NCT #: NCT03873779

FEASIBILITY STUDY TO EXPLORE THE SAFETY AND EFFICACY OF CRYOLIPOLYSIS FOLLOWED BY RADIOFREQUENCY TREATMENT FOR SUBMENTAL AND SUBMANDIBULAR CONTOURING

Investigational Plan

Sponsor	ZELTIQ, an Allergan Affiliate 4410 Rosewood Drive Pleasanton, CA 94588
Protocol Number:	ZA18-002
Protocol Version:	2.0
Protocol Date:	February 19, 2019
Product:	ZELTIQ CoolSculpting® System
Investigator/Co-Investigator(s):	PPD Innovation Research Center 4410 Rosewood Dr. Pleasanton, CA 94588
Sponsor Contact	PPD PH: PPD Fax: PPD

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INVESTIGATOR SIGNATURE PAGE

For protocol number ZA18-002

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 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

_____	_____	_____
Co- Investigator printed name	Signature	Date

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1. Protocol Summary

Title	Feasibility study to explore the safety and efficacy of cryolipolysis followed by radiofrequency treatment for submental and submandibular contouring
Design	Prospective, randomized, interventional cohort
Purpose	The purpose of this study is to evaluate the safety and efficacy of sequential use of CoolSculpting (Cryolipolysis) and radiofrequency treatment of the submental and submandibular area
Enrollment	Up to forty (40) subjects
Clinical Site	Up to three (3) investigational sites
Subject Population	Healthy adult men and women with skin fold thickness of > 1 cm in the submental and submandibular area who desire reduction of submental and submandibular fat
Primary Endpoint	Safety endpoint: Incidence of unanticipated adverse device effects (UADE). It is expected there will be zero UADEs. Efficacy Endpoint: Assessment of overall treatment outcome in submental and submandibular area using Investigator-graded Global Aesthetic Improvement Scale (IGAIS) at 12-weeks post final treatment.
Secondary Endpoint	Efficacy Endpoints: 1. Assessment of overall treatment outcome in submental and submandibular area using Subject-graded GAIS (SGAIS) administered at 12 weeks post-final treatment. 2. Subject Satisfaction as assessed by the Subject Self-Rating Scale score (SSRS). 3. Subject satisfaction as assessed by questionnaire administered at 12-weeks post treatment. 4. Reduction in fat layer thickness, as measured by caliper at 12 weeks post-final treatment.
Sponsor	ZELTIQ, an Allergan Affiliate 4410 Rosewood Drive Pleasanton, CA 94588

2. Introduction

2.1. Background

Fat reduction and body contouring procedures, which include invasive, minimally-invasive, and non-invasive procedures, have become increasingly popular aesthetic procedures. Patients who are obese and do not have specific fat bulges but require significant fat reduction to achieve aesthetic results are candidates for invasive and minimally-invasive procedures, such as liposuction and laser-assisted liposuction. Although effective at reducing fat, these invasive and minimally-invasive procedures involve significant patient pain, expense, downtime, and the risks typically associated with surgical procedures. As a result, patients who do not require significant fat reduction to achieve meaningful aesthetic results typically seek non-invasive fat reduction and body contouring procedures to avoid the pain, expense, downtime, and surgical risks associated with invasive and minimally-invasive procedures.

ZELTIQ Aesthetics has developed and commercialized a technology to non-invasively reduce subcutaneous fat. The ZELTIQ technology utilizes the sensitivity of fat cells to cold injury in order to selectively eliminate subcutaneous fat tissue without affecting the skin or other surrounding tissues. Termed cryolipolysis, this technology enables a non-invasive alternative for subcutaneous fat reduction through cellular apoptosis. The ZELTIQ CoolSculpting System, which is cleared for use in the United States for an indication of fat layer reduction in the flanks, abdomen, thighs, bra fat, back fat, banana roll, upper arms, and submental and submandibular areas through cold-assisted lipolysis, has been clinically proven to reduce fat bulges, allowing patients to achieve noticeable and measurable aesthetic results without the pain, expense, downtime, and risks associated with existing invasive and minimally-invasive procedures.


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2.2. Device Description

The CoolSculpting System is comprised of a control unit **(Figure 3**) which houses the system controller and power source, and detachable applicators such as the CoolMini (**Figure 4**), that are used to apply the cooling and/or warming to the treatment site. The vacuum applicators use vacuum pressure to draw tissue into the cup shaped applicator. Tissue drawn into the cup will be treated using a cooling parameter of -11˚C for up to 45 minutes.

Figure 3. CoolSculpting System Control Unit.

Figure 4: CoolMini Applicator.

2.3. Regulatory Status

The ZELTIQ System received market clearance on August 24, 2010 for "use as a non-invasive dermatological aesthetic treatment to affect the appearance of flanks" (DEN090002). On May 9, 2012, the ZELTIQ System received market clearance for treatment of the abdomen (K120023); on April 9, 2014 the System received market clearance for treatment of the thighs (K133212); and on September 24, 2015 the System received market clearance for treatment of the submental area (K151179). Subsequently, the System received clearance for bra fat, back fat and banana roll (K160259), upper arms (K162050), the submandibular area (K181740), and can affect the appearance of lax tissue after submental treatment (K172144). FDA clearance allows treatment duration of up to 120 minutes, and at temperatures as low as -15°C.

This study will investigate the use of the FDA-cleared ZELTIQ CoolSculpting System and the CoolMini vacuum applicator for treatment of subcutaneous fat in the submental and submandibular area followed by radiofrequency treatment either immediately post cryolipolysis

or 10-14 weeks later. Results from this clinical trial will be used to further support safety and efficacy of using the Zeltiq CoolSculpting System sequentially with radiofrequency for fat reduction/improved aesthetic outcome in the submental and submandibular areas.

3. Study Protocol

3.1. Design

Prospective, randomized, interventional cohort.

3.2. Study Duration

Enrollment and follow-up is expected to take up to six (6) months for each subject.

3.3. Physician Participants

Study investigators must be practicing medical physicians with experience in the use of the ZELTIQ CoolSculpting System and radiofrequency energy device.

3.4. Site Requirements

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

3.5. Subject Recruitment

Subjects who seek reduction of fat in the submental area and submandibular area will be recruited from the general population.

3.6. Sample Size

A maximum of forty (40) subjects will be treated at up to three investigational sites.

3.7. Subject Eligibility

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

Table 1. Eligibility criteria.

Inclusion Criteria a) Male or female subjects ≥22 years of age and ≤65 years of age. b) Treatment area skin fold thickness > 1cm (measured by caliper). c) Dissatisfaction with the treatment area expressed by the subject as a rating of 0, 1 or 2 using the Subject Self Rating Scale (SSRS) as determined at Screening visit. d) No weight change exceeding 5% of body weight in the preceding month. e) Agreement to maintain his/her weight (i.e., within 5%) by not making any major changes in diet or exercise routine during the course of the study. f) Subject has signed a written informed consent form.
Exclusion Criteria a) Body Mass Index ≥ 46.2 as determined at screening. b) Excessive skin laxity in the treatment area for which reduction of subcutaneous fat may, in the opinion of the investigator, result in an unacceptable aesthetic result. c) Prominent platysmal bands at rest which may interfere with assessment of treatment area. d) Evidence of any cause of enlargement in the treatment area other than localized subcutaneous fat, such as swollen lymph nodes or ptotic submandibular glands. e) Significant enlargement on the anterior neck that may prevent the proper placement of the applicator e.g. enlarged thyroid glands. f) Treatment with dermal fillers, chemical peels, radiofrequency or laser procedures that may affect contour in the treatment area within the past 6 months. g) Botulinum toxin, deoxycholic acid, or other aesthetic drug injections within the treatment area in the past 6 months. h) History of facial nerve paresis or paralysis (such as Bell's palsy). i) History of a fat reduction procedure (e.g., liposuction, surgery, lipolytic agents, etc.) or implant in or adjacent to the area of intended treatment. j) History of prior neck surgery, or prior surgery in the area of intended treatment. k) Current infection in and adjacent to treatment area.

l) Known history of cryoglobulinemia, cold urticaria, cold agglutinin disease or paroxysmal cold hemoglobinuria.
m) Known history of Raynaud's disease, or any known condition with a response to cold exposure that limits blood flow to the skin.
n) History of bleeding disorder or is taking any medication that in the investigator's opinion may increase the subject's risk of bruising.
o) Currently taking or has taken diet pills or weight control supplements within the past month.
p) Any dermatological conditions, such as scars in the location of the treatment area that may interfere with the treatment or evaluation.
q) Active implanted device such as a pacemaker, automatic implantable cardioverter/defibrillator (AICD), drug delivery system, or any other implantable electrical device.
r) Pregnant or intending to become pregnant in the next 6 months.
s) Lactating or has been lactating in the past 6 months.
t) Unable or unwilling to comply with the study requirements including remaining clean shaven for all study visits.
u) Currently enrolled in a clinical study of an unapproved investigational drug or device.
v) 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.

3.8. Informed Consent

Study candidates shall receive an explanation of the study objectives, possible risks and benefits of the study, and be given adequate time to read the information included in the informed consent document. Candidates will be given an opportunity to ask questions about any of the information contained in the informed consent. Candidates must verbally acknowledge understanding of the informed consent and sign the consent form accordingly. This form must have prior approval of the Institutional Review Board (IRB).

3.9. Screening Procedures

Screening Visit; Required; Day -45 to Day 0

The subject shall be consented for study participation as described in Section 3.8. After the informed consent is signed, subjects will be screened for eligibility. Each subject will be evaluated to determine that all eligibility criteria are met. The investigator or designee shall complete a brief medical history and examine the subject to confirm eligibility for the study.

1. Obtain height and weight.
2. Obtain Subject Self-Rating Scale score.
3. Visually assess and palpate the intended treatment area to determine if it is appropriate for treatment.
4. Assess oral cavity for current dental infection or evidence of dry mouth.
5. Assess function of the marginal mandibular nerve (grimace with ability to show lower teeth) and hypoglossal nerve (tongue does not deviate upon protrusion).
6. Assess upper neck to rule out enlarged lymph nodes or glands.
7. Measure the skin fold thickness of the intended treatment areas using a caliper.
8. Assess for dermatological conditions or implantable devices that may lead to exclusion of a subject from the study.
9. Document potential candidate's medication use (including over-the-counter medications, vitamins and herbs), Fitzpatrick Skin Type, race and ethnicity as well as any skin irregularities (e.g. moles, birth marks, scars, stretch marks, discoloration) at the intended treatment area.

All female subjects of childbearing potential will be assessed for the start date of their last menstrual cycle to determine if they may be pregnant. If unsure, a pregnancy test (urine) may be taken at the screening visit. If the subject is pregnant, she will be excluded from participation. Subjects will also be advised to avoid becoming pregnant during the course of the study by using a medically accepted form of contraception if they are sexually active. If the subject 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.

All subjects will be asked to maintain their weight by not making any major changes to their diet or exercise regimen during the course of the study. If a subject's weight change is more than 5% at 12 weeks after the final treatment, the subjects' data will be excluded from the primary effectiveness analyses. Subjects who do not maintain their weight within 5% will continue in the study, however their data will be excluded from efficacy analyses.

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

3.10. Study Enrollment

Study candidates who sign the informed consent and meet eligibility criteria a and desire to be in the study are considered enrolled.


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- Subject satisfaction as assessed by questionnaire administered at 12-weeks post-final treatment.

3.15. Statistical Analysis Plan

3.15.1. 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.

3.15.2. Analysis Population

Analysis Populations are defined as following:

Per-protocol Population (PP):

The Per-protocol Population will consist of all treated subjects followed for 12 weeks post final treatment and with weight change of no more than five percent at the time the 12-week post final treatment images are taken. Since a weight change of more than 5 percent will affect the images, the primary efficacy analysis will be performed based on this study population. Subjects who do not complete treatment will not be included in the primary and secondary efficacy analyses.

As-Treated Population (AT):

This population consists of all treated subjects regardless of whether they become pregnant or undergo weight change during the study.

Safety Population (SA):

This population will consist of all treated subjects with safety evaluation after the treatment. This population should be identical to the AT population. The safety data analyses will be performed based on the Safety Population.

Sample Size Requirement


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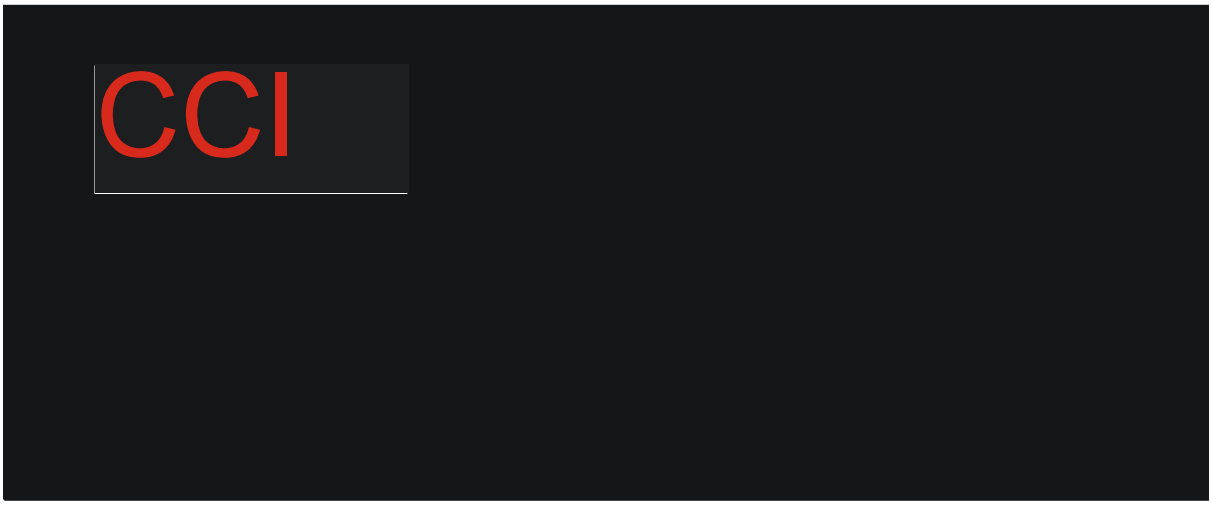

3.16. Protocol Adherence

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 or protocol deviation, as defined below.

Protocol Violation

Non-adherence to the protocol that may result in significant additional risk to the subject (e.g., enrollment of a subject 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 subject (e.g., subject missed visit). Protocol deviations are not required to be reported to the IRB; however, they must be recorded 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.

3.17. Adverse Events

Adverse events (AE) will be assessed continuously throughout the study. An adverse event is defined as any untoward medical occurrence in a subject, regardless of whether the event is related to the device.

All AEs and device deficiencies will be recorded on the corresponding CRF for the subject.

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.

Device Deficiencies

A device deficiency is defined in accordance with ISO 14155 as inadequacy of a medical device including issues 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 investigational site will document the event using the CRF. Device deficiencies will be documented throughout the study and appropriately managed and reported to regulatory authorities and IRBs as required by Federal regulations.

Serious Adverse Event (SAE)

Any untoward medical occurrence in a subject, regardless of whether the event is related to the device that:

a. results in death;
b. results in a life-threatening illness or injury;
c. results in a permanent impairment of a body structure or body function;
d. requires in-patient hospitalization or prolongation of existing hospitalization
e. results in medical or surgical intervention to prevent impairment to body structure or function;
f. results in fetal distress, fetal death, or a congenital abnormality/birth defect.

Unanticipated Adverse Device Effect (UADE)

Any serious adverse effect on health and safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The Investigator shall be responsible for determination of the causal relationship of all adverse events to the device and/or procedure. The Principal Investigator is responsible for monitoring the safety of the subjects enrolled.

The Sponsor is responsible for the ongoing safety evaluation of the product(s). The Sponsor shall be responsible for adjudication of all reported adverse events to determine whether the event is reportable under federal regulations (i.e., 21 CFR812.150[b][1]). The Sponsor will promptly notify all participating investigators and regulatory authorities, as appropriate, of findings that could affect adversely the safety of subjects, impact the conduct of the trial or alter the IRB's approval opinion to continue the trial.

3.18. Reportable Incidents

Serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) must be recorded and reported to the manufacturer of the study device and to the Sponsor or designee within 24 hours of knowledge of the event.

PPD
ZELTIQ, an Allergan Affiliate
4410 Rosewood Drive
Pleasanton, CA 94588
PPD (cell)
PPD (office)
PPD (fax)

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, 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.

4. Study Management and Quality Control

4.1. Study Data Collection

Standardized Case Report Forms (CRFs) will be provided to all participating sites. Data will be reviewed by the study monitor and Sponsor data management personnel to identify inconsistent or missing data and to ensure compliance with the study protocol.

4.2. Confidentiality

All information and data concerning study subjects 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.

Only authorized site staff, the study Sponsor or the Sponsor's designee and IRB will have access to these confidential files. A unique identification code will be assigned to each subject participating in this trial. All data used in the analysis, reporting and publication of this clinical trial will be maintained without identifiable reference to the subject. 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.

4.3. Investigator Responsibilities

4.3.1. General Responsibilities

Investigators are responsible for ensuring the investigation is conducted according to all signed agreements, the Investigational Plan, and applicable regulations. The investigator must protect the rights, safety, privacy and welfare of the subjects 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 governing institutional review board (IRB) provides 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 subject and that the study is not commenced until IRB approval has been obtained.

Device Accountability

Device accountability is not applicable for this non-significant risk study.

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.

4.3.2. 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, and a monitor
- 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 subjects
- Records of each subject'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 subject upon entering and during the course of the investigation and any relevant medical history and results of any diagnostic tests
- Record of each subject’s exposure to the device, including the date and time of use

- Investigational plan 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), or the reviewing IRB. 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, subject evaluations, study documentation and site monitoring.

4.3.3. 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 and no later than 10 working days 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 or violations of the investigational plan shall be reported to the Sponsor, and the IRB as required.
- Failure to obtain informed consent prior to use of a device in a subject 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.

4.4. Sponsor Responsibilities

4.4.1. General Responsibilities

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

IRB approval

Ensure IRB approval for the investigation. Ensure IRB approval for a supplemental application before beginning that portion of the investigation.

Investigators

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

Monitoring

Select monitors qualified by training and experience to monitoring the study and ensure proper monitoring of the investigation.

Investigational devices

Not applicable. This is a non-significant risk study

Data Management and Analysis

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

4.4.2. Training

Study Training

To ensure uniform data collection and protocol compliance, Sponsor personnel will provide an educational session to study site personnel as needed, which will cover the protocol, techniques for the identification of eligible subjects, 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, subject selection, informed consent, required clinical data and record keeping, etc.

Device Use and Procedure

Representatives of the Sponsor will train study site staff in use of the study device. Sponsor representatives may be present at study procedures.

4.4.3. 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, any specific recommendations made by the site's IRB and the signed Investigator Agreement.

Site Qualification Visit

A pre-study meeting will occur with the study site to evaluate the site's qualification to conduct the study.

Monitoring Visits

On-site monitoring visits 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. Monitoring visits will occur after enrollment of every 10 subjects and at a minimum one more visit before study close-out.

During monitoring visits, the monitor will compare subject records and other supporting documents with reports at the site 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 Investigational Plan is being followed, and only eligible subjects are being enrolled into the study.

- Deviations to the Investigational Plan have been reported to ZELTIQ and the IRB, as appropriate.
- Adverse events are promptly being reported.
- Information recorded in the case report forms and study reports are accurate, complete, legible and consistent with source documentation.
- Subjects failing to complete the clinical study and the reason for failure are recorded.
- Missed follow-up visits are noted in the study documentation.

Study Site Closeout

At the close of the study at a clinical site, the monitor will conduct site close out per Sponsor's standard procedure.

4.4.4. Final Report

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

4.4.5. Trial Registration

Prior to study initiation, the trial will be registered on a publicly accessible study database such as clinicaltrials.gov when applicable.

5. Data Ownership

ZELTIQ, 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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8. References

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2. Bernstein, E. F. & Bloom, J. D. (2017). Safety and Efficacy of Bilateral Submental Cryolipolysis with Quantified Three-Dimensional Imaging of Fat Reduction and Skin Tightening. *JAMA Facial Plastic Surgery.* April 2017.
3. Suh, D. H., Park, J. H., Jung, H. K., et al. (2017). Cryolipolysis for submental fat reduction in Asians. *Journal of Cosmetic and Laser Therapy*.
4. Fitzpatrick R, Geronemus R, Goldberg D, Kaminer M, et al. Multicenter study of noninvasive radiofrequency for periorbital tissue tightening. *Lasers Surg Med.* 2003;33:232-42.
5. Carruthers J, Fabi S, Weiss R. Monopolar Radiofrequency for Skin Tightening: Our Experience and a Review of the Literature. *Dermatol Surg.* 2014;40:S168-S173.

Signature: PPD

Email:

ZA18-002 Appendix A

Final Audit Report 2023-07-31

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