STUDY TITLE: A SINGLE-CENTER, PROSPECTIVE STUDY TO EVALUATE THE SAFETY AND EFFECTIVENESS OF MULTI -TREATMENT REGIMEN WITH ZELTIQ AESTHETICS, INC. RAPID ACOUSTIC PULSE (RAP)™ DEVICE FOR THE IMPROVEMENT IN THE APPEARANCE OF CELLULITE

PROTOCOL NUMBER: 2021-06

Rev: 02

DATE: MARCH 20, 2024

Contact: [redacted]
[redacted] Clinical Development, RESONIC™
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Sponsor:
ZELTIQ Aesthetics, Inc.
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Pleasanton, CA 94588

CONFIDENTIALITY STATEMENT

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This information cannot be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of ZELTIQ Aesthetics, Inc.

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INVESTIGATOR'S STATEMENT OF AGREEMENT

I have read the foregoing protocol and agree that it contains all necessary details for conducting the study. I will conduct the study as outlined herein and will complete the study within the time designated.

I agree to conduct this protocol in accordance with local regulations, external standards and applicable ICH and Good Clinical Practice (GCP) guidelines.

I will provide copies of the protocol, including any amendments, and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the ZELTIQ Aesthetics, Inc. device and the conduct of the study.

I further agree to provide access to ZELTIQ Aesthetics Inc, its designees, or regulatory authorities to any source documents from which case report form information may have been generated.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Principal Investigator
(Print name)

_____ _____

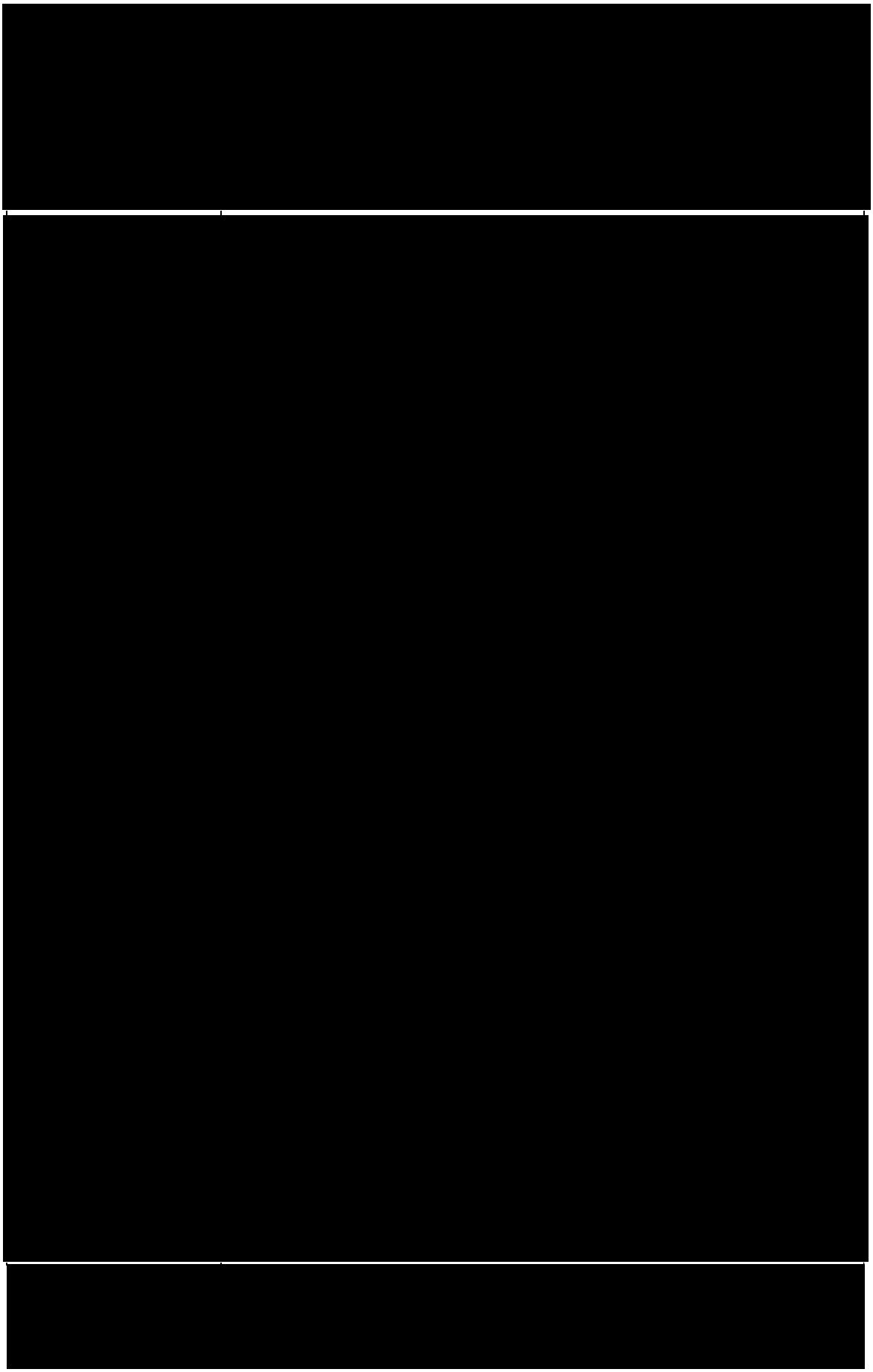
Principal Investigator Date
(Principal Investigator's signature)

CLINICAL SITE

STUDY SYNOPSIS

Purpose	The purpose of this single-site clinical study is to evaluate the safety and effectiveness of three (3) treatments sessions with the ZELTIQ Aesthetics, Inc. Rapid Acoustic Pulse (RAP) device for the improvement in the appearance of cellulite.
Primary Effectiveness Objective	• RAP treatment effectiveness: The primary effectiveness objective will demonstrate improvement in the appearance of cellulite as determined by correct identification of baseline vs 12-weeks post final treatment images [redacted] by at least 2 of 3 blinded independent physician reviewers (IPR).
Primary Safety Objective	• RAP treatment safety: The primary safety objective is to evaluate the safety of the RAP (Rapid Acoustic Pulse) device for cellulite treatments through the monitoring of the incidence of adverse events (AEs) and adverse device effects (ADEs); serious adverse events (SAEs) and SADEs (serious adverse device effects) and pain assessments.
Secondary Effectiveness Objective	• RAP treatment effectiveness: The secondary effectiveness objective is to demonstrate the improvement in the appearance of cellulite as determined by the study participants selecting "Agree" or "Strongly Agree" as answers to the Participant Satisfaction Survey (**Assessment 3**): when comparing side-by-side before and after photographs.
Test Device	ZELTIQ Aesthetics, Inc. Rapid Acoustic Pulse (RAP) device.
Treatment	Each cellulite treatment session will consist of RAP treatment [redacted] to bilateral thigh and/or buttock areas using the same treatment settings for both sides. The participants will have three (3) separate cellulite treatment sessions. The second treatment session will occur four (4) weeks post the initial treatment. The third treatment session will occur twelve (12) weeks post the second treatment.
Control	For each cellulite treatment area, the pre-treatment photos of the thighs and/or buttocks area will serve as a control.
Study Design	Non-significant risk, single-site, prospective clinical trial.
Planned Number of Sites / Countries	One clinical trial site located in the United States.

Planned Duration of Participant Engagement	Up to seventy-two (72) weeks [redacted]
Planned Number of Participants/ Treatment Areas	Up to 15 participants [redacted] (total of two thighs and/or buttocks per participant) The clinical site (CS) will recruit up to 15 participants. This will provide a total of up to thirty treatment areas.
Primary Effectiveness Endpoint	• Effectiveness Endpoint: An Independent Photo Review (IPR) panel will be asked to identify the 12-weeks post final treatment photographs from randomly placed side-by-side before and after photographs, for all participants who meet all the inclusion criteria and none of the exclusion criteria and complete the 12-weeks follow-up visit. The number of before and after photos correctly identified by at least 2 of 3 blinded reviewers from the IPR panel will be recorded. [redacted]
Primary Safety Endpoint	• RAP treatment safety endpoint: To demonstrate safety through the absence of unexpected adverse events (UAEs) and serious adverse events (SAEs) directly attributable to the RAP device or treatments.
Secondary Effectiveness Endpoint	• Effectiveness Endpoint: For all participants who meet all inclusion criteria and none of the exclusion criteria and are followed up at the 12-week timepoint post final treatment, [redacted] he study participants select "Agree" or "Strongly Agree" to the Participant Satisfaction Survey (**Assessment 3**): [redacted]
[redacted]	



[redacted]	
Inclusion Criteria	• Healthy candidates ages 18-50 years. • Seeking treatment of cellulite in the thigh and/or buttock areas. • Areas of moderate to severe cellulite on bilateral thigh and/or buttock using the Cellulite Dimple – At Rest Scale at Baseline with grades of 2 or 3 based on review of photos taken under the same lightening conditions planned for the trial. • Participant will not have had minimally invasive, invasive, or energy-based cellulite (liposuction, subcision, RF, laser, ESWT, cryo-lipolysis, muscle stimulation, etc.) treatments in the treatment areas in the prior 12 months. • Participant will not have used topical based cellulite treatments for prior 3 months and will not use during the trial. • Participant will not have used spray-on tanning treatments for 3 months prior to or during the term of the trial. • Participant must be able to provide written informed consent, understand and is willing to comply with all study-related procedures and follow-up visits.
Exclusion Criteria	• Participant is unwilling to have research photos and/or videos taken of treatment areas in the presence of or by Sponsor's research team. • Participant is unwilling to have RAP treatment provided in the presence of Sponsor's research team. • Participant is pregnant or planning to become pregnant during the duration of the study. • Participant is unwilling to commit to follow-up visits.

	• Metal or plastic implants (vascular stent, or implants in the hips, knees, etc.) in the treatment areas. • Active electronic implants such as pacemakers and defibrillators. • History of coagulopathy and/or on anticoagulant medication. • Skin disorders (skin infections or rashes, psoriasis, etc.) in the treatment areas. • Medical disorder that would hinder wound healing or immune response. • Any surgical procedure in the treatment areas in the prior 3 months or planned during the duration of the study. • Any other condition/disease/situation which, as deemed by the PI, would preclude participant from safely participating in or completing the study visits or that may confound study results.

INTRODUCTION

Overview

The Rapid Acoustic Pulse (RAP) is an electrohydraulic (EH) device designed to improve the appearance of cellulite. Devices using RAP technology have been successfully used in seven human clinical trials to accelerate laser-based tattoo removal, a proof of concept (POC) and pivotal clinical trials to improve the appearance of cellulite without the occurrence of device related UAEs or SAEs. The purpose of this single-site, multi-treatment clinical study is to evaluate the safety and effectiveness of ZELTIQ Aesthetics, Inc.'s Rapid Acoustic Pulse (RAP) device for the improvement of cellulite.

Cellulite

Cellulite is the often aesthetically displeasing rippling or dimpling of the skin most commonly located on the thighs and buttocks of women. Its appearance and texture are often likened by laypeople to that of "cottage cheese" or an orange peel [1].

In a paper discussing anatomical approaches to treating cellulite by Christman et al [1], "In normal skin, there is a support network of fibrous septa running through the subcutis, separating the adipose cells into chambers resembling a quilt. Magnetic resonance imaging demonstrates that in cellulite, these fibrous septa are contracted and sclerosed, ultimately tethering the skin at a fixed length. Concurrently, the adipose cells expand with weight gain or water absorption, promoting herniation, or outpouching of fat into the dermis. This results in skin dimpling creating the characteristic cellulite appearance. Two distinct morphologies of cellulite may be identified, sometimes coexisting in the same patient: 1) diffuse rippling in patients with increased adiposity and/or increased skin laxity and 2) dimpling, with discrete ellipsoid or linear depressions, in patients with good skin tone [1]."

Christman concluded, "It is crucial to consider the anatomy of the patient and the morphology of cellulite while choosing a treatment. Diffuse rippling represents increased adiposity and/or increased skin laxity which may stand to benefit from lipolytic and skin tightening modalities. Dimpling represents tethering by fibrous septa which may stand to improve from subcision by minimally invasive devices such as Cellfina [1]."

ZELTIQ Aesthetics, Inc.'s Rapid Acoustic Pulse (RAP) device with Cellulite Cartridge

ZELTIQ Aesthetics, Inc.'s Rapid Acoustic Pulse (RAP) technology was developed to improve the appearance of cellulite through microscopic disruption of the fibrous septa leading to an improvement in the appearance of cellulite dimples and ridges.

RAP comprises multiple components, including the console, handpiece, and the cable connecting the handpiece to the console. The disposable electrohydraulic cartridge is an electro-mechanical device that converts an electrical signal into mechanical (acoustical) energy. The RAP device produces [redacted] planar acoustic waves at a pulse rate of [redacted] This high pulse rate causes non-invasive fibrous structure disruption without cavitation damage or thermal degradation of the surrounding tissue that are seen with focused acoustic devices.

Physical Effects

RAP can induce physical effects in the form of disruption (i.e., subcision) of the fibrous structures that make up the extracellular matrix or in the case of subcutaneous tissue, the fibrous septa. These physical effects appear to be through shearing of the fibrous structures.

The high frequency wavefront's [redacted] play a critical role in shear-induced tissue injury. The greater the gradient, the more fibrotic disruption occurs [2]. Importantly, while shock-induced shearing might initiate disruption, individual high frequency acoustic waves do not produce sufficient shear to do so [3].

To produce enough fibrotic disruption from shearing, multiple acoustic shock waves need to be administered to the treatment site. For example, in a paper by Howard [4] of the mechanical effects of focused shock waves on tissue-mimicking structures, membrane disruption is observed to increase progressively as the number of shock waves increases. For example, kidney injury from shock waves during lithotripsy pervade the focal region of the kidney parenchyma after 1000 or 2000 shock waves [4].

However, it just not the number of shock waves that are important to affect tissue. If you provide one thousand shock waves to a kidney over a period of hours or days, there will be little if any tissue damage. [redacted]

[redacted]

[redacted]

The RAP improves the appearance of cellulite through disruption of the subcutaneous fibrous septa leading to a reduction in the severity of dimples and ridges.

Proof of Concept (POC) of Safety and Tolerability of RAP Cellulite Clinical Trial

In the proof-of-concept cellulite clinical trial that was initiated in June 2018 at SkinCare Physicians, the primary objectives of that study were to assess the safety and tolerability of the RAP treatment, and the secondary objective was to determine if the RAP treatment could provide improvement in appearance of cellulite.

Both thighs in five participants (10 treatment areas) having Grade II cellulite, were treated with the RAP device with [redacted] pulse rate. On one site, a single RAP treatment was provided. On the other site, a RAP treatment was given every three weeks for a total of three RAP treatments. Immediately after each RAP treatment, the treated areas were assessed for AEs. Additionally, the participants were asked about discomfort from the procedure. Finally, photographs of the treatment areas taken prior to, and at 12-weeks post the first treatment, were assessed to determine if the RAP treatment had the effect of improvement in the appearance of cellulite.

Results indicated there were no safety or discomfort issues resulting from the RAP treatments. Mild redness around hair follicles, which resolved within hours was the only side effect. There were no reports of erythema, swelling or bruising. [redacted]

Safety Conclusion

Given the safety and tolerability results of the Acoustic Wave Device (AWD) in the POC cellulite human clinical trial, the RAP device is anticipated to be safe and tolerable when used in this clinical trial. The RAP device that will be used in this study uses the same Rapid Acoustic Pulse technology that is the basis for ZELTIQ Aesthetics, Inc.'s AWD (Acoustic Wave Device) and RAP devices in earlier trials.

Pivotal Study of Safety and Efficacy of RAP Cellulite Clinical Trial

A multi-center, pivotal study was conducted to assess the safety and efficacy of the ZELTIQ Aesthetics, Inc. RAP device for the temporary improvement of cellulite on the treatment areas of thighs and/or buttocks. Sixty-seven participants enrolled in the study. Treatments were conducted at [redacted] Efficacy was documented at 12- weeks post treatment. No SAE or device related unexpected or SAE occurred during the study.

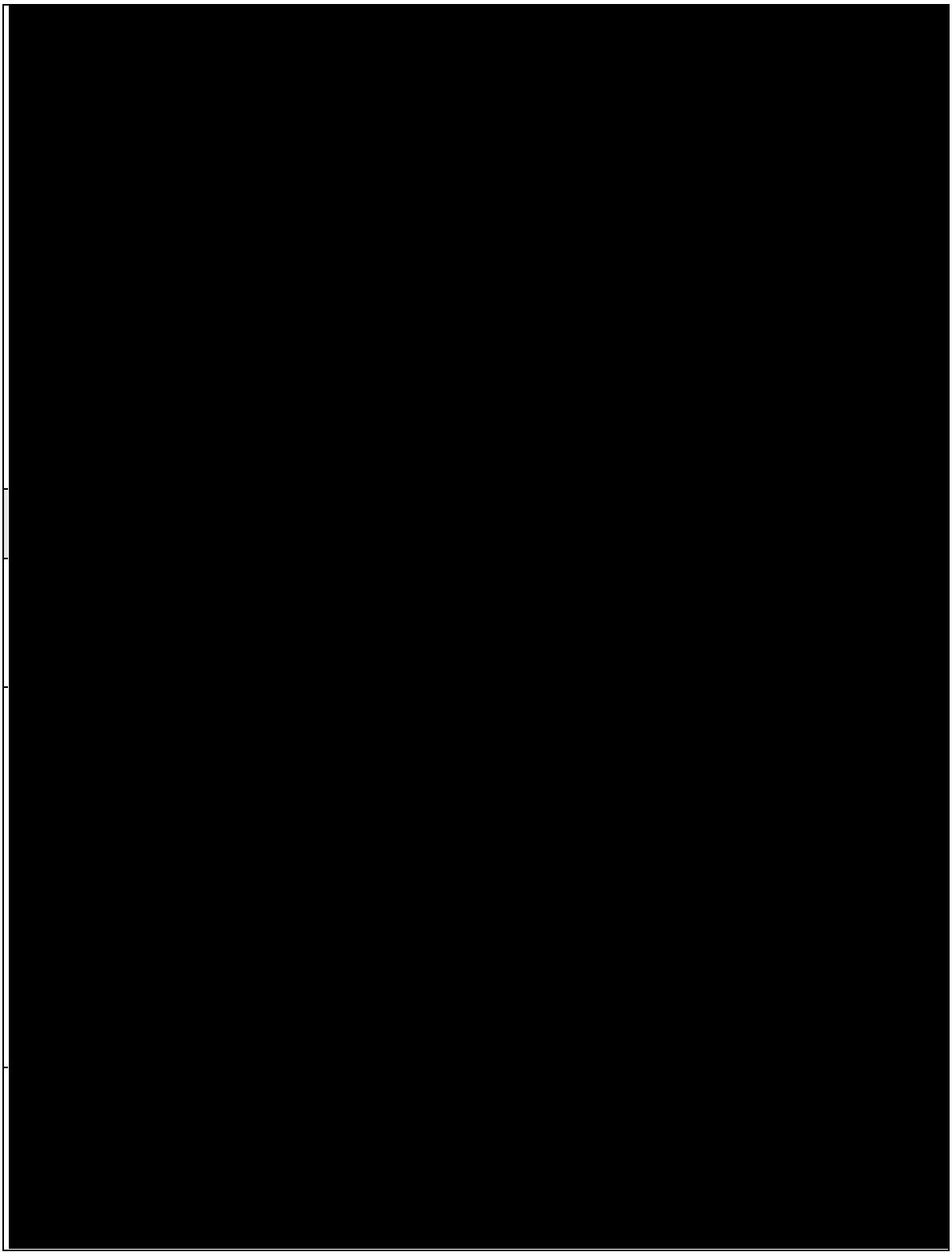
Short-term (12-week) analysis was conducted in fifty-six participants who completed a full treatment of the identified treatment areas and who completed the 12-week follow up visit. Serial clinical photographs were collected before RAP treatment under standardized conditions at the baseline (0-week) visit and at the short-term (12-week) follow-up visits. Photographs were assessed by blinded independent reviewers (IPR) to correctly identify the 12-weeks post-treatment photographs from randomly placed side-by-side comparison of before and after photographs. Additionally, the IPR graded the pre-treatment and post-treatment images using the simplified 6-point Cellulite Severity Scale (CSS) [3] and improvement using the Global Aesthetic Improvement Scale (GAIS). Safety assessments included evaluation of Adverse Events (AEs) via physician examination during and after the treatment.

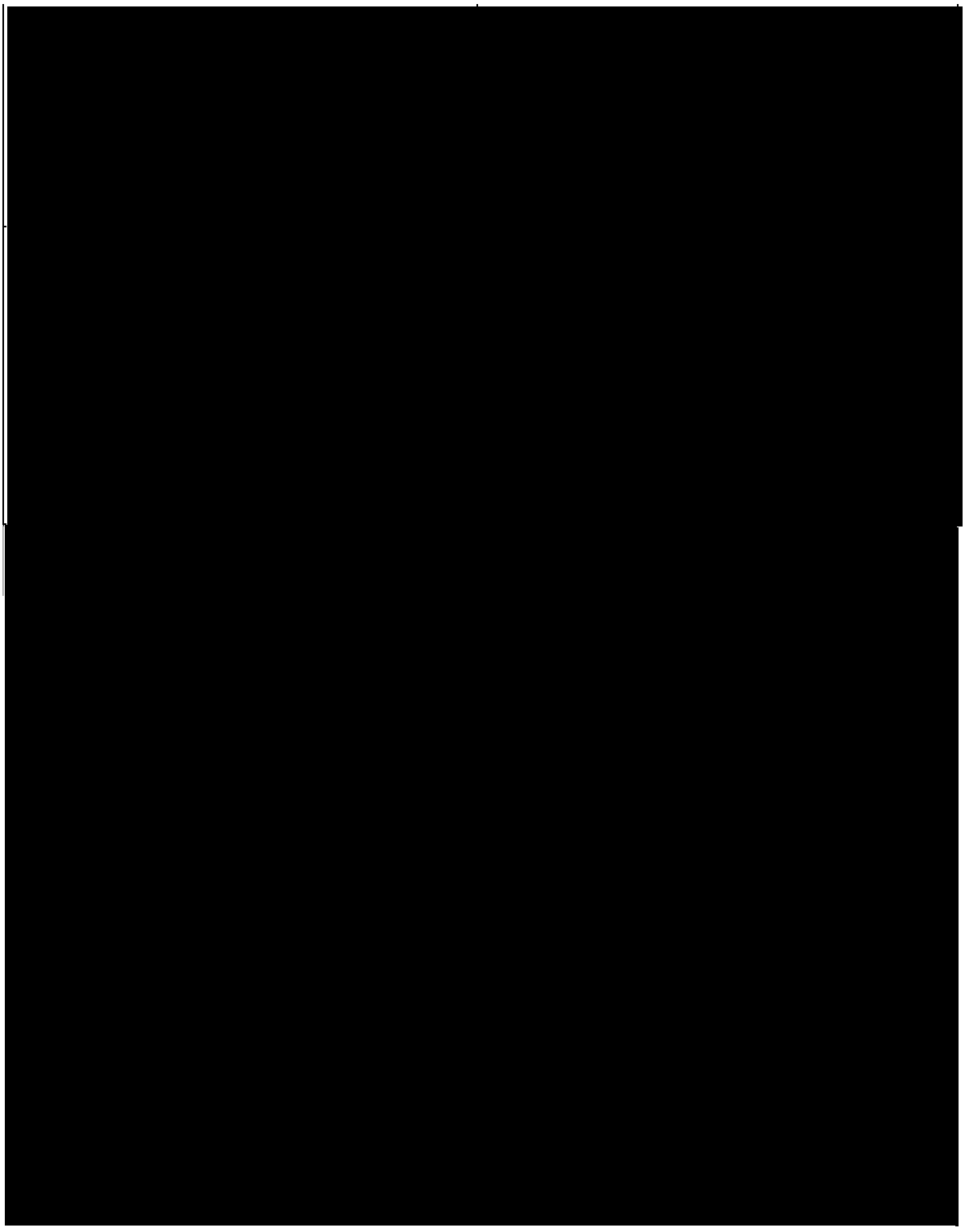
The short-term (12-week) results demonstrated that a single non-invasive acoustic subcision session can safely provide meaningful improvement in the appearance of cellulite in terms of depressions with minimal treatment pain and no post-treatment down time. The post-treatment photographs were correctly identified by blinded IPR from randomized pairs of pre/post-treatment photographs at a rate of 96.4%. Furthermore, the participants had a mean CSS reduction of 1.01 (a 29.5% reduction from baseline). Cellulite was graded as improved, much improved, or very much improved using the GAIS at 90.9% of treated locations. Finally, 92.9% of participants reported positive satisfaction responses. No device related unexpected or serious AEs were noted at treatment or follow-up. Overall average pain score during treatment was 2.4 (0-10 pain scale) and 0.3 immediately post-treatment.

Protocol 2021-06 Study Objectives and Endpoints

Primary Objectives	Primary Outcome Endpoints
RAP treatment effectiveness: The primary objective is to demonstrate improvement in the appearance of cellulite by blinded independent physician reviewers (IPR).	Effectiveness Endpoint: An IPR panel will be asked to identify the 12-weeks post final treatment photographs from randomly placed side-by-side before and after photographs, for all participants who meet the all inclusion criteria and none of the

	exclusion criteria and complete the 12-week follow-up visit. The number of before and after photos correctly identified by at least 2 of 3 blinded reviewers from the IPR panel will be recorded. [redacted]
RAP treatment safety: The promaryobjective is to evaluate the safety of the RAP device for cellulite treatments.	RAP treatment safety endpoint: The numbers and proportions of participants with AEs, SAEs, ADEs, SADEs, and unanticipated AEs or ADEs will be summarized. RAP treatment safety: The safety objective is to evaluate the safety of the RAP (Rapid Acoustic Pulse) device for cellulite treatments through the monitoring of the incidence of adverse events (AEs) and adverse device effects (ADEs); serious adverse events (SAEs) and SADEs (serious adverse device effects) and pain assessments.
Secondary Objectives	Secondary Outcome Endpoints
RAP treatment effectiveness: The secondary objective is to demonstrate the improvement in the appearance of cellulite as determined by the study participants.	For all participants who meet all inclusion criteria and none of the exclusion criteria and are followed up at the 12-week timepoint post final treatment, [redacted] In comparison to the pre-treatment photo, the 12-week photograph of the treatment area appears improved.
[redacted]	





STUDY DESIGN

This is a non-significant risk, single-center, prospective trial for safety, and effectiveness using ZELTIQ Aesthetics, Inc.'s RAP device for the improvement in the appearance of cellulite performed at 1 clinical research site in the United States.

Up to fifteen (15) healthy participants between the age of 18-50 will be enrolled in this study.

Participants who sign the informed consent form and meet all the eligibility criteria will be enrolled in the study. Each participant will undergo acoustic rapid pulse (RAP) treatments on both of their thighs and/or buttocks.

Total study duration is anticipated to be at or less than 72 weeks from the first participant visit to the last participant observation visit. A total of up to 7 visits are planned for this study [redacted].

Selection of Study Population

The clinical study can fulfill its objectives only if appropriate participants are enrolled.

The following criteria are designed to select participants for whom protocol requirements are considered appropriate.

Participants who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the study and assigned a participant No./ID in sequential order (i.e., 01, 02, 03, etc.)

Inclusion Criteria

- Healthy candidates ages 18-50 years
- Seeking treatment of cellulite in the thigh and/or buttock areas
- Areas of moderate to severe cellulite on bilateral thigh and/or buttock using the Cellulite Dimple – At Rest Scale at Baseline with grades of 2 or 3 based on review of photos taken under the same lightening conditions planned for the trial.
- Participant will not have had minimally invasive, invasive or energy-based cellulite (liposuction, subcision, RF, laser, ESWT, cryo-lipolysis, muscle stimulation, etc.) treatments in the treatment areas in the prior 12 months.
- Participant will not have used topical based cellulite treatments for prior 3 months and will not use during the trial.
- Participant will not have used spray-on tanning treatments for 3 months prior to or during the term of the trial.
- Participant must be able to provide written informed consent, understand and is willing to comply with all study-related procedures and follow-up visits.

Exclusion Criteria

- Participant is unwilling to have research photos and/or videos taken of treatment areas in the presence of Sponsor's research team.
- Participant is unwilling to have RAP treatment provided in the presence of Sponsor's research team.
- Participant is pregnant or planning to become pregnant during the duration of the study.
- Participant is unwilling to commit to follow-up visits.

- Metal or plastic implants (vascular stent, or implants in the hips, knees, etc.) in the treatment areas.
- Active electronic implants such as pacemakers or defibrillators.
- History of coagulopathy and/or on anticoagulant medication.
- Skin disorders (skin infections or rashes, psoriasis, etc.) in the treatment areas.
- Medical disorder that would hinder wound healing or immune response
- Any surgical procedure in the treatment areas in the prior 3 months or planned during the duration of the study.
- Any other condition/disease/situation which, as deemed by the PI, would preclude participant from safely participating in or completing the study visits or that may confound study results.

[redacted]

STUDY PROCEDURES

Study procedures as described in this section are outlined in the schedule of assessments. [redacted]

Study Visits

Visit 1 Baseline Screening and Consent Form (Day -30 to Day 0)

- Review study procedures, assessments and visit schedule with participants
- [redacted]
- Obtain informed consent
- Review of Inclusion/Exclusion criteria
- [redacted]
- Fitzpatrick Skin Type Scale **(Scale 2)**
- [redacted]
- Demographics and baseline characteristics (including weight and height)
- Limited physical exam, blood pressure and heart rate
- Review of medical history (3-year history)
- Urine pregnancy test for women of childbearing potential
- Concomitant medication
- 2D Photos of the treatment area
- [redacted]

[redacted]

Visit 2 Treatment

Pre-treatment Activities

- Review concomitant medication
- Take vital signs
- Urine pregnancy test for women of childbearing potential
- Adverse event evaluation
- Confirm eligibility
- [redacted]
- 2DPhotos of the treatment area taken pre and post marking
- [redacted]

Note: Visits 1 and 2 may be combined if feasible at time of screening and enrollment.

Treatment

- Administer treatment in accordance with Treatment Recommendations **(See Appendix A, Treatment Recommendations)**

Immediate Post-Treatment Activities

- Adverse event evaluation

[redacted]

Visit 3 Follow Up Visit 4-Weeks Post 1st Treatment (+/- 14 days) and 2nd Treatment

Pre-treatment Activities

- Review concomitant medication
- Take vital signs
- Weight
- Urine pregnancy test for women of childbearing potential
- Adverse event evaluation
- Confirm eligibility
- Collect Diary – Treatment 1
- [redacted]

[redacted] 2D Photos of the treatment area taken pre and post marking

[redacted]

Treatment

- Administer treatmen [redacted]

Immediate Post-Treatment Activities

- Adverse event evaluation

[redacted]

Visit 4 Follow Up Visit 12-Weeks Post 2nd Treatment (+/- 14 days) and 3rd Treatment

- Review concomitant medication
- Take vital signs
- Weight
- Urine pregnancy test for women of childbearing potential
- Adverse event evaluation
- Confirm eligibility
- [redacted]
- [redacted]
- 2D Photos of the treatment area taken pre and post marking

[redacted]

Treatment

- Administer treatment in accordance with Treatment Recommendations **(See Appendix A, Treatment Recommendations)**

Immediate Post-Treatment Activities

- Adverse event evaluation

[redacted]

Visit 5 Follow Up Visit 12- Weeks Post 3rd Treatment (+/- 14 days)

- Weight
- Review concomitant medication
- Adverse Event evaluation
- [redacted]
- 2D Photos of the treatment area

[redacted]

Visit 6 Follow Up Visit 26- Weeks Post 3rd Treatment (+/- 14 days)

- Weight
- Review concomitant medication
- Adverse Event evaluation
- Review Participant Pre and Post Treatment Instructions
- 2D Photos of the treatment area

[redacted]

Visit 7 Follow Up Visit 52- Weeks Post 3rdTreatment (+/- 14 days)

- Weight
- Review concomitant medication
- Adverse Event evaluation
- 2D Photos of the treatment area

[redacted]

* Local, national, or federal holidays may occur during the timeframe of this study, which may alter the follow up dates.

PHOTOGRAPHY

Baseline photographs will be taken under standardized lighting and equipment settings.

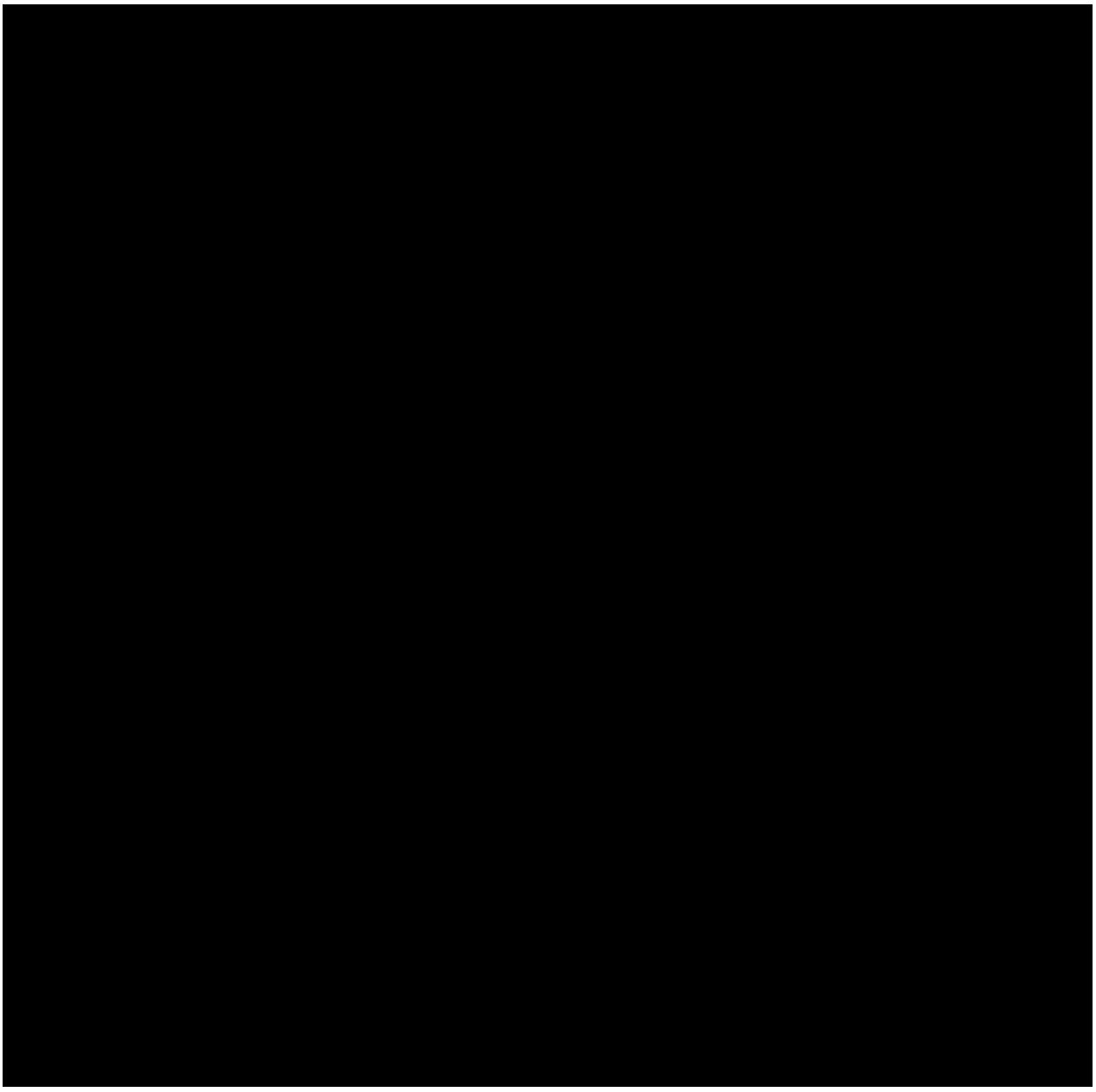
[redacted]

UNSCHEDULED VISITS
An unscheduled visit may be performed at any time during the study at the participant's request or as deemed necessary by the study investigator. The date and reason for the visit will be recorded in the source document.

PARTICIPANT WITHDRAWALAND EARLY TERMINATION
Participants may withdraw from the study at any time at their own request or withdrawn from at any time at the discretion of the Investigator for safety, behavioral, or administrative reasons. The Investigator should inquire about reason for withdrawal, request the participant to return for a final visit, and follow up with any unresolved adverse events. The Investigator should notify the Sponsor of any participants withdrawal or discontinuance.

RISKS AND BENEFITS

Clinical Benefit
There is no clinical benefit in this study. The participant may experience an improvement in the aesthetic appearance of the treated areas.



[redacted]

Risk Mitigations

The Investigator in this clinical study has been invited to participate in this study based on his/her previous experience with the use of energy-based systems and other novel modalities in aesthetic dermatology and plastic surgery. Experience with cosmetic treatments is the most critical element in managing participant risk in this trial. All other known risks will be disclosed to the participant via the informed consent process. Risks have been mitigated by the specific design employed in manufacturing the device.

REPORTING ADVERSE EVENTS AND COMPLICATIONS

Adverse Events

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs as detailed in this Section of the protocol.

At the treatment and follow-up visits, participants will be assessed for known physiological responses and adverse events.

Adverse Event (AE)

- An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that occurs or is reported by the participant to have occurred, or a worsening of a pre-existing condition. An adverse event may or may not be related to the study treatment.

- AEs will be elicited through direct questioning and participant reports. Any abnormality in physical examination findings that the investigator believes is clinically significant (CS) to the research participant and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant should not be recorded as an AE.

Adverse Device Effect (ADE)

- An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical

device as well as any event resulting from use error or from intentional misuse of the investigational medical device. This includes "comparator" if the comparator is a medical device.

1. Reporting of Adverse Events
    - Report initiation for all AEs and SAEs will begin at the time of the first treatment and continue until the end of the final study observation visit. All events will be followed to resolution or until the participant completes the study. A final assessment of outcome will be made at that time.
    - All AEs must be recorded in the participant's medical records and in the case report form. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is an SAE, the impact the event had on study treatment, the severity of the event, the causality of the event, whether treatment was given as a result of the event, and the outcome of the event.
2. Impact on Study Treatment

    - The impact the event had on the study treatment will be assessed as either: none, study treatment interrupted, study treatment discontinued, or not applicable. The "not applicable" assessment will be used only when the participant is in the observation phase of the protocol.

3. Causality Assessment

    - AEs will be assigned a relationship (causality) to the study treatment. The Investigator will be responsible for determining the relationship between an AE and the study treatment. The type of event, organ system affected, and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the study treatment. Relationship of AEs to study treatment will be classified as follows:

        i. Definitely related: This category applies to those AEs that the Investigator feels are incontrovertibly related to the study treatment. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study treatment; (2) it could not be reasonably explained by the known characteristics of the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant; (3) it follows a known response pattern to treatment with the study treatment.

        ii. Probably related: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study treatment. An AE may be considered probable if or when (must have three): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by participant's clinical state, environmental or toxic factors, or other therapies administered to the participant. (3) Disappears or is decreased upon

discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.

iii. Possibly related: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are judged unlikely but cannot be ruled out with certainty to the study treatment. An AE may be considered possible if or when (must have two): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by participant's clinical state, environmental or toxic factors, or other therapies administered to the participant. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.

iv. Remotely related: In general, this category can be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are judged likely to be unrelated to the study treatment. An AE may be considered unlikely if or when (must have two): (1) it does not follow a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by participant's clinical state, environmental or toxic factors, or other therapies administered to the participant. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It does not follow a known response pattern to treatment with the study treatment.

v. Unrelated: This category applies to those AEs which, after careful consideration at the time they are evaluated, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and determined with certainty to have no relationship to the study treatment.

4. Outcome Assessment

- The outcome of the event will be assessed as either: resolved, resolved with sequelae, ongoing, or death. Only one AE per participant is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given participant, only the primary cause of death will have an outcome of death.

5. Serious Adverse Events

- A Serious Adverse Event (SAE) is defined as any AE that:

i. Results in death

ii. Is life threatening (the participant is at immediate risk of dying from the adverse experience)

iii. Requires participant hospitalization or prolongs existing hospitalization

iv. Results in persistent or significant disability/incapacity

v. Is a congenital anomaly/birth defect
vi. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

6. Reporting SAEs

- The Investigator is required to report all SAEs that occur from RAP treatment through 30 days post end of study. Once the investigator becomes aware of an SAE, he/she must report the SAE to the Sponsor, ZELTIQ Aesthetics, Inc. ***within 24 hours***.
  - Contact Information:
    - Email: [redacted] and [redacted]
    - Phone: [redacted]

- The Sponsor ZELTIQ Aesthetics, Inc. may request additional supporting documentation as it becomes available, such as lab reports, electrocardiogram reports, discharge summary, hospital notes, etc., if applicable. Additional follow-up information as it becomes available must be reported to the same phone number and contact info listed at the beginning of this document.

- The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

7. SAE Follow-up
   - All participants experiencing an SAE, including discontinued participants, must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator, i.e., recovery, return to baseline status, no further improvement expected, or death.

   - For each SAE indicated as an unresolved event on the initial report, regardless of whether the participant completed the study or withdrew, the site should submit a follow-up report with updated information.

Device Malfunctions

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

Device malfunctions will be monitored and documented by the Sponsor for this study since they will be on-site for all treatments when the device is in use. If a malfunction occurs, reporting will be managed directly by the Sponsor per their Standard Operating Procedures.

STUDY PARTICIPANT INFORMED CONSENT

All eligible participants must sign the informed consent form prior to enrollment in the study. The participant and the Investigator or designee will discuss the benefits and risks of the study and review the participant consent form to ensure the participant understands

the scope of the study. It is the Investigator's or designee's responsibility to ensure that participants understand that participation in the study is voluntary, and that the quality of their medical care will not be adversely affected if they decline to participate in the study. Adequate time for any questions and explanations will be provided. Participant will have the opportunity to discuss the study with their surrogates and have time to think about it prior to participating. Participants may withdraw their consent at any time throughout the course of treatment. Once the participant understands the informed consent, he/she will be allowed to voluntarily agree to participate by signing the document. The investigator/designee is responsible for obtaining informed consent prior to enrollment in the study and ensuring that participant have a copy of the document for their records. The participant is considered enrolled in the study after the informed consent has been signed and it has been verified that the participant meets all inclusion criteria and none of the exclusion criteria.

RECORDS MANAGEMENT

Study Records Retention: Each site will maintain appropriate medical records for this study in accordance with institutional requirements including, but not limited to, hospital records, laboratory tests, pharmacy dispensing records, x-rays, and clinical charts. As part of study participation, each site will permit the Sponsor ZELTIQ Aesthetics, Inc., or its designee, to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of study safety and progress.

i. Essential documents, as listed below, must be retained by the site until at least 2 years after completion or termination of the investigation, or longer if advised by the Sponsor or designee.
ii. If the Investigator relocates, retires, or for any reason cannot keep study records, the records may be transferred to an acceptable designee. The Sponsor or its designee must be notified in writing of the name, address, and telephone number of the person designated to retain the study records. By signing the protocol, the Investigator agrees to adhere to the document retention procedures.
iii. Essential documents may include:

    1. IRB approvals for the study protocol and all amendments
    2. Participant's informed consent forms
    3. All source documents
    4. Case Report Forms
    5. Data change forms or data queries
    6. Monitoring logs and appointment schedules
    7. Investigators CVs, medical license information, and financial disclosure documentation

8. All sponsor representative/investigator correspondence, including telephone logs

9. Any other pertinent study documents

Protocol Deviations: Protocol deviations occur when there are variations in the approved study protocol, criteria, or procedure. An example of this would be a participant visit conducted outside the follow-up schedule. As protocol deviations may increase the risk or decrease the benefit of the intervention and/or affect the participant's rights, safety, welfare and/or integrity of the resultant data, investigators are required to record and report all incidences in a deviation log for adjudication during data analysis.

iv. All protocol deviations must be reported to Sponsor in a timely manner of their occurrence. Evaluation of the deviation and its impact on the study protocol will be adjudicated on a case-by-case basis. Data discrepancies or questions resulting from reported protocol deviations will be managed between Sponsor and the site investigator or their designee.

Protocol Violation: A violation is any non-adherence to the protocol that may result in significant additional risk to the participant (e.g., enrollment of a participant who does not meet the study criteria). A protocol violation can also be an event of non-adherence to GCPs that may impact participant safety (e.g., failure to obtain proper consent before performing study procedures). Violations should be reported to the study sponsor and the IRB within 5 working days if they occur.

INVESTIGATIONAL DEVICE ACCOUNTABILITY AND STORAGE

The Sponsor will maintain full device accountability. The Investigator will maintain adequate records documenting all materials received and returned, and shipping information of the device. All used materials will be discarded by the Investigator after each treatment has been completed.

REGULATORY AND ETHICAL COMPLIANCE

1. The Study will comply with all instructions, regulations, and agreements in this protocol. In addition, the study will comply with all local regulations, external standards and applicable ICH and Good Clinical Practice (GCP) guidelines.

2. Institutional Review Board: The site that is participating in this study must have this protocol and the associated informed consent approved through the IRB. Any amendments to the protocol or informed consent will be routed through IRB for approval prior to use.

3. Participant Confidentiality: Participant confidentiality for all data collected during the course of treatment will be maintained by the Investigator, on-site staff, and the Sponsor. All pictures of the participant's test areas will be de-identified, secure, privileged, and compliant with all HIPAA guidelines. A unique participant identification (ID) code will be assigned to each participant in the study. This ID code will be used throughout the course of treatment to ensure that no identifying

information exists on any Case Report Forms. The document which contains the participant ID key will be stored in a locked cabinet and will only be accessible by authorized study personnel. Private and confidential information about each participant will be preserved in any report or publication of the clinical investigation data.

4. Investigator Conflict of Interest: The proposed study will be conducted in accordance with signed investigator statements.

5. Funding Source: Funding for this study is provided by ZELTIQ Aesthetics, Inc.

6. Changes to Final Protocol: ZELTIQ Aesthetics, Inc. may amend the protocol at any time. All protocol modifications that could potentially affect data collection practices, study scope, participant safety, or scientific quality will be submitted to the IRB for approval prior to implementing the changes.

QUALITY ASSURANCE AND MONITORING

All participant data will be entered into a study database created and controlled by ZELTIQ Aesthetics, Inc.

The Sponsor will train the study site and be present at the initiation of treatment. The Sponsor will monitor the site at various intervals during the study. Monitoring activities may be on site or remote. Case Report Forms and source documents will be reviewed to verify adherence to the protocol; for completeness, accuracy, and consistency of data; and adhere to local regulations on the conduct of clinical research. The Sponsor will collect data throughout the study and at the end of the follow up period.

The investigational site will provide direct access to all trial-related site's source data/documents, and reports for the purpose of monitoring and auditing by ZELTIQ Aesthetics, Inc. or designee, and inspection by local and regulatory authorities (as appropriate).

The investigational site will have established standard operating procedures (SOPs) for quality management. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. The study will be conducted in accordance with procedures identified in the protocol.

The data and any research conducted will be controlled by ZELTIQ Aesthetics, Inc.

STUDY RESULTS/ANALYSIS

Sample Size Determination: Up to fifteen (15) participants will be enrolled and treated in this study. The sample size is based on clinical and practical exploratory considerations and not a formal statistical power.

Demographics and Baseline Characteristics: Demographic and baseline characteristics will include age, sex, ethnicity, race, gender identity, height, and weight, Fitzpatrick Skin Type, and Cellulite Dimple assessment of bilateral posterior thighs and/or buttocks.

Study Analysis Populations: The Full Analysis Set (FAS) will include all participants who meet all the inclusion and none of the exclusion criteria, received assigned three treatments with the device and completed the 12-week, follow-up visits per the protocol. The FAS will be treated as the primary analysis set.

Effectiveness Parameter Analysis: Descriptive statistics will be performed on the population per protocol, all participants completing the study without major protocol deviations. Descriptive statistics (i.e., mean, standard deviation, etc.) will be provided for all continuous variables, percentages and frequencies for all categorical variables collected in this study.

Summary tables will be used to present population characteristics at Baseline. For categorical parameters, the number and percentage of participants in each category will be presented. The denominator for percentage will be based on the number of participants appropriate for the purpose of analysis. For continuous parameters, descriptive statistics will include n (number of participants), mean, standard deviation, median, and range. No imputation will be used to account for missing data. No processing for outliers will be performed. Data will be presented as reported on the CRF. [redacted]

Safety Analysis: The Safety Analysis Set will consist of all enrolled participants who receive RAP treatment (started or completed).

Safety analyses will be performed in terms of incidence and severity of adverse events. These will be tabulated and a complete listing of all reports of adverse and/or unanticipated events will be presented.

SUSPENSION OR PREMATURE TERMINATION OF STUDY

The Sponsor reserves the right to suspend or prematurely terminate the study in its entirety or at an investigational site for significant and documented reasons. An Investigator, IRB, or regulatory authority may suspend or prematurely terminate participation in the clinical investigation for which they are responsible at any time in collaboration with the Sponsor.

PUBLICATION POLICY

Any investigator who wishes to develop a publication or presentation based on the results from this study must obtain written approval from ZELTIQ Aesthetics, Inc. prior to submission. ZELTIQ Aesthetics, Inc. may grant the investigator the freedom to publish any scientific or medical results deemed by the author to be of medical or scientific significance, provided that the information is scientifically sound, does not duplicate a previous or already planned publication, and is not being released prematurely.

STUDY COMPLETION

The IRB must be notified of completion of this study.

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TABLES
Timeline and Events Schedule

TABLE 1

3 TX Up to 15 participants	Baseline Screening	Treatment 1	Treatment 2	12 Week Follow up Post Tx 2 and Treatment 3	12 Week Follow up Post Last Treatment	26 Week Follow Up Post Last Treatment	52 Week Follow Up Post Last Treatment
Timeline	Visit 1 Day -30 to 0	Visit 2 Day 0	Visit 3 Wk 4 (/- 14 days)	Visit 4 Wk 12 (±14 Days)	Visit 5 Wk 24 (±14 Days)	Visit 6 Wk 38 (±14 Days)	Visit 7 Wk 64 (±14 Days)
Actions							
Informed Consent	X						
Inclusion/Exclusion	X						
Limited Physical Exam	X	X	X	X			
Medical History	X						
Con Meds	X	X	X	X	X	X	X
Urine Pregnancy Test	X	X	X	X			
[redacted]	[redacted]						
Fitzpatrick Skin Type Scale	X						
Weight	X			X	X	X	X
Height	X						
[redacted]							
Photos 2D	X	X	X	X	X	X	X
[redacted]							
RAP Treatment		X	X	X			
[redacted]							
AE Assessment (#Before TX) (After TX)		X#/	X#/	X#/	X	X	X
[redacted]							

Note: Visits 1 and 2 may be combined if feasible at time of screening and enrollment.

[redacted]

STUDY SCALES AND ASSESSMENTS

The following clinical scales and assessments will be used during the study:

[redacted]

Scale 2: Fitzpatrick Skin Type Scale - Investigator to establish participant skin type at Baseline using the six-category scale (I-VI); Fitzpatrick Skin Type Scale

Skin Photo type	Typical Features	Tanning Ability
I	Pale white skin, blue/hazel eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, always tans darkly
VI	Dark brown or black skin	Never burns, always tans darkly