# NON-INVASIVE FAT REDUCTION WITH CRYOLIPOLYSIS FOR JAWLINE CONTOURING

## Investigational Plan

| | |
|---|---|
| Sponsor | ZELTIQ, an Allergan Affiliate<br>4410 Rosewood Drive<br>Pleasanton, CA 94588 |
| Protocol Number: | ZA17-004 |
| Protocol Version: | 2.0 |
| Protocol Date: | July 31, 2018 |
| Product: | ZELTIQ CoolSculpting® System |
| Investigator/Co-Investigator(s): | [redacted] |
| Study Location(s): | Pacific Dermaesthetics<br>2425 Hemlock Street, Suite 200<br>Vancouver, BC V6H4E13<br>Canada |
| Sponsor Contact | [redacted] |

Summary of Changes to Protocol from Previous Version

| ZELTIQ Part Number | Protocol Version | Date |
|---|---|---|
| 208103-01 | 2.0 | July 25, 2018 |
| | | |
| **Affected Section (s)** | **Summary of Revisions Made** | **Rationale** |
| 2.1 and 2.2 | Added [redacted] applicator as an example of applicators. | To provide example of appropriate applicator types for the study. |
| 2.1 and 3.13 | Added 3-Week Follow-Up contact post each treatment visit. | To monitor any ongoing side effects and observations from the treatments. |
| 3.7 | Removed inclusion criterion C. | To allow enrollment of participants with smaller treatment areas. |
| 3.12.1 | Added the option of using a GelPad and liner, depending on the type of applicator used. | Depending on the type of applicator used in the study, various device components may be required. |
| 3.12.1 and 3.14 | Added the option of capturing thermal images of the treated area after completion of treatment. | To provide information regarding the cooling performance of the CoolSculpting system. |
| 3.12.2 | Made Treatment Visit #2 optional. | Depending on the aesthetic outcome from Treatment Visit #1, Treatment Visit #2 may not be necessary. |

INVESTIGATOR SIGNATURE PAGE

For protocol number ZA17-004

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 |

## RETURN PAGE TO SPONSOR

# Table of Contents

# 1. Protocol Summary

| | |
|---|---|
| Title | Non-Invasive Fat Reduction with Cryolipolysis for Jawline Contouring |
| Design | Prospective, non-randomized, interventional cohort |
| Purpose | The purpose of this study is to evaluate the safety and efficacy of non-invasive reduction of subcutaneous fat along the jawline with Cryolipolysis |
| Enrollment | Up to forty-five (45) subjects |
| Clinical Site | Up to three (3) investigational sites |
| Subject Population | Healthy adult men and women with skin fold thickness of > 1 cm on or below the jawline, and who desire reduction of jawline fat. |
| Primary Endpoint | [redacted] |
| Secondary Endpoints | [redacted] |
| Sponsor | ZELTIQ, an Allergan Affiliate<br>4410 Rosewood Drive<br>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.

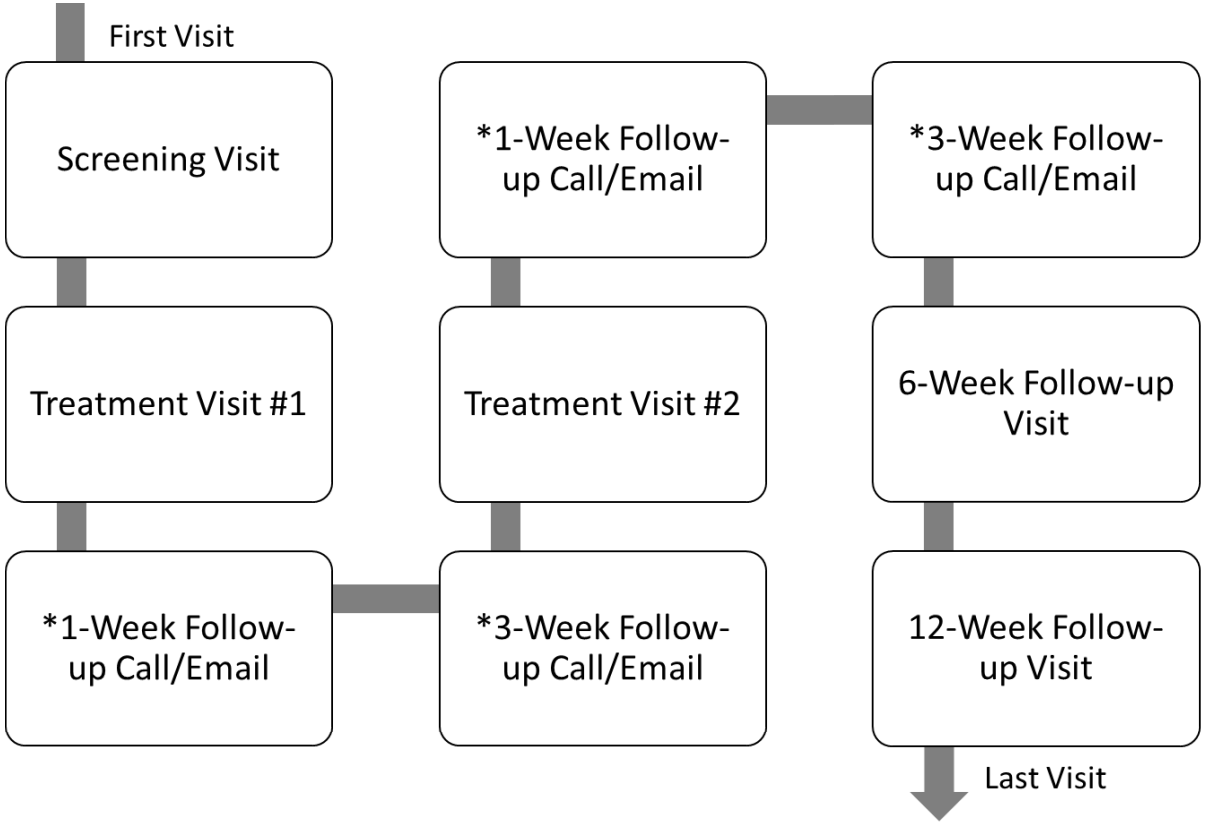
ZELTIQ Aesthetics has developed and commercialized a technology to non-invasively reduce subcutaneous fat. The ZELTIQ technology utilizes the sensitivity of fat cells to cold injury in order to selectively eliminate subcutaneous fat tissue without affecting the skin or other surrounding tissues. Termed 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, submental area and upper arms 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.

[redacted]. The purpose of this study is to further evaluate the safety and efficacy of non-invasive subcutaneous fat reduction along the jawline to provide a better aesthetic improvement to lower face contour. Anatomical areas along the mental region and mandible, such as submental area, submandibular area and jowls, will be treated using the ZELTIQ CoolSculpting System and an appropriate applicator (such as

[redacted]

a CoolMini or a [redacted] applicator) for fat layer reduction. In this study, subjects will receive up to 2 treatments at 6 weeks apart. [redacted] Subjects will be followed for 12 weeks after receiving final treatment. Follow-ups will be performed at the following time points: 1-week, 3-week, 6-weeks and 12-weeks post treatment. Final efficacy assessment will be performed at 12-weeks post 2nd treatment. **Figure 1** shows the overall study flow:

**Figure 1: Study Visit Flowchart.** All visits require subjects to return to the study site except for the 1-week and 3-week Follow-up phone/email.




*Follow-up conducted remotely via phone call or email

## *2.2. Device Description*

[redacted]

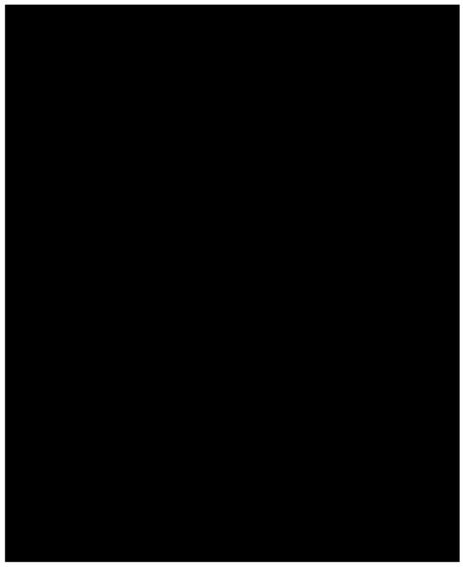


**Figure 2. CoolSculpting System Control Unit.**

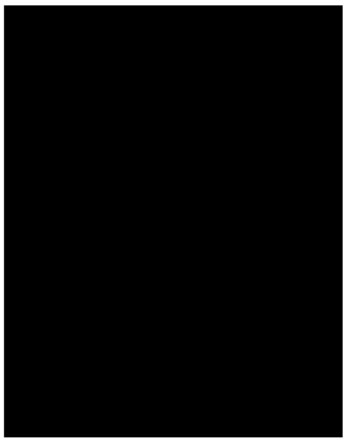


**Figure 3: CoolMini Applicator.**

### *2.3. Regulatory Status*

In Canada, the ZELTIQ CoolSculpting System is licensed ([redacted]) and approved for:

- Fat layer reduction through cold-assisted lipolysis
- Minimizing pain and thermal injury during laser and dermatological treatments
- Acting as a local anesthetic for procedures that induce minor local discomfort

The ZELTIQ system can also provide localized thermal therapy (hot or cold) to minimize pain for post-traumatic and/or post-surgical pain and to temporarily relieve minor aches and pains and muscle spasms. The optional massage function can also be used for temporary:

- Relief of minor muscle aches, pain and spasm
- Improvement in local circulation
- The CoolSculpting System also received Health Canada approval in September 2015 for colder temperatures and shorter treatment times.

## 3. Study Protocol

### *3.1. Design*

Prospective, non-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.

### *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, submandibular area or jowls will be recruited from the general population.

## *3.6. Sample Size*

A maximum of forty-five (45) 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 of the inclusion criteria and none of the exclusion criteria listed in **Table 1**.

**Table 1. Eligibility criteria.**

| |
|---|
| **Inclusion Criteria**<br>a) Male or female subjects ≥ 22 years of age and ≤ 65 years of age.<br>b) Treatment area skin fold thickness > 1cm (measured by caliper).<br>c) No weight change exceeding 5% of body weight in the preceding month.<br>d) 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.<br>e) Subject has signed a written informed consent form. |
| **Exclusion Criteria**<br>a) 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.<br>b) Prominent platysmal bands at rest which may interfere with assessment of treatment area.<br>c) Evidence of any cause of enlargement in the treatment area other than localized subcutaneous fat, such as swollen lymph nodes or ptotic submandibular glands.<br>d) Significant enlargement on the anterior neck that may prevent the proper placement of the applicator e.g. enlarged thyroid glands.<br>e) Treatment with dermal fillers, chemical peels, radiofrequency or laser procedures that may affect contour in the treatment area within the past 6 months.<br>f) Botulinum toxin, deoxycholic acid, or other aesthetic drug injections within the treatment area in the past 6 months.<br>g) History of facial nerve paresis or paralysis (such as Bell's palsy).<br>h) History of a fat reduction procedure (e.g., liposuction, surgery, lipolytic agents, etc.) or implant in or adjacent to the area of intended treatment.<br>i) History of prior neck surgery, or prior surgery in the area of intended treatment.<br>j) Current infection in and adjacent to treatment area.<br>k) Known history of cryoglobulinemia, cold urticaria, cold agglutinin disease or paroxysmal cold hemoglobinuria.<br>l) Known history of Raynaud's disease, or any known condition with a response to cold exposure that limits blood flow to the skin. |

m) History of bleeding disorder or is taking any medication that in the investigator's opinion may increase the subject's risk of bruising.
n) Currently taking or has taken diet pills or weight control supplements within the past month.
o) Any dermatological conditions, such as scars in the location of the treatment area that may interfere with the treatment or evaluation.
p) Active implanted device such as a pacemaker, defibrillator, or drug delivery system.
q) Pregnant or intending to become pregnant in the next 6 months.
r) Lactating or has been lactating in the past 6 months.
s) Unable or unwilling to comply with the study requirements.
t) Currently enrolled in a clinical study of an unapproved investigational drug or device.
u) 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. Visually assess and palpate the intended treatment area to determine if it is appropriate for treatment.
3. Measure the skin fold thickness of the intended treatment areas using a caliper.
4. Assess for dermatological conditions that may lead to exclusion of a subject from the study.

5. 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 or ultrasound measurements 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 last 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, meet eligibility criteria and undergo initiation of study treatment are considered enrolled. Study treatment initiation is defined as the initiation of the cooling cycle after the placement of the applicator on the intended treatment area on the scheduled treatment day.

## *3.11. Study Photography*

Study candidates who sign the informed consent and meet eligibility criteria will be required to have baseline photographs of the intended treatment area taken. Baseline photographs will be taken using a standardized system prior to receiving the first treatment, and may also have additional photographs taken at subsequent treatment visits. All subjects will return 12 weeks after final treatment to have photographs of the treated area taken before exiting the study, using the same system and setup as baseline photographs.

## *3.12. Study Treatment Procedures*

### 3.12.1. Treatment Visit #1; Required: Day 0

1. All female subjects of childbearing potential will be asked to take a pregnancy test (urine) at the treatment visit. Exclude subject from participation if the results are positive.
2. Review and verify the subject continues to meet all eligibility criteria.
3. Obtain weight.
4. Obtain baseline standardized photographs using standardized setup and settings. In addition, 3-dimensional image may be captured.

[redacted]

[redacted]

l. Clean the applicator per instructions in the Addendum to the User Manual.

8. Per Investigator's discretion, perform up to four additional cooling cycles to cover the intended treatment area [redacted] cycles per treatment visit). For additional cooling cycles, repeat Step 7 in Section 3.12.1
9. 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 unexpected effects (e.g., severe discomfort, severe and/or prolonged erythema, bruising, swelling; blistering, etc.) which may be related to the study.

### 3.12.2. Treatment Visit #2; Optional: Week 6 post-Treatment #1 (± 1 week)

Per the Investigator's discretion, subjects may receive a second treatment (up to 5 cooling cycles) after completion of the 6-week post-Treatment #1 follow-up evaluation.

1. All female subjects of childbearing potential will be asked to take a pregnancy test (urine) at the treatment visit. Exclude subject from participation if the results are positive.
2. Review and verify the subject continues to meet all eligibility criteria.
3. Obtain standardized photographs and 3-dimenstional images (optional).
4. Measure fat layer thickness of the treatment area with a commercially-available ultrasound device using a standardized protocol (optional).
5. Perform treatment as described in Section 3.12.1., #6-9.

## *3.13. Follow-up Procedures*

### 3.13.1. 1-Week Follow-Up Visit; Required: Day 7 (± 3 days)

A phone contact will take place one week after each treatment visit to evaluate the condition of the treatment area, pain score, and adverse events. If there are any observations reported at the phone follow-up, the subject will be contacted by phone weekly until resolution of symptoms is documented. If there is evidence that an adverse event may have occurred, the subject will be asked to come in for a visit so an appropriate evaluation can be done. Email may be used as an alternate method of contact.

### 3.13.2. 3-Week Follow-Up Visit; Required: Week3 (± 7 days)

A phone contact will take place three weeks after each treatment visit to evaluate the condition of the treatment area, pain score, and adverse events. If there are any observations reported at the phone follow-up, the subject will be contacted by phone weekly until resolution of symptoms is documented. If there is evidence that an adverse event may have occurred, the subject may be asked to come in for a visit so an appropriate evaluation can be done. Email may be used as an alternate method of contact.

### 3.13.3. 6-Week Follow-Up Visit; Required: Week 6 (± 7 days)

The following evaluations will be performed at the 6-week follow-up visit after Treatment Visit #1 and #2.

1. Obtain weight
2. Perform clinical assessment of the treatment area for any epidermal, dermal and subcutaneous findings (e.g., erythema, bruising, swelling, pigment changes).
3. Assess for alterations in sensation (e.g., numbness, tingling). Assess subject pain score using 0 – 10 scale.
4. Examine the oral cavity for evidence of dry mouth.
5. Assess lower face motor nerve function.
6. Assess for any adverse events.

### 3.13.4. 12-Week Final Follow-Up Evaluation; Required (12 weeks ± 14 days post final treatment)

The following evaluations will be performed at the 12-week follow-up visit after the final treatment visit:

1. Obtain weight.
2. Obtain photographs using standardized setup and settings. In addition, 3-dimensional images may be captured.
3. Measure fat layer thickness of the treatment area with a commercially-available ultrasound device using a standardized protocol.
4. Perform clinical assessment of the treatment areas for any epidermal, dermal and subcutaneous findings (e.g., erythema, bruising, swelling, pigment changes).
5. Assess for alterations in sensation (e.g., numbness, tingling). Assess subject pain score using 0 – 10 scale.
6. Examine the oral cavity for evidence of dry mouth.
7. Assess lower face motor nerve function.
8. Assess for any adverse events.

9. Administer subject questionnaire to obtain subject feedback on overall satisfaction.

### 3.13.5. Optional Follow-Up Evaluations (up to 4 within study period)

The full evaluation is not required at optional follow-up visits; the extent of the assessment will be at the discretion of the investigator.

Table 2 summarizes study schedule and events at each visit.

## Table 2. Schedule of Assessments

| | | | Post-Treatment Visit #1 | | | | Post-Treatment Visit #2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening (< 1 hr) | Treatment Visit #1 (< 4 hrs) | 1 Wk Follow-Up (< 1 hr) | 3 Wk Follow-Up (< 1 hr) | 6 Wk Follow-Up AND Treatment Visit #2 (< 4 hrs) | | 1 Wk Follow-Up (< 1 hr) | 3 Wk Follow-Up (< 1 hr) | 6 Wk Follow-Up | 12 Wk Follow-Up (< 1 hr) | Optional ** Follow-Up |
| Time Frame | Day - 45 to 0 | Day 0 | Day 7 (+/- 3 days) | Day 21 (+/- 7 days) | Week 6 (+/- 7 days) | | Day 7 (+/- 3 days) | Day 21 (+/- 7 days) | Week 6 (+/- 7 days) | Week 12 (+/- 14 days) | Open |
| | | | | | 6 Wk | Tx #2 | | | | | |
| Informed Consent* | X | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | X | | | | | |
| Pregnancy Test | X | X | | | | X | | | | | |
| Medical History | X | | | | | | | | | | |
| Tx Site Assessment | X | X | | | X | | | | X | X | |
| Height | X | | | | | | | | | | |
| Weight | X | X | | | X | | | | X | X | |
| Photography | | X | | | X*** | | | | X*** | X | |
| 3-D Photography | | X*** | | | X*** | | | | X*** | X*** | |
| Thermal Imaging | | X*** | | | | X*** | | | | | |
| Caliper Measurement | X | | | | | | | | | | |
| Ultrasound Measurement | | X | | | X*** | | | | X*** | X | |
| Treatment | | X | | | | X | | | | | |
| Pain Assessment | | X | X | X | X | X | X | X | X | X | |
| AE Assessment | | X | X | X | X | X | X | X | X | X | |
| Subject Survey | | | | | | | | | | X | |

* Informed consent to be signed by subject prior to the collection of any data or completion of any study procedures.
** Investigator discretion as to timing and extent of follow-up assessment for optional visits.
*** Optional

## *3.14. Assessments*

Study-related assessments are described below.

### 3.14.1. Safety Assessments

The primary safety endpoint is the rate of device- or procedure-related adverse events 12 weeks post 2nd treatment. Safety will be monitored by documentation of adverse events and clinical assessment of the treatment site.

### 3.14.2. Photography

All pre-treatment and post-treatment photographs will be taken using the same method. A series of baseline and follow-up photographs of the treatment area will be taken using standardized set up, lighting, and camera settings to ensure consistency. Subsequent to basic processing, the photographs may be cropped or re-sized for comparison purposes but otherwise will not be re-touched or manipulated in any way except for normal processing for equalization of color and exposure. Any re-sizing of photographs is intended to account for differences in camera-to-subject distance only. Any cropping of photos is intended to ensure that pre- and post-treatment follow-up images are aligned both vertically and horizontally. Cropping and/or re-sizing of the photographs will be performed using the same methods for all study photographs.

Image files will be stored electronically by ZELTIQ and indexed by subject study identification code. Copies of subject photographic data will be filed at the clinical site.

[redacted]

In addition to standard photography, 3-Dimensional photographs and thermal imaging may also be captured. Three-Dimensional photography may be performed using a commercially available photography system, such as the Canfield VECTRA or similar device. Thermal images may be captured using a commercially available system, such as a FLIR or similar device.

### 3.14.3. Caliper Measurement

Caliper measurements of the treatment areas will be taken at the screening visit.

### 3.14.4. Ultrasound Measurement

Ultrasounds will be performed by a qualified representative of the sponsor.

[redacted]

### 3.14.5. Subject Satisfaction

Subject satisfaction data will be collected via a written questionnaire at the 12-week post-final treatment. This questionnaire will be composed of 5-point Likert scale questions, as well as free-text responses. Subjects will be asked to determine overall satisfaction with the treatment. The choices will be: 1) very dissatisfied; 2) dissatisfied; 3) not sure 4) satisfied; 5) very satisfied.

## *3.15. Endpoints*

The objective of this study is to further evaluate the safety and efficacy of the ZELTIQ CoolSculpting System to contour along the jawline.

### 3.15.1. Primary Endpoints

The primary endpoints of the study will be defined as follows:

[redacted]

[redacted]

### 3.15.2. Secondary Endpoints

Secondary endpoints in the study are as follows:

[redacted]

## *3.16. Statistical Analysis Plan*

### 3.16.1. 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.

### 3.16.2. 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 last 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**

The sample size of this study (45) was selected as it is thought to be appropriate to provide preliminary information regarding safety and efficacy of using the CoolMini vacuum applicator for contouring along the jawline.

### 3.16.3. Endpoint Analysis

**Primary Safety Endpoint:**

The primary safety endpoint is measurement of unanticipated adverse device effects. All adverse events reported during and following the treatment will be included in the safety analysis. The frequency and proportion of subjects reporting each type of adverse event will be tabulated by relationship with the treatment and severity of the event.

**Primary Efficacy Endpoint: Photographic Review**

[redacted]

**Secondary Endpoint: Reduction in Fat Layer Thickness as Measured by Ultrasound**

[redacted]

[redacted]

[redacted]

**Secondary Endpoint: Subject Satisfaction**

The number and percentage of subjects will be summarized for each possible point grade of the satisfaction questionnaire at 12-weeks. The percentage of subjects who responded as satisfied or very satisfied will be provided, [redacted] subjects who responded as dissatisfied or very dissatisfied will also be calculated.

## *3.17. 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, or protocol exemption, 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.

## *3.18. 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.

**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.

**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.

## *3.19. Reportable Incidents*

Serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) must be reported within 24 hours of knowledge of the event to the Sponsor:

[redacted]

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.

# 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 not 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 at regular intervals.

During monitoring visits, the monitor will compare subject records and other supporting documents with reports at the site to determine that:

**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.

# 6. Publication Policy

Participating investigators and/or Institutions may publish information or data collected or produced as a result of participation in appropriate scientific conference or journals or other professional publications subject to written permission from the Sponsor, provided that drafts of the material are provided to the Sponsor for purposes of review and comment at least sixty (60) days prior to the first submission for publication or public release. Investigators may not publish information regarding site-specific data until a multicenter study report has been published.

# 7. Risk/Benefit Analysis

The Sponsor has undertaken a comprehensive risk-benefit analysis.

## *7.1. Benefits*

Fat reduction in the treatment area is anticipated to provide an aesthetic benefit and the use of this non-invasive system may eliminate the need for an invasive procedure that requires anesthesia or recovery time. Considering the number of surgical procedures performed for the removal of fat each year (1.5 million procedures worldwide, according to the 2016 International Society of Aesthetic Plastic Surgeons Biennial Global Survey), the use of such a non-invasive procedure has the potential to significantly reduce the incidence of complications and post-surgical limitations associated with those procedures.

## *7.2. Risks*

Although this study presents minimal risks to the subject, there is the potential for some risk when any medical procedure is performed.

**Anticipated Device Effects**

These are known effects of the ZELTIQ Procedure, previously recorded in prior studies as transient and/or temporary effects related to the cold application and/or vacuum pressure inherent in the treatment. Anticipated effects of the device which will not be considered adverse events include:

- inflammation of the subcutaneous fat layer, which is a desired effect of the procedure;
- sensations of coldness, stinging, burning, pinching, or pressure associated with placement of the applicator and the initiation of the cold treatment;
- known skin effects (e.g., blanching; erythema, bruising, purpura, petechiae, swelling, discomfort, tenderness, or soreness at the treatment site, all mild to moderate in nature) which are temporary effects that resolve spontaneously shortly after the procedure;
- localized sensory changes (e.g., numbness, tingling) at the treatment area resolving within 12 weeks of the procedure;

**Adverse Effects**

The following summarizes the potential adverse effects in this study:

| Potential Adverse Effect | Description |
|---|---|
| Severe Bruising | The appearance of ecchymosis (purple colored spots or patches > 1cm); purpura (3-4 mm to 1cm); or petechiae (pin point red dots, < 3-4 mm) that is rated as severe by the investigator; |
| Prolonged Bruising | Bruising lasting longer than 1 month |
| Severe Erythema | The appearance of erythema (redness) that is rated as severe by the investigator |
| Prolonged erythema | Erythema lasting longer than 2 weeks. |
| Severe Swelling | The appearance of swelling (edema) that is rated as severe by the investigator |
| Prolonged swelling | Swelling lasting longer than 1 month. Prolonged swelling can lead to sensation of fullness in the back of the throat. |
| First Degree Burn | A first degree burn is superficial and causes local inflammation of the skin. The inflammation is characterized by pain, redness, and mild swelling. The skin may be very tender to touch. |
| Second Degree Burn | Second degree burns are deeper and in addition to the pain, redness and inflammation, there is also blistering of the skin. |

| | |
|---|---|
| Third Degree Burn | Third degree burns are deeper still, involving all layers of the skin. Because the nerves and blood vessels are damaged, third degree burns appear white, leathery and tend to be relatively painless. |
| Cold-induced panniculitis | Severe inflammation which requires medical or surgical intervention |
| Skin Pigmentary Changes | The appearance of hyperpigmentation or hypopigmentation in the treatment area. |
| Infection | Infection at the treatment site, diagnosed by a physician and requiring medical intervention. |
| Discomfort During Procedure | Discomfort reported during the procedure that is intolerable to the subject and results in an interruption or discontinuation of the procedure |
| Discomfort Post Procedure | Significant discomfort, pain, cramping, tenderness, soreness, muscle spasm following the procedure which results in medical intervention (physician visit and/or prescription pain reliever) |
| Prolonged Sensory Alteration Post Procedure | Sensory changes (numbness, tingling, burning sensation) that are prolonged (i.e., lasting longer than 12 weeks). |
| Sensory Alteration Requiring Medical Intervention | Sensory changes (pain, burning, stinging, hypersensitivity) with a severity warranting medical intervention. |
| Vasovagal Symptoms | The occurrence of symptoms of anxiety, lightheadedness, dizziness, nausea, sweating, near syncope, or syncope (fainting). |
| Motor nerve injury | Injury to the lower face motor nerves such as marginal mandibular nerve (lower lip weakness) or hypoglossal nerve (tongue deviation). |
| Xerostomia | Injury to the submandibular or parotid gland as evidenced by the subjective decrease in saliva production. |
| Subcutaneous Induration | Generalized hardness and/or discrete nodules within the treatment area, which may develop after the treatment and may present with pain and/or discomfort. |
| Paradoxical Hyperplasia | Visibly enlarged tissue volume within the treatment area that may develop within 2 - 5 months after treatment. Surgical intervention may be required. |
| Contour Irregularity | Significant indentation or contour irregularity in the treatment area that would require surgical correction. |
| Allergic/Irritant Contact Dermatitis | Itchy rashes and skin peeling that may result from prolonged exposure to gel or applicator pressure |
| Other | Any other untoward medical event determined by the investigator to be an adverse event, regardless of the relationship to the device or treatment. |