being in the study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by the University or may be billed to the patient's insurance company. The University and the study sponsor do not normally provide any other form of compensation for injury.

31) Economic Burden to Subjects

The patient will need to come to the dermatology clinic for the PDT treatments. As such, they will need to pay for the expense of travel. Although this may be offset by compensation for participation in the study, the patient will need to pay for the travel expense ahead of receiving their compensation.

32) Consent Process

Written consent will be obtained from patients at the UC Davis outpatient Dermatology clinic in Sacramento. We will be following the SOP: Informed Consent Process for Research. After obtaining consent, there will be a two-week waiting period before initiating treatment so that the patient may begin using only

Dove soap and stop using any other products to their face. If the patient is using systemic treatment they will have to wait 4 weeks before participating, and if the patient is using topical treatment they will have to wait 2 weeks before participating. Patient will also be provided a moisturizer and sunscreen to use as needed. Patient will be encouraged to use sunscreen following PDT treatments.

Only English-speaking, adult subjects who are not cognitively impaired and are able to consent will be recruited.

33) Process to Document Consent in Writing

Written documentation of consent process will be obtained (please see attached Consent document). This includes signing of the standardized consent form and HIPPA as well as an additional consent form that outlines permission to use photographs/recordings for publications/conferences/training purposes. In combination, this consent process will follow UCDHS policies related to this studya and allow use of photographs obtained for conferences/trainings /publications.

34) Drugs or Devices

Aminolevulinic acid (ALA) and the Blu-U unit are routinely used for delivering PDT treatments in the dermatology clinic. The Levulan Kerasticks and Demo Levulan Kerasticks will be at the Investigational Drug Services (IDS), a Division of the Pharmacy Departmen at the University of California, Davis. IDS dispenses the Kerasticks upon the investigators' request. They will be used as per the UC Davis Department of Dermatology protocol for PDT treatments. PDT is not an investigational drug or device.

Levulan Keastick is approved by the FDA for the treatment of actinic keratosis. The FDA has exempeted this protocol from the IND regulations.

References:

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7. Lee, J.W., et al., *Topical photodynamic therapy with methyl aminolevulinate may be an alternative therapeutic option for the recalcitrant Malassezia folliculitis.* International Journal of Dermatology, 2011. **50**(4): p. 488-490.
8. Biel, M.A., *Photodynamic therapy of bacterial and fungal biofilm infections.*

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Figure 1. Schematic for the split-face study. The C and M groups will be randomized to the right or the left side of the face by binary randomization.

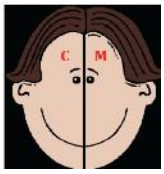

Figure 2. Seborrheic Dermatitis PDT Study Protocol

Recruit total of 12 subjects
Binary randomization for treatment of right versus left face as the control

Visit 0

1. Medical history and inclusion/exclusion criteria
2. sign the consent forms

2-10 week interval

Visit 1

1. Urine pregnancy test for female subjects. If the woman is postmenopausal or if the woman does not have a uterus, then they will be exempted from pregnancy testing
2. Facial photography for SASI-F grading and erythema and scale grading
3. Swab facial sites for microbiome analysis
4. Measure facial sebum production rates with SebuMeter®
5. Apply ALA to treatment side and sham ALA to control side
6. Incubate ALA for one hour
7. Expose to blue light per UC Davis Dept of Dermatology standard protocol

2-4 week interval

Visit 2

1. Urine pregnancy test for female subjects. If the woman is postmenopausal or if the woman does not have a uterus, then they will be exempted from pregnancy testing
2. Facial photography for SASI-F grading and erythema and scale grading
3. Measure facial sebum production rates with SebuMeter®
4. Apply ALA to treatment side and sham ALA to control side
5. Incubate ALA for one hour
6. Expose to blue light per UC Davis Dept of Dermatology standard protocol

2-4 week interval

Visit 3

1. Facial photography for SASI-F grading and erythema and scale grading
2. Swab facial sites for microbiome analysis
3. Measure facial sebum production rates with SebuMeter®

END OF STUDY