Information Cover Page

Zeltiq Aesthetics Protocol ZA18-003

A Feasibility Study to Evaluate Electromagnetic Muscle Stimulation and CoolSculpting for Abdominal Contouring

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A FEASIBILITY STUDY TO EVALUATE ELECTROMAGNETIC MUSCLE STIMULATION AND COOLSCULPTING FOR ABDOMINAL CONTOURING

Investigational Plan

Sponsor	ZELTIQ Aesthetics, an Allergan affiliate 4410 Rosewood Dr. Pleasanton, CA 94588
Protocol Number:	ZA18-003
Protocol Version:	2.0 February 22, 2019
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Summary of Changes to Protocol from Previous Version

ZELTIQ Part Number	Protocol Version	Date
[redacted]	Version 01	October 3, 2018
	Version 02	February 22, 2019
Affected Section (s)	**Summary of Revisions Made**	**Rationale**
Protocol Summary	Corrected typographical error for the number of clinical sites from six to five.	Administrative change
1.2, 1.3	EMS devices description was corrected. Other minor formatting changes	EMS devices are nonsignificant risk devices, and FDA clearance is not required for their use in the study.
1.2	EMS treatment will be conducted prior to or post CoolSculpting	Reflects the study design for Cohort 4.
2.7(g)	A new inclusion criterion has been added to specify criteria for eligibility specifically for the new Cohort 4.	Cohort 4 will consist exclusively of Cohort 3 participants who have completed CoolSculpting treatment.
Table 2	Modified format and removed specific requirement for enrollment by Cohort	Sponsor will decide number of participants for each Cohort
2.12.1(e) 2.12.2(e)	Modified procedure to allow up to two applicators.	It is common in current commercial treatment practice to use 2 applicators
2.12.2(i)	Revised description of pain score from average to maximum pain score	Changed to improve participant's comprehension of assessment.
2.12.1, 2.12.2, 2.12.4	Added use of a support arm with EMS device	Support arm may be supplied with EMS device and is an optional tool for the clinician
2.12.4	Added Cohort 4	Assess effects of EMS post-CoolSculpting
2.12.5	Corrected reference to photographs to 2.14	Administrative correction
[redacted]	[redacted]	[redacted]
2.18	Added description of the requirement for documentation of device deficiencies Updated description of investigator reporting time lines for adverse event reporting.	This is a requirement in accordance with ISO 14155 Reporting time line consistent with company procedure.
6.2	Hernia was added to the list of risks	This potential adverse event was inadvertently not listed in Version 1. It is not a new risk, it is a recognized and documented rare side effect.
6.2	The description of the Adverse Effect, Discomfort During the Procedure was corrected.	The description provided in the protocol was for post-procedure discomfort. The amended description is for intra-procedure discomfort.

INVESTIGATOR SIGNATURE PAGE

For protocol number ZA18-003

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

Protocol Summary

Title	A Feasibility Study to Evaluate Electromagnetic Muscle Stimulation and CoolSculpting for Abdominal Contouring
Design	Prospective, multi-center, non-randomized, feasibility study
Purpose	[redacted]
Enrollment	Up to sixty (60) subjects
Clinical site(s)	Up to five (5) investigational sites
Subject Population	Healthy adult men and women aged 22 – 65 who desire abdominal subcutaneous fat reduction and abdominal toning.
Primary Endpoints	*Efficacy endpoint:* Comparison of pre-treatment- and 12-week post-final treatment photographs to assess visible changes in the abdomen. *Safety endpoint:* Incidence of unanticipated adverse device effects (UADE). It is expected there will be zero UADEs.
Secondary Endpoints	The secondary endpoints in the study are: 1. Reduction in abdominal circumference as measured by 3-Dimensional imaging. 2. Subject- graded Global Aesthetic Improvement Scale at 12-week post-final treatment follow-up.
Sponsor	ZELTIQ Aesthetics, an Allergan affiliate 4410 Rosewood Dr. Pleasanton, CA 94588

1. Introduction

1.1 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 discomfort, 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 for cold-assisted lipolysis. The ZELTIQ CoolSculpting technology is based on the sensitivity of fat cells to cold injury in order to selectively eliminate subcutaneous fat tissue without affecting the skin or other surrounding tissues. The technology, cryolipolysis, enables a non-invasive alternative for subcutaneous fat reduction through cellular apoptosis. The ZELTIQ CoolSculpting System is cleared for use in the United States for the indication of cold-assisted lipolysis of various body areas, including the abdomen, flanks, thighs, submental and submandibular areas, back fat, bra fat, and banana roll. It 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.

Clinical studies of the CoolSculpting System used on the abdomen have demonstrated the treatment to be safe and effective for the reduction of subcutaneous fat. Subjects in a recent study rated their satisfaction with the CoolSculpting procedure at 73% and 89% indicated they would recommend the procedure. [1]

While the CoolSculpting procedure is successful in reducing subcutaneous fat in the abdomen, ZELTIQ Aesthetics is exploring the concept of combining other non-invasive aesthetic treatment modalities to enhance and/or improve the contouring effects of CoolSculpting.

[redacted] Electromagnetic muscle stimulation (EMS), also known as neuromuscular electrical stimulation (NMES) is the elicitation of muscle contraction using electric impulses. The impulses mimic the action potential that comes from the central nervous system, causing the muscles to contract. [2]

EMS devices are frequently used in physical therapy or rehabilitation settings to strengthen and tone muscles damaged by illness or disease but they may also be used for other purposes. [3] High intensity EMS devices can elicit stronger, more effective muscle contractions believed to increase muscle strength and endurance. EMS has received an increasing amount of attention in the last few years from fitness enthusiasts as various manufacturers promote the technology for muscle strengthening, firming and improvement in muscle tone specifically in the abdomen, buttocks and thighs. [4]

[redacted]

1.2 Device Descriptions

EMS Devices

Electromagnetic (EMS) devices that may be used in this evaluation produce electromagnetic muscle stimulation by a non-contact magnetic field in tissue. Each device under consideration for use in this study has the same indications for use and similar technological characteristics and principles of operation. Figure 1 below depicts a representative EMS device.

[redacted]

Figure 1. Representative EMS Device

[redacted]

All EMS devices considered for use in the proposed evaluation have the following indications:

- Improvement of abdominal tone, strengthening of the abdominal muscles, development of firmer abdomen.

EMS devices utilized in this study will be operated in accordance with the manufacturer's Instructions for Use.

CoolSculpting System

[redacted] Both the control unit and the applicators are cleared by the FDA and are commercially available.

Safety features are built into the device to avoid any unexpected excursions in temperature. The device will automatically shut down if the thermal exposure at the skin interface exceeds specified criteria.

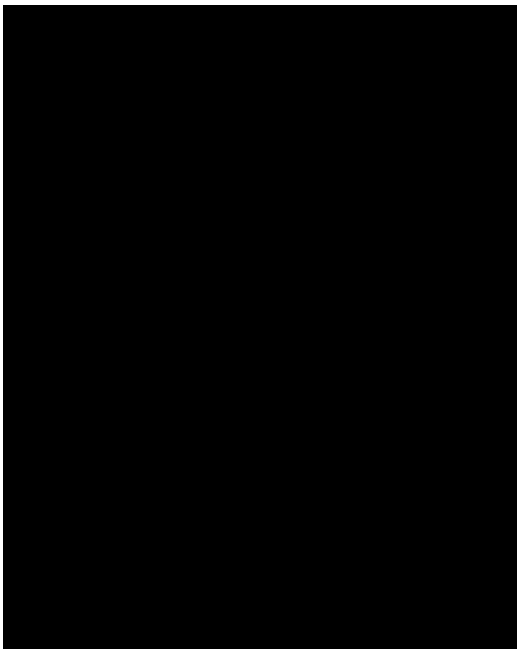
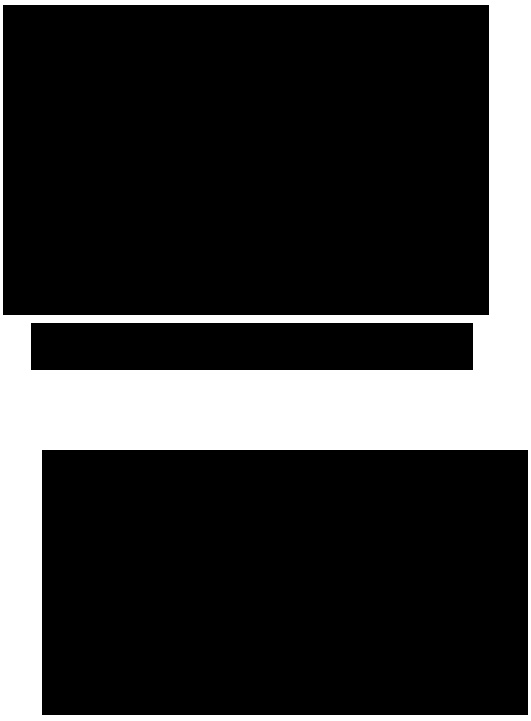


Figure 2: ZELTIQ CoolSculpting System control unit.



[redacted]

The materials used for patient-contacting surfaces are all common materials with a history of use in medical and/or skin-contact consumer applications or have been tested for biocompatibility.

1.3 Regulatory Status

The EMS devices that may be used in the proposed evaluation are non-significant risk devices. [redacted] Other devices under consideration for use in this study may not be FDA cleared, and will have similar technological characteristics and principles of operation, and have passed all performance and safety testing.

The ZELTIQ CoolSculpting 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). [redacted]

The device was also previously cleared for cooling as a method to minimize localized pain and thermal injury during laser and dermatological treatments under: K060407 (initial clearance), K063715 (clearance for warming and massage), K072152 (clearance for flat and belt applicators), K080118 (clearance for vacuum applicator), and K090094 (clearance for commercial device).

2. Study Protocol

2.1 Design

Prospective, multi-center, non-randomized, feasibility study

2.2 Study Duration

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

2.3 Physician Participants

Study Investigators must be practicing medical physicians with experience in the use of the CoolSculpting System and EMS devices.

2.4 Site Requirements

Site Investigators must have at least one study coordinator with experience in conducting aesthetic research and with sufficient time to perform study activities.

2.5 Subject Recruitment

Patients who seek reduction of fat layer in the abdomen, and/or who wish to have adjunctive treatment for abdominal firming and toning will be recruited for this study.

2.6 Sample Size

A maximum of sixty (60) subjects will be included in the study.

2.7 Subject Eligibility

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

Table 1. Eligibility criteria.

Inclusion Criteria
a) Male and female subjects ≥ 22 years of age and ≤65 years of age.
b) Subject has not had weight change exceeding 5% of body weight in the preceding month.
c) Subject agrees to maintain her weight (i.e., within 5%) by not making any major changes in diet or exercise routine during the course of the study.

d) Subject agrees to refrain from any new abdominal training exercises during the course of the study.
e) BMI ≤ 30 kg/m^2 as determined at screening.
f) Abdominal skin fold thickness 2.0 to 5.0 cm, as measured by caliper below umbilicus.
g) Cohort 4 only: Subject participated in protocol ZA18-003 in Cohort 3, and received the CoolSculpting treatment no more than 6 months prior.
h) Subject has read and signed a written informed consent form.

Exclusion Criteria

a) Subject has had a surgical procedure(s) in the area of intended treatment.
b) Subject has had an invasive fat reduction procedure (e.g., liposuction, mesotherapy) in the area of intended treatment.
c) Subject has had a non-invasive fat reduction, body contouring and/or skin tightening procedure in the area of intended treatment within the past 12 months.
d) Subject has numbness, tingling or other altered sensation in the treatment area.
e) Subject needs to administer or has a known history of subcutaneous injections into the area of intended treatment (e.g., heparin, insulin) within the past month.
f) Subject has not had an intrauterine contraceptive device inserted or removed within the past month.
g) Subject has a known history of cryoglobulinemia, cold urticaria, cold agglutinin disease, or paroxysmal cold hemoglobinuria
h) Subject has a known history of Raynaud's disease, or any known condition with a response to cold exposure that limits blood flow to the skin.
i) Subject has a history of bleeding disorder or is taking any medication that in the Investigator's opinion may increase the subject's risk of bruising.
j) Subject has known sensitivity or allergy to isopropyl alcohol and propylene glycol, or latex.
k) Subject is taking or has taken diet pills or supplements within the past month.
l) Subject has any dermatological conditions, such as moderate to excessive skin laxity, or scars in the location of the treatment sites, that may interfere with the treatment or evaluation (stretch marks is not an exclusion).
m) Subject has a metal implant or active implanted device such as a pacemaker, defibrillator, or drug delivery system.
n) Subject has been involved in any type of abdominal muscle training program within the previous 6 months.
o) Subject has pulmonary insufficiency.
p) Subject has a cardiac disorder.

q) Subject has a malignant tumor.
r) Subject has been diagnosed with epilepsy.
s) Subject currently has a fever.
t) Subject is pregnant or intending to become pregnant during the study period (in the next 9 months).
u) Subject is lactating or has been lactating in the past 6 months.
v) Subject is unable or unwilling to comply with the study requirements.
w) Subject is currently enrolled in a clinical study of any other investigational drug or device.
x) 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.

2.8 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).

2.9 Screening Procedures

Once informed consent is obtained, interested subjects will undergo screening.

Screening Visit; Required; Day -60 to Day 0

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

1. Obtain height and weight.
2. Calculate BMI
3. Assess for any medical conditions that would lead to exclusion of a subject from the study.
4. 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.

5. 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 taken or any other efficacy assessment performed.

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. Subjects who do not maintain their weight within 5% will still continue in the study. However, if the weight change is more than 5% after the final treatment, the subjects' data will be excluded from the per protocol data analysis. All subjects will be asked to avoid sun tanning during the course of the study.

After completion of the screening procedures and confirmation of eligibility, subjects will be assigned to one of four treatment groups described in **Table 2** below.

Table 2. Treatment Cohorts

Cohort 1	Cohort 2	Cohort 3	Cohort 4
EMS only (4 sessions)	EMS (4 sessions) *followed by* CoolSculpting (3-6 cycles)	CoolSculpting only (3-6 cycles)	CoolSculpting (3-6 cycles) *followed by* EMS (4 sessions)

Subjects that do not meet all eligibility criteria will be excluded from further participation in the study.

2.10 Enrollment

Study candidates who sign the informed consent form, meet eligibility criteria, and undergo initiation of study treatment are considered enrolled. Study treatment initiation is defined as the initiation of treatment with a study device after the placement of the applicator on the intended treatment area on the scheduled treatment day.

2.11 Photo Visit; Required, day -30 to 0

All subjects will have their photos taken within 30 days prior to study treatment.

a) Obtain weight.
b) Obtain baseline 3-Dimensional photographs of the abdomen using Vectra or similar imaging system.
c) Obtain baseline photographs of the treatment area using standardized setup and settings.

2.12 Study Treatment

Treatment Visit 1; Required; Day 0

Treatment instructions for the four (4) interventional cohorts are described below:

2.12.1 COHORT 1

For subjects assigned to receive EMS as a stand-alone intervention **(Cohort 1),** preparation activities are described in steps 2.12.1 a) through k):

a) Review inclusion and exclusion criteria.
b) Repeat pregnancy test for female subjects of childbearing potential (urine). Exclude subject from participation if the results are positive.
c) If the subjects meet all of the inclusion criteria and none of the exclusion criteria, then proceed with the study treatment.
d) Obtain weight prior to first EMS treatment.
e) Apply EMS device per manufacturer's Instructions for Use, and place one or two applicators in the center of treatment area.
f) Support the EMS device with treatment arm, pillows or straps as needed.

g) Initiate treatment using recommended program for abdominal toning and firming supplied by manufacturer.
h) Record the highest % energy utilized for the EMS treatment.
i) At the conclusion of the EMS treatment, the site(s) will be examined for any epidermal, dermal, or subcutaneous findings (e.g., blanching, erythema, bruising, swelling); alterations in sensation (e.g., numbness, tingling).
j) [redacted]
k) Three (3) additional EMS treatment visits will be scheduled wherein the intervention will be repeated for a total of 4 treatment sessions to occur within a two-week period. Treatment Visits 2, 3 and 4 will be performed as specified in **Section 2.12.1 a) through j).**

2.12.2 COHORT 2

For subjects assigned to receive EMS treatments prior to CoolSculpting **(Cohort 2)**, follow steps in **Section 2.12.2 a) through k):**

a) Review inclusion and exclusion criteria.
b) Repeat pregnancy test for female subjects of childbearing potential (urine). Exclude subject from participation if the results are positive.
c) If the subjects meet all of the inclusion criteria and none of the exclusion criteria, then proceed with the study treatment.
d) Obtain weight prior to first EMS treatment.
e) Apply EMS device per manufacturer's Instructions for Use, and place one or two applicators in the center of the treatment area.
f) Support the EMS device with treatment arm, pillows or straps as needed.
g) Initiate treatment using recommended program for abdominal toning and firming supplied by manufacturer.
h) Record the highest % energy utilized for the EMS treatment.
i) At the conclusion of the EMS treatment, the site(s) will be examined for any epidermal, dermal, or subcutaneous findings (e.g., blanching, erythema, bruising, swelling); alterations in sensation (e.g., numbness, tingling).
j) [redacted]

k) Three (3) additional EMS treatment visits will be scheduled wherein the intervention will be repeated for a total of 4 treatment sessions to occur within a two-week period. Treatment Visits 2, 3 and 4 will be performed as specified in Section 2.12.2 a) through j).

l) At the conclusion of the 4th EMS treatment or within 7 days, the subject will receive multiple CoolSculpting cycles per the Investigator's discretion. Cooling cycles may be applied to the upper or lower abdomen or in both areas. CoolSculpting treatments will be performed using a minimum of 3 cycles and will not exceed 6 cycles. Per Investigator discretion, CoolSculpting cycles may be performed simultaneously (dual-sculpting method).

i. Obtain subject's weight.

[redacted]

x. Immediately post treatment, the treatment site will be examined for any epidermal, dermal or subcutaneous findings (e.g., blanching, erythema, bruising, swelling), and alterations in sensation (e.g., numbness, tingling).

xi. [redacted]

xii.

[redacted]

2.12.3 COHORT 3

For subjects assigned to **Cohort 3,** all CoolSculpting cycles will be completed in a single visit.

a) Review inclusion and exclusion criteria.
b) Repeat pregnancy test for female subjects of childbearing potential (urine). Exclude subject from participation if the results are positive.
c) If the subjects meet all of the inclusion criteria and none of the exclusion criteria, then proceed with the study treatment.
d) Obtain weight.
e) Use template to mark the treatment areas on the abdomen.
f) Apply a new gasket onto applicator, then, attach the contour.

[redacted]

n) Immediately post treatment, the treatment site will be examined for any epidermal, dermal or subcutaneous findings (e.g., blanching, erythema, bruising, swelling), and alterations in sensation (e.g., numbness, tingling).
o) [redacted]

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

2.12.4 COHORT 4

For subjects assigned to **Cohort 4**, all CoolSculpting cycles will be completed in a single visit as part of prior participation in Cohort 3 of this protocol. For these subjects assigned to receive EMS treatments, follow steps **in Section 2.12.4 a) through k):**

a) Review inclusion and exclusion criteria.
b) Repeat pregnancy test for female subjects of childbearing potential (urine). Exclude subject from participation if the results are positive.
c) If the subjects meet all of the inclusion criteria and none of the exclusion criteria, then proceed with the study treatment.
d) Obtain weight prior to first EMS treatment.
e) Apply EMS device per manufacturer's Instructions for Use, and place one or two applicators in the center of the treatment area.
f) Support the EMS device with treatment arm, pillows or straps as needed.
g) Initiate treatment using recommended program for abdominal toning and firming supplied by manufacturer.
h) Record the highest % energy utilized for the EMS treatment.
i) At the conclusion of the EMS treatment, the site(s) will be examined for any epidermal, dermal, or subcutaneous findings (e.g., blanching, erythema, bruising, swelling); alterations in sensation (e.g., numbness, tingling). [redacted]
k) Three (3) additional EMS treatment visits will be scheduled wherein the intervention will be repeated for a total of 4 treatment sessions to occur within a two-week period. Treatment Visits 2, 3 and 4 will be performed as specified in **Section 2.12.4 a) through j)**.

2.12.5 Additional EMS Treatment Visits; Required

EMS Treatment Visit 2 (Cohorts 1, 2 and 4); Required; during Week 1 following first EMS treatment

a) Review and verify the subject continues to meet all eligibility criteria.

b) Repeat pregnancy test for female subjects of childbearing potential (urine). Exclude subject from participation if the results are positive.
c) Perform EMS treatment as described in **Section 2.12.1 a) through j).**

EMS Treatment Visit 3 (Cohorts 1, 2 and 4); Required; during Week 2 following first EMS treatment

a) Review and verify the subject continues to meet all eligibility criteria.
b) Repeat pregnancy test for female subjects of childbearing potential (urine). Exclude subject from participation if the results are positive.
c) Perform EMS treatment as described in **Section 2.12.1 a) through j)**.

EMS Treatment Visit 4 (Cohorts 1, 2 and 4); Required; during Week 2 following first EMS treatment

a) Review and verify the subject continues to meet all eligibility criteria.
b) Repeat pregnancy test for female subjects of childbearing potential (urine). Exclude subject from participation if the results are positive.
c) Perform EMS treatment as described in **Section 2.12.1 a) through j).**
d) Obtain 3-Dimensional photographs of the abdomen using Vectra or similar imaging system.
e) Obtain photographs of the treatment area using standardized setup and settings (Optional). See Section 2.14 for details.

2.13 Follow-up Procedures

Subjects who receive study treatment with the study devices will be required to complete all follow-up visits and assessments (2-Week, 4-Week and 12-Week).

2.13.1 Two-Week Post-Final Treatment Follow-Up; Day 14 ± 3 days

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

2.13.2 Four-Week Post-Final Treatment Follow-Up; 4 Weeks ± 1 week;

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

i. Obtain weight.
ii. Clinical assessment of the treatment area for any epidermal, dermal, and subcutaneous findings (e.g., erythema, bruising, swelling, pigment changes) as well as alterations in sensation (e.g., numbness, tingling).
iii. Assessment of any adverse events.
iv. Obtain 3-Dimensional photographs of the abdomen using Vectra or similar imaging system.
v. Obtain photographs of the treatment area using standardized setup and settings, optional. See Section 2.14 for details.

2.13.3 Twelve-week Post Final Treatment Follow-Up Visit; 12 Weeks ± 2 weeks

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

i. Obtain weight.
ii. Clinical assessment of the treatment area for any epidermal, dermal, and subcutaneous findings (e.g., erythema, bruising, swelling, pigment changes) as well as alterations in sensation (e.g., numbness, tingling).
iii. Assessment of any adverse events.
iv. Obtain 3-Dimensional photographs of the abdomen using Vectra or similar imaging system.
v. Obtain photographs of the treatment area using standardized setup and settings. See Section 2.14 for details.
vi. Subject to complete Global Aesthetic Improvement Scale.

2.13.4 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 the study schedule and events at each visit.

Table 3. Schedule of Visits

	Screening (< 1hr)	Photo Visit (<1hr)	EMS Treatment #1 (<2hrs)	EMS Treatment #2 (<2hrs)	EMS Treatment #3 (<2hrs)	EMS Treatment #4 (<2hrs)	CoolSculpting Treatment (<4hrs)	2-Wk Post Tx Phone Follow-Up (<30 min)	4-Wk Post-Tx Follow-Up (< 1 hr)	12-Wk Post-Tx Follow-Up (< 1 hr)	Optional Follow-Up*****
Time Frame	Day -60 to 0	Day -30 to 1	Day 0	Week 1	Week 2	Week 2	Day 0- Day 10 ±3 days	Week 2-3****	(4 ± 1 weeks)	(12 ± 2 weeks)	Open
Informed Consent***	X										
Eligibility Criteria	X		X	X	X	X	X				
Medical History	X										
Tx Site Assessment	X		X	X	X	X	X		X	X	
Height	X										
Weight	X	X	X				X		X	X	
BMI	X										
3D Photography		X				X			X	X	
Standardized Photography		X				X#			X#	X	
CoolSculpting							X**				
EMS			X*	X*	X*	X*					
Pain Assessment			X	X	X	X	X	X	X	X	
AE Assessment			X	X	X	X		X	X	X	
Subject GAIS										X	

* EMS treatment visits 1, 2, 3, 4 apply to Cohorts 1, 2 and 4 only.
** Cohort 2 after EMS and Cohort 3.
*** Informed Consent to be signed by subject prior to the collection of any data or initiation of any study procedures.
**** 2-week F/U timing is dependent on cohort assignment.
***** Investigator discretion as to timing and extent of follow-up assessment for optional visits.
# Optional

2.14 Assessments

Study-related assessments are described below.

2.14.1 Global Aesthetic Improvement Scale (GAIS-Independent)

Independent physician(s) experienced in body contouring treatment will be asked to rate the improvement observed in the subject's treated area between 12-week post final treatment images and baseline images, using the Global Aesthetic Improvement Scale:

- 3 = Very much improved
- 2 = Much improved
- 1= Improved
- 0 = No change
- -1 = Worse
- -2 = Much worse
- -3 = Very much worse

2.14.2 Global Aesthetic Improvement Scale (GAIS-Subject)

At 12-weeks post-final treatment, subjects will be asked to rate the improvement observed in the treated area using the Global Aesthetic Improvement Scale:

- 3 = Very much improved
- 2 = Much improved
- 1 = Improved
- 0 = No change
- -1 = Worse
- -2 = Much worse
- -3 = Very much worse

2.14.3 Photography

Three-Dimensional (3-D) photography will be used in this evaluation. 3-D photography may be performed using a commercially available photography system, such as the Canfield VECTRA or similar device.

In addition, standardized photos of the treatment areas will be obtained at pre-treatment and 12-week visits, using standardized setup, lighting, and camera settings

to ensure consistency. All standard photographs will be captured at fixed angles and posture. Using a series of pre-determined markings on the floor, the photographer will position the camera at the pre-determined reference points to ensure that the reproduction ratio and focal distance are maintained throughout the image series during the study. Subjects will use a Foot Positioning Guide (FPG) for each body angle. During follow-up visits, the photographer will re-align subjects on the FPG by referencing baseline images. The photos will be used in the Independent GAIS evaluation

2.14.4 Circumference Measurements

Subjects will undergo 3-D imaging. The imaging will be used to calculate abdomen circumference using the 3-D imaging manufacturer's software tools.

2.15 Endpoints

[redacted]

2.15.1 Primary Endpoints

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

- *Efficacy endpoint:* Comparison of pre-treatment and 12-week post-final treatment photographs to assess visible changes in the abdomen.

- *Safety endpoint:* Incidence of unanticipated adverse device effects (UADE). It is expected there will be zero UADEs.

2.15.2 Secondary Endpoints

The secondary endpoints in the study are:

- Reduction in abdominal circumference as measured by 3-Dimensional imaging.
- Subject Global Aesthetic Improvement Scale at 12-weeks post-final follow-up visit.

2.15.3 Exploratory Assessments:

Additional analyses, which may be performed, include:

[redacted]

2.16 Statistical Analysis Plan

2.16.1 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 deviation, 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.

2.16.2 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 and with weight change of no more than five percent (5%) of total body weight at the time the 12-week images are taken compared to the weight taken at the photo visit. Since significant weight change 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 efficacy analyses.

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

2.16.3 Endpoint Analysis

Primary Endpoints:

The primary efficacy endpoint will be evaluated by a comparison of pre-treatment and 12-week post-final treatment photographs to assess visible changes in the abdomen. Independent physician(s) experienced in body contouring treatment will be asked to rate the improvement observed in the subject's treated area between 12-week post final treatment images and baseline images, using the Global Aesthetic Improvement Scale.

The primary safety endpoint is the incidence of Unanticipated Adverse Device Effects (UADE). The number and percentage of subjects experiencing each AE Term will be descriptively summarized.

Secondary Endpoints:

Circumference
Circumference measurements obtained using 3-D imaging pre-treatment and at the 12-week post-final visit will be analyzed using the imaging manufacturer's software tools.

Global Aesthetic Improvement Scale
At 12-weeks post-final treatment, the subject will be asked to rate the improvement observed in the treated area using the Global Aesthetic Improvement Scale. The questionnaire is scored on a 7-point scale with 3 = Very much improved, 2 = Much improved, 1 = Improved, 0 = No change, -1 = Worse, -2 = Much worse, and -3 = Very much worse.

The number and percentage of subjects will be summarized for each possible point grade of the survey at 12 weeks. The percentage of subjects who noted some improvement will be tabulated, and the corresponding exact 95% confidence interval (per binomial distribution) will be calculated.

2.17 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 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 within 5 working days and reported to the IRB per IRB guidelines.

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.

2.18 Adverse Events

Adverse events (AEs) will be assessed continuously throughout the study. An adverse event is defined as any untoward medical occurrence in a participant, 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 (AE)

Any sign, symptom, or disease in a study participant 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 participant, regardless of whether the event is related to the device that:

a. results in death;

b. results in a life-threatening illness or injury;

The term life threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. results in a permanent impairment of a body structure or body function;
    - Impairment of body function means a substantial disruption of a person's ability to conduct normal life functions.
    - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial impairment.

d. requires in-patient hospitalization or prolongation of existing hospitalization;
   - In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

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.

Time Period and Frequency for Collecting AE and SAE Information

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

Medical occurrences that begin after signing of informed consent and before administration of study treatment will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.

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 participants.

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 participants enrolled.

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.

Sponsor Contact:

Lori Brandt
Director, Clinical Trial Management
ZELTIQ Aesthetics, an Allergan affiliate
4410 Rosewood Dr.
Pleasanton, CA 94588
[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.

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.

3. Study Management and Quality Control

3.1 Study Data Collection

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

3.2 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, IRB and FDA will have access to these confidential files. All data used in the analysis, reporting and publication of this clinical trial will be maintained without identifiable reference to the 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.

3.3 Investigator Responsibilities

General Responsibilities

Investigators are responsible for ensuring the investigation is conducted according to all signed agreements, the Investigational Plan, and applicable FDA 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 21 CFR 812 and other applicable regulations, including but not limited to:

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

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

Device Accountability: The Investigator is responsible for controlling all investigational device(s) stored at their site, including supervision of device use, disposal of the device or returning the device as instructed by the Sponsor. (21 CFR 812.110 & 812.140 (2))

Financial Disclosure: Investigators shall provide financial disclosure according to federal regulations (21 CFR 54).

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.

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, or 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 devices
- 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 devices, 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.

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.

3.4 Sponsor Responsibilities

General Responsibilities:

As the Sponsor, ZELTIQ Aesthetics assumes overall responsibility for the conduct of the study. ZELTIQ Aesthetics assumes all responsibilities per 21 CFR 812 and other applicable regulations, and shall:

IRB approval: Ensure IRB approval for the investigation before shipping the device to any Investigator.

Investigators: Select Investigators qualified by training and experience, and providing them with the information they need to conduct the investigation properly (21 CFR 812.43). Obtain a signed Investigator Agreement (21 CFR 812.43(c)) 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 monitoring the study (21 CFR 812.43), and ensure proper monitoring of the investigation. (21 CFR 812.46)

Investigational devices: Provide devices only to qualified Investigators (21 CFR 812.43). No study site may receive shipment of study devices until the following documents are received by the Sponsor:

- Signed Investigator's Letter of Agreement
- Signed Clinical Site Agreement
- Investigator current curriculum vitae

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

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 Investigational Plan, 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 devices and protocol, applicable regulations and requirements, and expectations of the study, enrollment expectations, subject selection, informed consent, required clinical data and record keeping, etc.

Investigational Device Use: Representatives of the Sponsor will train Investigators in use of the study device prior to study initiation. Sponsor representatives may be present at study procedures.

Site Monitoring

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

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

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 minimum once 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
- Device accountability is being maintained
- 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

Clinical monitors will provide feedback to the site regarding protocol or study compliance.

Study Site Closeout

At the close of the study at an investigational site, the monitor will ensure that all case report forms have been monitored and retrieved and that the Investigator's files are accurate and complete. The monitor will ensure that all investigational devices and study supplies are accounted for, and provide for appropriate disposition of any remaining supplies. The monitor will review record retention requirements with the

Investigator and any remaining Investigator obligations are reviewed and ensure that all applicable requirements are met for the study. The monitor will prepare a report of the site closeout visit.

Final Report

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

4. 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.

5. 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.

6. Risk/Benefit Analysis

The Sponsor has undertaken a comprehensive risk-benefit analysis.

6.1 Benefits

Abdominal muscle toning and contouring in the treatment area is anticipated to provide an aesthetic benefit and this non-invasive device accomplishes the desired effect without anesthesia and with minimal recovery time. Furthermore, the results of this study will help in the development of the optimal aesthetic procedure for fat removal with cryolipolysis followed by EMS. Considering the number of body contouring 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.

6.2 Risks

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

Anticipated Device Effects from CoolSculpting procedure:

These are known effects of the ZELTIQ Procedure, previously noted in prior studies as transient and/or temporary effects related to 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;
- transient, localized sensory changes (e.g., numbness, tingling) resolving within 12 weeks of the procedure;

Anticipated Device Effects of EMS:

- muscular pain in the treatment area
- temporary muscle spasm
- temporary joint or tendon pain
- local erythema and/or skin redness
- skin irritation and burns under the electrodes may cause possible allergic skin reaction to tape or gel

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 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.
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 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).

Potential Adverse Effect	Description
Gastrointestinal Symptoms	Nausea, bloating, or diarrhea temporally related to the procedure (within the first few hours after the procedure)
Contour Irregularity	Significant indentation or contour irregularity in the treatment area that would require surgical intervention.
Skin surface irregularities	Significant indentation or rippling which develops 1 month after treatment that would require medical intervention.
Allergic/Irritant Contact Dermatitis	Itchy rashes and skin peeling that may result from prolonged exposure to gel or gelpad, foam borders or applicator pressure
Subcutaneous Induration	Hardness within the treatment area, either as generalized firmness or discrete nodules.
Hernia	Creation or exacerbation of hernia. Hernia is defined as a protrusion of an organ or the fascia of an organ through the wall of the cavity that normally contains it.
Paradoxical Hyperplasia	Visibly enlarged tissue volume within the treatment area which may develop 2-5 months after treatment. Surgical intervention may be required.
Other	Any other untoward medical event determined by the Investigator to be an adverse event, regardless of the relationship to the device or treatment.

7. Selected References

1. Krueger, N., Mai, S. V., Luebberding, S., & Sadick, N. S. (2014). Cryolipolysis for noninvasive body contouring: clinical efficacy and patient satisfaction. *Clinical, cosmetic and investigational dermatology*, *7*, 201.

2. Maffiuletti NA, Minetto MA, Farina D, Bottinelli R. Electrical stimulation for neuromuscular testing and training: state-of-the art and unresolved issues. Eur J Appl Physiol. 2011 Oct;111(10):2391-7.

3. Leon-Salas WD, Rizk H, Mo C, et al. A Dual Mode Pulsed Electro-Magnetic Cell Stimulator Produces Acceleration of Myogenic Differentiation. *Recent patents on biotechnology*. 2013;7(1):71-81.

4. Jacob CI, Paskova K. Safety and efficacy of a novel high-intensity focused electromagnetic technology device for noninvasive abdominal body shaping. J Cosmet Dermatol. 2018;00:1-5.