1) Protocol Title

The Use of Microneedles to Expedite Treatment Time in Photodynamic Therapy

2) Author of Protocol

☒ UC Davis Researcher
☐ Researcher from other institution
☐ Private Sponsor
☐ Cooperative Group
☐ Other: _____

3) IRB Review History

This is a new IRB protocol however it is in follow-up of a previously IRB approved study titled "The Use of Microneedles in Photodynamic Therapy" (IRB# 282150).

4) Objectives

Investigate whether pretreatment with microneedles can decrease the required incubation times of the topical aminoleveulininc acid (ALA) prior to exposure to blue light photodynamic therapy.

5) Background

Photodynamic therapy (PDT) is an established treatment for actinic keratoses (AK). The current standard of care of PDT application at the UC Davis Department of Dermatology, includes pre-treatment of the area with topical aminolevulinic acid (ALA) for 1 hour, followed by treatment with blue light.

Our group conducted a pilot study at UC Davis titled "The Use of Microneedles in Photodynamic Therapy". The global aim of this pilot study was to investigate how microneedles can facilitate the penetration and efficacy of photodynamic therapy, and specifically to investigate whether pretreatment with microneedles enhances penetration of topical aminolevulinic acid (ALA) that is FDA approved and marketed as Levulan® Kerasticks by DUSA Pharmaceuticals, Inc.

This pilot study thus far has demonstrated that microneedles enhance penetration of topical ALA as compared to the control group. More impressively the study has demonstrated that pre-treatment using microneedles with ALA with 20 minute incubation demonstrated equal outcomes as the control group without microneedle treatment and 1 hour incubation.

This demonstration of equal efficacy with decreased incubation time is important as it alleviates one of the major barriers to PDT which is the time needed for administration of this therapy. This is now a follow-up study where we will used reduced incubation times for both the microneedle and sham microneedles treatment sites such that the study will be head to head along incubation times.

6) Inclusion and Exclusion Criteria

Inclusion criteria:

1. 18 years of age and older
2. Subjects has actinic keratoses and qualifies for photodynamic therapy
3. Do not meet any of the exclusion criteria

Exclusion criteria:

1. Subjects who smoke
2. Subjects who have a photosensitizing condition such as lupus, porphyria, or similar condition
3. Subjects who have established allergy to topical ALA
4. Subjects who have had a documented nonmelanoma skin cancer on the face over the past 6 months.

7) Number of Subjects

A total of 30 subjects will be randomized into two treatment groups of 15 subjects each. This number was calculated based on a power analysis that revealed that 12 subjects were needed in each group to have a 95% power to detect a 25% difference in the clearance of actinic keratoses between the split face treatment groups with the α at 0.05. Each of the microneedle treatment groups (10 min and 20 min) will consist of split-face comparisons of control topical application of aminolevulinic (sham microneedles). We will recruit 30 subjects to allow for a 20% dropout rate.

8) Recruitment Methods

Potential subjects will be identified from the existing patient base at the UC Davis Department of Dermatology and will be recruited during their clinic visit. In addition, potential subjects that have been evaluated, informed, and referred for photodynamic therapy by a UC Davis dermatologist will be subsequently approached formally to participate in the study prior to their follow up in the photodynamic therapy clinic either by telephone (see script) or in person.

We will indicate that the patients will receive the same options for care regardless of whether they decide to participate or not participate in the study. They will be reassured that their clinical care will be provided to the same level whether they participate or not.

We request a waiver of HIPAA authorization for research for the purposes of screening and recruitment of subjects via electronic medical records.

The size of the potential study population is so large that it would not be practicable to obtain consent.

The screening procedures pose no more than minimal risk to participants (including risks to privacy). The only record linking the participants and the research data would be the consent document, and the main risk of research would be a breach of confidentiality [45 CFR 46. 117 (c)(1)].

All subjects enrolled in the study are assigned a unique subject ID. All PHI recorded will be linked the subject ID only. A key matching each subject with their IDs is kept separate from recorded PHI. All paper study documents are kept in locked cabinets in locked offices only accessible by authorized personnel. Electronic data is password-protected and kept on secure servers.

All PHI will be destroyed at the earliest opportunity consistent with the study.

PHI will not be inappropriately reused or disclosed to any other person or entity other than those approved in this study.

9) Compensation to the Subjects

The subjects will be paid a total of $30 dollars for their participation in the entire study. The subjects will receive $15 for the first day of participation and $15 for their 1 month follow-up visit. Subjects who drop out of the study or are withdrawn will be given a prorated sum.

10) Study Timelines

Subjects will be treated with PDT on day 1 of the study and will be seen for a follow-up visit one month post-treatment. The first study visit may last up to one hour. The subsequent visit will last about 30 minutes.

11) Study Endpoints

The primary endpoint will be the difference in the percentage of complete clearance of the actinic keratoses as an intraindividual comparison between the treatment groups using the paired t-test.

The secondary endpoint will be any pain associated with the microneedle pretreatment and with the application of the PDT.

12) Procedures Involved

After the subject has been consented, the Treatment Visit will commence. Subjects will be randomized into one of two groups. Group 1 will be the 10-minute topical ALA (Levulan® Kerasticks) incubation group. Group 2 will be the 20-minute topical ALA incubation group. All of the subjects will be randomized by binary randomization into each of the treatment groups and then undergo secondary binary randomization for application of the microneedle treatment (vs. sham microneedle treatment) to the right or left side of the entire face.

The subject's face will be cleansed followed by photographic imaging of the face. Next, a Transepidermal Water Loss Meter (Tewameter) will be used to measure the water evaporation gradient on the skin, known as the transepidermal water loss (TEWL). The Tewameter is a non-invasive and painless device that has been widely used for the study of skin barrier function (Figure 3). Each device has a flat-top electrode (approximate diameter of 1cm) that will come in contact with the skin surface during measurements. The device in held in place for a few seconds while it takes its measurement. This device does not deliver any energy to the skin and works by measuring the density gradient of the water evaporation from the skin indirectly by the two pairs of sensors (temperature and relative humidity) inside the hollow cylinder. This is an open chamber measurement. The open chamber measurement method is the only method to assess the transepidermal waterloss continuously without influencing its micro environment. A microprocessor analyzes the values and expresses the evaporation rate in $g/h/m^2$. The subjects will not experience discomfort during and after the measurements. The electrode tip will be cleaned with alcohol wipes before and after use with each subject. Measurements will be made on the right and left forehead and on the right and left cheeks.

Then the face will be subjected to microneedle pretreatment. The microneedle pretreatment will consist of rolling the microneedles or sham microneedles into the skin for several seconds on the sides of the face that have respectively been randomized to the microneedle or control treatment. Sham microneedles will consist of a flat roller without the presence of the microneedles. The microneedles are solid and are long enough to penetrate the stratum corneum and enter the epidermis. Microneedles that are 650 micrometers in length have been shown to induce minimal pain that was rated a 1 out of 10 on a visual analog pain scale (results of IRB# 282150). For this study, subjects will rate pain on a visual analog scale after pretreatment as well.

Then, TEWL measurements will be obtained with the Tewameter again from the right and left face (forehead and cheeks).

Next, topical ALA will be applied. Topical ALA is an FDA-approved product for use in photodynamic therapy. Photodynamic therapy will be done per the usual protocol used at the dermatology clinic.

Follow-up visits will be at one month post-treatment.

During the follow-up visit the patient will be asked about side effects or any adverse events. Imaging will be performed with a non-invasive photographic setup that will be provided by Brigh-Tex Bio-Photonics. To perform the imaging, the study subjects place their face on a chin rest and a series of images are taken of their face that involve blue light and white light (www.btbp.org) similar to how this was used in the previous study (IRB #282150).A sample image from their website is included as figure below:

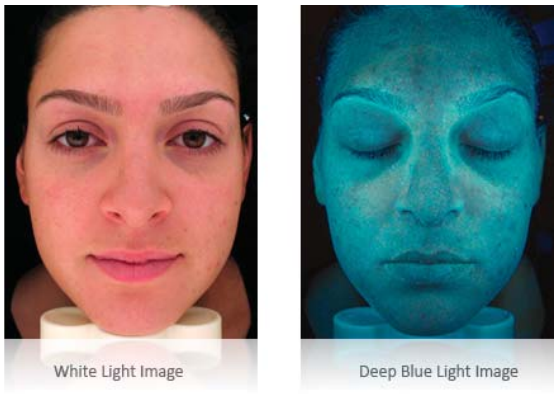

Figure 1: Example of Whole Face Imaging

13) Data and Specimen Banking

No tissue will be removed or collected as a part of this investigation.

14) Data Management and Confidentiality

Each of the subjects' signed consents will be filed in a locked cabinet within a locked room. All of the subjects will be entered into the data analysis sheets as codes and a separate password protected file will contain the key for these codes. All of the files will be saved on computers that will be within locked rooms.

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 pain or blisters. All of the treatments are done with topical aminolevulinic acid, which has already undergone safety testing and received FDA approval for the treatment of actinic keratoses.

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

However, the subject 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 and these 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.

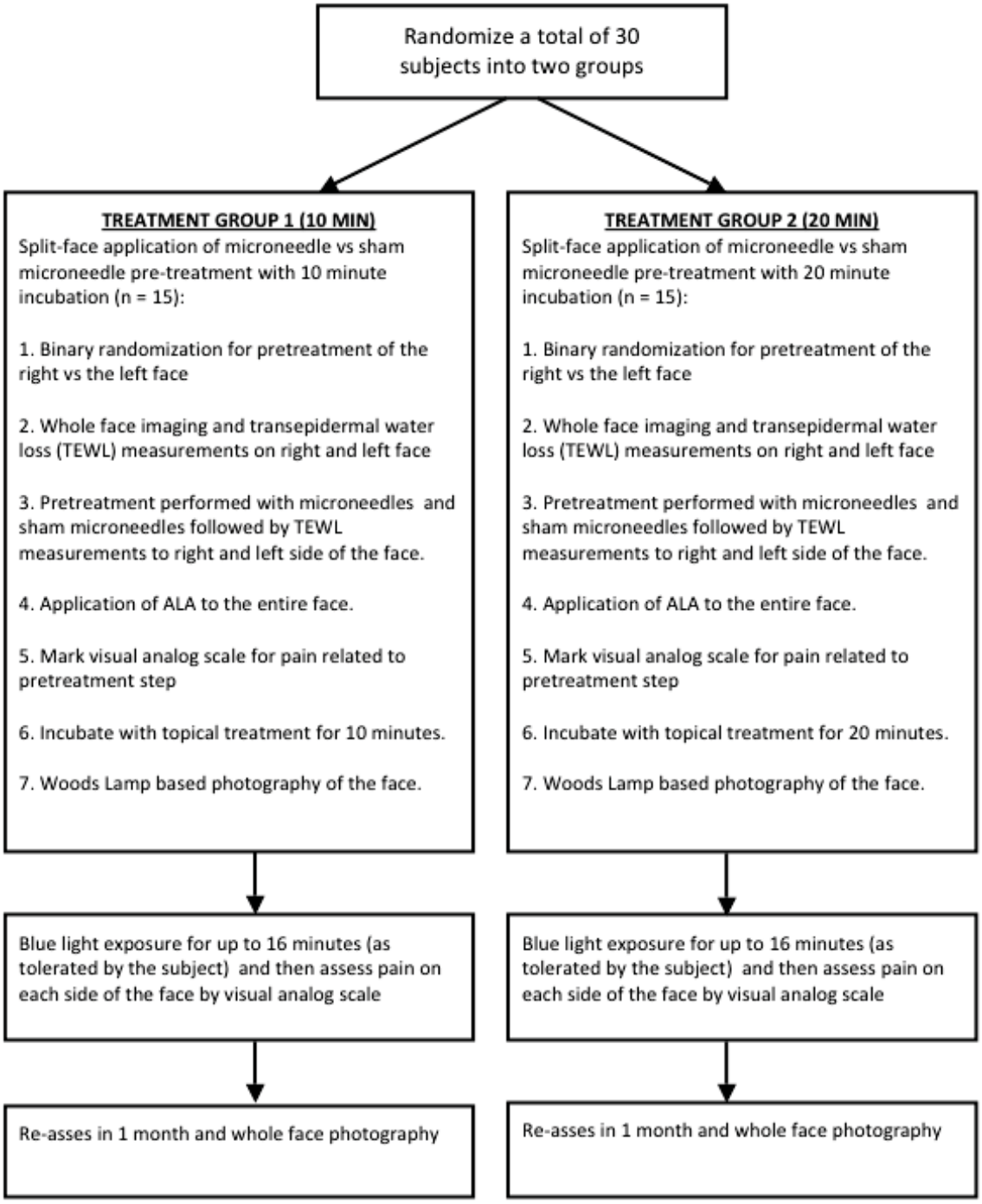

Figure 2: Protocol Flow Schematic

16) Withdrawal of Subjects

Subjects may be withdrawn by the investigators at any time at their discretion. If a subject chooses to withdraw from this trial at any point, he or she will be treated for actinic keratoses per current standard of care.

17) Risks to Subjects

There is a low chance for any physical, psychological, social or legal injury from the participation. The subject will be warned of the standard risks of treatment with topical aminolevulinic acid including erythema, pain, blisters, increased temporary photosensitivity for 36 hours after treatments, and risk for hyperpigmentation and hypopigmentation.

These reactions 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 aminolevulinic acid. This can be adequately managed with topical steroids and topical antibiotics for any secondary infection.

18) Potential Benefits to Subjects

Each subject involved has potential to derive benefit in this study as they may see regression of their actinic keratoses as part of the study result. Also, the outcome of the research may lead to the development of methods for painless anesthesia that may benefit the subject in the future.

19) Vulnerable Populations

No vulnerable populations will be recruited for this study.

20) Multi-Site Research

This is a single center study.

21) Setting

The study will be performed at the UC Davis Dermatology Clinic (3301 C Street, Sacramento, CA 95816).

22) Resources Available

This is an investigator-initiated study. Funding will be provided through departmental funds.

The Dermatology department and clinic at UC Davis are available for use and that will consist of sufficient personnel to conduct the study. The UC Davis Department of Dermatology has two dedicated clinical research exam rooms and waiting rooms. Therefore that is sufficient personnel and space to conduct the study.

The personnel involved in this study, their qualification and their roles are as follows:

Dermatology Physician at the UC Davis Department of Dermatology.
- Experience in AK clinical care and research
- Role: PI, Study design, all aspects of the study procedures including application of microneedles, topical ALA, and photodynamic therapy

Dermatology resident at UC Davis Department of Dermatology
- Dermatology resident with experience in AK clinical care and research
- Role: Study design, all aspects of the study procedures including application of microneedles, topical ALA, and photodynamic therapy

Junior Specialist at the UC Davis Department of Dermatology
- Role: IRB submissions, organization of subject visits, consent of study subjects, operation of Tewameter and photography instrumentation, collection of data

Clinical Research Coordinator at the UC Davis Department of Dermatology
- Role: IRB submissions, organization of subject visits, consent of study subjects, operation of Tewameter and photography instrumentation, collection of data

Clinical Research Associate at the UC Davis Department of Dermatology
- Role: IRB submissions, organization of subject visits, consent of study subjects, operation of Tewameter and photography instrumentation, collection of data

Volunteer Researcher and Visiting Medical Student Researcher
- Role: consent of study subjects, operation of Tewameter and photography instrumentation, operation of collection of data

23) Provisions to Protect the Privacy Interests of Subjects

All of the subject information will be coded to allow for efficient data analysis without using the actual subjects' names or medical record numbers. The data will be input into password protected files that are stored on computers that require password entry. The key for the subject codes will also be saved as a password protected file. Furthermore, the computers will be located within a locked room such that there are three levels of security (one for the password protected file, the second level for the password protected computer, and the third for the locked room). All paper consents will be maintained within a locked cabinet within a locked room.

We plan to eventually publish our data as a clinical report and so we will keep all of the consent files in a locked cabinet and all of the data in a locked room for at least five years. After the five years, we will destroy all of the consents and we will delete the file that contains the key to link the codes to specific subjects.

24) Compensation for Research-Related Injury

There is a low chance for any physical, psychological, social or legal injury from the participation. The subject will be warned of the standard risks of treatment with topical aminolevulinic acid including erythema, pain, blisters, increased temporary photosensitivity for 36 hours after treatments, and risk for hyperpigmentation and hypopigmentation.

These reactions 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 aminolevulinic acid. This can be adequately managed with topical steroids and topical antibiotics for any secondary infection.

25) Economic Burden to Subjects

The subject may incur costs associated with travel to and from the UC Davis Dermatology clinic. The blue light exposure portion of the therapy will not be covered through the research study and this portion may be billed to the subject's insurance. The subject will be made aware of this.

26) Consent Process

We will obtain written informed consent from all subjects. The consent process will take place at the UC Davis Dermatology Clinic. We will follow the Informed Consent Process for Research (HRP-090).

We will not be enrolling children and adults who are cognitively impaired or unable to consent.

27) Process to Document Consent in Writing

We will be following Written Documentation of Consent/Assent (HRP-091).

28) Drugs or Devices

Pre-sterilized microneedles will be used with each subject. The MTS Roller^{TM} MR2 (200 micrometer in length) is available from Clinical Resolution Laboratory, Inc. (product information attached). These microneedles are already approved for use in Europe and are in the process of seeking Class I exemption status from the FDA since they are shorter than existing class I exempt microneedles, such as the microneedles that were used in the previous IRB approved study and were 650 micrometers in length (IRB #282150). We would like to use the microneedles from Clinical Resolution Laboratory, Inc. as they are designed as a roller allowing for greater ease and efficiency with the pre-treatment for both the investigator and the subject. The previous microneedles were used as a stamp method and do not come in a roller design. Because the microneedle roller we would like to use for this study is more than three times shorter than the previously used microneedles, they are safer than the existing class I microneedle (3M Microchannel Skin System).

Furthermore, each microneedle roller from Clinical Resolution Laboratory, Inc. is prepacked in sterilized form. Because the handles are made of a plastic polymer base and the needles are made of stainless steel, the microneedle rollers will be sterilized with the liquid chemical sterilization protocol provided as a service to the UC Davis Dermatology Clinic after each use prior to use on the next subject. There are no hollow bores to any of the needles and all needles are solid. The FDA provides guidance in that devices that are minimal risk are at the discretion of the IRB and do not require an IDE. We believe that this is true especially since these microneedles are shorter than microneedles that are already classified as Class I exempt devices. We have attached the information sheets for both the MTS Roller^{TM} CR2 device that we would like to use in this study and the 3M Microchannel Skin System which was used in our previous study.

Transepidermal Water Loss Meter: Measurements will be performed with non-invasive devices that have been widely used for the study of skin barrier function (Figure 3). Each device has a flat-top electrode (approximate diameter of 1cm) that will come in contact with the skin surface during measurements. The subjects will not experience discomfort during and after the measurements. The electrode tip will be cleaned with alcohol wipes between subjects.

Figure 3: Tewameter TM 300 (Courage and Khazaka ®, Cologne, Germany). http://www.courage-khazaka.de/index.php/en/products/scientific/139-tewameter#tm1