TITLE PAGE

Protocol Number: C-16-EV09

Protocol Title: A Single-Center, 2-Arm Study of the Enlighten™ and Excel V™ Lasers for Lentigines on the Hands

Sponsor: Cutera, Inc.
3240 Bayshore Boulevard
Brisbane, CA 94005

[redacted]

Principal Investigator: Kelly Stankiewicz, MD FAAD

[redacted]

Site: DuPage Medical Group
2155 City Gate Lane
Suite 225
Naperville, IL 60563
(630) 547-5040

Version, Date: Version 1.0 Dated April 06, 2016

Statement of Compliance

The study will be conducted in accordance with the design and specific provisions of this IRB approved protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Protocol Signature Page – Principal Investigator

[redacted]

Study Title: ***A Single-Center 2-Arm Study of the Excel V™ and Enlighten™ Lasers for Lentigines on the Hands***

Protocol Version 1.0, Dated Apr 06, 2016

I have received and read the protocol dated **April 06, 2016** and agree to adhere to the requirements. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or informed consent form must first be approved by Cutera, Inc. and the Institutional Review Board (IRB), except those changes necessary to eliminate apparent immediate hazards to subjects. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding their role in the study. I will ensure that the study is conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements, and with the reviewing IRB requirements. I agree to commence this study only after documented IRB approval is obtained.

Principal Investigator

_____ _____

Signature Date

_____

Printed Name

Table of Contents

Protocol Summary

Title	A Single-Center 2-Arm Study of the Enlighten and Excel V Laser for Lentigines on the Hands
Objective	To evaluate the effectiveness and safety in a clinic setting of two laser systems for improvement of lentigines on the hands: 1. Cutera Enlighten [redacted] 2. Cutera Excel V [redacted]
Study Design	A single-center prospective, open-label, 2-armed uncontrolled study.
Enrollment	Up to 12 subjects in each arm
Primary Endpoint	• Reduction of the number of lentigines at 4 weeks [redacted] post-final treatment [redacted]
Secondary Endpoints	• Degree of improvement in [redacted] skin texture, and overall appearance of the hands at 4 weeks [redacted] post-final treatment. • Subject satisfaction at 4 weeks [redacted] post-final treatment. • Incidence and severity of adverse effects during the study period [redacted]
Subject Population	Female or male subjects, age 30 to 90 years, Fitzpatrick skin types I-III
Planned Schedule	First subject enrolled: April 2016 Last subject last visit: June 2016 (Enlighten cohort) October 2016 (Excel V cohort)

1 BACKGROUND INFORMATION

Non-invasive treatment options are in high demand by patients wanting to improve the appearance of their skin without surgical intervention. As a result, patients now have a variety of options for non-invasive skin treatments, from laser and light-based treatments to devices that utilize ultrasound and radiofrequency, however this was not always the case. Initial skin improvement procedures utilized ablative lasers, such as the carbon dioxide (CO_2) and erbium:yttrium-aluminum-garnet (Er:YAG), and resulted in substantial improvement in skin appearance, texture, rhytides and laxity[1-3]. However, since ablative treatments destroy the epidermal layer of the skin in order to penetrate and heat the deeper dermal layers, ample post-procedure recovery time is required and patients may experience side effects lasting for a few weeks. Furthermore, hypo- or hyperpigmentation, prolonged wound healing and even scarring can occur following ablative procedures [4-6]. Treatment methods with less risk of side effects and post-treatment down time are in high demand. As such, the choices are vast and varied, ranging from fractional non-ablative laser devices to those that use radiofrequency [7-15]. Fractional lasers inflict microscopic zones of thermal damage in the dermal layers of the skin without destruction of the epidermis, thereby reducing recovery time significantly as compared to ablative procedures[16]. Treatment with non-fractional, non-ablative laser devices requires little to no post-procedure recovery time. Nonablative lasers of various wavelengths are effective for improvement of skin appearance based on the principle of selective photothermolysis, whereby laser light is absorbed by hemoglobin in blood vessels and melanin in pigment-producing skin cells [17, 18]. Absorption of laser light by these molecular chromophores results in the production of heat, leading to destruction of unwanted blood vessels and pigment cells. Heat production within the dermis by the laser light also results in immediate collagen contraction and heat-induced wound healing that, over time, causes a cascade of cellular events leading to new collagen production and improved skin appearance [8, 10, 19-23].

[redacted]

[redacted]

[redacted]

2 STUDY PURPOSE AND OBJECTIVES

The purpose of this study is to evaluate the effectiveness and safety in a clinic setting of two laser systems for the treatment of lentigines (liver spots, age spots, or dark sun spots) on the hands:

- Cutera Enlighten dual wavelength 532 nm [redacted] and/or 1064 nm Nd: YAG picosecond pulse duration laser
- Cutera Excel V dual wavelength 532nm [redacted] long pulsed laser and/or 1064 nm Nd: YAG

The objectives of this study are to:

1) Evaluate the reduction of the number of lentigines on the hands, the improvement of [redacted] skin texture, and overall appearance, and customer satisfaction 4 weeks following treatment with one of the two study lasers.
2) Evaluate the rate of adverse events experienced by the study subjects.

3 STUDY DESIGN

This is a single-center prospective, 2-armed, open-label, uncontrolled study in up to 24 male or female subjects per arm, age 30 to 90 years who desire non-ablative laser treatment for treatment of lentigines of the hand, and additionally to evaluate the improvement of skin texture, and overall appearance of the skin.

Subjects will be assigned to a treatment arm using a random number generator.

[redacted]

Subjects will be instructed to maintain the same skin care regimen as before enrollment in the study, use daily sunscreen on the hands of SPF 50 or higher as approved by the study doctor and practice strict, diligent prevention of sun exposure.

3.1 Study Endpoints

3.1.1 Primary Endpoint

- Percent reduction in the number of hand lentigines at 4 weeks [redacted] post-final treatment as assessed by [redacted] physician.

3.1.2 Secondary Endpoints

- Degree of improvement in skin texture of the hands at 4 weeks [redacted] post-final treatment as assessed by a [redacted] physician using the Physician's Global Assessment scale.
- Degree of improvement in overall appearance of the hands at 4 weeks [redacted] post-final treatment as assessed by a [redacted] physician using the Physician's Global Assessment scale.
- Subject satisfaction at 4 weeks [redacted] post-final treatment.
- Incidence and severity of adverse device effects during the study period

3.2 Study Duration

[redacted]

[redacted].

The screening and first laser treatment may be combined into one visit provided that the informed consent process has been completed (see Section 12.2) and the subject has signed the IRB-approved Informed Consent Form prior to the commencement of any study-related procedures and device treatments.

3.3 Study Assessments

3.3.1 Percent Reduction in the Number of Lentigines

[redacted] physician at the study site will be asked to perform an assessment of baseline and 4 weeks post-treatment subject photographs. [redacted]

[redacted]

[redacted]

3.3.2 Physician's Global Assessment Scale

At 4 weeks post-final treatment, the [redacted] investigator will be asked to rate the degree of improvement observed in the skin with regards to skin texture, and overall appearance. Each of the 2 improvement categories will be assesses using the Physician's Global Assessment Scale:

4 = Very Significant Improvement [redacted]
3 = Significant Improvement [redacted]
2 = Moderate Improvement [redacted]

1 = Mild Improvement [redacted]
0 = No Change [redacted]

3.3.3 Subject Assessments

3.3.4 *At 4 weeks post-final treatment, subjects will be asked to complete a questionnaire to rate their level of satisfaction with the laser treatment outcome and the overall laser treatment procedure* [redacted]

[redacted]

[redacted]

3.4 Photographs

Standardized digital photographs will be taken of each subject's hand(s) at baseline, prior to all laser treatments, immediately after each laser treatment, and at the end of study visit. [redacted]

3.5 Study Discontinuation

The sponsor (Cutera, Inc.) has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following: incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects; subject enrollment is unsatisfactory; number of protocol deviations is unacceptable; data recording is inaccurate or incomplete; or questionable study site compliance with ICH-E6, Good Clinical Practice.

3.6 Investigator Selection

The investigator will be invited to participate in the study based on his/her medical specialty, experience conducting clinical research studies and experience in the use of light-based devices for aesthetic indications. Access to potential study subjects and the investigator's sincere interest in this study along with expressed willingness to cooperate with the study process and requirements will also be considered.

4 STUDY POPULATION

4.1 Study Subject Recruitment and Selection including procedures for randomization

[redacted] male or female subjects who desire laser treatment for lentigines on the hand(s) will be studied for each of the laser treatments. Subjects will be recruited to participate from the local population. Subjects may also be recruited from the investigator's existing patient database or from patients who present themselves to the study site requesting treatment. Only subjects who meet all eligibility criteria and who provide written informed

consent will be enrolled into the study. After verification of eligibility, there will be randomization into one laser group.

4.2 Subject Selection

Each subject will be evaluated by the investigator to assess his/her suitability for entry into the study according to the following inclusion and exclusion criteria.

4.2.1 Inclusion Criteria

To be included in the study, subjects must meet all of the following Inclusion Criteria:

1. Female or Male, 30-90 years of age (inclusive).
2. Fitzpatrick Skin Type I – III.
3. Desires non-invasive and non-ablative treatment of lentigines on the hand(s).
4. Have 4 or more lentigines on the hand(s).
5. Subject must be able to read, understand and sign the Informed Consent Form.
6. Must be willing and able to adhere to the treatment and follow-up schedule and post-treatment care instructions.
7. Willing to have very limited sun exposure and use an approved sunscreen of SPF 50 or higher on the treatment area every day for the duration of the study, including the follow-up period.
8. Willing to have digital photographs taken of the treatment area and agree to use of photographs for presentation, educational or marketing purposes.
9. Agree to not undergo any other procedure(s) for treatment of lentigines during the study, including but not limited to chemical peel, laser and light based device treatment, and home-use device treatment.
10. Agree to not undergo any injection of botulinum toxin, collagen, hyaluronic acid filler or other dermal filler to the treatment area during the study.

4.2.2 Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following Exclusion Criteria:

1. Participation in a clinical trial of another device or drug in the target area within 6 months prior to enrollment or during the study.
2. Any type of prior cosmetic treatment to the target area within 6 months of study participation, such as laser or light-based procedures or surgery.
3. Systemic use of retinoid, such as isotretinoin, within 6 months of study participation.
4. Use of topical medications on the hands, such as antibiotics, benzoyl peroxide, retinoids (isotretinoin), corticosteroids, hydroquinone, or products containing dihydroxyacetone or alpha-hydroxy with concentration > 8%, within 1 month of participation.
5. History of malignant tumors in the target area.
6. Skin abnormalities in the target area, e.g., cuts, scrapes, wounds, scars, large moles.
7. Pregnant.
8. Having an infection, dermatitis, or a rash in the treatment area.

9. History of keloid scarring, hypertrophic scarring or of abnormal wound healing.
10. Any use of medication that is known to increase sensitivity to light according to investigator's discretion.
11. History of radiation to the treatment area or undergoing systemic chemotherapy for the treatment of cancer.
12. History of pigmentary disorders, particularly tendency for hyper- or hypo-pigmentation.
13. Anytime in life, having have used gold therapy (gold salts) for disorders such as rheumatologic disease or lupus.
14. Excessively tanned in areas to be treated or unable/unlikely to refrain from tanning during the study.
15. In the opinion of the investigator, any physical or mental condition which might make it unsafe for the subject to participate in this study or which requires systematic therapy that could interfere with this research study.

4.3 Subject Discontinuation Criteria

Participation in this study is completely voluntary and a subject can choose to withdraw from the study at any time. In addition, a subject can be discontinued for any of the following reasons: the principal investigator decides that continuing in the study would not be in the subject's best interest, a subject is noncompliant with the protocol, a subject has a serious reaction to the treatment, or the study is stopped by the study sponsor. In addition, subjects will be discontinued from the study if s/he develops any of the exclusion criteria.

5 STUDY PROCEDURES

[redacted]

5.1 Screening Visit

The following procedures will be performed prior to the first laser treatment for both types of laser treatments:

1. Informed consent.
2. Investigator assessment of treatment area for study eligibility.
3. Review of medical history.
4. Subject will be randomly assigned to either the Enlighten cohort or the Excel V cohort.
5. Assessment of concomitant medications.
6. Pre-treatment digital photographs of the subject's treatment area will be taken.
7. Provide and explain the before / after treatment instructions to the subject.

Once it has been determined that the subject meets all criteria to be included in the study and informed consent has been obtained, the subject will be enrolled in the study.

5.2 Laser Treatment Visit(s)

[redacted]

[redacted]

Table 1 [redacted]

[redacted]		

[redacted]

[redacted]		

9. [redacted]

[redacted]

[redacted]

5.3 Final Follow-Up Visit

The follow-up visit will occur at approximately 4 weeks [redacted].

The following procedures will be performed at the follow-up visit:

1. Assessment of concomitant medications: Assess and record any additions, changes and/or deletions in prescription and nonprescription concomitant medications since the previous study visit.
2. Assess for any new procedure related adverse effects or changes to previously recorded adverse effects.
3. Digital photographs of the treated area(s) will be taken.
4. [redacted] Physician's Global Assessment of Improvement
5. Subject will be asked to complete and return the Subject Questionnaire.

6 ADVERSE EVENTS

[redacted]

[redacted]

[redacted]

[redacted]

6.1 Reporting of Adverse Events

If any serious adverse event (SAE), anticipated or unanticipated, occurs at any time during or after the use of the device within the study period, the investigator must report it to Cutera within 24 hours using the Cutera Serious Adverse Event Report Form.

If the SAE is unanticipated in nature, severity or degree of incidence, Cutera will notify all events that fulfill the following criteria to the Institutional Review Board (IRB) within ten (10) working days using the IRB Unanticipated Problem/Event Report Form:

- **Serious** (i.e., death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect) [21 CFR 312.32(a)], **AND**
- **Unexpected** (i.e., not described in the Informed Consent Document), **AND**
- **Related** to the study design, procedures, or device (possibly, probably or definitely related, or unknown).

OR

- Any event that, in the opinion of the investigator, may adversely affect the rights, welfare or safety of subjects in the study.

6.2 Follow-up of Subjects after AEs

All reported AEs should be followed until resolution or until the subject's participation in the study ends. All AEs assessed by the investigator as probably related or possibly related to the study device should be followed until they resolve or until the investigator assesses them as "chronic" or "stable". Resolutions of such events are to be documented on the appropriate CRF pages. All AEs that result in permanent discontinuation from this clinical trial, whether serious or not, should also be reported on the Subject Non-Completion of Study Form.

7 POTENTIAL RISKS / BENEFITS

7.1 Potential Risks

[redacted]

7.2 Potential Benefits

The subjects may or may not benefit from the treatment. There is no guarantee of success.

7.3 Risk Management

The investigator participating in this study was chosen based on extensive and safe experience with the use of lasers in dermatology applications. This is the most critical element in managing subject risk. In addition, study investigators will be trained on the use of both the Cutera Enlighten and Excel V laser systems by a representative of Cutera.

8 TRAINING AND MONITORING

[redacted]

9 DATA ANALYSIS PLAN

9.1 Sample Size Calculation

The planned sample size of up to 24 subjects for each laser cohort was determined based on clinical judgment to provide sufficient information to evaluate reduction in the number of lentigines in the hands.

9.2 Data Analysis

Descriptive statistics and 95% confidence intervals and will be calculated for percent reduction in the number of hand lentigines, at 4 weeks [redacted]

Descriptive statistics and 95% confidence intervals and will be calculated separately for improvement in skin texture, and overall appearance of the hands, based on the Physician's Global Improvement Assessment evaluation, and also for the Subject Satisfaction Scale evaluations.

Safety measures include the incidence of treatment-related AEs, the proportion of subjects who prematurely terminate from the study due to a treatment-related AE [redacted]

10 INFORMED CONSENT

[redacted]

[redacted]

[redacted]

[redacted]

11 DATA COLLECTION AND RECORD KEEPING

[redacted]

[redacted]

12 SUBJECT CONFIDENTIALITY

This study preserves the confidentiality of all subjects under the HIPAA Privacy Rule. The following safeguards will be in place to protect the privacy of the individuals who are the subjects of the health information to be used in the research and the confidentiality of that information:

[redacted]

[redacted]

[redacted]

13 PUBLICATION POLICY

[redacted]

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. It is the responsibility of the sponsor to register this trial in ClinicalTrials.gov. Any clinical trial starting enrollment after September 27, 2007 must be registered either on or before the onset of patient enrollment.

REFERENCES