

TITLE PAGE

Protocol Number: C-16-EV10

Protocol Title: A Single-Center Open-Label Study of 1064 nm Nd:YAG for Nonablative Skin Rejuvenation

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Version, Date: Version 1.0 Dated February 22, 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).

NOTE: The confidential information in the following document is provided to you as an Investigator, potential Investigator, or consultant for review by you, your staff, and applicable Institutional Review Board. By accepting this document, you agree that the information contained herein will not be disclosed to others, without written authorization from Cutera, Inc. except to the extent necessary to obtain informed consent from those persons to whom the device will be administered.

Protocol Signature Page – Principal Investigator

PROTOCOL C-16-EV10

Study Title: *A Single-Center Open-Label Study of 1064 nm [REDACTED] Laser for Nonablative Skin Rejuvenation*

Protocol Version 1.0, Dated February 22, 2016

I have received and read the protocol dated **February 22, 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, 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 Institutional Review Board (IRB) requirements. I agree to commence this study only after documented IRB approval is obtained.

Principal
Investigator

Signature

Date

Printed Name

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Protocol Summary

Title	A Single-Center Open-Label Study of 1064 nm [REDACTED] Laser for Nonablative Skin Rejuvenation
Objective	To evaluate the efficacy and safety of the Cutera excel V Laser Genesis/ 1064 nm [REDACTED] laser for skin rejuvenation.
Study Design	A single-center prospective, open-label uncontrolled study.
Enrollment	15 subjects
Primary Endpoint	<ul style="list-style-type: none">• Degree of improvement at 12 weeks post-final treatment as assessed by independent blinded reviewers (Physician's Global Assessment).
Secondary Endpoints	<ul style="list-style-type: none">• [REDACTED][REDACTED][REDACTED][REDACTED][REDACTED][REDACTED]
Subject Population	Female or male subjects, age 35 to 55 years, Fitzpatrick skin types I-IV
Planned Schedule	First subject enrolled: March 15, 2016 Last subject last visit: January 15, 2017

1 PURPOSE

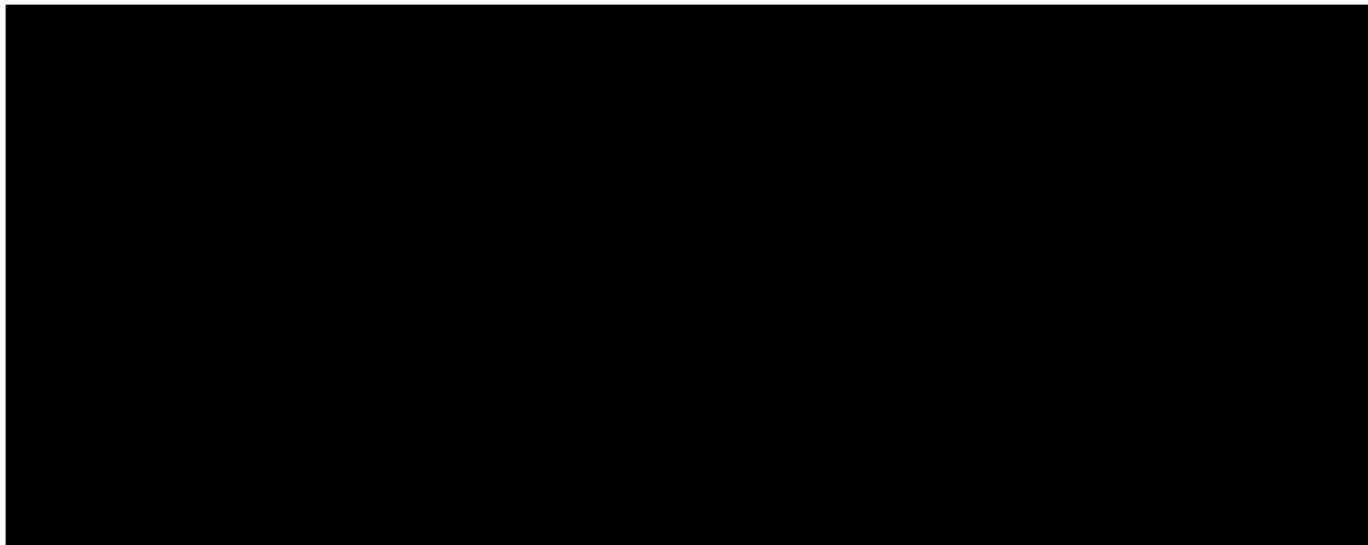
The purpose of this investigation is to evaluate the safety and efficacy of the Cutera excel V Laser Genesis procedure utilizing the 1064nm [REDACTED] laser for skin rejuvenation, specifically improvement of overall skin quality including rhytides, lentigines, erythema, telangiectasia and skin texture.

2 BACKGROUND INFORMATION

2.1 Photo-Rejuvenation

Non-invasive treatment options are in high demand by patients wanting to improve their appearance without surgical intervention. As a result, patients now have a variety of options for non-invasive skin rejuvenation, from laser and light-based treatments to devices that utilize ultrasound and radiofrequency, however this was not always the case. Initial skin rejuvenation procedures utilized ablative lasers, such as the carbon dioxide (CO₂) 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 skin rejuvenation 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].

2.2 Study Device



[REDACTED]		
[REDACTED]	[REDACTED]	[REDACTED]

3 STUDY OBJECTIVES

The objectives of this study are:

- 1) To evaluate safety of the Cutera excel V Laser Genesis procedure utilizing 1064 nm [REDACTED] laser for skin rejuvenation treatment;
- 2) To evaluate efficacy of the Cutera excel V laser for skin rejuvenation, in particular, improvement of rhytides, lentigines, erythema, telangiectasia and skin texture.

4 STUDY DESIGN

This is a single-center prospective, open-label uncontrolled study in 15 male or female subjects, age 35 to 55 years who desire non-ablative laser treatment for facial photo-rejuvenation, specifically improvement of rhytides, lentigines, erythema, telangiectasia and skin texture. Subjects will receive [REDACTED] laser treatments [REDACTED] and complete [REDACTED] follow-up visits; [REDACTED] at 12 weeks post-final treatment.

[REDACTED]

4.1 Study Endpoints

4.1.1 Efficacy endpoints

4.1.1.1 Primary Efficacy Endpoint

- Degree of improvement at 12 weeks post-final treatment as assessed by independent blinded reviewers (Physician's Global Assessment).

4.1.1.2 [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

4.1.2 Safety Endpoint

- Incidence and severity of adverse device effects during the study period, including subject pain level during laser treatment.

4.2 Study Duration

Subjects enrolled will be asked to participate for [REDACTED] : one screening visit, [REDACTED] laser treatment visits, [REDACTED] | [REDACTED] follow-up visits; [REDACTED] 12 weeks post-final treatment.

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.

4.3 Study Effectiveness Assessments

4.3.1 Blinded Assessments

4.3.1.1 Blinded Reviewer's Global Assessment of Improvement

Independent, blinded physician reviewers will be asked to perform an assessment of subject photographs at baseline, [REDACTED] and 12 weeks post-final treatment. The arrangement of each subject's pair of baseline and

post-final treatment photographs will be randomized such that the baseline photograph will be randomly assigned to the left or right side of the page. The order of subject photograph pairs will also be randomized. The reviewers will be blinded to the treatment parameters used, the subject data, the temporal order of photographs (before and after), and follow-up time point.

The reviewers will be asked to first determine the temporal order of each photograph pair, then rate the degree of improvement observed in the post-treatment photograph using the Physician's Global Assessment of Improvement Scale:

4 = Very Significant Improvement [REDACTED]

3 = Significant Improvement [REDACTED]

2 = Moderate Improvement [REDACTED]

1 = Mild Improvement [REDACTED]

0 = No Change [REDACTED]

4.3.1.2 [REDACTED]

4.3.2 [REDACTED]

[REDACTED] [REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

4.3.3.2 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.4 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.5 Study Safety Assessments

4.5.1 Incidence and Severity of Adverse Events:

Following the first laser treatment, adverse device effects (ADEs) will be assessed post-treatment and at each subsequent subject visit using the following scale:

- 1= mild: requires minimal or no treatment and does not interfere with the Subject's daily activities.
- 2= moderate: may cause some interference with functioning.
- 3= severe: interrupts Subject's usual daily activity and may require treatment.

4.5.2 Treatment-related Discomfort

Subjects will be asked to rate the average amount of discomfort experienced during laser treatment using the Pain Rating Scale found in Appendix 2.

4.6 Photographs

Standardized digital photographs will be taken of each subject's face at baseline, prior to all laser treatments and at both follow-up visits. Any jewelry will be removed from the area being photographed. Hair will be pulled away from the face with a headband and subject will have recently cleansed skin. Facial photographs will be obtained from 3 angles: with the subject facing forward, 45° to the right and 45° to the left. Photographs will be taken in the same windowless room equipped with adequate lighting. The room lighting, camera positioning and subject positioning should be consistent for all study visit photographs. Digital camera settings should remain the same for all photographs and the highest resolution settings should be utilized.

4.7 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.

4.8 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.

5 STUDY POPULATION

5.1 Study Subject Recruitment and Selection

Twenty male or female subjects, ages 35 to 55, with Fitzpatrick Skin Type I-IV (see Appendix 4 for skin type classification) who desire laser treatment for facial wrinkles or photo-rejuvenation will be studied. 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.

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.

5.1.1 Inclusion Criteria

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

1.	Female or Male, 35 to 55 years of age (inclusive).
2.	Fitzpatrick Skin Type I – IV (Appendix 4).
3.	Desires non-invasive and non-ablative treatment of skin-aging or photo-rejuvenation of the skin.
4.	Have signs of moderate skin aging, including presence of mild to moderate rhytides around eyes and upper lip, multiple lentigines, diffuse erythema or telangiectasia, and a score between 4 and 7 (inclusive) on the Fitzpatrick Wrinkle Classification Scale (Appendix 3).
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 30 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 skin rejuvenation 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 during the study.
11.	Post-menopausal or surgically sterilized, or using a medically acceptable form of birth control at least 3 months prior to enrollment and during the entire course of the study, and no plans to become pregnant or to father a child for the duration of the study.

5.1.2 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 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.	Prior injection to the face of botulinum toxin, collagen, hyaluronic acid filler or other dermal filler within 6 months of study participation, as applicable.
4.	Systemic use of retinoid, such as isotretinoin, or corticosteroid, as applicable, within 6 months of study participation.
5.	Use of topical medications on the face, such as antibiotics, benzoyl peroxide, retinoids (isotretinoin), corticosteroids, hydroquinone, or products containing dihydroxyacetone or alpha-hydroxy with concentration > 8%, within 1 month of participation.
6.	History of malignant tumors in the target area.
7.	Skin abnormalities in the target area, e.g., cuts, scrapes, wounds, scars, large moles.
8.	Pregnant and/or breastfeeding.
9.	Having an infection, dermatitis or a rash in the treatment area.
10.	Significant concurrent illness, such as diabetes mellitus or cardiovascular disease, e.g., uncontrolled hypertension.
11.	Suffering from coagulation disorders, or taking prescription anticoagulation medication which might make study participation unsafe according to Investigator's discretion.
12.	History of keloid scarring, hypertrophic scarring or of abnormal wound healing.
13.	History of immunosuppression/immune deficiency disorders or currently using immunosuppressive medications.
14.	History of vitiligo, eczema, or psoriasis.
15.	History of connective tissue disease, such as systemic lupus erythematosus or scleroderma.
16.	History of seizure disorders due to light.
17.	Any use of medication that is known to increase sensitivity to light according to Investigator's discretion.
18.	History of disease stimulated by heat, such as recurrent herpes simplex and/or herpes zoster (shingles) in the treatment area, unless treatment is conducted following a prophylactic regimen

19.	History of radiation to the treatment area or undergoing systemic chemotherapy for the treatment of cancer.
20.	History of pigmentary disorders, particularly tendency for hyper- or hypo-pigmentation.
21.	Anytime in life, having have used gold therapy (gold salts) for disorders such as rheumatologic disease or lupus.
22.	Excessively tanned in areas to be treated or unable/unlikely to refrain from tanning during the study.
23.	Current smoker or history of smoking within 6 months of study participation.
24.	As per the Investigator's discretion, any physical or mental condition which might make it unsafe for the subject to participate in this study.

5.2 Subject Numbering

If a subject meets the study eligibility criteria and is willing to participate, the subject will be assigned a study subject identification number. This number is comprised of a sequential subject number and the subject initials (first and last names).

5.3 Subject Discontinuation Criteria

If possible, every subject should remain in the study until completion of the required follow-up period. However, participation in this study is completely voluntary and a subject can choose to withdraw from the study at any time. Decision to withdraw will not affect or prejudice the subject's continued medical care in any way. In those instances, the investigator will attempt to obtain a final clinical assessment and an adverse device effect evaluation for the subject prior to this withdrawal. A subject will be considered lost to follow-up only after three unsuccessful, documented attempts to contact the subject have been made.

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, a subject develops any of the exclusion criteria during the study period or the study is stopped by the study sponsor.

6 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

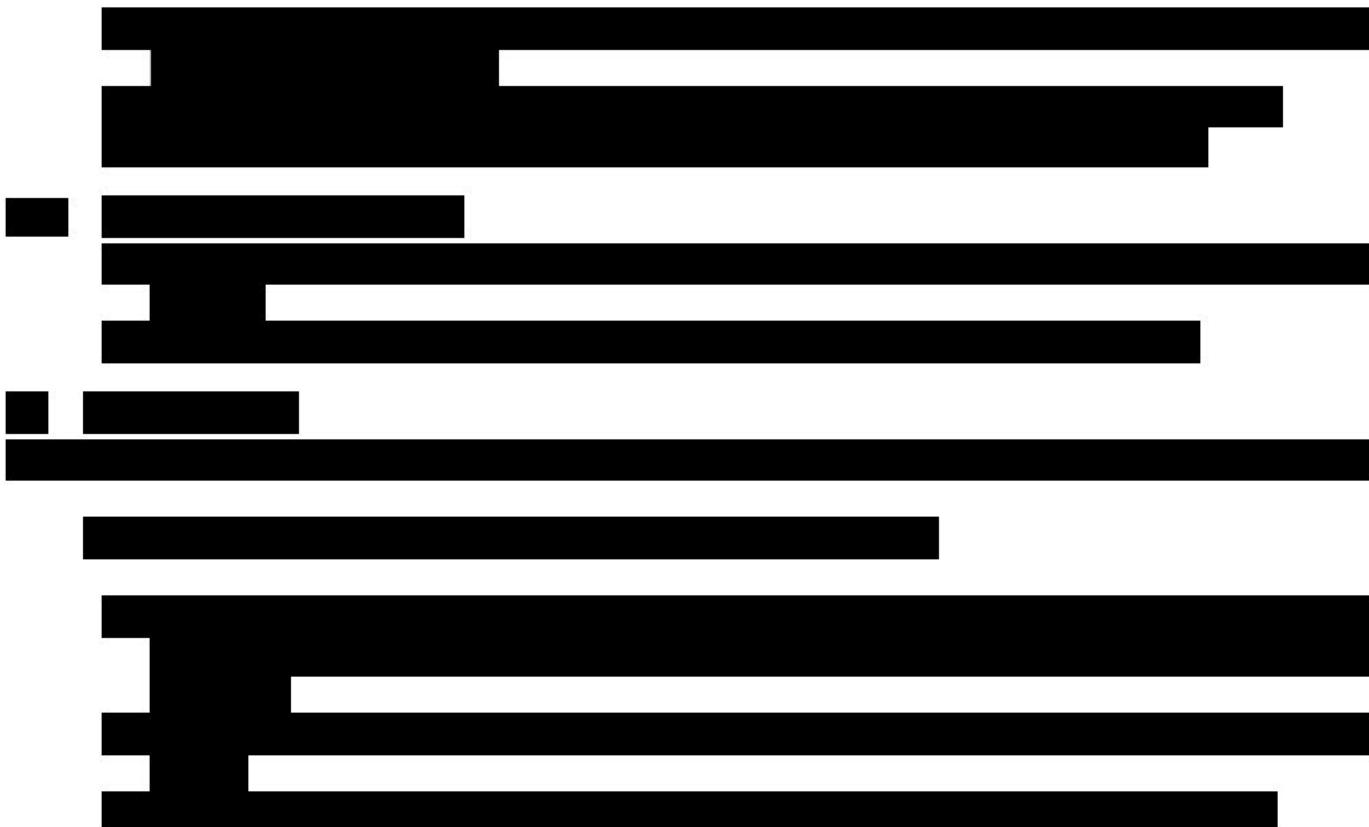
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6.2





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7 ADVERSE DEVICE EFFECTS

7.1 Definitions

[REDACTED]

[REDACTED]

7.2 Recording ADEs and SADEs

All ADEs/SADEs will be: (1) evaluated and must be recorded in the subject's medical chart and in the study case report forms (CRFs); (2) monitored and tracked from the time of the first treatment with the Cutera ExcelV laser system.

At each contact with the subject, the investigator must seek information on ADEs/SADEs by specific questioning and, as appropriate, by examination. ADEs/SADEs may be observed by the investigator and/or clinical research staff, elicited from the subject and/or family member or volunteered by the subject. All observed and volunteered adverse signs and symptoms, anticipated or unanticipated, regardless of severity or frequency, will be recorded in the case histories (medical chart and CRFs). Included in the description should be the nature of the sign or symptom, the date of onset, date of resolution (duration), the severity, anticipated or unanticipated, the relationship to study treatment or other therapy, the action taken (if any), and the outcome.

All SADEs, anticipated or unanticipated, must be reported to Cutera immediately but not later than 5 working days. The SADE must be recorded in: (1) the AE CRF and (2) a written report must be submitted to Cutera within five (5) working days after the investigator first learns of the event and is to include a full description of the event and sequelae, in the format detailed by the Cutera Serious Adverse Device Effect Form.

7.3 Follow-up of Subjects after ADEs and SADEs:

All reported ADEs/SADEs should be followed until resolution or until the subject's participation in the study ends. Resolutions of ADEs/SADEs are to be documented on the appropriate CRFs. All ADEs 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.

8 POTENTIAL RISKS / BENEFITS

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

For more information, contact the Office of the Vice President for Research and the Office of the Vice President for Student Affairs.

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8.2 Potential Benefits

The subjects may or may not benefit from the treatment with the study device. Potential benefit of laser treatment for photo-rejuvenation is improved appearance of skin, diminished appearance of rhytides, improvement in telangiectasia and lightening of lentigines. There is no guarantee of success.

9 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 the Cutera excelV laser system by a representative of Cutera.

10 DATA ANALYSIS PLAN

10.1 Sample Size

Up to [REDACTED] subjects will be enrolled in this safety and efficacy study.

10.2 Demographics and Subject Characteristics at Baseline

Subject demographics, medical history, concomitant medications will be tabulated and summarized descriptively.

10.3 Statistical Analysis Methods

10.3.1 Analysis Sets

The efficacy analysis set will include all subjects who received at least one laser treatment session and complete a follow-up visit. The safety analysis set will include all subjects enrolled in the study who had at least one laser treatment session.

Missing data will not be imputed for efficacy or safety endpoints.

10.3.2 Analysis of Primary Endpoint

Formal statistical analysis is not planned for this study. The primary efficacy endpoint data, blinded reviewer degree of improvement at 12 weeks post-final treatment, will be summarized descriptively.



10.3.4 Safety Analyses

Safety variables will be analyzed descriptively.

The safety variables for this study are:

1. Subject discomfort (pain) during treatment (to be descriptively displayed).

2. Incidence and severity of adverse effects during study duration (to be displayed descriptively as counts and frequency distributions).

Enrolled subjects who received at least one treatment will be included in the safety analyses. Device-related and procedure-related adverse effects (AEs) and subjects who prematurely terminate from the study due to an adverse device effect, including the treatment-related pain ratings, as reported on case report forms will be tabulated and analyzed. For a given AE term, counting will be done by subject, not by event, i.e. for a subject reporting the same AE more than once, the event will be counted only once, at the most severe and most-related occurrence. The number and percentage of subjects experiencing each AE Term will be descriptively summarized. Statistical hypothesis testing will not be performed for safety data.

11 [REDACTED]

[REDACTED]

[REDACTED]

12 STUDY MANAGEMENT AND ADMINISTRATIVE PROCEDURES

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

12.3 Protocol Compliance

The principal investigator must comply with all terms of the protocol.

12.3.1 Protocol Amendments

Neither the principal investigator nor the sponsor will modify or alter this protocol without first obtaining the concurrence of the other party (with the exception of amendments which involves mitigating a medical emergency or immediate health risk to the subject). The party initiating an amendment must confirm it clearly in writing and it must be signed and dated by the sponsor and the principal investigator. IRB approval must be obtained before implementation of an amendment.

12.3.2 Protocol Deviations

All protocol deviations must be clearly described on the case report form (i.e., Cutera Protocol Deviation Form). Deviations from the protocol may include but are not limited to subject's failure to attend scheduled visit during a visit window, use of out of range treatment parameters and incomplete or incorrect study procedures. Any medical emergency or immediate health risk to the subject which results in a protocol deviation and must be reported to the sponsor within 5 working days

Significant protocol deviations must be reported to IRB according to their policies.

12.4 Study Personnel

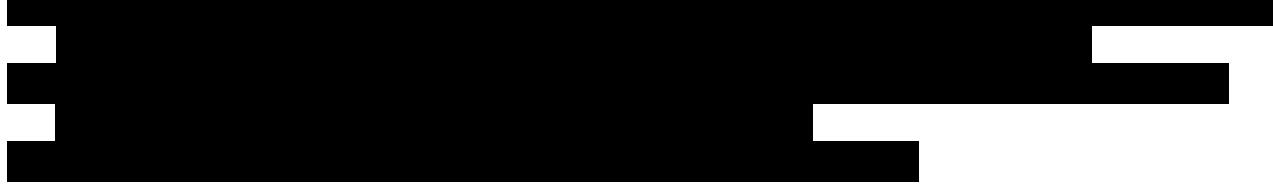
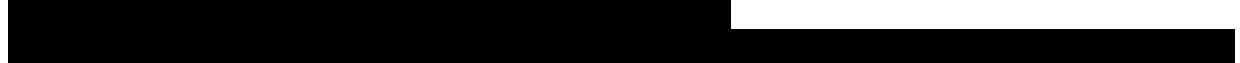
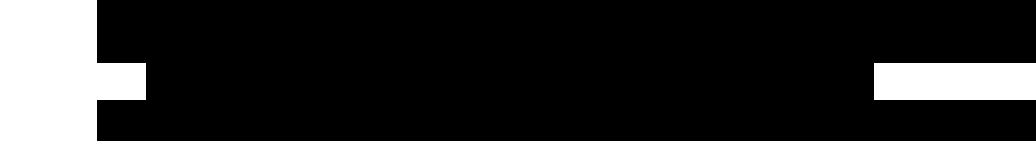
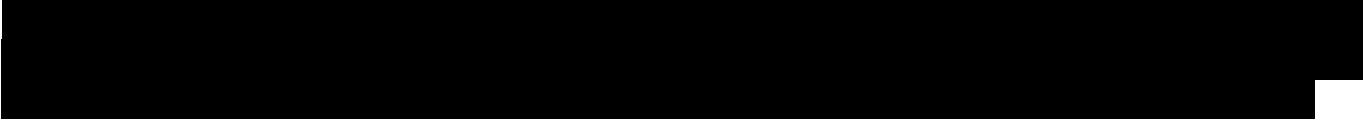
Prior to the start of the study, the investigator must supply the sponsor with a list of the names and curricula vitae that describe the professional backgrounds of the clinically responsible study investigators (principal, sub-investigators), research nurses, and other possible participants (e.g. medical doctor, nurse, etc.).

12.5 Disclosure of Financial Interest

Each investigator [principal and sub-investigator(s)] is required to disclose sufficient accurate financial information to the sponsor, to allow sponsor to submit complete and accurate certification or disclosure statements.

12.6 Data Collection, Record Keeping and Storage

The principal investigator is responsible for assuring that all study records including case report forms



13 SUBJECT CONFIDENTIALITY

This study preserves the confidentiality of all subjects under the Health Insurance Portability and Accountability Act of 1996 (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]

[REDACTED]

14 PUBLICATION POLICY

The investigator shall have the right to publish the results of the study. Unless mutually agreed upon in writing, prior to submission for publication of any manuscript, poster, presentation, abstract or other written or oral material describing the results of the study, the investigator shall allow sponsor to review manuscript, poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any patentable information is disclosed. At the sponsor's request, the investigator shall withhold any publication or presentation to permit sponsor to seek patent protection and to remove any confidential information from all publications.

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.

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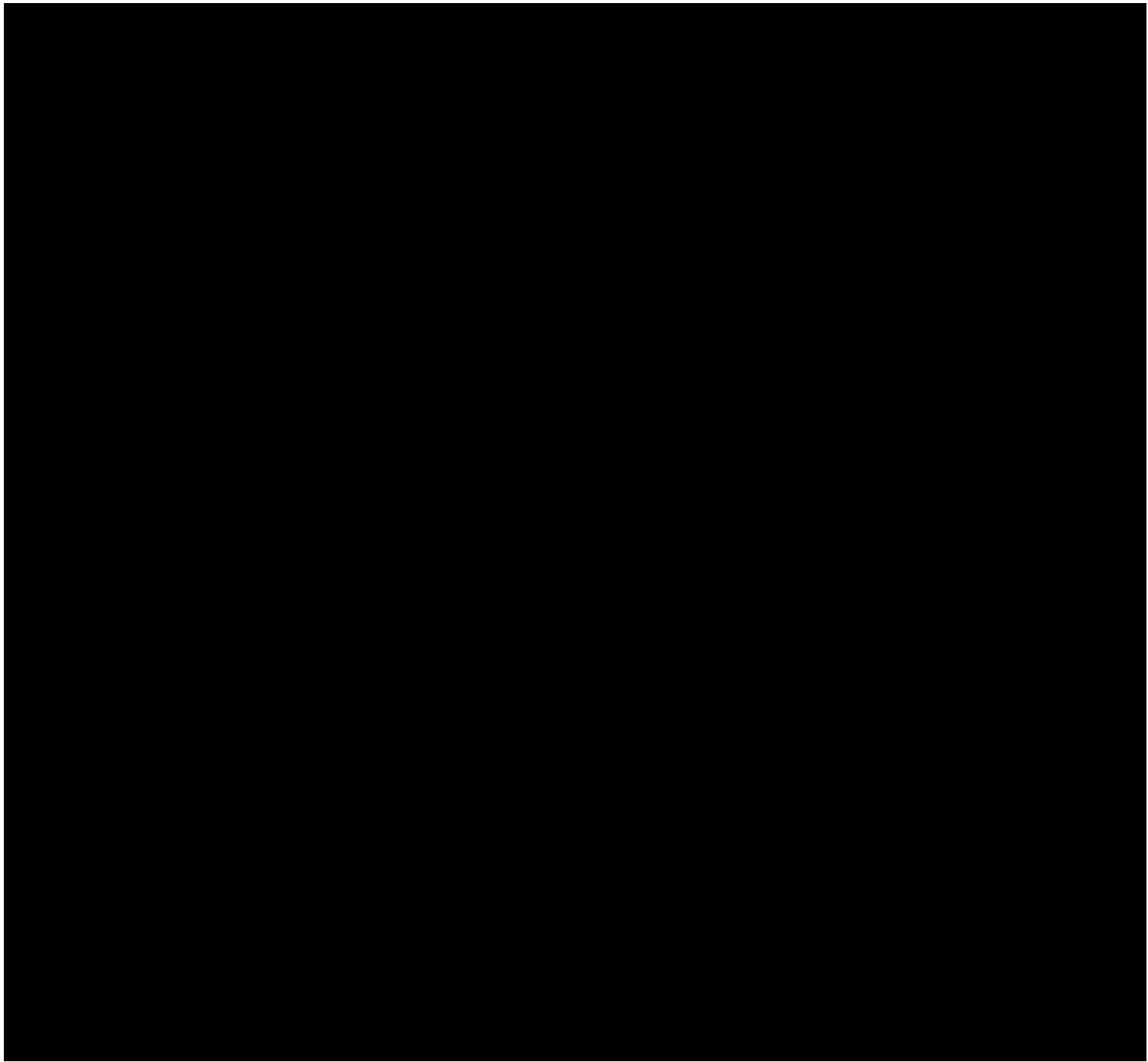
■ XXXXXXXXXX

10. **What is the primary purpose of the *Journal of Clinical Endocrinology and Metabolism*?**

—

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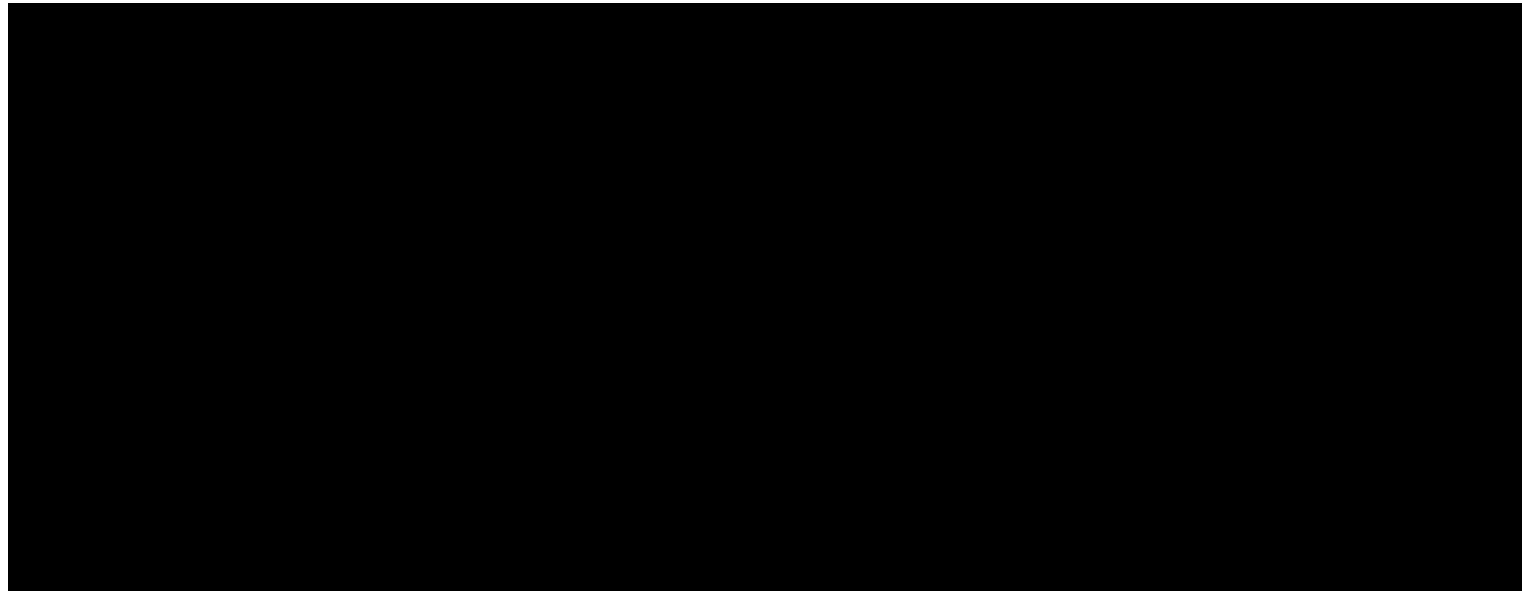


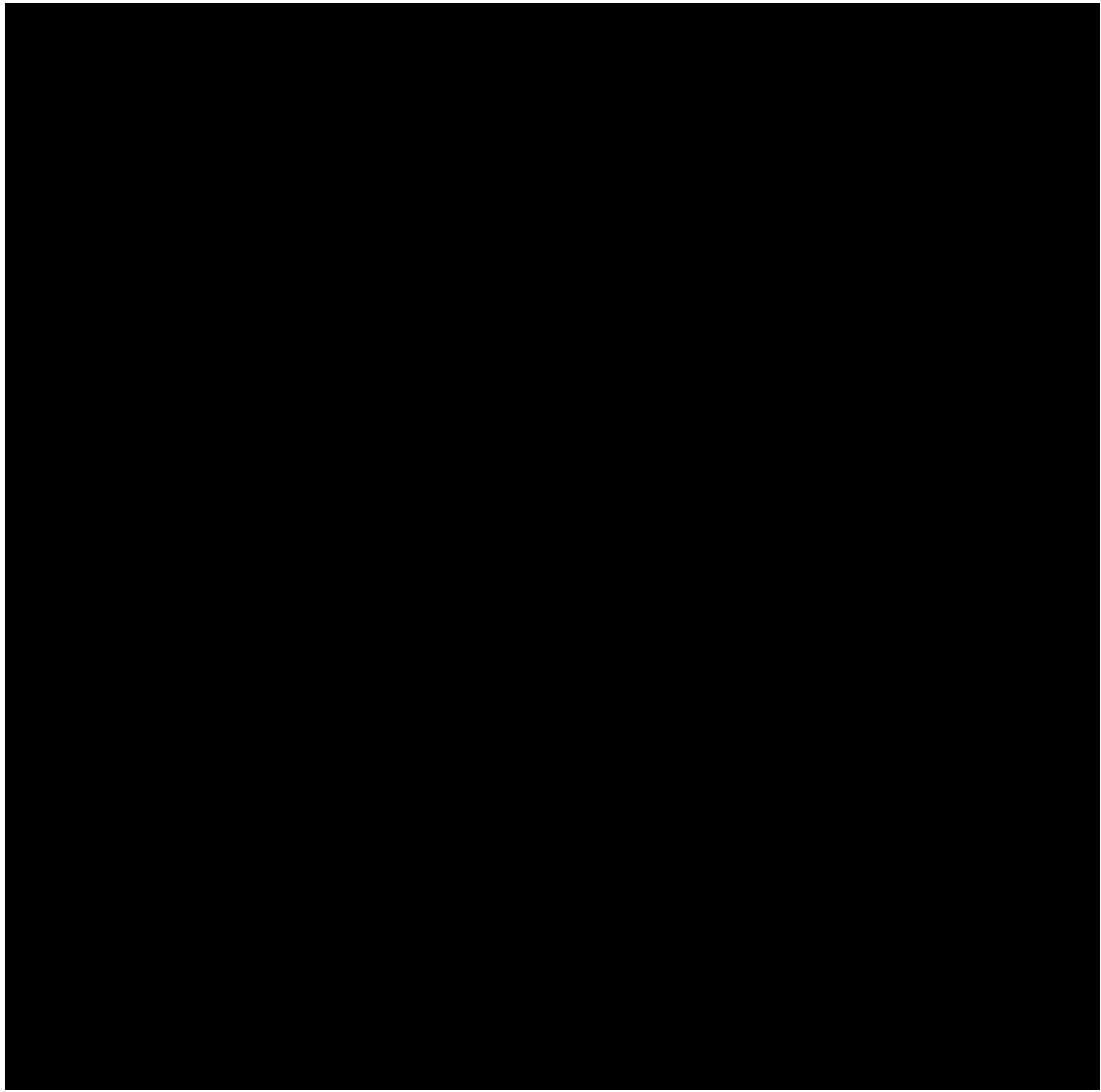


[REDACTED]

[REDACTED]

[REDACTED]





For more information, contact the Office of the Vice President for Research and Economic Development at 319-273-2500 or research@uiowa.edu.

ANSWER

■ [REDACTED]

1 [REDACTED]

1 | Page

1. **What is the primary purpose of the study?** (Please select one)

I [REDACTED]

— 1 —

— [REDACTED]

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[REDACTED]

