TITLE PAGE

Protocol Number: C-16-EN12

Protocol Title: A Single-Center, Open-Label Exploratory Study of a Novel Laser for Skin Rejuvenation

Sponsor:
Cutera, Inc.
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Principal Investigator:
[redacted]

Version, Date: Version 2.0 September 28, 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 Sheet – Principal Investigator

PROTOCOL C-16-EN12

Study Title: ***A Single-Center, Open-Label Exploratory Study of a Novel Laser for Skin Rejuvenation***

Protocol Version 2.0, September 28, 2016

I have received and read the protocol dated **September 28, 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

TABLE OF CONTENTS

Protocol Summary

Title	A Single-Center, Open-Label Exploratory Study of a Novel Laser for Skin Rejuvenation
Objective	1. To evaluate the safety of an investigational version of the enlighten™ 532nm /1064nm/670nm laser for photo-rejuvenation. 2. To evaluate the efficacy of an investigational version of the enlighten™ 532nm /1064nm/670nm laser for photo-rejuvenation.
Study Design	A single-center prospective, open-label uncontrolled exploratory study. Subjects will receive [redacted] laser treatments, [redacted] and will be followed at 2[redacted] 12 weeks [redacted]) post-final treatment. In addition, after each treatment, subjects will complete a 3 day post treatment phone follow-up. [redacted]
Enrollment	A maximum of 20 subjects
Study Endpoints	• Incidence and severity of adverse device effects at 2 weeks post-first treatment. • Incidence and severity of adverse device effects during the study period, including subject pain level during laser treatment. • Degree of improvement in the treated are at 12 weeks post-final treatment as assessed by the Investigator (Physician's Global Assessment of Improvement). [redacted]
Subject Population	Female or male subjects, age 18 to 75 years, Fitzpatrick skin types I-VI
Planned Schedule	First subject enrolled: September2016 Last subject last visit: August 2018

1 PURPOSE

The purpose of this exploratory investigation is to evaluate the safety and efficacy of an investigational version of the Cutera enlighten™ laser for skin rejuvenation, specifically improvement of acne scars, fine rhytides, lentigines, pigmentation, erythema and skin texture. The version of the laser under investigation allows the user to treat using a wavelength between 660 nm – 690 nm as well as 532 nm or 1064 nm.

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 (CO_2) and erbium:yttrium-aluminum-garnet (Er:YAG), and resulted in substantial improvement in skin appearance, texture, rhytides and laxity[1-3]. 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 non-ablative laser devices to those that use radiofrequency [7-15].

Laser therapy often includes the use of pulsed lasers, namely Q-Switched or Quality-Switched (QS) lasers which produce nanosecond laser pulses by suddenly releasing all of the excited-state energy from the laser medium [16]. This concept is based on the principle of selective photothermolysis which imply: (1) the use of the wavelength matching the absorption spectra of the pigment; and (2) the delivery of the heat to target pigment particle within pulse duration shorter than its thermal relaxation time [17]. This allows selective destruction of target chromophore in the skin with minimal damage to the surrounding tissue.

Nanosecond QS lasers have been widely used for more than 20 years as a safe and effective treatment for skin rejuvenation [18-24]. Laser wavelengths and pulse durations currently available for nanosecond QS laser treatment of pigmented lesions include 532 nm Nd:YAG, 1064 nm Nd:YAG, 755 nm Alexandrite and 694 nm Ruby with pulse durations from 5 to 10 ns (Nd:YAG), 50 to 70 ns (Alexandrite) 25 to 30 ns (Ruby). These wavelengths in the visible and infrared ranges are appropriate for the absorption spectrum of melanin. Melanin, the target pigment for these lasers, is largely present in basal keratinocytes in benign pigmented lesions. During laser procedures, the melanosomes, the organelle which hold the melanin in melanocytes, are rapidly heated [25, 26]. This rapid heating and evaporation of the melanosomes in the skin result in vacuolization.

The current proposed exploratory clinical study described herein intends to evaluate the safety and effectiveness of the investigational laser and the optimal range of treatment parameters for use in skin rejuvenation.

2.2 Study Device

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3 STUDY OBJECTIVES

The objective of this study is to evaluate efficacy and safety of treatment with the investigational version of the Cutera enlighten™ laser with 670nm wavelength for photo-rejuvenation.

4 STUDY DESIGN

This is a single-center prospective, open-label, uncontrolled feasibility study in up to 20 male or female subjects, age 18 to 75 years who desire laser treatment for photo-rejuvenation, specifically improvement of acne lesions and scars, fine rhytides, lentigines or pigmentation, diffused redness erythema and skin texture. Subjects may be treated on the face and/or body (such as, but not limited to, hand, forearm, chest or décolleté).

Subjects will receive [redacted] laser treatments, [redacted] and will be followed at [redacted] 12 weeks post final treatment [redacted]). The number of treatments as well as the interval between treatments will be determined at the Investigator's discretion. In addition, subjects will complete a 3-day post treatment phone survey after each treatment. [redacted]

[redacted]

4.1 Study Endpoints

4.1.1 Exploratory Endpoints

4.1.1.1 Safety Endpoints

- Incidence and severity of adverse device effects at 2 weeks post-first treatment.
- Incidence and severity of adverse device effects during the study period, including subject pain level during laser treatment.

4.1.1.2 Efficacy Endpoints

- Degree of improvement in the treated area at 12 weeks post-final treatment as assessed by the Investigator (Physician's Global Assessment of Improvement).
- [redacted]

4.2 Study Duration

Subjects enrolled in this trial will participate for approximately 5 to 16 months, [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.

4.3 Study Effectiveness Assessments

4.3.1 Investigator Assessments

4.3.1.1 Investigator's Global Assessment of Improvement

At 12 weeks post-final treatment, the Investigator will be asked to rate the degree of improvement in the appearance of the subject's treated area from baseline using the Physician's Global Assessment Scale:

4 = Very Significant or Complete Clearing ([redacted]
3 = Significant Clearing [redacted]
2 = Moderate Clearing ([redacted]
1 = Mild Clearing [redacted]
0 = No Clearing [redacted]

4.3.2 Subject Assessments

4.3.2.1 [redacted]

[redacted]

[redacted]

4.4 Study Safety Assessments

4.4.1 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.

4.4.2 Treatment-related Discomfort

After each laser treatment, subjects will be asked to rate the average amount of discomfort experienced during treatment and immediately after laser treatment.

4.4.3 Phone Follow-up

Phone follow-up will be conducted for all subjects by the Investigator's staff at 3 days after each laser treatment. Data recorded on the phone follow-up questionnaire will be evaluated for adverse events, event duration and adverse event resolution. The Phone Follow-up Questionnaire is presented in **Appendix 5**.

4.5 Photographs

Standardized digital photographs will be taken of each subject's treatment area at baseline, prior to all laser treatments and at each follow-up. Any jewelry will be removed from the area being photographed. For facial photographs, hair will be pulled away from the face with a headband and subject will have recently cleansed skin. Photographs will be taken prior to all laser treatments and at each follow-up visit. Facial photographs will be obtained from 3 angles: with the subject facing forward, 90° to the right and 90° 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.

4.6 Study Discontinuation

Cutera, Inc. (the sponsor) 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.

4.7 Investigator Selection

The Investigator will be invited to participate in the study based on his or 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 was also considered.

5 Study Population

5.1 Study Subject Recruitment and Selection

Up to 20 male or female subjects, ages 18 to 75, with Fitzpatrick Skin Type I-VI who desire laser treatment for skin rejuvenation on the face. 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, 18 to 75 years of age (inclusive).
2.	Fitzpatrick Skin Type I – VI **(Appendix 2).**
3.	Desires photo-rejuvenation of the skin or improvement in the appearance of acne scarring.
4.	Subject has visible signs of acne scarring or moderate sun-damaged and/or aging skin in the treatment area with visible areas acne lesions and scars, fine rhytides, lentigines or pigmentation, diffused redness erythema and skin texture
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), including injectable agents, for skin rejuvenation during the study and has no intention of having such procedures performed during the course of the study.
10.	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.

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 drug, or device administered to the target area, 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 of botulinum toxin, collagen, hyaluronic acid filler or other dermal filler within 6 months of study participation.
4.	History of malignant tumors in the target area.
5.	Skin abnormalities in the target area, e.g., cuts, scrapes, wounds, large moles.
6.	Pregnant and/or breastfeeding.
7.	Having an infection, dermatitis or a rash in the treatment area.
8.	Significant concurrent illness, such as diabetes mellitus or cardiovascular disease, e.g., uncontrolled hypertension.

9.	History of keloid scarring, hypertrophic scarring or of abnormal wound healing.
10.	History of immunosuppression/immune deficiency disorders or currently using immunosuppressive medications per investigator's discretion.
11.	History of vitiligo, eczema, or psoriasis.
12.	History of connective tissue disease, such as systemic lupus erythematosus or scleroderma.
13.	History of seizure disorders due to light.
14.	Any use of medication that is known to increase sensitivity to light according to Investigator's discretion.
15.	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
16.	History of pigmentary disorders, particularly tendency for hyper- or hypo-pigmentation.
17.	Systemic use of retinoid, such as isotretinoin, as applicable, within 6 months of study participation.
18.	Topical use of retinoid, such as isotretinoin, as applicable, on the treatment area within 1 month of participation.
19.	Anytime in life, having have used gold therapy (gold salts) for disorders such as rheumatologic disease or lupus.
20.	Excessively tanned in areas to be treated or unable/unlikely to refrain from tanning during the study.
21.	Current smoker or history of smoking within 6 months of study participation.
22.	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.

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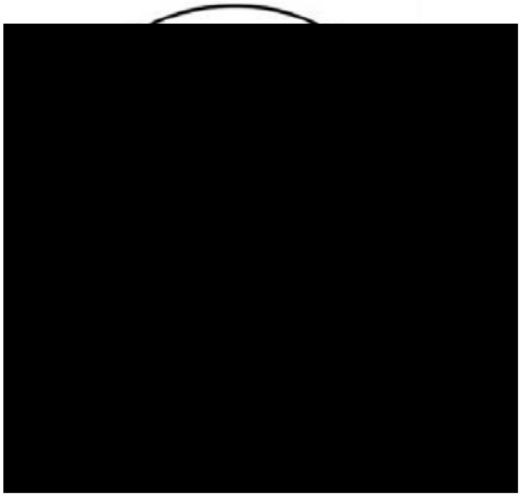

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7 ADVERSE DEVICE EFFECTS

7.1. Definitions

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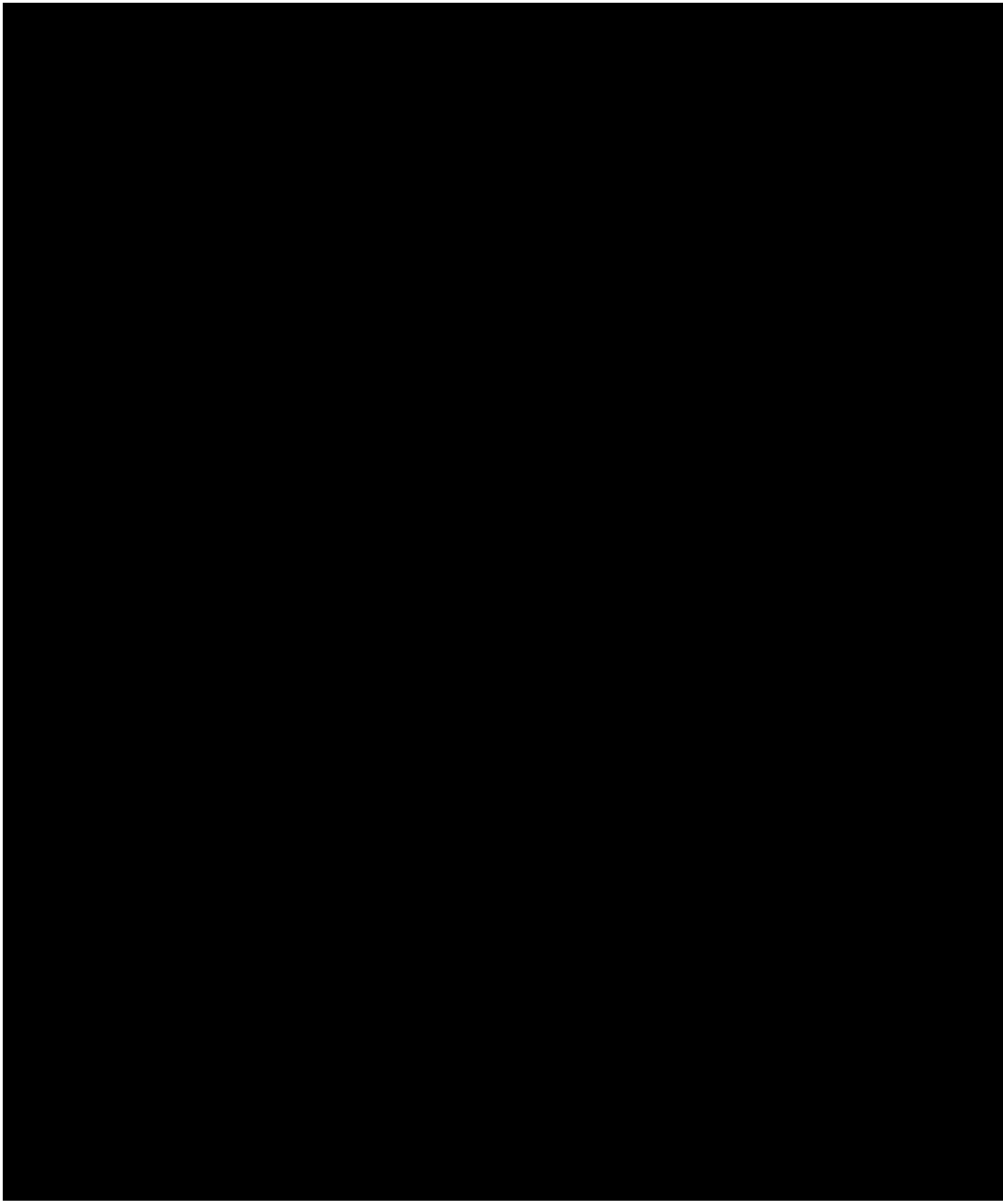

7.2 Recording ADEs and SADEs

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 Enlighten 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

8.1 [redacted]

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[redacted].

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 treated area. 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 Enlighten laser system by a representative of Cutera.

10 DATA ANALYSIS PLAN

10.1 Sample Size

Up to 20 subjects will be enrolled in this exploratory 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

This is an exploratory study to evaluate safety and efficacy of the investigational enlighten device, therefore, formal statistical analyses are not planned.

Outcome measures will be assessed around multiple endpoints. These measures will be: degree of improvement as assessed by the Investigator, [redacted] and safety. Additional assessments may also be performed but are not considered part of the analysis (i.e. subject post-treatment questionnaire). The specific assessment tools, collection method and time points are listed herein.

10.3.1 Analysis Sets

The efficacy analysis set will include all subjects who received at least one laser treatment session and complete at least one 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.

10.3.1.1 Efficacy Analyses

Descriptive statistics such as mean, standard deviation, median and range will be performed for:

- The degree of improvement at 12 weeks post-final treatment as assessed by the Investigator, using the Physician's Global Assessment tool.
- [redacted]

10.3.1.2 Safety Analyses

The safety variables for this study are:

- Incidence and severity of adverse effects during study duration (to be displayed descriptively as counts and frequency distributions)
- Subject discomfort (pain) during treatment (to be descriptively displayed).

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.

Interim analyses of adverse events and adverse device effect incidence and severity will be performed when all treated subjects have completed the 12 week post-final treatment visit. At the conclusion of the study, complete analyses of the safety variables will be displayed descriptively.

11 SUBJECT PAYMENT

12 STUDY MANAGEMENT AND ADMINISTRATIVE PROCEDURES

[redacted]

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[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

[redacted]

[redacted]

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[redacted]

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:

The subjects will be informed by the investigator or the investigator's designee that their medical records will be kept as confidential as possible but may be subject to review by: (1) Cutera, or its representative; (2) reviewing IRB; and/or (3) by appropriate regulatory bodies (e.g. the US Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies).

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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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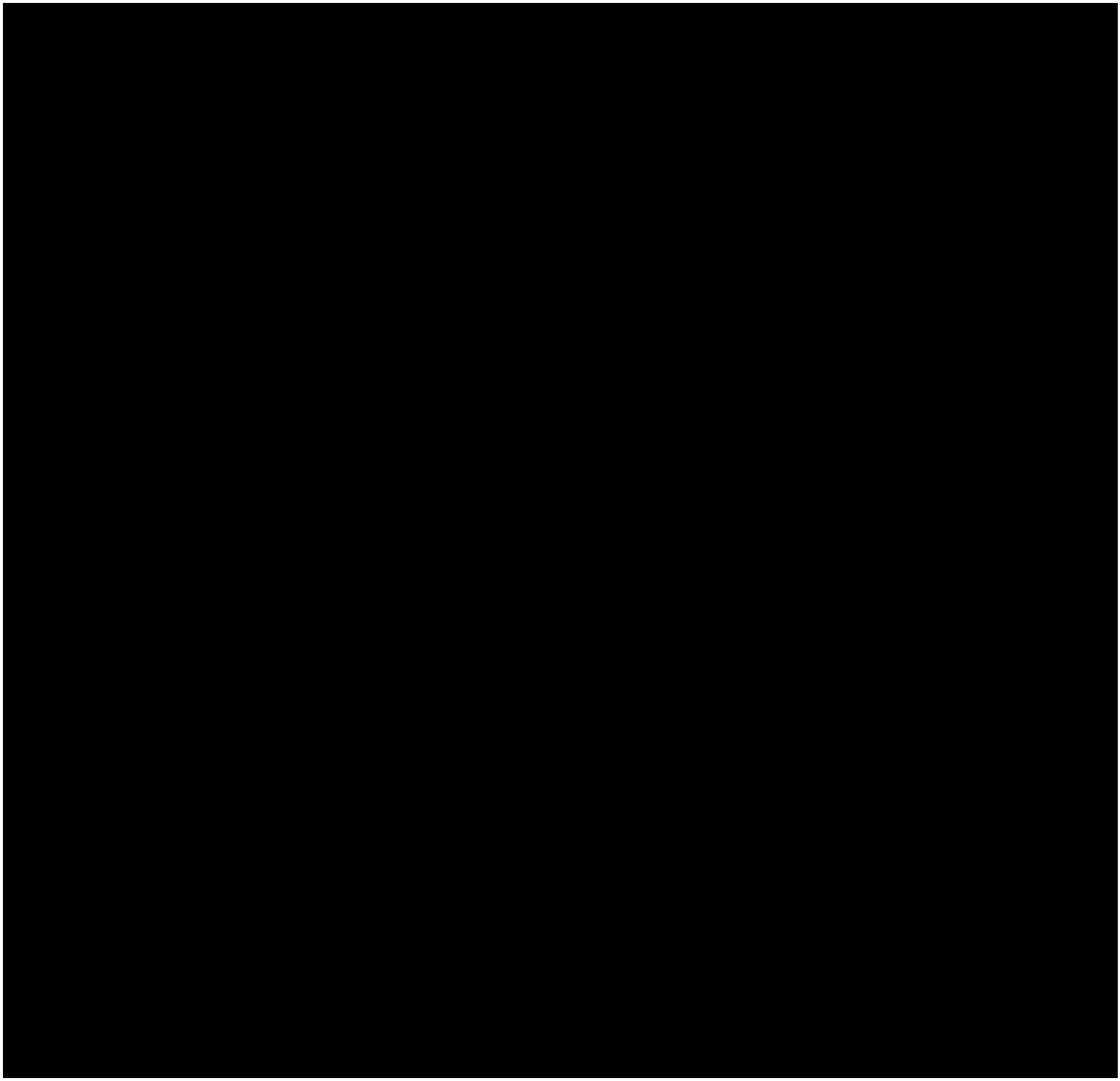

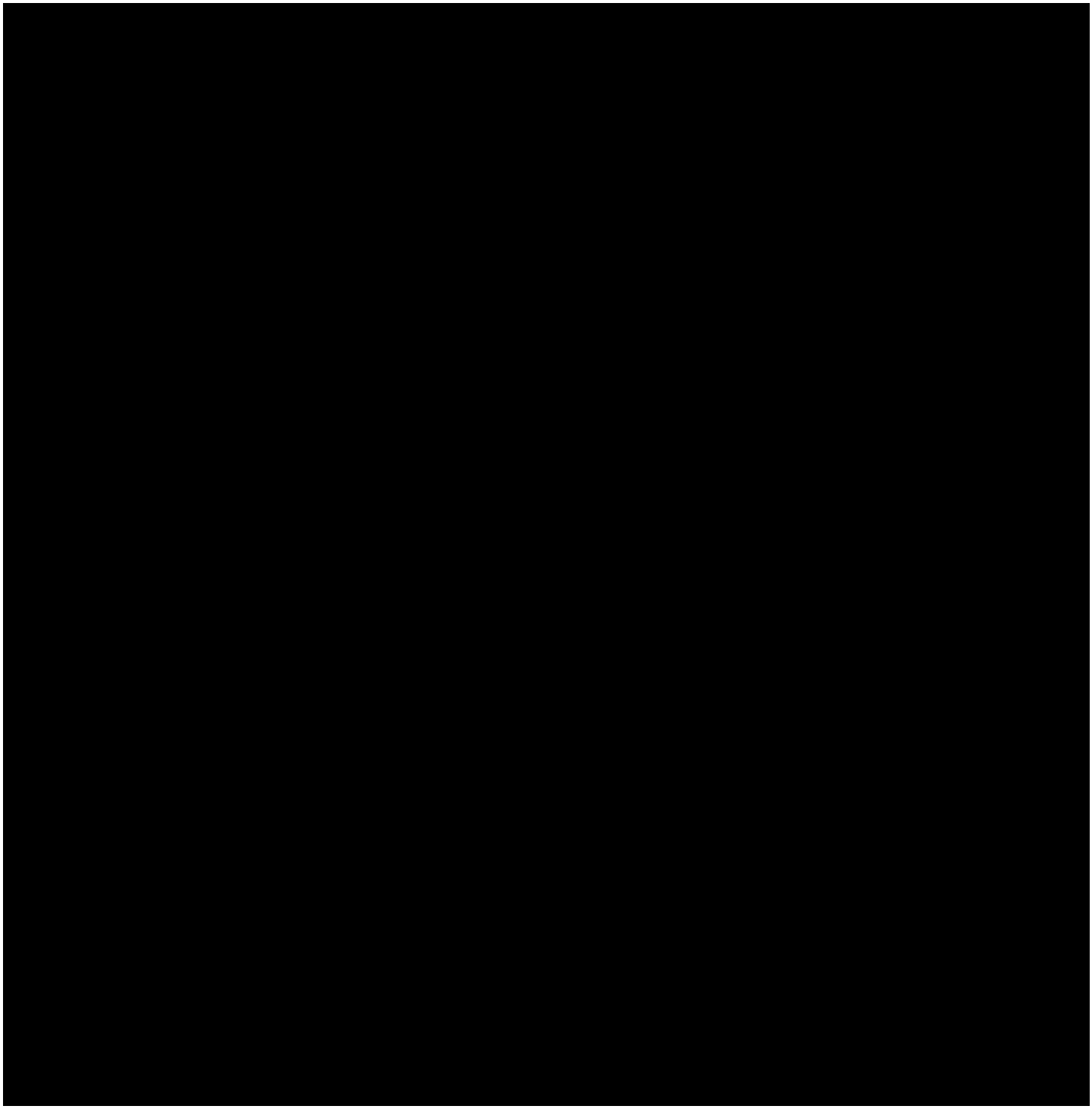

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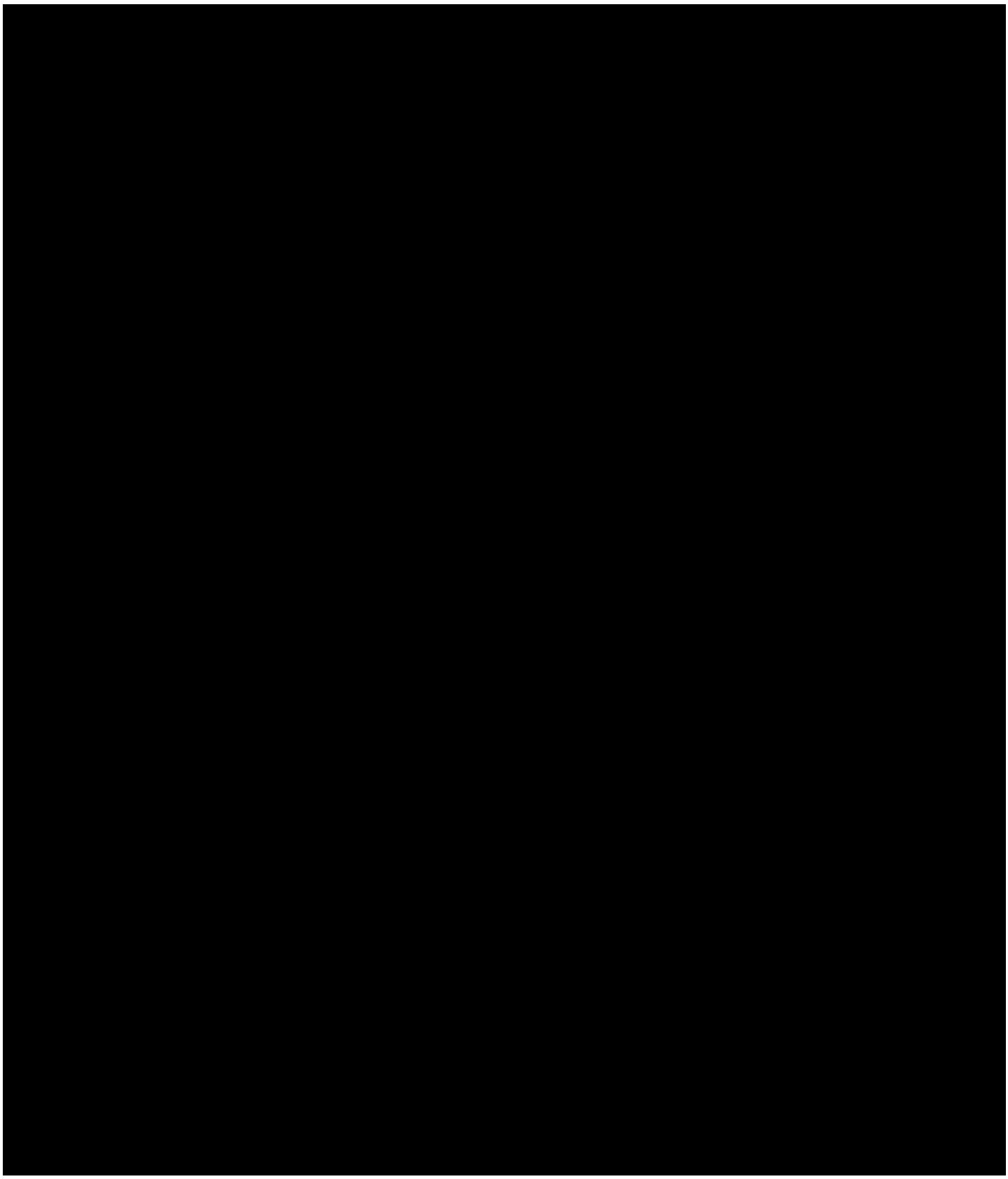

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