Information Cover Page

Zeltiq Aesthetics Protocol ZA16-005

DualSculpting the Upper Arms Using Vacuum Applicators and a Customized Treatment Approach

NCT02939105

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DUALSCULPTING THE UPPER ARMS USING VACUUM APPLICATORS AND A CUSTOMIZED TREATMENT APPROACH

Investigational Plan

Sponsor	ZELTIQ Aesthetics 4698 Willow Rd. Pleasanton, CA 94588
Protocol Number:	ZA16-005
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Sponsor:

Print Name and Title	Signature	Date

Investigator:

Print Name and Title	Signature	Date

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1. Protocol Summary

Title	DualSculpting the Upper Arms Using Vacuum Applicators and a Customized Treatment Approach
Design	Single-center, prospective, non-randomized, interventional cohort
Purpose	Evaluate the safety and efficacy of the ZELTIQ CoolSculpting System using specialized vacuum applicators for non-invasive subcutaneous fat reduction of the upper arms.
Enrollment	Up to 15 subjects enrolled
Clinical Sites	One investigational site
Subject population	Healthy adult women and men with clearly visible fat on the upper arms that they wish to have reduced
Primary Endpoints	• Safety endpoint: The primary safety endpoint is the rate of unanticipated adverse device effects (UADE). It is expected there will be zero UADEs. • Effectiveness endpoint: Correct identification of pre-treatment vs. 12-week post-final treatment images by at least two out of three blinded, independent reviewers. Success will be defined as at least 70% correct identification of the pre-treatment images.
Additional Assessments	• Subject satisfaction as assessed by questionnaire administered at 12 weeks post-final treatment. • Assessment of fat reduction using various methods, which may include; ultrasound, caliper and circumference measurements.
Sponsor	ZELTIQ Aesthetics, Inc. 4698 Willow Rd. 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. [redacted]

The purpose of this study is to evaluate the safety and efficacy of the ZELTIQ CoolSculpting System using vacuum applicators for non-invasive subcutaneous fat reduction in the upper arms. [redacted] vacuum applicators will be used in this study to provide a customized treatment approach for each subject's upper arm dimensions.

2.2. Device Description

The study treatments will be performed using the ZELTIQ CoolSculpting System. [redacted]

[redacted]

This study will evaluate the safety and efficacy of the vacuum applicators to treat the upper arms. The subjects will receive bilateral treatment. [redacted] At the investigator's discretion, an additional cooling cycle may be delivered to cover the treatment area (up to two cycles per each upper arm).

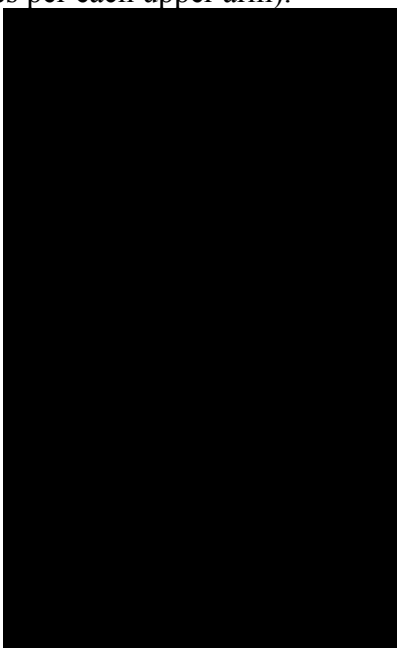

Figure 1: Cleared ZELTIQ System control unit.

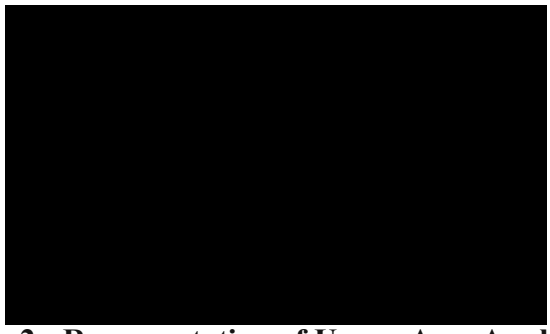

Figure 2: Representation of Upper Arm Applicator

2.3. Regulatory Status

In Canada, the ZELTIQ CoolSculpting System is licensed (License #78510) 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 five (5) months for each subject.

3.3. Physician Participants

Study investigators must be practicing medical physicians with experience in body contouring treatments.

3.4. Site Requirements

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

3.5. Subject Recruitment

Subjects who seek reduction of fat in the upper arm will be recruited from the general population.

3.6. Sample Size

A maximum of fifteen (15) subjects will be treated at one investigational site.

3.7. Patient 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) Male or female subjects ≥ 22 years of age and ≤ 65 years of age.
b) Subject has clearly visible fat sufficient for treatment on the upper arm, which in the investigator's opinion, may benefit from the treatment.
c) No weight change exceeding 5% in the preceding month.
d) Subject agrees to maintain his/her weight (i.e., within 5% of total body weight) by not making any major changes in their diet or exercise routine during the course of the study.
e) Subject has read and signed the study written informed consent form.
Exclusion Criteria
a) History of a fat reduction procedure (e.g., liposuction, surgery, lipolytic agents, etc.), or implants in or adjacent to the area of intended treatment.
b) History of prior surgery in the arms.
c) Known history of cryoglobulinemia, cold urticaria, cold agglutinin disease, or paroxysmal cold hemoglobinuria.
d) Known history of Raynaud's disease, or any known condition with a response to cold exposure that limits blood flow to the skin.
e) History of bleeding disorder or is taking any medication that in the investigator's opinion may increase the subject's risk of bruising.
f) History of carpal tunnel syndrome, compartment syndrome or deep vein thrombosis in the upper extremities.
g) Currently taking or has taken diet pills or weight control supplements within the past month.
h) Any dermatological conditions, such as scars, infection, in the location of the treatment area that may interfere with the treatment or evaluation.
i) Active implanted device such as a pacemaker, defibrillator, or drug delivery system.
j) Pregnant or intending to become pregnant in the next 5 months.

k) Lactating or has been lactating in the past 6 months.
l) Unable or unwilling to comply with the study requirements.
m) Currently enrolled in a clinical study of any other unapproved investigational drug or device. 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.

3.9. Screening Procedures

3.9.1. Screening Visit; Required; Day -60 to Day 0

All subjects screened for the study must be documented on the Screening Log.

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 measurement of upper arm length, distance from peak of bulge to elbow, and circumference at peak of bulge. (Optional)
3. Visually assess and palpate the intended treatment area to determine if it is appropriate for treatment.
4. Assess for dermatological conditions that may lead to exclusion of a subject from the study.
5. Obtain photos of both right and left arms. (Optional)
6. Document potential candidate's medication use (including over-the-counter medications, vitamins and herbs), Fitzpatrick Skin Type, and ethnicity as well as any skin irregularities (e.g. moles, birth marks, scars, stretch marks, discoloration) at the intended treatment area.

7. All female subjects of childbearing potential will be asked to take a pregnancy test (urine) prior to being treated. If the subject is pregnant, she will be excluded from participation.

Female subjects of childbearing potential will 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 and circumference taken. Female subjects of childbearing potential will be assessed for the start date of their last menstrual cycle.

All subjects will be asked to maintain their weight by not making any major changes to their diet or exercise routine during the course of the study. If the weight change is more than 5% of total body weight at 12 weeks after the treatment, the subjects' data will be excluded from the primary effectiveness analyses. Subjects who do not maintain their weight within 5% of total body weight 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. 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 cold therapy after the placement of the applicator on the intended treatment area on the scheduled treatment day.

3.11. Study Treatment

3.11.1. Treatment Visit; Required; Day 0

1. Review inclusion and exclusion criteria.
2. Administer pregnancy test for female subjects of childbearing potential (urine). Exclude subject from participation if the results are positive.

3. If the subject meets all of the inclusion criteria and none of the exclusion criteria, they will be enrolled in the study and proceed with the treatment.
4. Obtain baseline photographs of both right and left arms using the standardized setup and settings. Photos will be taken of each arm from the front and the back.
5. Obtain weight.
6. Mark the intended treatment areas.
7. Optional ultrasound measurements of the fat layer in each upper arm may be obtained using a standardized ultrasound fat measurement protocol.
8. Optional caliper measurements of the treatment areas may be obtained.
9. Optional circumference measurements of the upper arms may be obtained.
10. Determine arm to be treated first based on randomization scheme.
11. [redacted]
12. [redacted]
13. [redacted]
14. [redacted] A securement system may be used to hold the applicator in place. [redacted]
15. [redacted]
16. The subject's level of comfort will be assessed during treatment using a standard scale of 0-10, 0 being no pain and 10 being worst pain imaginable. If discomfort is intolerable, the treatment will be discontinued until the subject is comfortable and treatment, at the discretion of the investigator, can be resumed. Discomfort that results in either a temporary or permanent cessation of the treatment is to be documented as an adverse event.
17. Assess for sensory/motor alteration (such as numbness, tingling in hands/fingers) outside of the treatment area. If present, reposition subject and/or applicator. Reapply applicator as needed.
18. At the conclusion of the treatment, the investigator or designated staff member will examine the treatment site for any epidermal, dermal or subcutaneous findings (e.g., blanching, erythema, bruising, swelling); alterations in sensation (e.g., numbness, tingling) and pain score will be assessed. The subject will be assessed for any sensory alteration outside of the treatment area.
19. [redacted]

[redacted]

20. At the investigator's discretion, an additional cooling cycle may be delivered to cover the treatment area (up to two cycles per each upper arm). For additional cooling cycle, repeat steps 12 through 19.
21. Repeat steps 11 through 20 on the contralateral arm. Treatments may be concurrently on each arm or consecutively.

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. Follow-up Procedures

3.12.1. One-Week Follow-Up Contact; Required: (Day 7 +/- 3 days)

Clinical site staff will contact (via phone or email) subjects one week after treatment for assessment of the treatment areas, pain score, and adverse events. Subjects will be assessed for any sensory alteration outside of the treatment areas. 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 may be asked to come in for a visit so an appropriate evaluation can be done.

3.12.2. Four-week Follow-Up Evaluation; Required (Day 28 +/- 7 days)

The following evaluations will be performed at the 4-week follow-up visit:

1. Obtain weight.
2. Obtain photos of both treated arms using the same standardized setup and settings as the pre-treatment photographs (optional).
3. Perform clinical assessment of the treatment areas. Evaluate for any epidermal, dermal and subcutaneous findings (e.g., erythema, bruising, swelling, pigment changes) as well as alterations in sensation (e.g., numbness, tingling). Assess for sensory alteration outside of the treatment areas.
4. Assess for adverse events.

3.12.3. Twelve-Week Follow-Up Evaluation; Required (Day 84 +/- 14 days)

The following evaluations will be performed at the 12-week visit.

1. Obtain weight.
2. Obtain photos of both treated arms using the same standardized setup and settings as the pre-treatment photographs.
3. Optional ultrasound measurements of the fat layer in each upper arm may be obtained using a standardized ultrasound fat measurement protocol.
4. Optional caliper measurements of the treatment areas may be obtained.
5. Optional circumference measurements of the upper arms may be obtained.
6. Perform clinical assessment of each of the treatment areas (right and left upper arms). Evaluate for any epidermal, dermal and subcutaneous findings (e.g., erythema, bruising, swelling, pigment changes) as well as alterations in sensation (e.g., numbness, tingling). Assess for sensory alteration outside of the treatment areas.
7. Administer subject satisfaction questionnaire.
8. Assess for adverse events.

3.12.4. 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 3 summarizes study schedule and events at each visit.

Table 3. Study Schedule

Study Task	Screening Visit (< 1 hr)	Treatment #1 (</= 3 hrs)	1-Week Follow-Up (< 1/2 hr)	4-Week Follow-up (<1/2 hr)	12-Week Follow-up (<1 hr)	Optional Follow-Up*
	Day -60 to 0	Day 0	(+/- 3 days)	(+/- 7 days)	(+/- 14 days)	Open
Informed Consent	X					
Eligibility Criteria	X	X				
Pregnancy Test		X				
Medical History	X					
Clinical Assessment	X	X		X	X	
Height	X					
Weight	X	X		X	X	

Photography	X**	X		X**	X	
Ultrasound (optional)		X			X	
Caliper Measurement (optional)		X			X	
Circumference Measurement (optional)		X			X	
Treatment		X				
Pain Assessment		X	X	X	X	
AE Assessment		X	X	X	X	
Subject Questionnaire					X	

*Investigator discretion as to extent of follow-up assessment for optional visits.
**Photography is optional at 4-week visit.

3.13. Assessments

Study-related assessments are described below.

3.13.1. Safety Assessments

The primary safety endpoint is the rate of device- or procedure-related adverse events 12 weeks post-final treatment. Safety will be monitored by documentation of adverse events and clinical assessment of the treatment sites. Post-treatment sensory changes outside of treatment areas will also be documented and assessed.

3.13.2. Photography

A series of baseline and follow-up photographs of the treatment areas will be taken using standardized set up, lighting, and camera settings to ensure consistency. The subject's faces will not be on the photographs. No other identifiable subject information will be recorded on the photographs. The photographs may be cropped or re-sized for comparison purposes but otherwise will not be re-touched or altered in any way. Image files will be stored electronically by ZELTIQ and indexed by subject identifier. Copies of subject photographic data will be filed at the clinical site.

Photos will be reviewed by a blinded independent panel of physician reviewers with expertise in the areas of dermatology and/or plastic surgery. All photographs will be blinded by removing the subject identification and dates of the photographs. The reviewers will be presented with two series of photographs for each treatment area, the pre-treatment and the post-treatment series, and asked to select the series representing the pre-treatment photographs. The order in which the photographs are presented will be randomized by subject. The order in which the pre- and post-treatment series

are presented will also be randomized. The reviewers will be asked to select the baseline photograph series for each treatment area and record their data on individual data collection forms provided by the Sponsor.

3.13.3. Optional Ultrasound Measurement

Ultrasound images may be collected pre-treatment and at each specified follow-up time point. The images will be collected by a qualified representative of the sponsor or site personnel. [redacted] Copies of subject-arm ultrasound data will be filed at the clinical site. Standardized techniques of obtaining images will be used to ensure consistency throughout the study.

3.13.4. Optional Caliper Measurement

Caliper measurements of the treatment areas may be taken at pre-treatment and at 12-weeks post final treatment. After the treatment area is identified and marked, the thickness of fat layer will be measured using a caliper at the middle of the fat bulge. For each treatment area, three (3) measurements will be taken and recorded. [redacted]

3.13.5. Optional Circumference Measurement

Circumference data may be collected pre-treatment and at 12-weeks post-treatment. [redacted]

3.13.6. Subject Satisfaction

Subject satisfaction data will be collected via a written questionnaire at the final 12-week follow-up visit.

3.14. Endpoints

The objective of this study is to evaluate the safety and efficacy of the CoolSculpting System for non-invasive subcutaneous fat reduction in the upper arms.

3.14.1. Primary Endpoints

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

- Safety endpoint: incidence of device- or procedure-related adverse events
- Efficacy endpoint: Correct identification of pre-treatment vs. 12-week post-final treatment images by two out of three blinded independent reviewers. Success will be defined as at least 70% correct identification of the pre-treatment images.

3.14.2. Other Assessments

Additional assessments to be performed in the study are as follows:

- Subject satisfaction as assessed by questionnaire administered at 12 weeks post-treatment.
- Assessment of fat reduction using various methods, which may include; ultrasound, caliper and circumference measurements.

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 the treated subjects followed for 12 weeks and with weight change of no more than five percent of total

body weight at the time the 12-week 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 on the upper arm will not be included in the efficacy analyses.

As-Treated Population (AT):
This population consists of all treated subjects regardless of weight change, etc.

Safety Population (SA):
This population will consist of all the 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.

3.15.3. Endpoint Analysis

3.15.3.1. Primary Safety Endpoint:

The primary safety endpoint is measurement of all device- or procedure-related adverse events. All adverse events reported during and following the treatment will be included in the safety analysis.

3.15.3.2. Primary Efficacy Endpoint: Photographic Evaluation

The primary efficacy endpoint is the correct identification of pre- vs 12-week post-treatment images. Since weight change will affect the image, the analysis will be based on the evaluation of the PP population, i.e. treated subjects followed for 12 weeks who did not became pregnant, and with weight change of no more than 5% at the 12-week visit. [redacted]

3.15.3.3. Other Assessments:

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 with satisfied or very satisfied responses will be provided, and the corresponding exact 95% confidence interval (per binomial distribution) will be calculated. The percentage and the exact 95% confidence interval of

dissatisfied responses (dissatisfied or very dissatisfied) will also be calculated.

Other Assessments of Fat Reduction
Fat reduction may be assessed using other various methods, which may include; ultrasound, caliper and circumference measurements.

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, 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.

Protocol Exemption

[redacted]

Exemptions should be reported promptly to the IRB given the severity and circumstances of the incident; within 30 days from knowledge of the event is sufficient.

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.

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 CFR 812.150[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 reported within 24 hours of knowledge of the event to the Sponsor:

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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 Information Protection Act (HIPA) of 2004.

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 in their countries. 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.

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)

- 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
- 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 the investigational plan shall be reported to the Sponsor and the IRB.
- 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 patient base and can provide sufficient staff and documentation support to conduct the study properly.

Monitoring

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

Investigational devices

Not applicable. Devices used in this investigation are commercial devices.

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 to be used in the study.

Device Use

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, applicable regulations, 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 qualifications.

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.

Study Site Closeout

At the close of the study at a clinical site, the monitor may make a final on-site visit. Closeout monitoring will be conducted per Sponsor's procedures.

4.4.4. Final Report

A final report will be prepared at the conclusion of the trial.

4.4.5. Trial Registration

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

5. 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.

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 will 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 (1.3 million procedures worldwide, according to the 2011 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 bruising (purple discoloration); purpura (purple colored spots or patches); or petechiae (pin point red dots) that is rated as severe by the investigator;
Prolonged Bruising	Bruising lasting longer that 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.
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

Potential Adverse Effect	Description
	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 Pigment 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 Alterations Post Procedure	Sensory changes (numbness, tingling, burning sensation) that are prolonged (i.e., lasting longer than 12 weeks).
Sensory Alterations Requiring Medical Intervention	Sensory changes (pain, burning, stinging, hypersensitivity) with a severity warranting medical intervention.
Sensory Alteration Outside Treatment Area Post-Treatment	Sensory or motor nerve alteration (such as numbness or tingling in the fingers or hands) that does not resolve within twenty minutes following applicator removal.
Vasovagal Symptoms	The occurrence of symptoms of anxiety, lightheadedness, dizziness, nausea, sweating, near syncope, or syncope (fainting).
Nerve injury	Injury to the arm motor nerves such as ulnar, radial, or brachial nerves that innervate the upper and lower arm, hand and fingers.
Contour Irregularity	Significant indentation or contour irregularity in the treatment area that would require surgical intervention.
Allergic/Irritant Contact Dermatitis	Itchy rashes and skin peeling that may result from prolonged exposure to gel or gelpad, or applicator pressure
Subcutaneous Indurations	Hardness within the treatment area, either as general firmness or discrete nodules.

Potential Adverse Effect	**Description**
Paradoxical Hyperplasia	Visibly enlarged tissue volume within the treatment area which may develop 2-5 months after treatment. Surgical intervention may be required.
Deep Vein Thrombosis	The occurrence of a blood clot that forms in a vein
Compartment Syndrome	Increased pressure within a compartment, such as arm or hand, causing pain, tingling or burning sensations within the area.
Other	Any other untoward medical event determined by the investigator to be an adverse event, regardless of the relationship to the device or treatment.