Feasibility Study of CoolSculpting Effects on Cellulite Appearance

Sponsor	ZELTIQ Aesthetics 4410 Rosewood Dr. Pleasanton, CA 94588
Protocol Number:	ZA20-002
Protocol Version:	4.0
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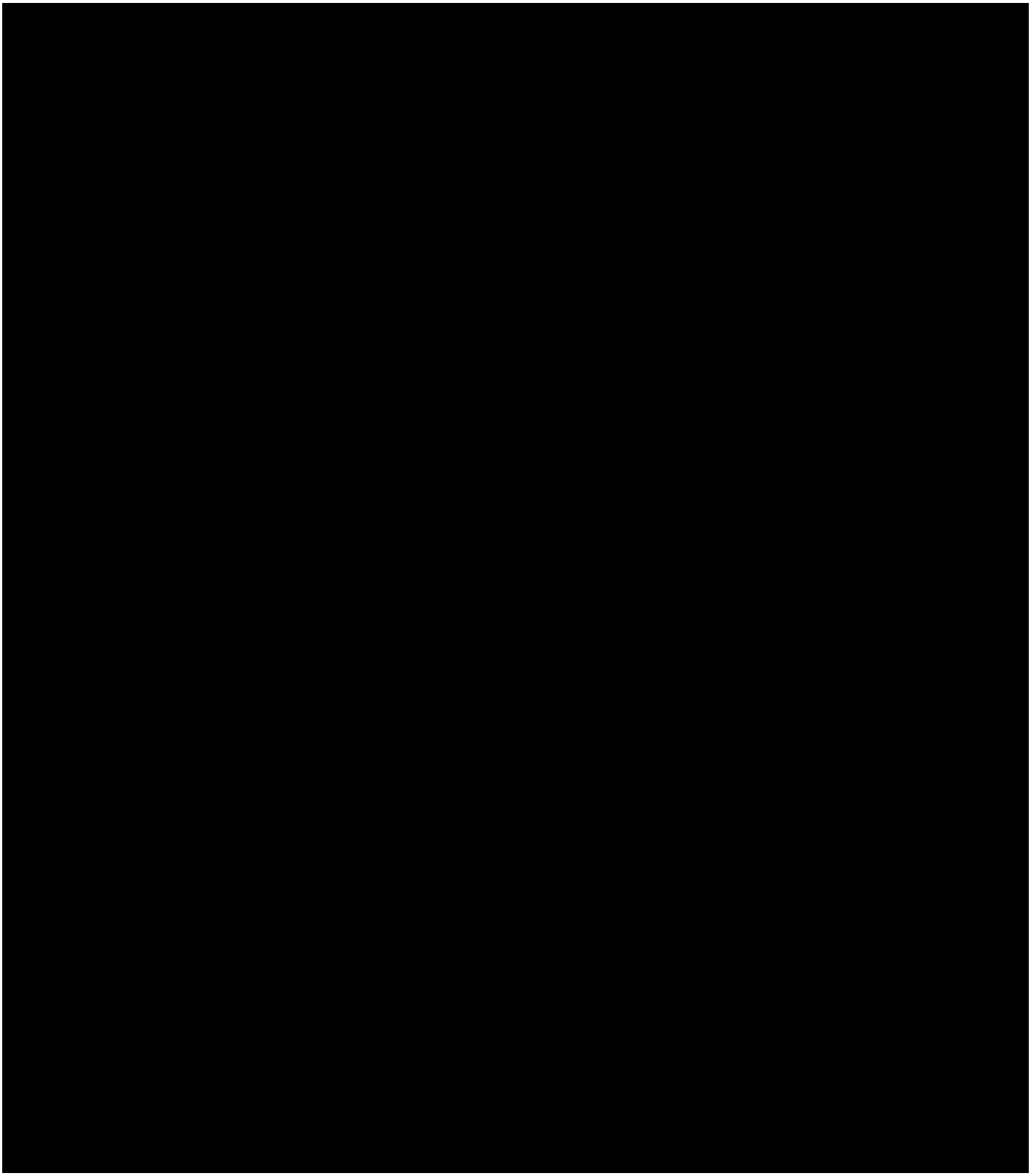
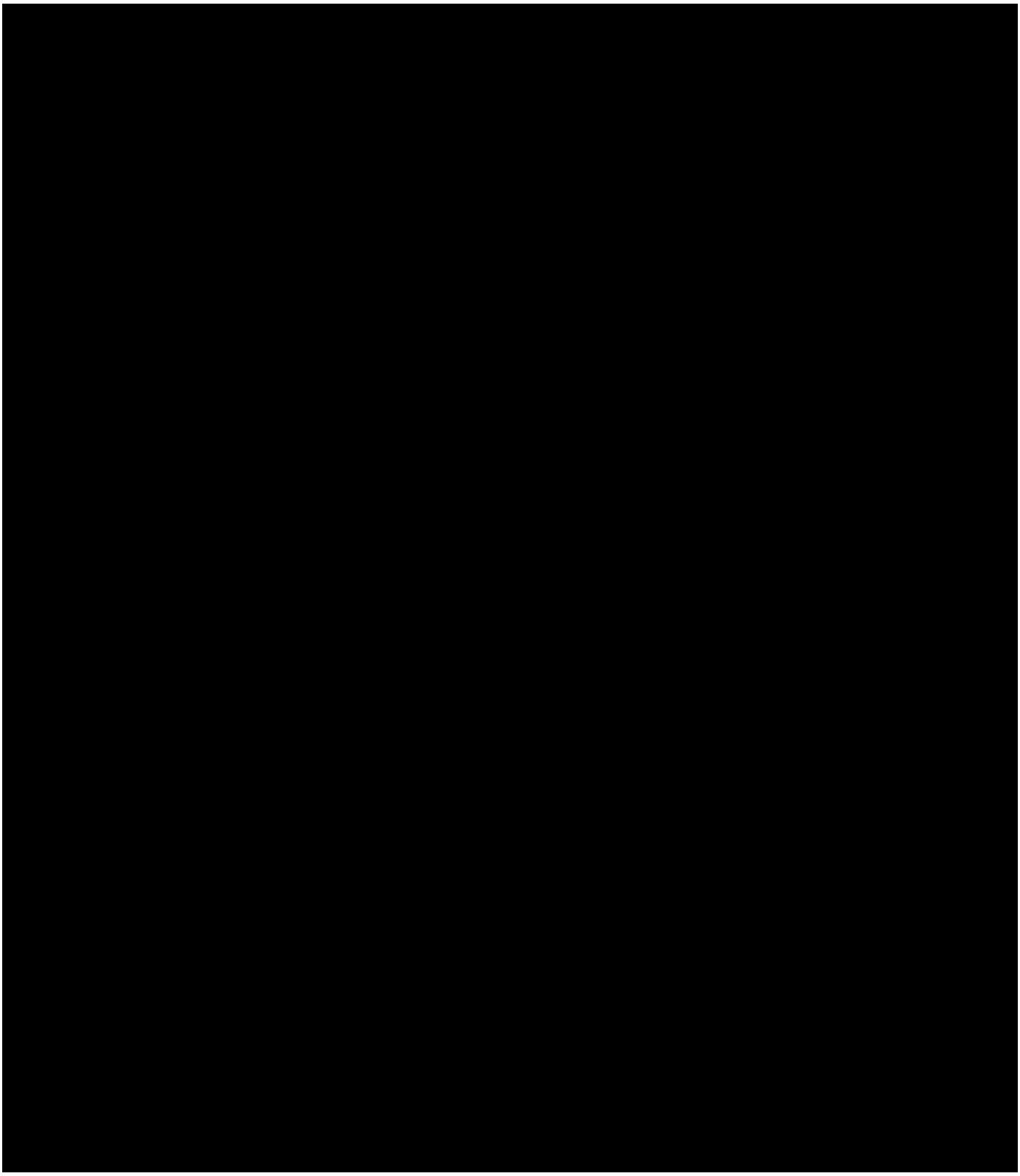
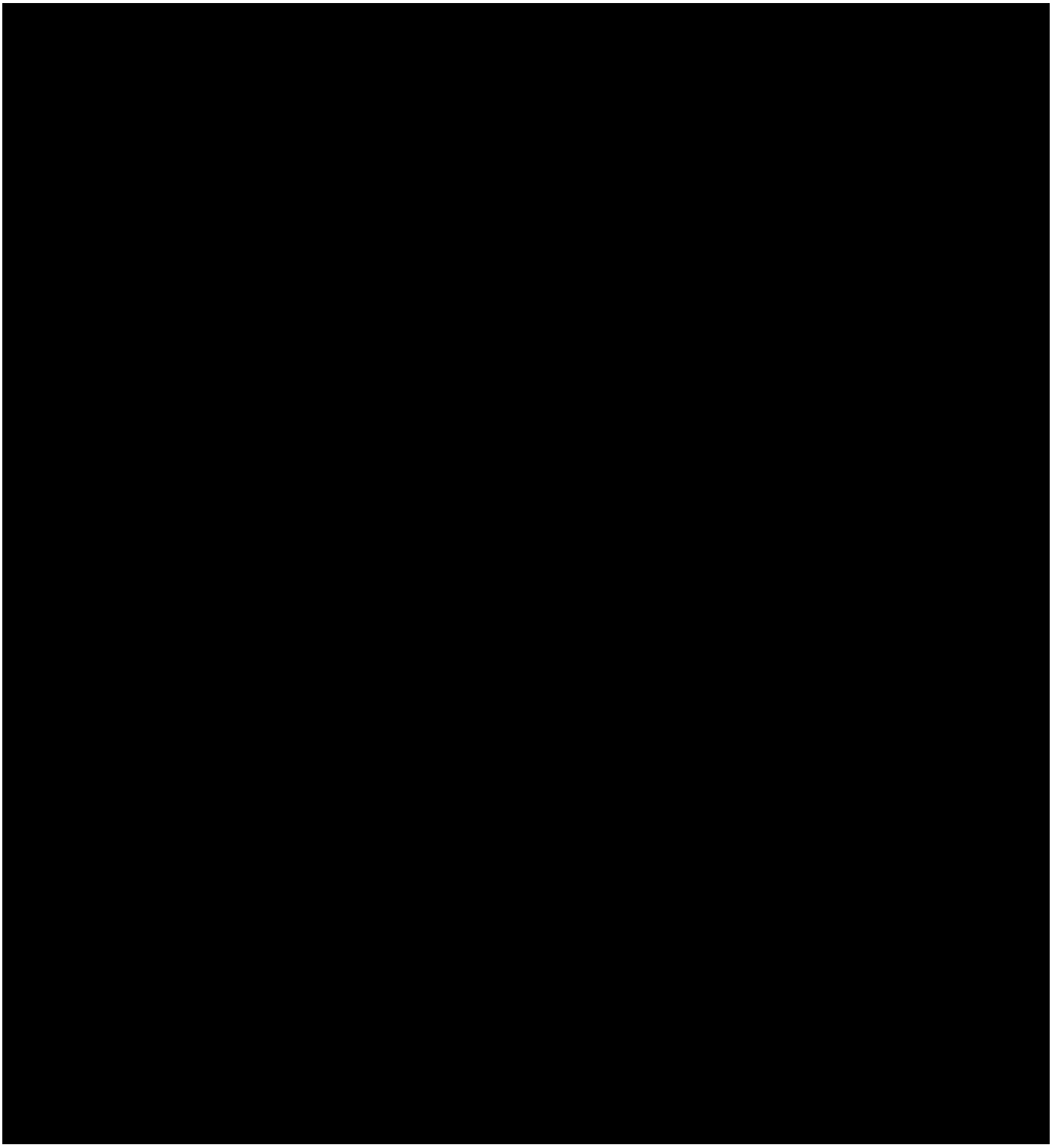
Product(s)	CoolSculpting system
Sponsor Contact:	[redacted] CoolSculpting PH: [redacted]
Medical Safety Physician	[redacted] Device Medical Safety PH: [redacted]







INVESTIGATOR SIGNATURE PAGE

For protocol number ZA20-002

I agree to:

- Implement and conduct this study diligently and in strict compliance with this protocol, GCP, and all applicable laws and regulations.
- Maintain all information supplied by the Sponsor, ZELTIQ Aesthetics, an Allergan affiliate, in confidence and, when this information is submitted to an Institutional Review Board (IRB) or Ethics Committee (EC), or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

_____	_____	_____
Investigator printed name	Signature	Date
_____	_____	_____
Investigator printed name	Signature	Date

RETURN PAGE TO SPONSOR

Table of Contents

1. Protocol Summary

Title	Feasibility study of CoolSculpting Effects on Cellulite Appearance
Design	Prospective, open label, interventional feasibility study
Objective/Purpose	Evaluate the effects of the CoolSculpting System and applicators for effects on the appearance of cellulite in the thigh.
Enrollment	Up to two hundred (200) subjects
Clinical sites	Up to fifteen (15) investigational sites
Participant/ Subject Population	Healthy adult women aged 22 – 65 with clearly visible cellulite on their thighs that they wish to have reduced.
Treatment:	[redacted]
Primary Endpoints	Safety endpoint: The frequency of device and procedure-related adverse events (AEs), including device-related serious adverse events (SADEs) and unanticipated adverse events, will be summarized. Efficacy endpoint: 1. Comparison of baseline and 12-week post-final treatment photographs to assess visible changes in appearance of the treated areas.
[redacted]	
Sponsor	ZELTIQ Aesthetics 4410 Rosewood Dr. Pleasanton, CA 94588

2. Introduction

2.1. Background

Cellulite is a common condition that occurs in a large proportion of the female population. It is a benign condition which manifests in lumpy, dimpled flesh on the thighs, hips, buttocks and abdomen. Cellulite is a multifactorial disease of the skin, fat, and connective tissues. The anatomical structure of the skin/fat layer includes vertical fibers of connective tissue (fibrous septa) which tether the skin to subcutaneous fascia. When fat cells enlarge and the dermal layer thins and loses elastin, the fat layer bulges, causing the undesirable appearance of dimples and waviness.

ZELTIQ Aesthetics has developed and commercialized cryolipolysis technology for non-invasive cold-assisted lipolysis. The CoolSculpting technology is based on the sensitivity of fat cells to cold injury in order to selectively eliminate subcutaneous fat tissue. The CoolSculpting System is cleared for use in the United States for the indication of cold-assisted lipolysis of the thighs, flank, abdomen, submental and submandibular areas, bra fat, back fat, and banana roll; as well as temporary reduction of cellulite.

Mild to moderate improvement in cellulite following the CoolSculpting procedure has been reported in the literature.[1] The technology reduces subcutaneous fat which minimizes bulging of the fat layer and reduces the rippled appearance in the skin. It is thought that controlled cooling may stimulate collagen and elastin production in the skin, improving the appearance of cellulite. The purpose of this study is to further evaluate the CoolSculpting System for non-invasive treatment of cellulite.

2.2 Regulatory Status

The CoolSculpting System has been cleared in the United States for use as an aesthetic treatment to affect the appearance of the flanks (DEN090002), the abdomen (K120023), the thighs (K133212), the submental area (K151179), and bra fat, back fat, and banana roll (K160259). Additionally, the System has been cleared for flexible treatment parameter ranges (K142491).

The device was also previously cleared for cooling as a method to minimize localized pain and thermal injury during laser and dermatological treatments under: K060407 (initial clearance), K063715 (clearance for warming and massage), K072152 (clearance for flat and belt applicators),

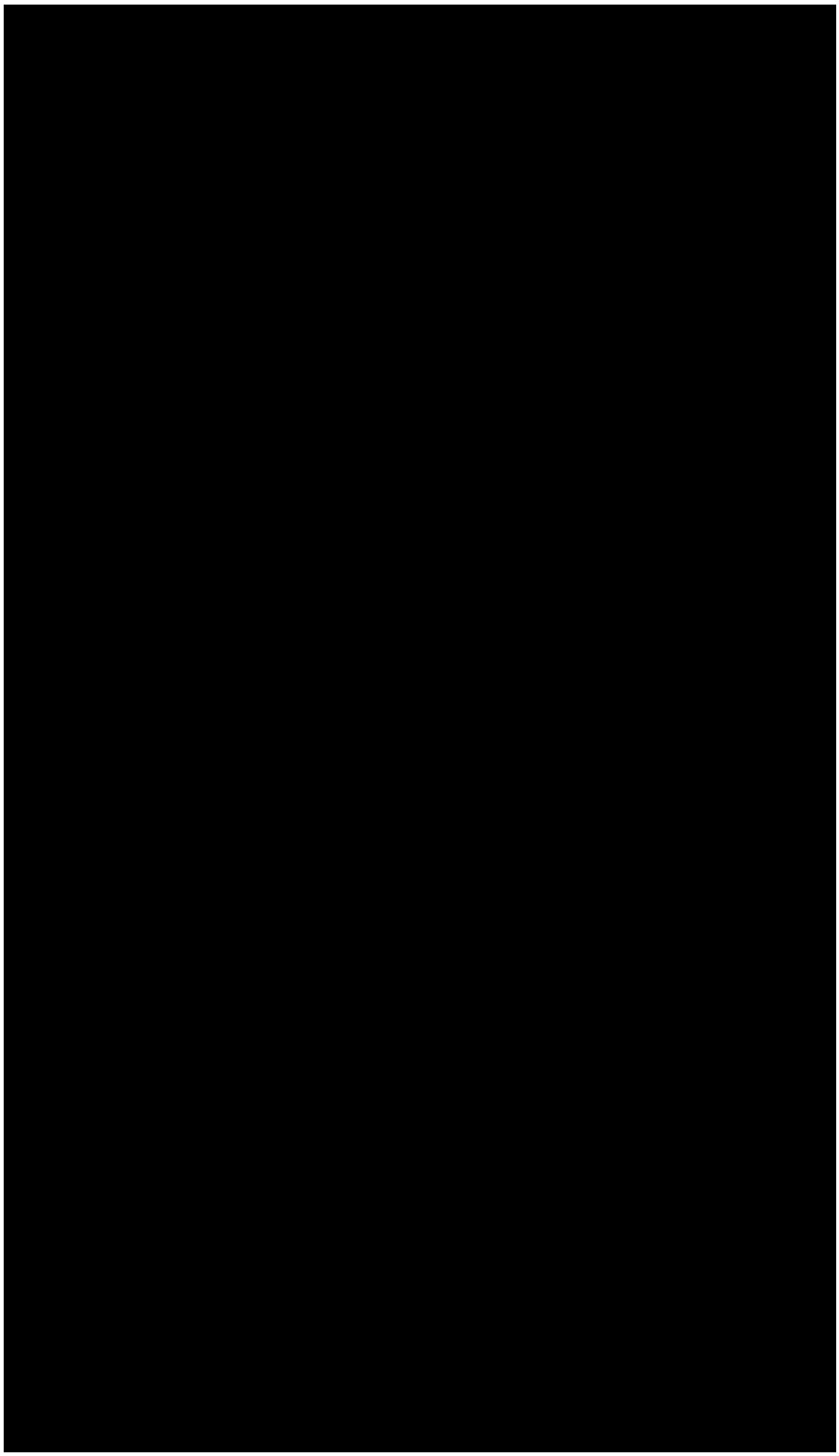
[1] Carruthers J, Stevens WG, Carruthers A, Humphrey S. Cryolipolysis and skin tightening. Dermatol Surg. 2014 Dec;40 Suppl 12:S184-9.

K080118 (clearance for vacuum applicator), and K090094 (clearance for commercial device).

This study will investigate the use of the FDA-cleared CoolSculpting System for treatment of cellulite in the thigh area. Results from this study will be used in development of future studies for an indication approval.

2.4 Device Description

The CoolSculpting System is comprised of a control unit (Figure 1), which houses the system controller and power source, and a detachable applicator which is used to apply cooling and/or warming to the treatment site. The study treatments will be performed using the CoolSculpting System with either a surface applicator (Figure 2) or a vacuum applicator (Figure 3), depending on applicator conformity and tissue quality of the treatment area. The surface applicator has a flat cooling surface that is placed on the treatment area. The vacuum applicator uses vacuum pressure to draw tissue into the cup shaped applicator; tissue is then cooled inside the cup in a controlled manner.



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3 Study Objectives

The objective of this study is to evaluate the effects of the CoolSculpting System and applicators for effects on the appearance of cellulite in the thigh.

4 [redacted]

4.1 Study Design

Up to fifteen sites will enroll up to 200 eligible subjects. Enrollment and follow-up is expected to take up to 12 months for each subject. The study duration is expected to be up to 2 years.

4.2 Investigator Qualifications

To participate in this study, an investigator must have an active medical license and board certification in dermatology and/or plastic surgery. The investigator must undergo training on the study device(s) prior to study initiation.

Site investigators must have at least one study coordinator with experience in conducting aesthetic research and with sufficient time to conduct the study.

4.3 Study Population

4.3.1 Target Patient Population

Patients with cellulite on the anterior, lateral or posterior thighs that they wish to have reduced will be recruited to participate in this study

4.3.2 Subject Eligibility

To be eligible to participate, subjects must meet all of the inclusion criteria and none of the exclusion criteria listed in Table 1.

Table 1. Eligibility criteria.

Inclusion Criteria
a) Female subjects ≥ 22 years of age and < 65 years of age.
b) Subject has clearly visible cellulite on the intended treatment area (thighs), which in the Investigator's opinion, may benefit from the treatment.
c) Subject has not had weight change exceeding 5% in the preceding month.
d) Subject agrees to maintain her weight (i.e., within 5%) by not making any major changes in diet or exercise routine during the course of the study.
e) Subject has read and signed a written informed consent form.
Exclusion Criteria
a) Subject has had a surgical procedure(s) in the area of intended treatment.
b) Subject has had an invasive fat reduction procedure (e.g., liposuction, mesotherapy) in the area of intended treatment.
c) Subject has had a non-invasive fat reduction, body contouring, cellulite reduction and/or skin tightening procedure in the area of intended treatment within the past 4 months.
d) Presence of significant suntan in the thighs.
e) Inability to avoid sun exposure in the thighs.
f) Subject has a history of hernia in or adjacent to the areas to be treated.
g) Subject needs to administer or has a known history of subcutaneous injections into the area of intended treatment (e.g., heparin, insulin) within the past month.
h) Subject has a known history of cryoglobulinemia, cold urticaria, cold agglutinin disease, or paroxysmal cold hemoglobinuria.
i) Subject has a known history of Raynaud's disease, or any known condition with a response to cold exposure that limits blood flow to the skin.
j) Subject has a history of bleeding disorder or is taking any medication that in the Investigator's opinion may increase the subject's risk of bruising.
k) Subject has known sensitivity or allergy to isopropyl alcohol and propylene glycol.
l) Subject is taking or has taken diet pills or supplements within the past month.
m) Subject has any dermatological conditions, such as moderate to excessive skin laxity, or scars in the location of the treatment sites, that may interfere with the treatment or evaluation (stretch marks is not an exclusion).
n) Subject has an active implanted device such as a pacemaker, defibrillator, implants (e.g. buttock implants), or drug delivery system.

o) Subject is pregnant or intending to become pregnant during the study period (in the next 9 months).
p) Subject is lactating or has been lactating in the past 6 months.
q) Subject is unable or unwilling to comply with the study requirements.
r) Subject is currently enrolled in a clinical study of any other unapproved investigational drug or device.
s) Any other condition or laboratory value that would, in the professional opinion of the Investigator, potentially affect the subject's response or the integrity of the data or would pose an unacceptable risk to the subject.

4.3.3 Vulnerable Populations

Children, pregnant women, fetuses, neonates and prisoners are not included in this study.

5 Study Conduct and Procedures

5.1 Subject Recruitment

Study candidates who seek reduction of cellulite in the thighs will be recruited from the general population.

[redacted]

5.2 Informed Consent

Subjects will be recruited from the Investigator's clinical practice and via IRB/EC approved advertising. Once the patient's potential eligibility has been determined, the Investigator or designee trained to the protocol will explain the nature and scope of the study, risks and benefits of participation, answer questions for the subject, and invite the subject to participate. The study will be explained in lay terms. Subjects will be consented for optional skin biopsies prior to study enrollment. If the patient agrees to participate, the IRB/EC-approved informed consent will be signed and dated by the patient and the Investigator or designee. A copy of the signed and dated informed consent will be provided to the study subject.

5.3 Screening Procedures

5.3.1 Screening Visit; Required; Day -30 to Day 0

After the informed consent is signed, subjects will be screened for eligibility. Each subject will be evaluated to determine that all selection criteria are met. The Investigator or designee shall complete a brief medical history and examine the subject to confirm eligibility for the study.

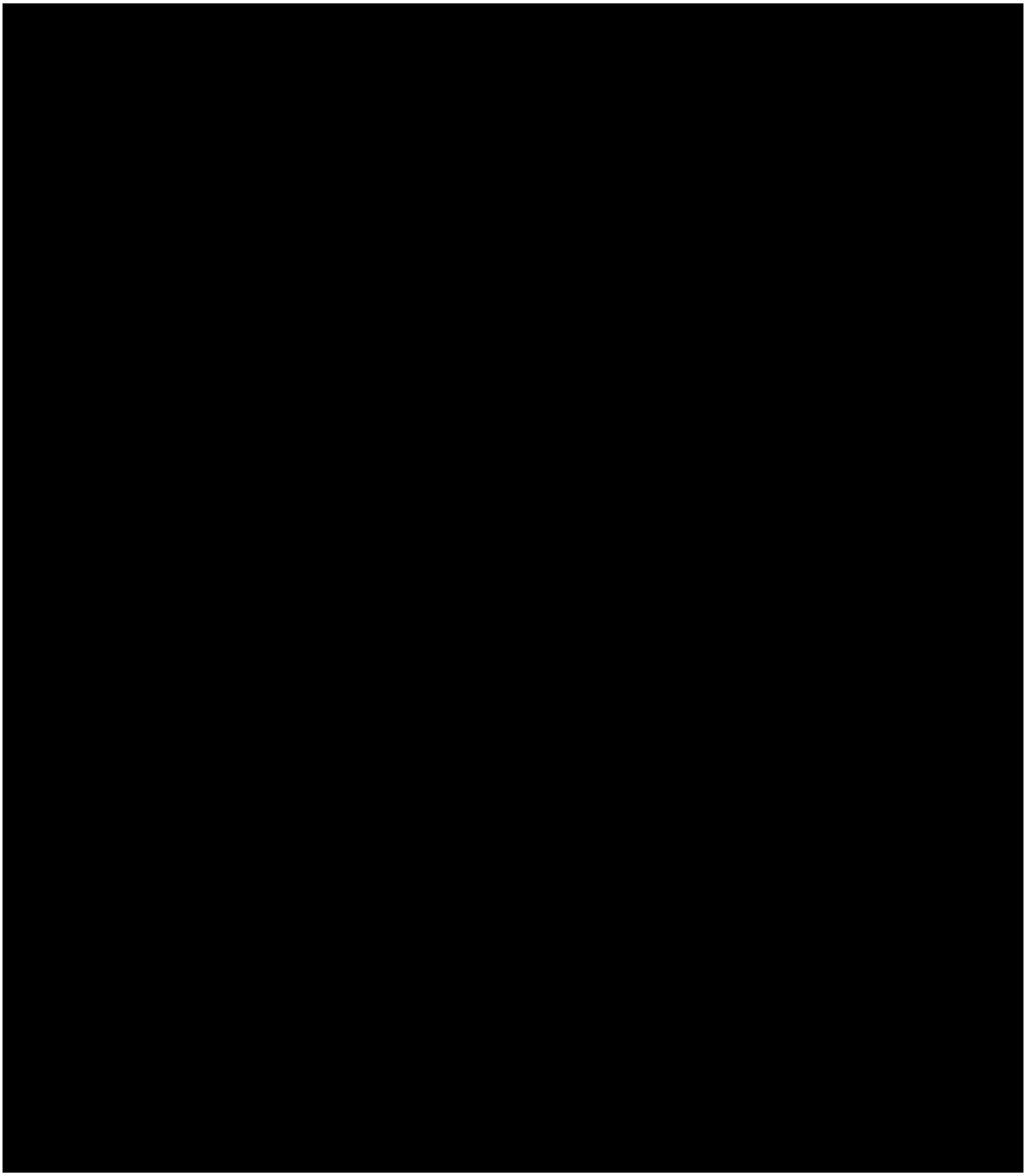
Female participants of childbearing potential will be advised to avoid becoming pregnant during the study by using a medically accepted form of contraception if they are sexually active. If the participant becomes pregnant during the course of the study, she will not be treated subsequently with the study device or be required to have follow-up photographs taken. Female participants of childbearing potential will be assessed for the start date of their last menstrual cycle.

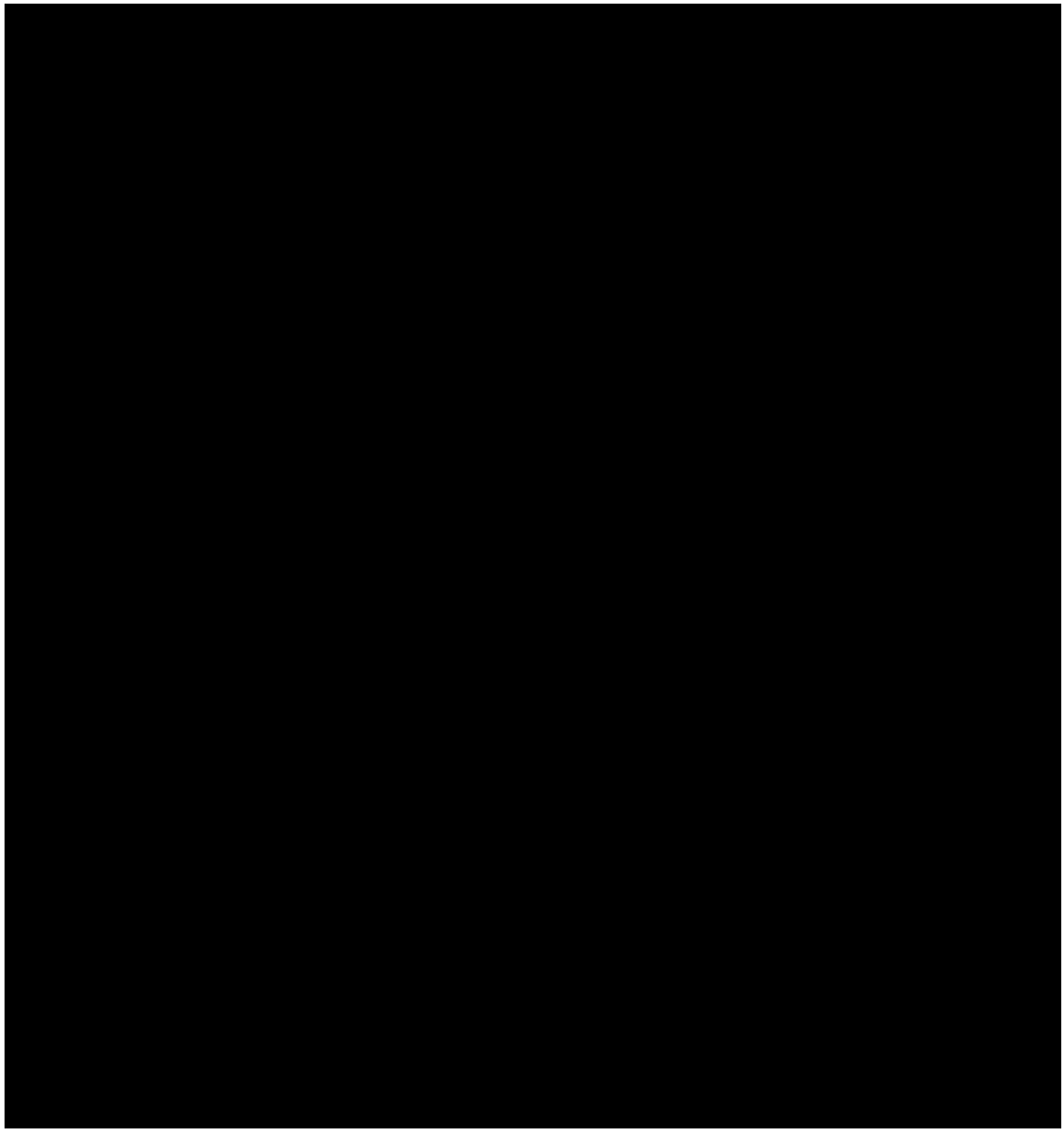
All participants will be asked to maintain their weight by not making any major changes to their diet or exercise routine during the study. Participants who do not

maintain their weight within 5% of their baseline body weight will continue in the study but will be excluded from the primary effectiveness analyses.

Participants who meet all inclusion criteria and none of the exclusion criteria shall be eligible to participate in the study and the first treatment will be scheduled.

5.4





The need for post-treatment care is not expected for this study. Subjects will be encouraged to call the study site if they experience any unusual effects (e.g., severe discomfort, severe and/or prolonged erythema, bruising, swelling; blistering, etc.) which may be related to the study.

[redacted]

5.4.2 Follow-up Procedures

Subjects who receive study treatment with the device will be required to complete all follow-up visits and assessments. Subjects are required to undergo follow-up visits and assessments after each treatment visit at 1-, 3- and 6-. After completing the final treatment subject will complete follow-up assessment at 1-, 3- 6 and 12-Week as specified in the protocol. Subjects may also be asked to return for optional 24, and 36 weeks visits after the final treatment.

[redacted]

5.4.2.1 One-Week Post-Treatment Follow-Up; Day 7 ± 3 days

Clinical site staff will contact (via phone call or email) subjects one week after each treatment visit for assessment of the treatment area, pain score, and adverse events. If there are any observations reported, the study site should obtain a resolution date of the symptoms. If there is evidence that an adverse event may have occurred, the subject, at the discretion of the Investigator, may be asked to come in for an optional visit for appropriate evaluation.

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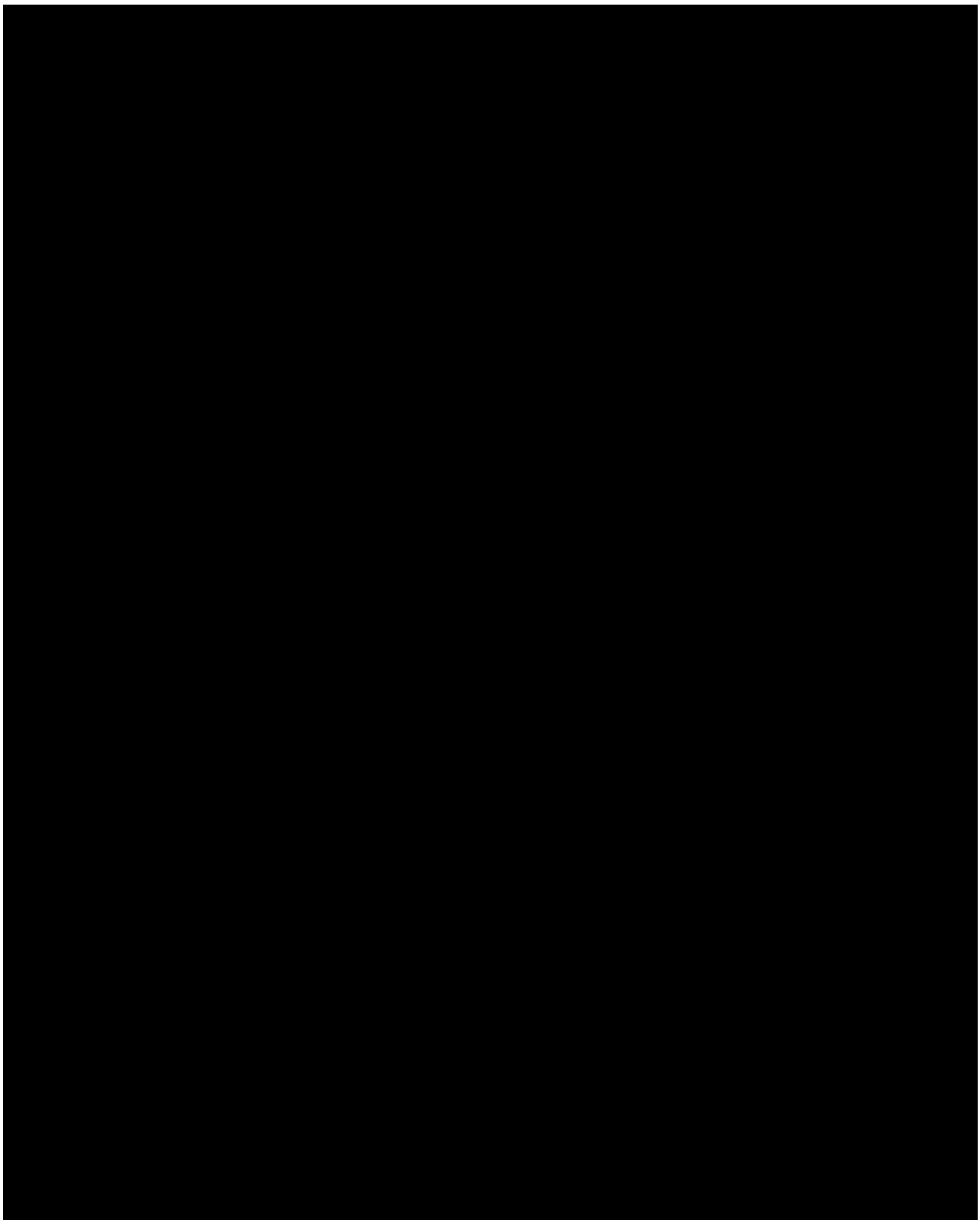

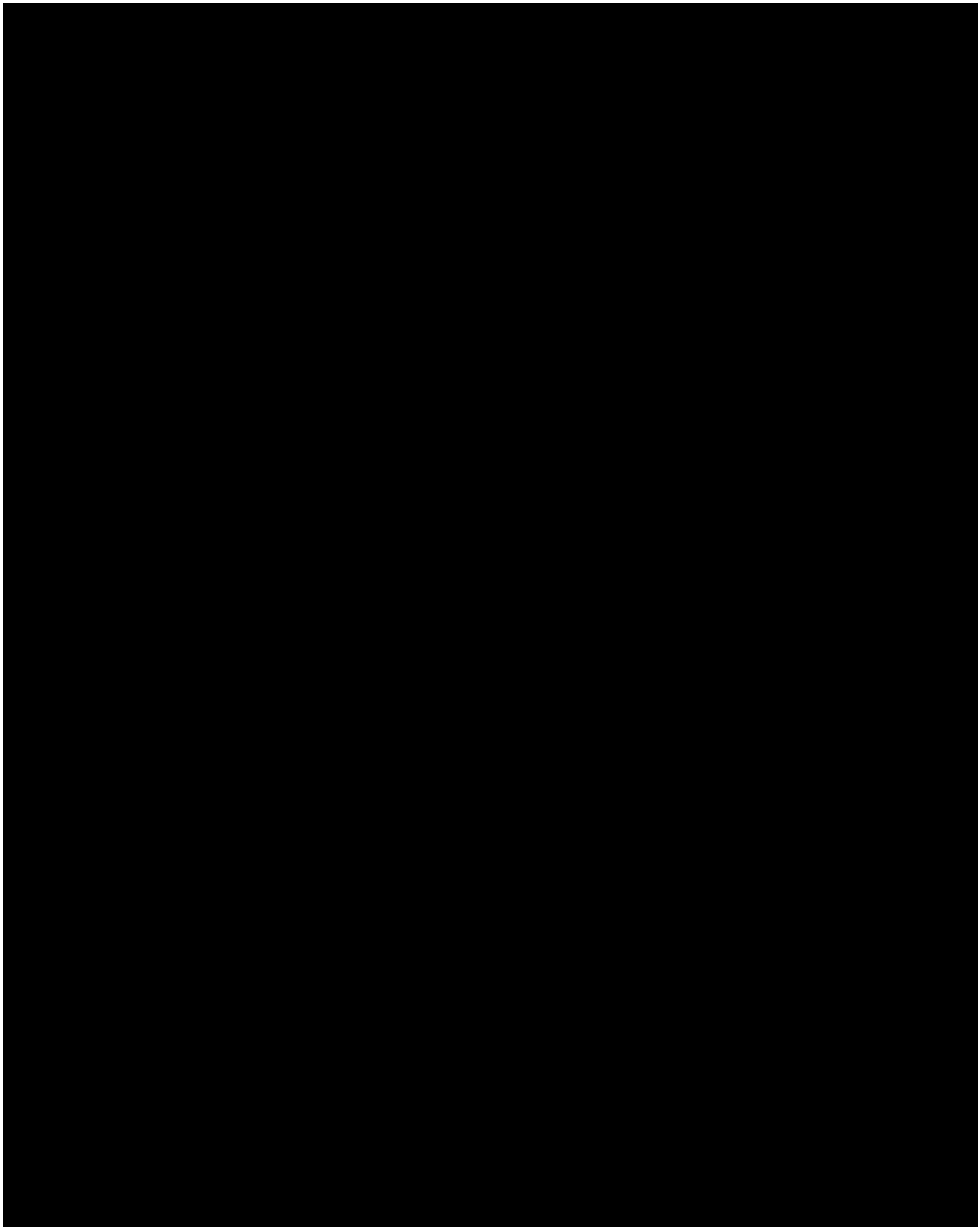

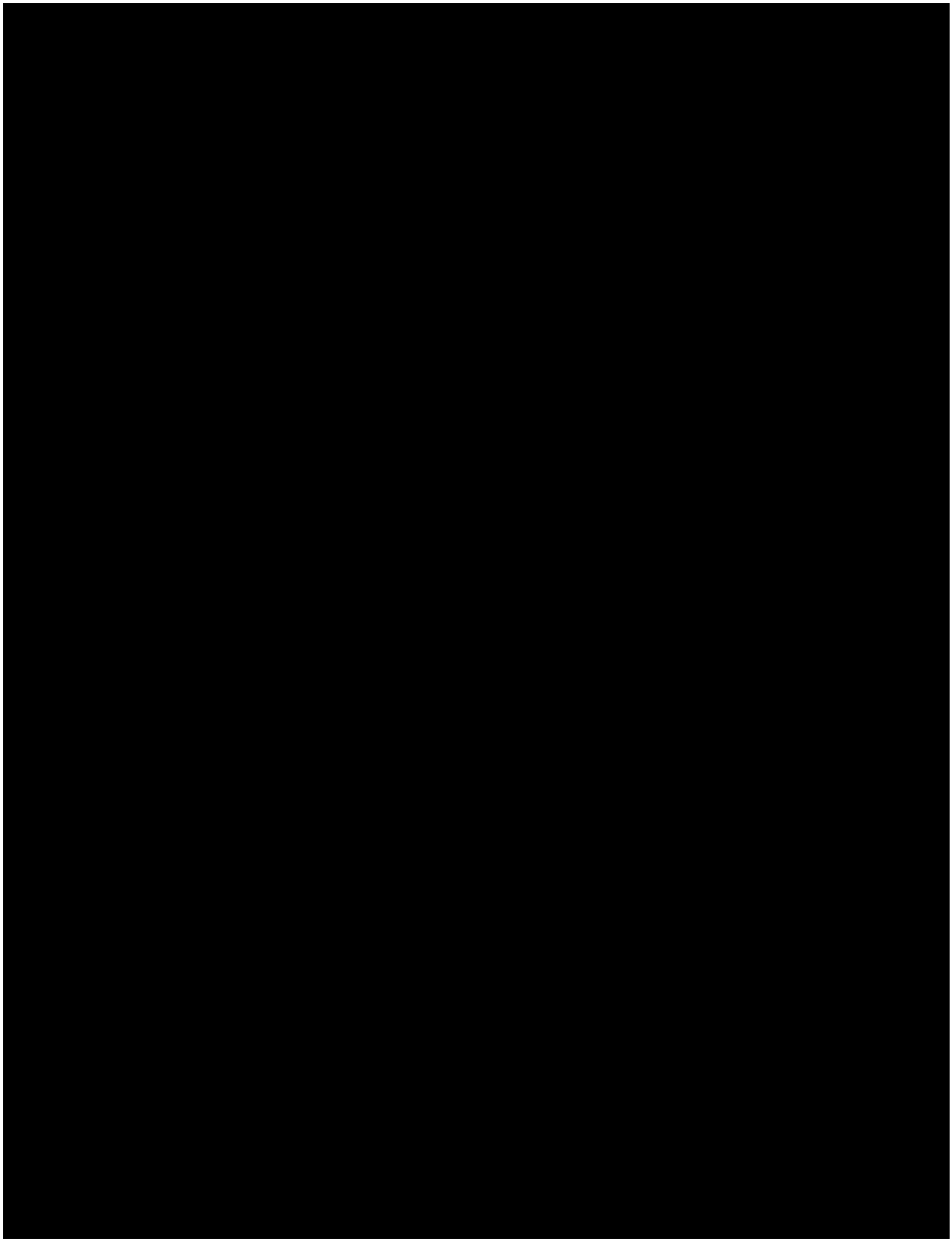

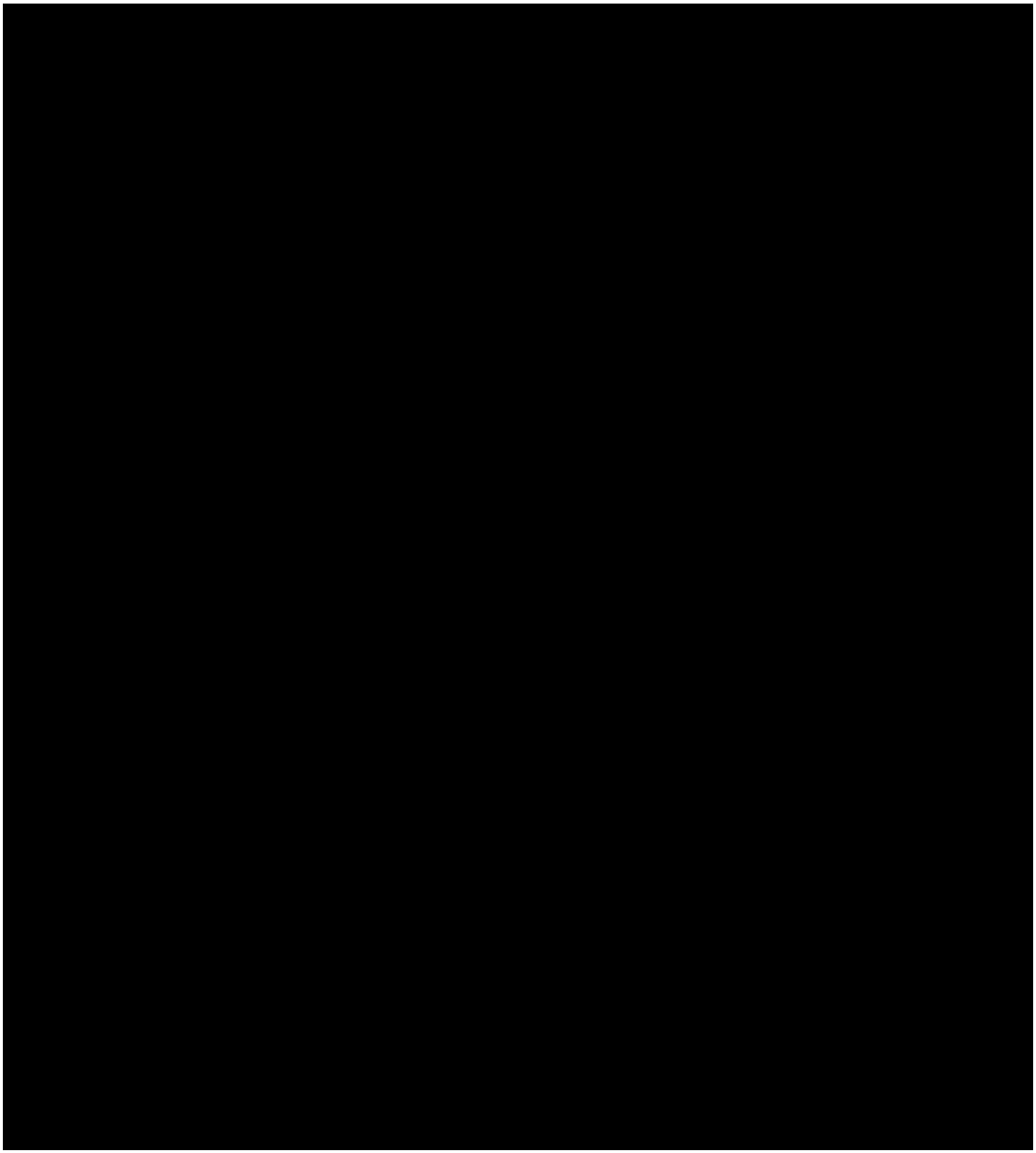

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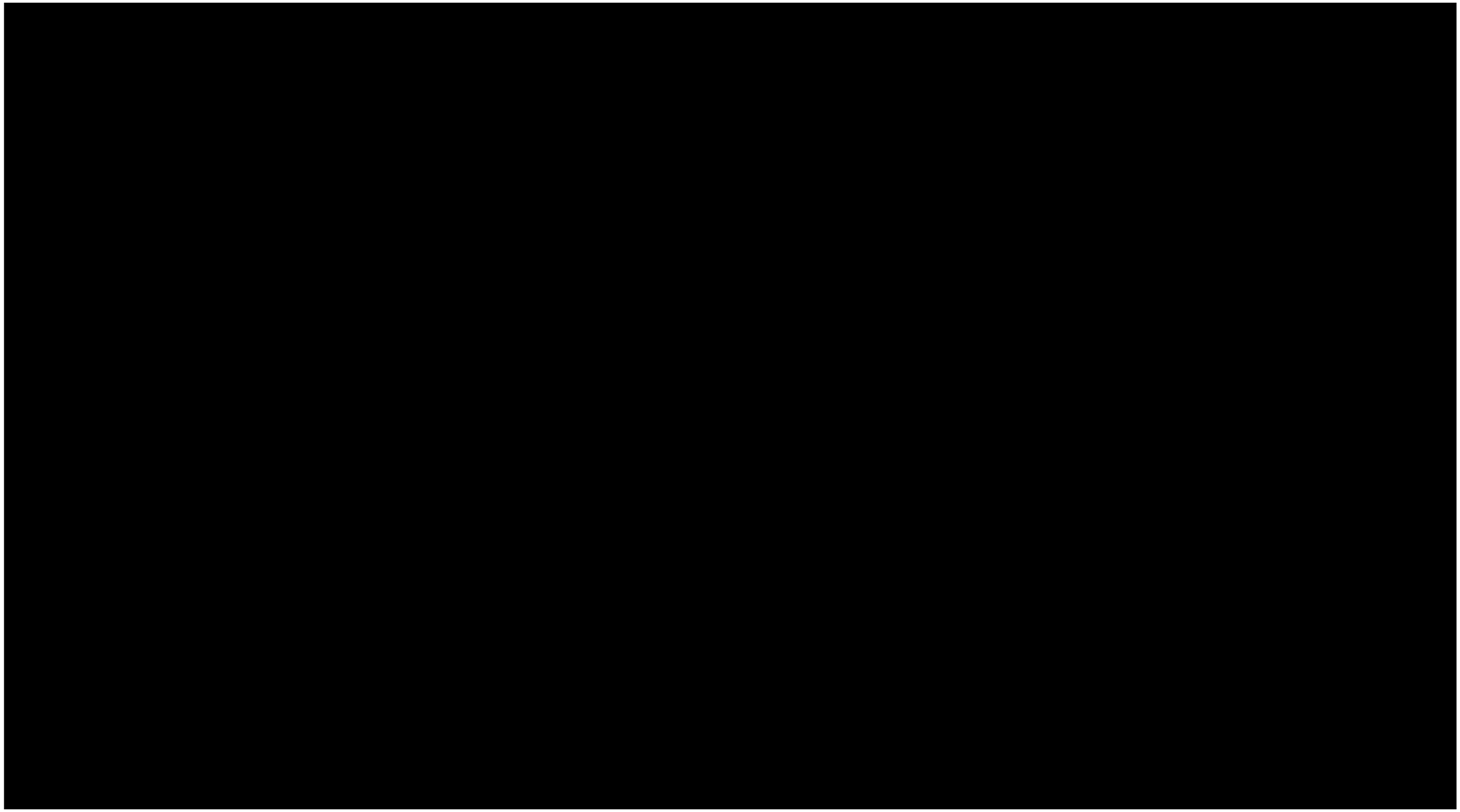
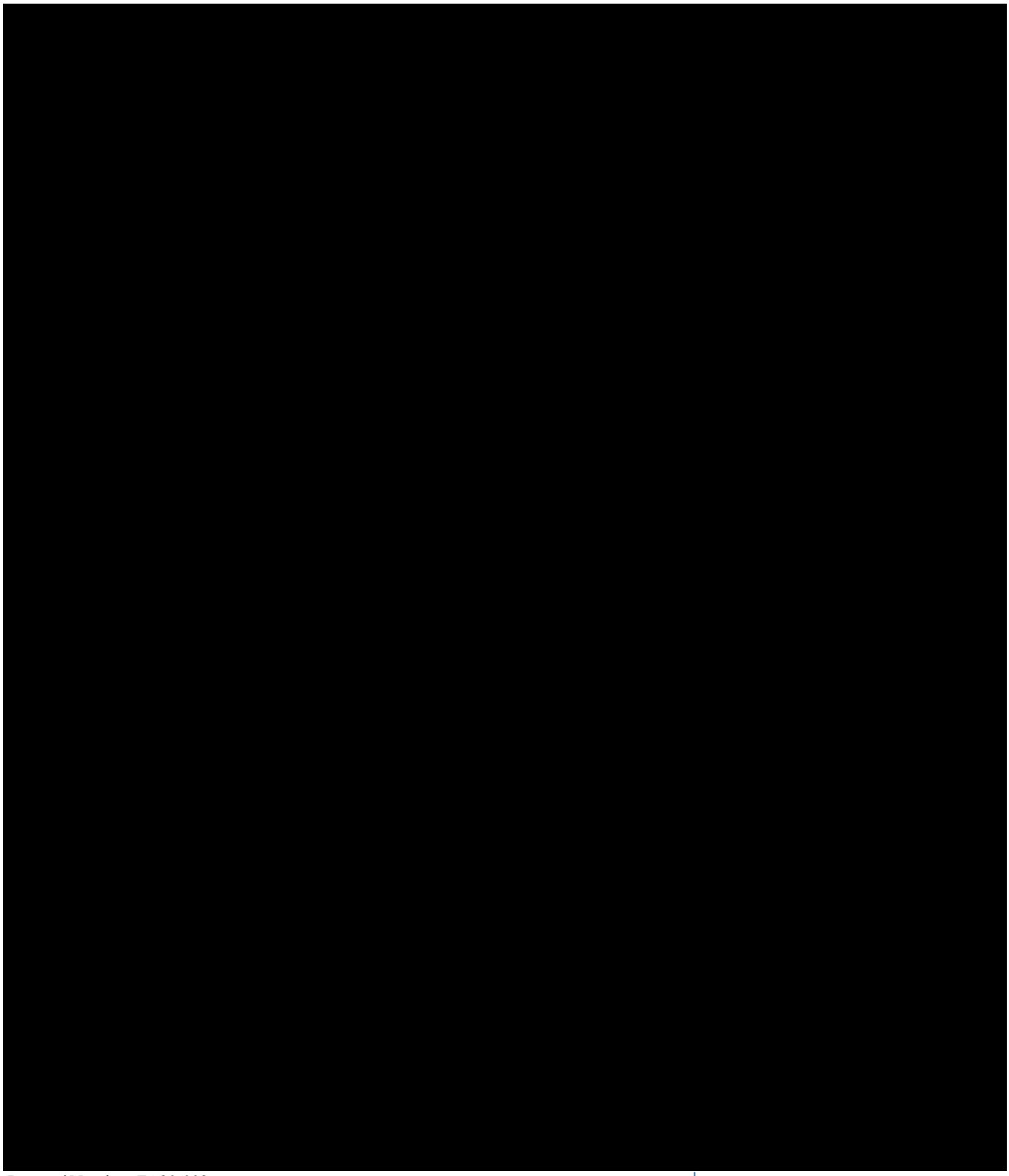
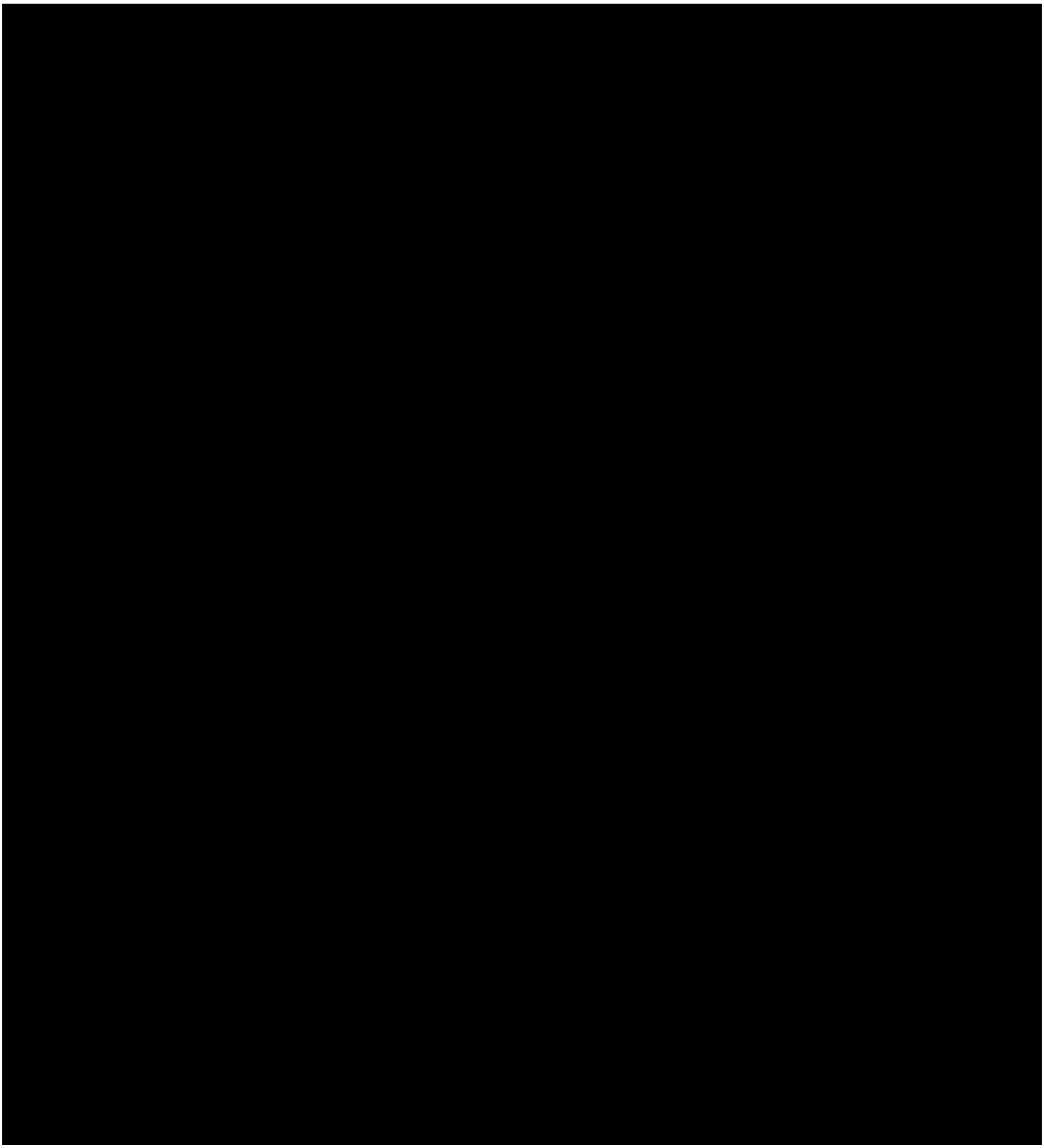
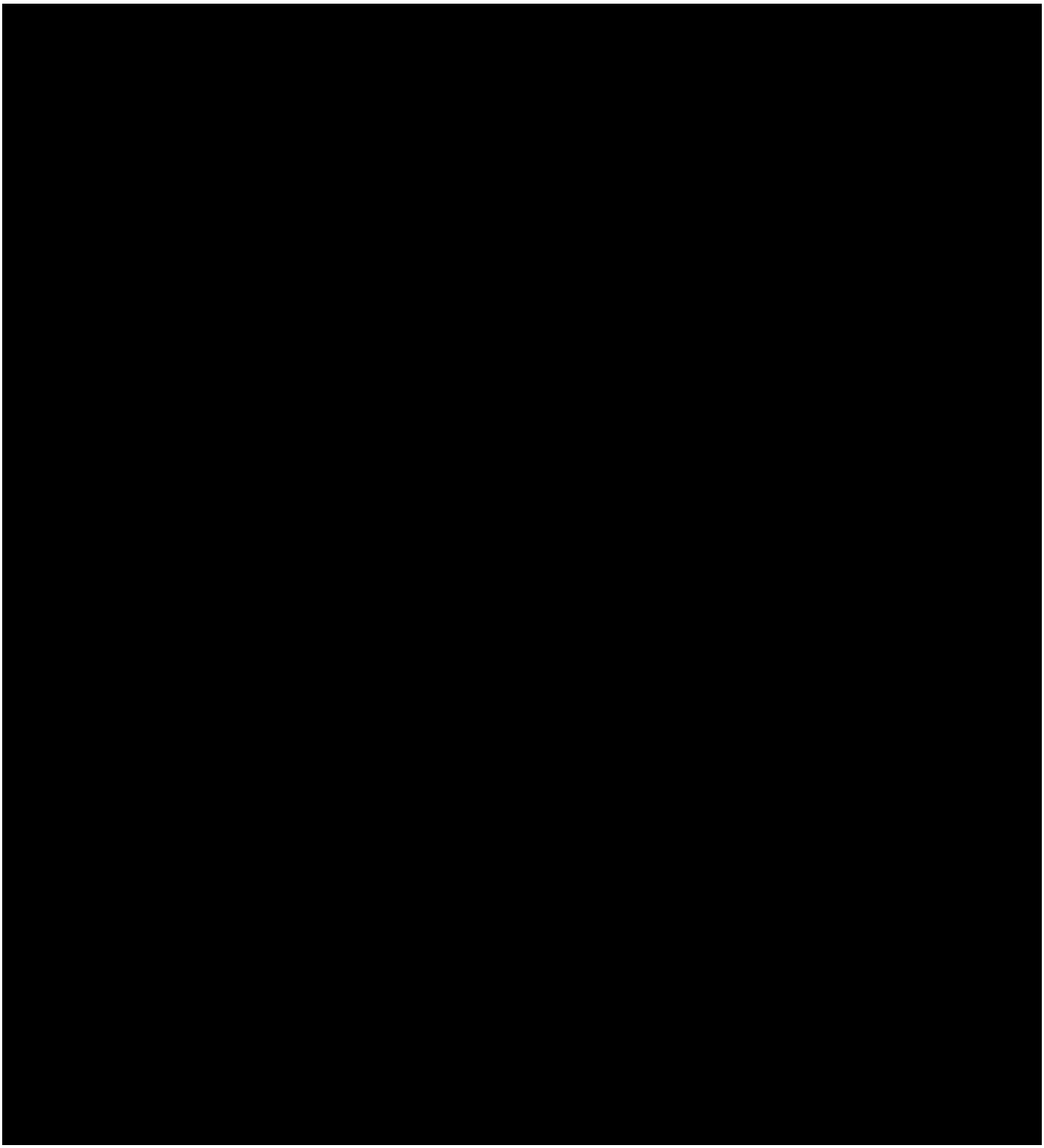
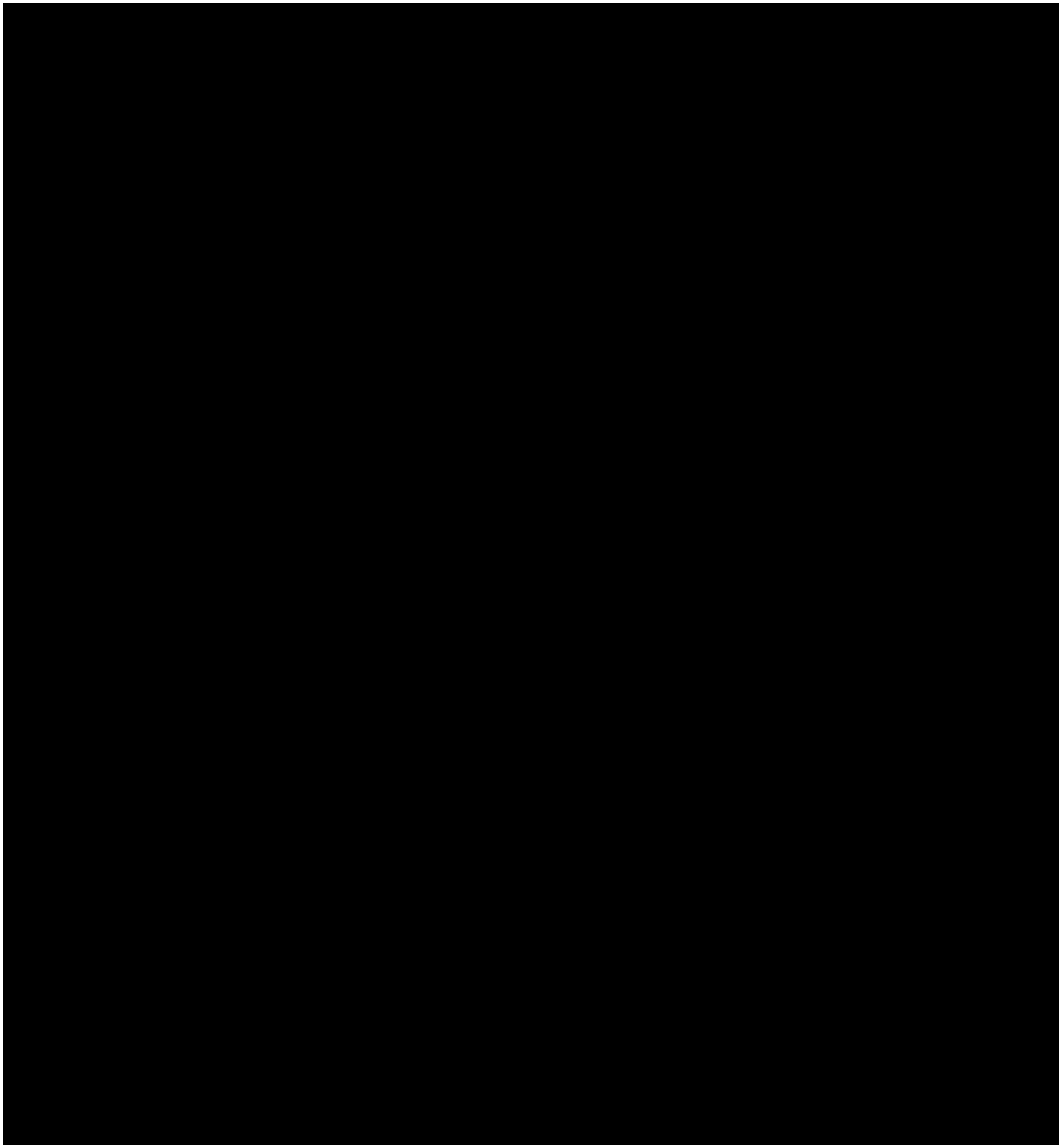
Table 3 summarizes the schedule of visits during the Follow-Up Phase of the study and the assessments to be performed at each visit. The Follow-Up Phase of the study starts after the completion of the final treatment. After the final treatment, a 1 week follow up will be conducted remotely, followed by 3-, 6- and 12 -Weeks Follow-Up Visits. To study the long-term effect of the treatment, subject may be asked to return for 24- and 36-Weeks follow-up (Optional).

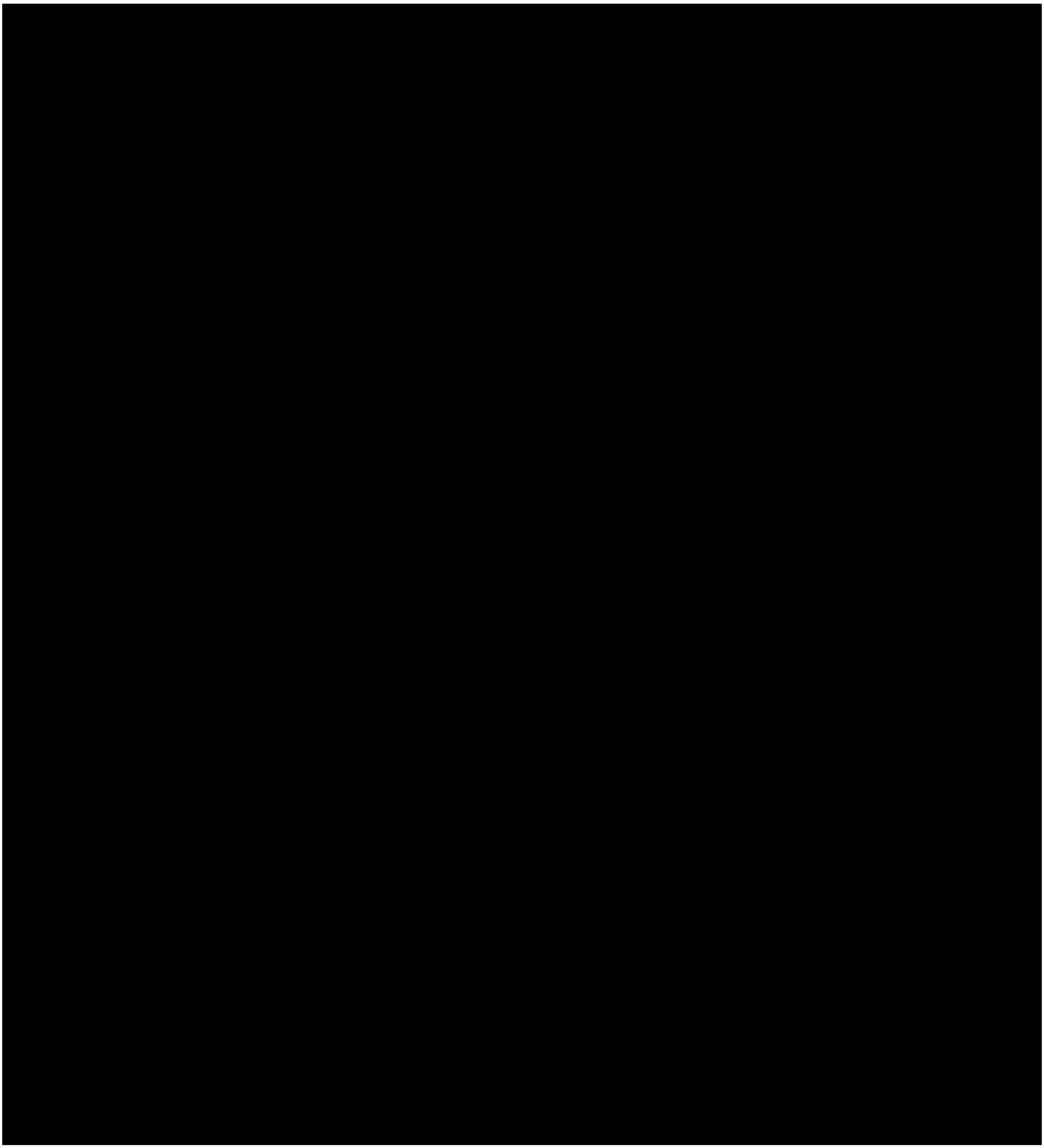












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6 Statistical Methodology and Analyses

6.1 Primary Endpoints

The primary endpoints of the study are defined as follows:

- Safety Endpoint: The frequency of device and procedure-related adverse events (AEs), including device-related serious adverse events (SADEs) and unanticipated adverse events, will be summarized.
- Efficacy Endpoint: Comparison of baseline and 12-week post-final treatment photographs to assess visible changes in the treated areas.

6.2 Statistical Methods: Overall Plan

Data will be summarized based on the nature of the data. Dichotomous (e.g., gender, independent photographic review) and ordinal (e.g., Fitzpatrick Skin type) data will be tabulated by category. The mean, standard error, maximum and minimum will be tabulated for continuous data (e.g., age). The significance level will be two-sided 0.05 for all statistical tests.

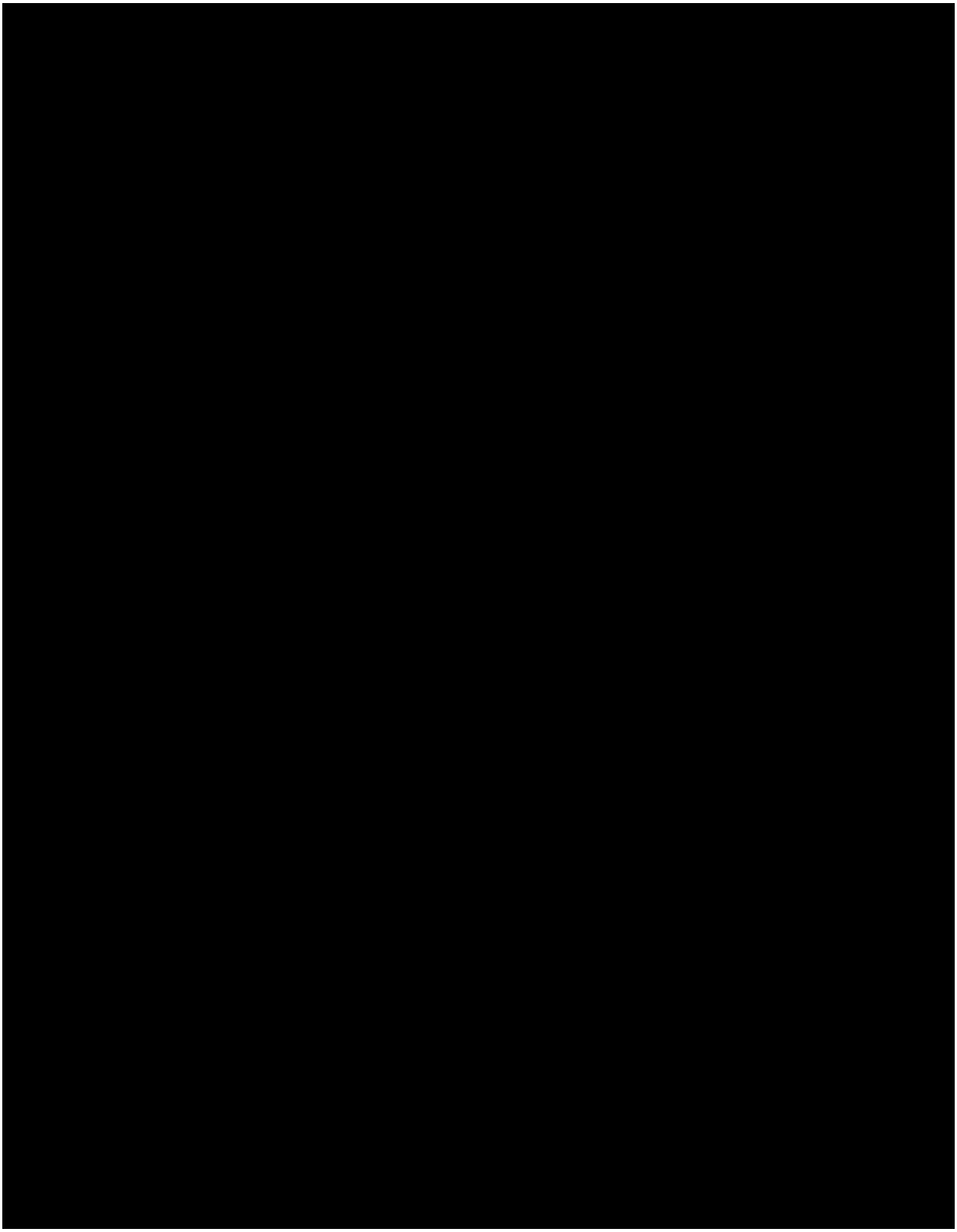
6.3 Analysis Cohorts

6.3.1 Safety Cohort

This cohort will consist of all the treated participants with safety evaluation after the treatment. This cohort should be identical to the As Treated (AT) cohort. The safety data analyses will be performed based on the Safety Cohort.

6.3.2 Effectiveness Cohorts

Two groups of subjects will be identified for the analysis of effectiveness endpoints: Per Protocol Cohort and the As Treated Cohort. All analyses of effectiveness will be



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6.3.4 Missing Data Handling

In general, no imputation for missing data will be made. Data will be analyzed "as-is" where subjects with missing data not being included in the analysis.

6.3.5 Data Pooling

Data are assumed to be poolable across sites due to: 1) use of the same study protocol, 2) equivalent training of all sites in the study protocol and use of the investigational device, 3) use of the same CRF at each site, and 4) use of Independent Evaluator(s).

[redacted]

7 Adverse Events

Adverse events (AE) will be collected and assessed continuously throughout the study. An AE is defined in accordance with ISO 14155 as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in study participants, users, or other persons temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Disease signs and symptoms that existed prior to the study treatment are not considered AEs unless the condition recurs after the patient has recovered from the pre-existing condition or the condition worsens in intensity or frequency during the study.

Adverse events will be monitored throughout the study beginning with signing of informed consent. At each post-baseline visit, the investigator will begin querying for AEs by asking each patient a general, non-directed question such as "Have you had any changes to your condition since your last visit?" Previous AEs and changes in therapy/concomitant medications are to be updated. Directed questioning and examination will then be done as

appropriate. All AEs and clinically significant abnormal laboratory findings will be documented on the appropriate CRF.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any designees are responsible for detecting, collecting and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study until the event has resolved or until 30 days after the completion of the study.

7.1 Adverse Device Effect (ADE)

Any sign, symptom, or disease in a study subject that occurs during the course of a clinical trial that is determined by the Investigator to have a causal relationship or possible causal relationship with the device under investigation. This definition includes any AE s resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error (per ISO 62366) or from intentional misuse of the investigational medical device.

7.1.1 Serious Adverse Device Effect (SADE)

A serious adverse device effect (SADE) is defined in accordance with ISO 14155 as “an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.”

7.1.2 Unanticipated Serious Adverse Device Effect (USADE)

An unanticipated serious adverse device effect (USADE) is defined in accordance with ISO 14155 as “any serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.” The investigator is to consult the IFU for anticipated risks or anticipated AEs.

7.1.3 Serious Adverse Event (SAE)

An SAE is defined in accordance with ISO 14155 as an AE that:

1. Led to death
2. Led to serious deterioration in the health of the patient, that either resulted in:
   a. a life-threatening illness or injury, or
   b. a permanent impairment of a body structure or a body function, or
   c. inpatient or prolonged hospitalization, or

d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, or
e. led to fetal distress, fetal death or a congenital abnormality or birth defect

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.

7.1.4 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs from the signing of the Informed Consent Form (ICF) until the last follow-up visit will be collected at the time points specified in the schedule of activities, and as observed or reported spontaneously by study participants.

Medical occurrences that begin after signing of informed consent and before administration of study treatment will be recorded as an AE on the appropriate CRF.

All SAEs will be recorded and submitted to the Sponsor or designee within 24 hours of learning about the event using the SAE form. All non-serious AEs related to the devices used in the study, as well as Device Complaints, will be submitted to the Sponsor within 7 working days. The investigator will submit any updates on these events to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the final visit of the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly report the event to the Sponsor.

7.1.5 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about possible AEs.

7.1.6 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization based on investigator's assessment, the event is otherwise explained, the participant is lost to follow-up or until 30 days after completion of the study.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as

possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

7.1.7 Reportable Serious Adverse Events (SAEs)

Serious adverse events (SAEs and SADEs) as well as unanticipated adverse device effects (UADEs) /unanticipated serious adverse device effects (USADE) must be reported within 24 hours of knowledge of the event to the Sponsor.

All adverse events observed by the investigator or reported by the subject will be recorded on the appropriate CRF, irrespective of the relationship to the investigational device used in the study. Medically significant adverse events will be followed until resolved or considered stable at investigator's discretion. For each event, the investigator will record a description, dates of onset and resolution, severity, and relationship to the investigational device. The investigator may be required to provide follow-up information as-needed to fulfill requirements for regulatory reporting.

Any adverse event that results in withdrawal from the study must be reported to the Sponsor after the decision to withdraw the subject is made.

Any death occurring during the study must be reported to the Sponsor within 24 hours.

If an event is classified as an SADE or a UADE/USADE, the Sponsor will determine if there is an unreasonable risk to the patients within the study. In the event a UADE/USADE is reported during this study, it will be reported to the IRB and to the regulatory agencies as appropriate according to the relevant standard operating procedures and law of the country where the trial is performed.

7.1.8 Assessment of Severity

Severity of adverse events will be determined using the following scale:

- Mild: Event that is easily tolerated and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: Events that interfere with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. It is usually alleviated with additional specific therapeutic intervention.
- Severe: Event that is incapacitating, with inability to work and do

the usual activities of daily living, or significantly affects clinical status. This may require intensive therapeutic intervention.

7.1.9 Assessment of Relatedness

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relatedness.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the investigator's brochure and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of relatedness.
- For each AE/SAE, there are 4 levels of relatedness, as follows:
    - Not related
    - Possible
    - Probable
    - Definite relationship

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of relatedness for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of relatedness in light of follow-up information and send an SAE follow-up report with the updated relatedness assessment.
- The relatedness assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator will determine the relationship of each adverse event to the study device using the question: "Is there a reasonable possibility that the event may be related to treatment with the device? Answer 'yes' or 'no' for each adverse event."

The guideline below should be used to consider relatedness:

For a “not related” assessment, the adverse event:

- May be judged to be due to extraneous causes such as disease or environment or toxic factors
- May be judged to be due to the subject's clinical state or other therapy being administered
- Is not biologically plausible
- Does not reappear or worsen when the investigational device is re-administered
- Does not follow a temporal sequence from treatment with the investigational device,

For an assessment of relatedness (including, probable and possible assessments) there is a reasonable possibility that the event may have been caused by the investigational device, the adverse event:

- Follows a temporal sequence from treatment with the device.
- Is a known response to the device based on clinical or nonclinical data.
- Could not be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapy administered.
- Disappears or decreases upon cessation of the use of the device.
- Reappears or worsens when the device is re-administered.

7.1.10 Serious Adverse Event Reporting Procedures

All serious adverse events must be reported to the Sponsor within 24 hours of discovery or notification of the event and according to IEC/IRB requirements and the institution at which the study is conducted, if applicable. Serious adverse event information and any follow-up information will be recorded on a Serious Adverse Event Form and transmitted to the Sponsor using the contact information provided

by the Sponsor. Note that for each device used in this study, a separate SAE form and contact information will be used. The Sponsor is responsible for evaluating and reporting any serious adverse event and unexpected serious adverse reactions in accordance with all applicable laws and standards.

Serious Adverse Event Reporting

Serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) must be recorded and reported to the Sponsor or designee within 24 hours of knowledge of the event by the clinical study site to the following contact:

[redacted] - CoolSculpting
Fax: [redacted]
Email: [redacted]

Any additional information regarding the serious adverse event should be submitted to the sponsor in a follow-up form within 24 hours of awareness. The Sponsor is responsible for regulatory reporting and notifying the IRB, as required.

Other adverse events, deemed by the Investigator to be non-serious, should be provided to the Sponsor as soon as possible and not later than 1 week after knowledge of the event. This will be forwarded to the Product Surveillance team within 24 hours of receipt by the Sponsor Contact.

Additional information obtained by the Clinical Site regarding any adverse event, both serious and non-serious, will be reported to the Sponsor within 24 hours of awareness.

Safety Monitoring Considerations

If an adverse event occurs that in the judgment of the investigator represents a potential risk for new subjects, the investigator will contact the Sponsor within 1 working day after becoming aware of the event.

A full reporting of the event shall be provided within 10 working days of the event. The Sponsor is then responsible for notifying the IRB/EC, as required.

7.1.11 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment through the duration of the pregnancy.
- If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and the Allergan Pregnancy Surveillance Form will be completed.

- If a female of childbearing potential becomes pregnant during the study, the investigator should notify the participant's physician that the participant may have been treated with the investigational device and exit the participant from the study.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8 Device Tracking

The Sponsor will send the Investigator investigational devices. The Investigator must house study devices in an appropriate, secure location.

The Sponsor will track sending and receiving of devices to/from the Investigator. The Investigator must track receipt and final disposition of the devices, and maintain accurate records of the use of the device on each study subject.

In addition, for IDE studies, the Investigator must maintain records of receipt, use and disposition of all devices on a device accountability log which will be monitored by the Sponsor and a copy collected at the end of the study. An accurate record of the date the device was used on each subject must be available for inspection at any time.

8.1 Device Packaging and Labeling

Clinical study devices will be packaged and labeled according to the country's regulatory requirements.

The study device or its immediate package, will be labeled per the requirements of 21CFR 812.5(a).

9 Device Deficiencies and Malfunctions

A device deficiency is defined in accordance with ISO 14155 as "inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance." Device deficiencies include malfunctions, use errors, and inadequate labeling.

If a device deficiency occurs, the investigator will notify the Sponsor. Device deficiencies shall be documented throughout the study and appropriately managed and reported to regulatory authorities and IRBs as required by national regulations.

10 Ethical and Regulatory Considerations

10.1 Compliance with Good Clinical Practice

This study will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice (GCP) guidelines and with other applicable regulations. The Investigator and all study staff will conduct the study in compliance with this protocol. Voluntary informed consent will be given by every subject prior to the initiation of any study-related procedures. The rights, safety and well-being of the study subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training and experience to perform their assigned responsibilities.

10.2 Institutional Review Board (IRB) and Informed Consent

Before study initiation, the Investigator must have written and dated approval from the IRB/EC for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The Investigator should also provide the IRB/EC with a copy of the product labeling, information to be provided to subjects and any updates. The Investigator will submit documentation of the IRB/EC approval to the Sponsor. Copies of all correspondence with the IRB/EC regarding this study must be sent to the Sponsor.

The IRB/EC-approved consent form must include all elements required by FDA, state, and local regulations, and may include appropriate additional elements.

The Investigator/designee will explain the study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The Investigator must provide the subject with a copy of the consent form in a language the subject understands. The Investigator will maintain documentation that informed consent was obtained prior to the initiation of any study-specific procedures.

Withdrawal of IRB/EC approval of the Investigator's part in the investigation must be reported to the Sponsor within 5 working days.

10.3 Protocol Adherence

The study investigators are responsible for performing the study in compliance with the protocol. Non-adherence to the protocol is to be classified as a protocol violation, protocol deviation, as defined below.

Protocol Violation

Non-adherence to the protocol that may result in significant additional risk to the participant (e.g., enrollment of a participant who does not meet the study criteria). Or, non-adherence to Good Clinical Practices (GCP) that may impact patient safety (e.g., failure to obtain proper

consent prior to performing study procedures). Violations should be reported to the study Sponsor and the IRB within 5 working days if they occur.

Protocol Deviation

Non-adherence to study procedures which does not result in additional risk to the participant (e.g., participant missed visit). Protocol deviations are not required to be reported to the IRB; however, they must be recorded and addressed on the study case report forms and may be reported and reviewed in conjunction with the progress report as part of the annual review process.

Protocol Waivers

Waivers, exceptions or any intentional deviation from the approved protocol are not permitted in the study.

10.4 Protocol Amendments

Amendments to the study protocol can be made only by the study Sponsor. A revised protocol can be put into place only after governing IRB/EC approval. All administrative letters must be submitted to the IRB/EC for their information.

New or altered consent forms required by the IRB due to a protocol change must be used for any subsequent subject enrollment and when the IRB requires, signed by subjects currently enrolled in the study.

11 Study Management and Quality Control

11.1 Study Data Collection

The Sponsor will supply Case Report Forms (CRFs) to all participating sites for this study.

A CRF is required and will be completed for each included subject. The Investigator has ultimate responsibility for the collection and reporting of all data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the Investigator to attest that the data contained therein are true.

Paper Based CRFs

Demographic, Screening (Inclusion/Exclusion), Treatment, Follow Up, Adverse Event, Protocol Deviation, and Study Termination Data will be recorded on paper Case Report Forms (CRFs) developed by the Sponsor. Completed CRFs will be monitored by the Sponsor or a designee at

defined intervals and the original CRFs will be collected. Copies will remain filed at the investigational sites. The data will then be reviewed by the Sponsor and entered into a study database. Data queries will be issued as necessary to clarify discrepancies.

11.2 Data Management

Data management activities will be performed in accordance with internal Sponsor SOPs for handling data in non-significant risk studies conducted under abbreviated IDE requirements.

11.2.1 Data Receipt and Data Entry

The monitor will collect clinical study related documents including Case Report Forms (CRFs), Data Clarification Forms (DCFs), and any other clinical documents from clinical sites and transmit the documents to the Sponsor as appropriate.

11.3 Confidentiality

All information and data concerning study participants will be considered confidential, and handled in compliance with all applicable regulations including the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

The investigator is responsible for ensuring the confidentiality of subjects throughout the trial. A unique identification code will be assigned to each subject participating in this trial. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity.

Only authorized site staff, the study Sponsor or the Sponsor's designee, IRB/EC or regulatory authorities will have access to these confidential files. All data used in the analysis, reporting and publication of this clinical trial will be maintained without identifiable reference to the participant. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique participant code and will not reveal the participant's identity.

11.4 Quality Assurance Audits

Sponsor representatives or designees may conduct site quality assurance (QA) audits during the study. The Investigator must agree to provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the FDA or other regulatory authorities, the Investigator must give the inspector direct access to relevant documents and to discuss any findings with the inspector. The Investigator must notify Sponsor in the event of a FDA site audit.

11.5 Investigator Responsibilities

11.5.1 General Responsibilities

Investigators are responsible for ensuring the investigation is conducted according to all signed agreements, the Protocol, and applicable FDA regulations. The investigator must protect the rights, safety, privacy and welfare of the participants under the Investigator's care. Investigators will assume overall responsibility and accountability for study site staff and for the clinical data obtained during the study. The investigator assumes all responsibilities per applicable regulations, including but not limited to:

IRB approval: The investigator may not begin the study until the FDA and the governing institutional review board (IRB) provide written approval of the study protocol and consent form. The investigator is also responsible for fulfilling any conditions of approval imposed by the IRB.

Informed Consent: The investigator must ensure that informed consent is obtained from each prospective study participant in accordance with 21 CFR Part 50 and that the study is not commenced until FDA and IRB approvals have been obtained.

Financial Disclosure: Investigators shall provide financial disclosure according to federal regulations.

Study Coordinator: To assure proper execution of the study protocol, each investigator must identify a study coordinator for the site who will work with and under the authority of the investigator to assure that study requirements are fulfilled as appropriate.

11.5.2 Investigator Records

The investigator and study staff must maintain accurate, complete, and current records relating to the conduct of the investigation. Records must be retained for a period of two years following (1) the date the investigation was completed or terminated, or (2) the records are no longer required to support a regulatory submission or completion of a product development protocol, whichever is longer. Participating investigators shall maintain the following:

- All correspondence with the Sponsor, another investigator, the IRB, a monitor, or the FDA
- Records of all persons authorized to conduct the study (e.g. Delegation of Duties/Signature Authorization, CV)
- Records of receipt, use or disposition of the device
- Informed Consent documentation for all enrolled participants

- Records of each participant's case history, including study-required Case Report Forms and source documentation (e.g. physician notes, lab reports, study worksheets, clinic charts)
- All relevant observations of adverse device effects
- Records of any protocol deviations
- The condition of each participant upon entering and during the course of the investigation and any relevant medical history and results of any diagnostic tests
- Record of each participant's exposure to the device, including the date and time of use
- Protocol with all amendments
- Current IRB approved informed consent and all previously approved versions
- Signed Investigator Agreement
- Investigators will be responsible for the accurate and timely completion of CRFs during the trial.

These records must be available and suitable for inspection at any time by Sponsor representatives (monitor), the reviewing IRB, or FDA. The Investigator will supply access to study-related medical records, original laboratory data, and other records and data as they relate to the trial. The investigator will ensure that both he/she and his/her study staff have adequate time and resources to devote to the study, including study enrollment, participant evaluations, study documentation and site monitoring.

11.5.3 Investigator Reports

The investigator is responsible for preparation and submission of the following reports:

- Report of any unanticipated adverse device effects shall be submitted to the Sponsor within 24 hours after the Investigator first learns of the effect
- Withdrawal of IRB approval of the investigator's part in the investigation shall be reported to the Sponsor within 5 working days
- Progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB annually. Alternatively, the Sponsor may prepare the report.
- Deviations from the protocol shall be reported to the Sponsor and the IRB
- Failure to obtain informed consent prior to use of a device in a participant shall be reported to the Sponsor and IRB within 5 working days after the use occurs

- A final report shall be submitted to the Sponsor and IRB within 3 months after termination or completion of the investigation, or the investigator's part of the investigation.

11.6 Sponsor Responsibilities

11.6.1 General Responsibilities:

As the Sponsor, ZELTIQ Aesthetics assumes overall responsibility for the conduct of the study including assurance that the study satisfies applicable regulatory requirements. ZELTIQ Aesthetics assumes all responsibilities per applicable regulations, and shall:

IRB approval: Ensure IRB approval for the investigation. No IDE application is necessary for this study.

Investigators: Select investigators qualified by training and experience, and providing them with the information they need to conduct the study properly. Obtain a signed Investigator Agreement from each participating investigator. Study sites will be evaluated to ensure that they have an adequate participant base and can provide sufficient staff and documentation support to conduct the study properly.

Monitoring: Select monitors qualified by training and experience and ensure proper monitoring of the study.

Data Management and analysis: Ensure data collection, verification, analysis, records storage, etc. Sponsor will assist with presentation(s) and/or publication(s).

Essential Document Records: Maintain all Essential Documents pertaining to the study per ISO 14155:2011. Records must be retained for a period of two years following (1) the date the investigation was completed or terminated, or (2) the records are no longer required to support a regulatory submission or completion of a product development protocol, whichever is longer.

Study Training: To ensure uniform data collection and protocol compliance, Sponsor personnel will provide an educational session to study site personnel which will cover the Protocol, techniques for the identification of eligible participants, data collection and form completion, and the device directions for use. The investigator and study staff will be trained on the study device and protocol, applicable regulations and requirements, and expectations of the study, enrollment expectations, participant selection, informed consent, required clinical data and record keeping, etc.

Device Use: Representatives of the Sponsor will train investigators in use of the study device.

11.6.2 Site Monitoring

The Sponsor will ensure that qualified clinical monitors are available to monitor and oversee the conduct of the trial and that monitoring is performed in accordance with the Sponsor's approved procedures or third-party procedures approved by the Sponsor.

The clinical monitors will evaluate compliance with the protocol and applicable regulations, any specific recommendations made by the site's IRB and the signed Investigator Agreement.

Monitoring Visits

Monitoring will assess the progress of the clinical study and identify any concerns that result from device performance or review of the investigator's study records, study management documents, and informed consent documents.

Monitoring will ensure continued protocol compliance, accurate data reporting, and adequate accounting of shipments of study devices.

The endpoint of this clinical study involves data captured at the 12-Week follow-up visit. Therefore, monitoring will occur after the 12-Week follow-up visits are completed at each site. Monitoring will occur at each site prior to study closeout.

During monitoring visits, the monitor will review participant records and other supporting documents to determine that:

- The facilities used by the investigation continue to be acceptable for the purposes of the clinical study
- Informed consent was properly obtained and documented for all enrolled study participants
- The protocol is being followed, and only eligible participants are being enrolled into the study
- Deviations to the Protocol have been reported to the Sponsor and the IRB, as appropriate
- Adverse events are promptly being reported
- Device accountability is being maintained
- Information recorded in the case report forms and study reports are accurate, complete, legible and consistent with source documentation
- Participants failing to complete the clinical study and the reason for failure are recorded
- Missed follow-up visits are noted in the study documentation

Clinical monitors will provide feedback to the site regarding protocol or study compliance. If monitoring reveals significant Investigator noncompliance with the study agreements, protocol, applicable regulations, IRB approval conditions, the monitor will notify Sponsor Clinical Management. Action will be taken to secure compliance, and if further compliance problems persist, or the issue is deemed serious (i.e. endangering patient welfare or safety), the site may be removed from the study and/or the investigator disqualified from future studies.

Study Site Closeout

At the close of the study at an investigational site, the monitor will conduct a final visit to ensure that all case report forms have been monitored and retrieved and that the investigator's files are accurate and complete. The monitor will ensure that all investigational devices and study supplies are accounted for, and provide for appropriate disposition of any remaining supplies. The monitor will review record retention requirements with the investigator and any remaining investigator obligations are reviewed and ensure that all applicable requirements are met for the study. The monitor will prepare a report of the site closeout visit. The closeout visit may be combined with a final monitoring visit.

11.6.3 Final Report

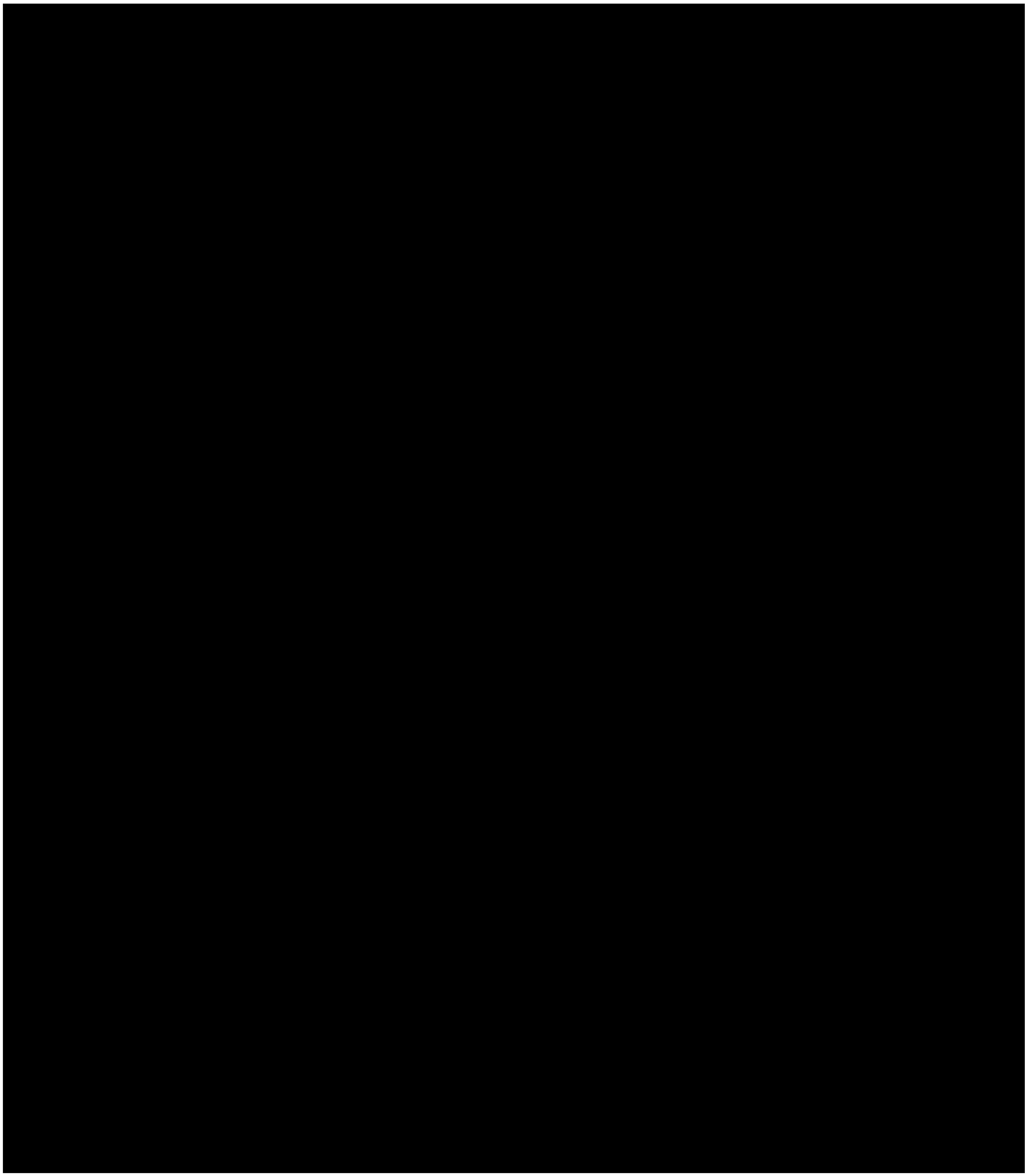
A final report will be prepared at the conclusion of the trial. Copies of the final report will be provided to each investigator and to the respective IRBs.

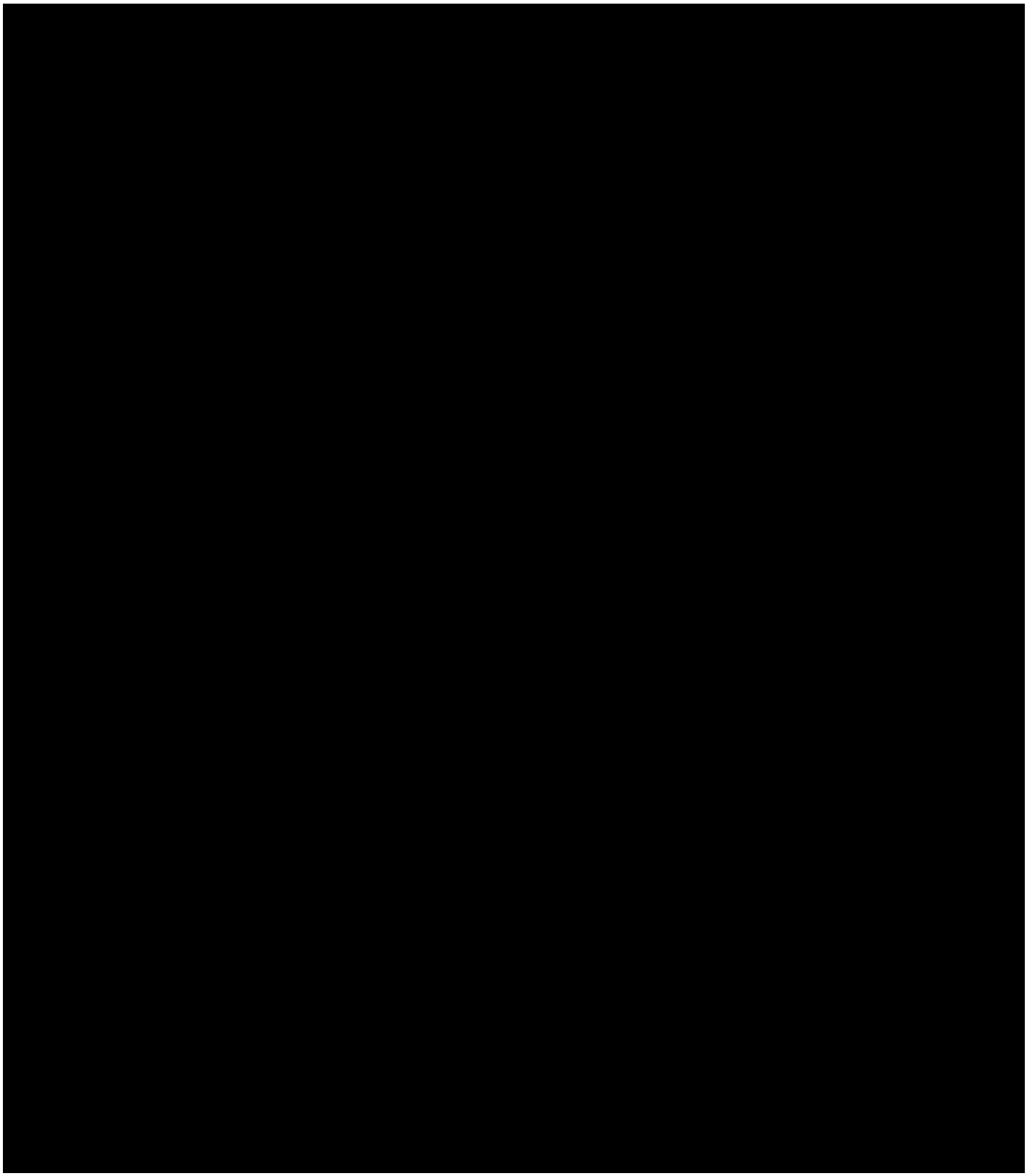
11.6.4 Trial Registration

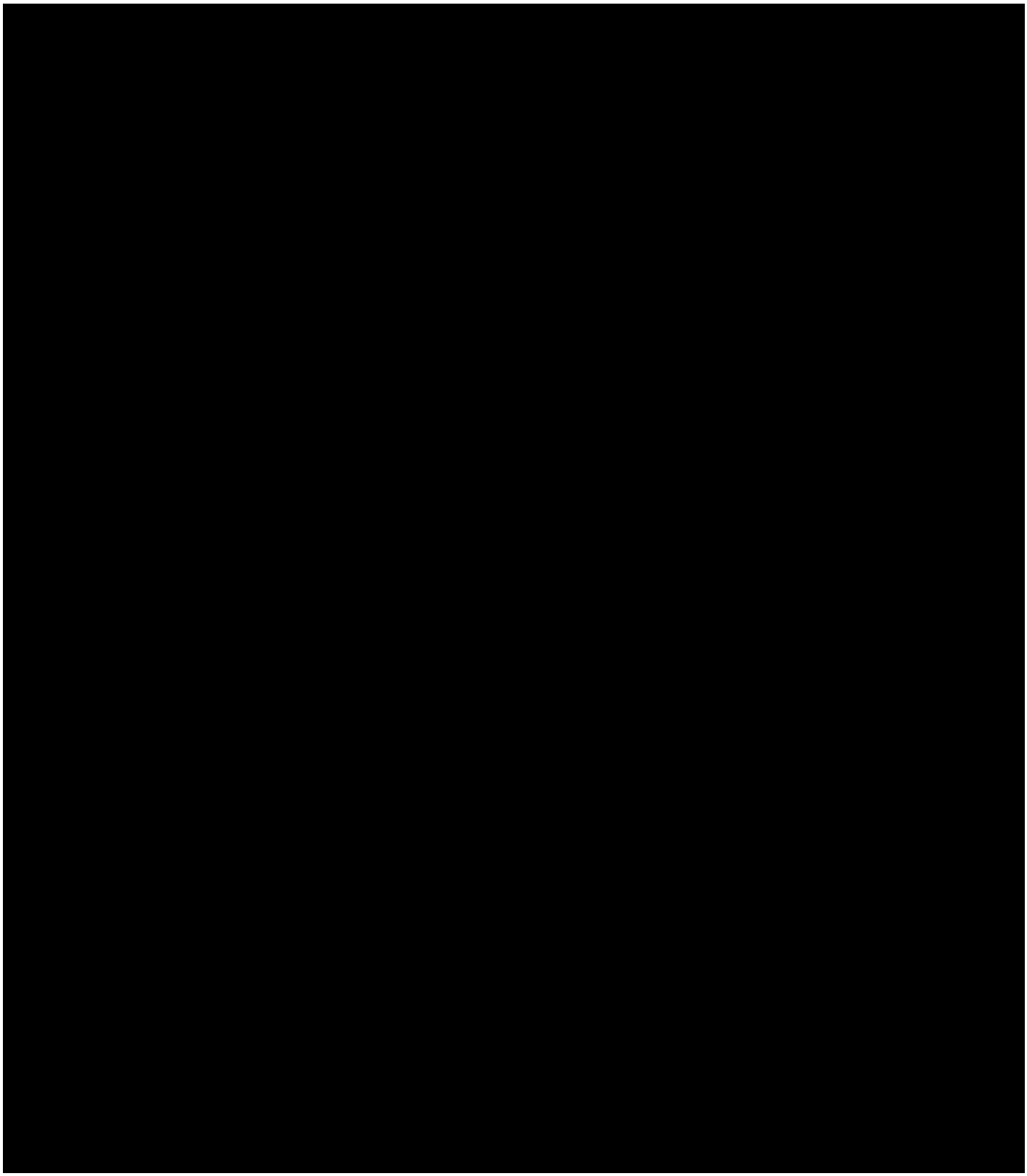
When appropriate, prior to study initiation, the trial will be registered on a publicly accessible study database such as clinicaltrials.gov.

12 Data Ownership

ZELTIQ Aesthetics, the study Sponsor, retains ownership of all data generated in this study, and controls the use of the data for purposes of regulatory submissions to the US and/or other governments. Investigator(s) and institution(s) (which shall include their employees, agents, and representatives) may not issue or disseminate any press release or statement, nor initiate any communication of information regarding this study (written or oral) to the communications media or third parties without the prior written consent of the Sponsor.







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Signature

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