STUDY TITLE: A MULTI-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

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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 SITES

PPD

PPD

PPD

PPD

STUDY SYNOPSIS

Purpose	The purpose of this multi-site clinical study is to evaluate the safety and effectiveness of two (2) treatment sessions with the ZELTIQ Aesthetics, Inc. Rapid Acoustic Pulse (RAP) device for the improvement in the appearance of cellulite.
Primary Effectiveness Objective	• 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.
Secondary Objectives	• Evaluate the safety of the RAP device for cellulite treatments after each treatment and at each follow up visit. • The secondary effectiveness objective: will demonstrate improvement in the appearance of cellulite as determined by the study participants completing the Participant Satisfaction Survey (**Assessment 3**) when comparing side-by-side baseline vs 12-weeks post final treatment images.
Test Device	ZELTIQ Aesthetics, Inc. Rapid Acoustic Pulse (RAP) device.
Treatment	Each cellulite treatment session will consist of RAP treatment delivered at 100Hz to bilateral thigh and/or buttock areas using the same treatment settings for both sides. The participants will have two (2) separate cellulite treatment sessions. The second treatment session will occur four (4) weeks after the initial treatment.
Control	The pre-treatment photos of the thighs and/or buttocks area will serve as a control.
Study Design	Non-significant risk, multi-site, prospective clinical trial.
Planned Number of Sites / Countries	Four (4) clinical trial sites located in the United States.
Planned Duration of Participant Engagement	Up to sixty (60) weeks (including baseline/screening, two treatment visits, and 12-, 26- and 52-weeks post last treatment follow up visits)
Planned Number of Participants/ Treatment Areas	Up to sixty (60) participants/120 body areas, (total of two (2) thighs and/or buttocks per participant). Each combined buttock/thigh area is considered a treatment area. Each clinical site (CS) will recruit up to fifteen (15) participants. 7-15 cellulite areas (e.g., dimples) will be treated per each

	thigh/buttock. This will provide a total of up to thirty (30) treatment areas (i.e. thighs/buttocks) per clinical study site.
Primary Effectiveness Endpoint	• Primary Effectiveness Endpoint: Correct identification of baseline vs 12-weeks post-final treatment images of the treated body area(s) by at least two out of three blinded, independent reviewers. The primary effectiveness endpoint will be met if ≥ 70% of the before and after photos treatment are correctly identified at 12-weeks post final treatment.
Secondary Endpoints	• RAP treatment safety: The numbers and proportions of participants with AEs, SAEs, ADEs, SADEs, and unanticipated AEs or ADEs after each treatment and at each follow up visit will be summarized. • Secondary Effectiveness Endpoint: The secondary effectiveness endpoint will measure 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 baseline vs 12-weeks post final treatment session images.
Additional Assessments/ Measurements	• Treatment tolerability: RAP treatment discomfort will be assessed after each thigh and/or buttock area treatment session has been completed. The overall average pain per participant and combined participant data will be summarized. • Treatment Effectiveness: An additional measurement to demonstrate the improvement in the appearance of cellulite may be performed using the Cellulite Dimple – At Rest Scale **(Scale 1)**. Baseline photos and 12-weeks follow-up photos of the treatment areas (e.g., thighs/buttocks) may be assessed using the Cellulite Dimple – At Rest Scale and determined as the score agreed to by at least 2 of 3 IPR or the average, rounded to nearest whole number, of all three IPR Cellulite Scores if there is no agreement. Treatment effectiveness will be met if the treatment areas (e.g., thighs/buttocks), of all participants with a Cellulite Score of ≥ 2 at the baseline visit, have a mean reduction in Cellulite Score of ≥ 1 at the 12-weeks post final treatment follow-up visit and optionally at the 4-, 26- and 52- weeks post treatment follow up visits. • Treatment Effectiveness: An additional effectiveness endpoint will measure 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 baseline vs 4 weeks post first treatment session images

	and 12-, 26- and 52-weeks post last treatment follow up visits, when comparing baseline and post-treatment photos. • Treatment Effectiveness: Baseline and follow-up photos of the treatment areas (e.g., thighs/buttocks) may be assessed for correct identification of baseline vs 26- and 52-weeks post-final treatment images of the treated body area(s) by at least two out of three blinded, independent reviewers. • Global Aesthetic Improvement Scale (GAIS) (**Assessment 5**): this endpoint will be met if there is an average improvement in the cellulite appearance using the GAIS as determined by the Investigator at the 4 weeks post first treatment and at 12-, 26-,and 52-weeks post treatment follow up visits, when comparing baseline and post-treatment photos. • Body Q™ (**Assessment 4**) Participant assessments: All participants will complete pre-treatment assessments using a series of Body Q™ surveys including Appraisal of Cellulite, Satisfaction with Buttocks and Satisfaction with Hip and Outer Thigh. All participants who are followed up at the 4-weeks post first treatment and 12-, 26- and 52-weeks timepoint post final treatment will complete the series of Body Q™ surveys.
Exploratory Assessments	• Skin laxity: An IPR panel may assess and grade baseline laxity using the At Rest Skin Laxity Scale, Buttocks and Posterior Thigh **(Scale 3)** by viewing baseline photos. The IPR may then assess laxity improvement of those participants with confirmed baseline laxity by comparing baseline and post treatment photos. The percentage of participants that demonstrate an improvement in skin laxity of the treated areas (e.g., thighs/buttocks), as graded by IPR when comparing baseline and 12-weeks post final treatment photos and optionally at the 4-, 26- and 52- weeks follow up visits will be noted. • Dermal layer measurements: Ultra-sound skin analysis may be used to visualize the dermal layer of the skin at baseline and at 4 weeks post first treatment visit and at 12-, 26- and 52-weeks post final treatment visit. • Dimple/depth/volume which may present as but not limited to, round or oval defects, depressions, valleys, linear depressions, or linear elevations or ridges) may be assessed at the 4-weeks post first treatment and 12-, 26- and 52-weeks post final treatment visit for all or some participants using before and after photos taken with a 3D camera system i.e., Cherry Imaging system.
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 lighting 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 (e.g., thighs/buttocks) 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 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 six 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 safety issues. The purpose of this multi-site, multi-treatment clinical study is to evaluate the safety and effectiveness of two (2) treatment sessions of the ZELTIQ Aesthetics, Inc. 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 0.25 – 12 MPa planar acoustic waves at a pulse rate of 50 - 100 Hz. 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.

CCI

[redacted]

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. Therefore, in addition to the number of acoustic pulses, the acoustic pulse rate at which the acoustic pulses are provided is critical.

The reason for this is that human skin is an anisotropic, nonlinear viscoelastic, loading history–dependent material [5]. At a given acoustic pulse rate, the slower the relaxation time for the tissue, the more tissue degradation from cumulative shock-induced shearing will accumulate (“A cumulative shear mechanism”) [3]. What that means is that at a pulse rate slower than the tissue relaxation time, there typically is no accumulated disruption. However, if the pulse rate is faster than the tissue relaxation time, membrane disruption is observed to increase progressively as the number of shock waves increases [4].

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 50Hz 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. In terms of discomfort, an estimated 97% of greater than approximately 400 one-minute treatment areas treated with the RAP device were scored as 0 (no pain) when the participants were asked about pain on a 0-10 scale. The maximum overall pain score of 4 was seen for only one RAP treatment site. In terms of effectiveness, comparison of pretreatment and 12-weeks post treatment photographs provide evidence that a single (~ 20 minute) RAP treatment provides improvement in the appearance in cellulite.

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 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 50 Hz. 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.

At the long-term follow-up visit, forty-two participants were available for evaluation. The number of participants lost to follow up was due in large part to the COVID-19 pandemic (i.e., stay-at-home orders, lockdowns, and participant self-quarantine). The 60-week long-term mean CSS reduction was **1.09** (a 34.1% reduction from the baseline) compared to the 12-week mean CSS reduction of **1.01** (a 29.5% reduction from baseline). The difference between short-term (mean 12-week, range 11-15 weeks) and long-term (mean 60-weeks, range 52-67 weeks) mean CSS reduction scores were not significant (*t*-test, unpaired, two-tailed, $p = 0.5202$, $t = 0.6454$, df=96). The long-term post-treatment photographs were correctly identified from randomized pairs of pre/post-treatment photographs at a rate of **95.2%** compared to the 12-week rate of **96.4%.** A Mann-Whitney test found there was no significant difference between these rates (U = 1162, $p < 0.9999$, Mdn1 = 1.00 (n = 56), Mdn2 = 1.0 (n = 42)). Finally, at the long-term visit, **100%** of participants reported positive satisfaction responses compared to the 12-week visit where **92.9%** of the participants reported positive satisfaction responses. A Kolmogorov-Smirnov test indicated the differences between the two groups were non-significant (D=0.4, P=0.8095). No device related unexpected or serious AEs were noted at treatment or follow-up.

PROTOCOL 2022-01 STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Outcome Endpoint
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	Effectiveness Endpoint: Correct identification of baseline vs 12-weeks post-final treatment images of the treated body area(s) by at least two out of three blinded, independent reviewers. The primary effectiveness endpoint will be met if ≥ 70% of the before and after photos treatment are correctly identified.
Secondary Objectives	Secondary Outcome Endpoints
• Evaluate the safety of the RAP device for cellulite treatments after each	• RAP treatment safety: The numbers and proportions of participants with AEs,

treatment and at each follow up visit.by monitoring of the frequency of adverse events (AEs), adverse device effects (ADEs); serious adverse events (SAEs) and SADEs (serious adverse device effects) • Demonstrate improvement in the appearance of cellulite as determined by the study participants completing the Participant Satisfaction Survey (**Assessment 3**) when comparing side-by-side baseline vs 12-weeks post final treatment images.	SAEs, ADEs, SADEs, and unanticipated AEs or ADEs after each treatment and at each follow up visit will be summarized. • RAP treatment effectiveness: The secondary effectiveness endpoint will 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 baseline vs the 12-weeks post final treatment images.
Additional Assessments/Measurements	Additional Summaries/Endpoints
Demonstrate improvement in the appearance of cellulite as determined by the study participants completing the Participant Satisfaction Survey (**Assessment 3**) when comparing side-by-side baseline vs 4-weeks post first treatment images and baseline vs 26- and 52- week post final treatment images.	Demonstrate 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 baseline vs 4-weeks post first treatment and 26- and 52- weeks post final treatment images.
Treatment tolerability: RAP treatment pain/discomfort will be assessed after each thigh and/or buttock area treatment session has been completed.	The overall average pain per participant and combined participant data will be summarized.
Treatment Effectiveness: An additional measurement to demonstrate the improvement in the appearance of cellulite for each cohort, may be performed using the Cellulite Dimple – At Rest Scale.	Baseline photos and 12-weeks follow-up photos of the treatment areas (e.g., thighs/buttocks) may be assessed using the Cellulite Dimple – At Rest Scale and determined as the score agreed to by at least 2 of 3 IPR or the average, rounded to nearest whole number, of all three IPR Cellulite Scores if there is no agreement. Treatment effectiveness will be met if the treatment areas (e.g., thighs/buttocks), of all participants with a Cellulite Score of ≥ 2 at the baseline visit, have a mean reduction in Cellulite Score of ≥ 1 at the 12-weeks follow-up visit and optionally at the optionally at the 4 weeks post first treatment visit and 26- and 52- weeks follow up visits will be noted.

Global Aesthetic Improvement as assessed by the PI.	This endpoint will be met if there is an average improvement in the cellulite appearance using the GAIS as determined by the Investigator at the 4 weeks post first treatment, 12-, 26- and 52- weeks post final treatment visit, when comparing baseline and post-treatment photos.
Treatment Effectiveness: An additional measurement to demonstrate improvement in the appearance of cellulite as determined by correct identification of baseline vs 26- and 52-weeks post final treatment images.	Baseline and follow-up photos of the treatment areas (e.g., thighs/buttocks) may be assessed for correct identification of baseline vs 26- and 52-weeks post-final treatment images of the treated body area(s) by at least two out of three blinded, independent reviewers.
Participant Body Q™ surveys including Appraisal of Cellulite, Satisfaction with Buttocks and Satisfaction with Hip and Outer Thigh.	All participants will complete pre-treatment assessments using a series of Body Q™ surveys. All participants who are followed up at the 4- weeks post first treatment and 12-, 26- and 52-weeks timepoint post final treatment will complete the series of Body Q™ surveys.
Exploratory Assessments	Exploratory Endpoints
Skin laxity	An IPR panel may assess and grade baseline laxity using the At Rest Skin Laxity Scale, Buttocks and Posterior Thigh **(Scale 3)** by viewing baseline photos. The IPR will then assess laxity improvement of those participants with confirmed baseline laxity by comparing baseline and post treatment photos. The percentage of participants that demonstrate an improvement in skin laxity of the treated areas (e.g., thighs/buttocks), as graded by IPR when comparing baseline and 12-weeks post final treatment photos and optionally at the 4-, 26- and 52- weeks follow up visits will be noted.
Dermal layer measurements	Ultra-sound skin analysis may be used to visualize the dermal layer of the skin at baseline, 4-weeks post first treatment and 12-, 26- or 52- weeks post final treatment visit.

Dimple/ depth/volume changes	Dimple/depth/volume which may present as but not limited to, round or oval defects, depressions, valleys, linear depressions, or linear elevations or ridges) may be assessed at baseline, the 4 weeks post first treatment visit or at the 12-, 26- or 52-weeks post final treatment visit for all or some participants using before and after photos taken with a 3D camera system i.e., Cherry Imaging system.

STUDY DESIGN

This is a non-significant risk, multi-center, multi-treatment (2 treatment sessions) prospective trial for safety, and effectiveness using ZELTIQ Aesthetics, Inc.'s RAP device for the improvement in the appearance of cellulite performed at up to four (4) clinical research sites in the United States.

Up to sixty (60) 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) treatment sessions on both of their thighs and/or buttocks.

Total study duration is anticipated to be at or less than 60 weeks from the first participant visit to the last participant observation visit. A total of up to six (6) visits are planned for this study as shown in Table 1.

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 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.

Treatment Recommendations (Please also see Appendix A for specific treatment information.)

Areas identified as cellulite may present as but not limited to, round or oval defects, depressions, valleys, linear depressions, or linear elevations or ridges, will be treated with 100Hz repetition rate.

Each dose delivered is equivalent to one minute of treatment. An additional dose may be delivered to severe areas. The number of treatment areas (e.g., dimples) is based on the

PI's and participant's assessment of the thigh and/or buttock, but no fewer than 7 and no more than 15 dimples will be treated per thigh/buttock.

STUDY PROCEDURES

Study procedures as described in this section are outlined in the schedule of assessments. **(Table 1)**

Study Visits

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

- Review study procedures, assessments and visit schedule with participants
- Review Participant Pre and Post Treatment Instructions
- Obtain informed consent
- Review of Inclusion/Exclusion criteria
- Cellulite Dimple – At Rest Scale **(Scale 1)** for study inclusion
- Fitzpatrick Skin Type Scale **(Scale 2)**
- Skin Ultrasound of the treatment area (Optional)
- 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
- 3D Photos of treatment areas (Optional)
- Body Q Surveys x 3 **(Assessment 4)**

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
- Mark treatment areas (e.g. dimples). **(See Appendix A Treatment Recommendations)**
- 2D Photos of the treatment area taken pre and post marking
- 3D Photos of treatment areas (e.g thighs/buttocks) taken pre and post marking (Optional)

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
- Participant to complete Procedure Tolerability Questionnaire **(Assessment 1)** using the Numeric Pain Scale (**Assessment 2**)
- Review Participant Post Treatment Instructions
- Provide 14 Day Diary to participant
- Instruct participant on completion of diary

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
- Mark treatment areas (e.g dimples). **(See Appendix A Treatment Recommendations)**
- 2D Photos of the treatment area taken pre and post marking
- 3D Photos of treatment areas taken pre and post marking (Optional)
- Skin Ultrasound (Optional)
- Participant Satisfaction Survey **(Assessment 3)**
- Body Q Surveys x 3 **(Assessment 4)**
- GAIS evaluation by PI

Treatment

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

Immediate Post-Treatment Activities

- Adverse event evaluation
- Participant to complete Procedure Tolerability Questionnaire **(Assessment 1)** using the Numeric Pain Scale (**Assessment 2**)
- Review Participant Pre and Post Treatment Instructions
- Provide 14 Day Diary to participant
- Instruct participant on completion of diary

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

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

- 3D Photos of the treatment area (Optional)
- Skin Ultrasound (Optional)
- Collect Diary – Treatment 2
- Participant Satisfaction Survey **(Assessment 3)**
- Body Q Surveys x 3 **(Assessment 4)**
- GAIS evaluation by PI

Visit 5 Follow Up Visit 26-Weeks Post 2nd Treatment (+/- 14 days)

- Weight
- Review concomitant medication
- Adverse Event evaluation
- Review Participant Pre and Post Treatment Instructions
- 2D Photos of the treatment area
- 3D Photos of the treatment area (Optional)
- Skin Ultrasound (Optional)
- Participant Satisfaction Survey **(Assessment 3)**
- Body Q Surveys x 3 **(Assessment 4)**
- GAIS evaluation by PI

Visit 6 Follow Up Visit 52- Weeks Post 2nd Treatment (+/- 14 days)

- Weight
- Review concomitant medication
- Adverse Event evaluation
- 2D Photos of the treatment area
- 3D Photos of the treatment area (Optional)
- Skin Ultrasound (Optional)
- Participant Satisfaction Survey **(Assessment 3)**
- Body Q Surveys x 3 **(Assessment 4)**
- GAIS evaluation by PI

* 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. These photographs will serve as control images for the assessment of 4-, 12-, 26-, and 52-weeks post final treatment assessment. 3-D photographs may be taken at baseline and at each follow up visit.

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 WITHDRAWL AND 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.

Known Physiological Responses of RAP Treatment

Known Physiological Responses:
There are known effects of the Rapid Acoustic Pulse (RAP) treatment, recorded in prior studies as transient and/or temporary effects related to the delivery of the acoustic pulses inherent in the treatment, which include:

- Sensations of cold related to gel pad application
- Sensations associated with initiation of the RAP treatment on the skin may include stinging, tingling, or pinching or similar sensations.
- Known skin effects (e.g., erythema (redness), redness around the hair follicles (folliculitis), bruising (contusion, petechiae, pinpoint red dots/bleeding, purpura), edema (swelling), pain, heat, micro-blistering (caused by acoustic skin friction), scratches, crustiness, scaliness, itchiness, scabbing or hair removal) at the treatment site, all mild to moderate in nature, and which are temporary effects that resolve spontaneously shortly after the procedure.

These responses should not be reported as adverse events (AEs) unless the criteria below are met (Table 2-1).

When Known Physiological Responses should be considered Adverse Events
If known physiological response is considered severe, prolonged, results in treatment interruption or discontinuation and/or requires medical intervention as outlined below, then the event should be evaluated as a potential AE.

Table 2.1 Guidance for AE Criteria for Known Physiological Responses

Known Physiological Response	Criteria for AE Reporting	Description for AE criteria
Bruising	Severe or prolonged	Severe: Bruising/contusion (purple discoloration); purpura (purple-colored spots or patches); or petechiae (pinpoint red dots/bleeding) that cause disruption to the participant's daily activities as assessed by the study investigator.

		Prolonged: Bruising lasting longer than 1 month.
Erythema	Severe or prolonged	Severe: Erythema (redness), folliculitis (redness around the hair follicles) that causes disruption to the participant's daily activities as assessed by the study investigator. Prolonged: Erythema lasting longer than 2 weeks.
Edema	Severe or prolonged	Severe: The appearance of edema (swelling) that causes disruption to the participant's daily activities as assessed by the study investigator. Prolonged: Swelling lasting more than 1 month.
Topical skin issues	Severe or prolonged	Severe heat, micro-blistering, scratches, crustiness, scaliness, itchiness, or scabbing that causes disruption to the participant's daily activities as assessed by the study investigator. Prolonged: topical skin issues that last for more than 90 days
Pain/discomfort during procedure	Discontinuation of treatment or requiring medical intervention	Pain/discomfort reported during the procedure that is intolerable to the participant or results in discontinuation of the procedure and medical intervention.
Pain/discomfort post procedure	Requiring medical intervention	Significant pain or discomfort, following the procedure which results in medical intervention (unplanned physician visit and/or prescription pain reliever).

In addition to the known physiological responses that meet the criteria of reporting as an AE (Table 2.1), other reported AEs with RAP treatment are presented in Table 2-2.

Table 2.2 Other Reported Adverse Events

Adverse Event	**Description for AE criteria**
Hypopigmentation	Spotty changes in skin color resulting in temporary lightening of the skin
Hyperpigmentation	Spotty changes in skin color resulting in temporary darkening of the skin
Abrasion/desquamation	Area of skin that is rubbed/scraped/peeled away, due to acoustic friction
Muscle spasm	Involuntary muscle cramping

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 considered to be a 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: PPD and PPD
       - Phone: PPD

- 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. Participants 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 the participant has 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:

ii. Advised by the Sponsor or designee. 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.

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 sixty 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 following populations are defined for statistical analyses:

Population	Description
Enrolled	The enrolled population will consist of all participants who sign the informed consent
Safety	The safety population will consist of all enrolled participants who receive a Resonic treatment session (started or completed).
Evaluable	The evaluable population for the primary endpoint will consist of all treated participants who completed the Resonic treatment plan to the bilateral buttocks and/or thighs.

Effectiveness Parameter Analysis: Correct identification of baseline vs 12-weeks post-final treatment images of the treated body area(s) by at least two out of three blinded, independent reviewers.

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. Subgroup analyses will consist of gender, age, and the Cellulite Dimple – At Rest Scale.

Safety Analysis: The numbers and proportions of participants with AEs, SAEs, ADEs, SADEs, and unanticipated AEs or ADEs after each treatment and at each follow up visit will be summarized.

SUSPENSION OR PREMATURE TERMINATION OF STUDY

The Sponsor reserves the right to suspend or prematurely terminate the study in its entirely 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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[9] A. C. Elliot, *WINKS SDA Statisical Data Analysis,* CreateSpace Independent Publishing Platform; 7th edition, 2013.

TABLES
Timeline and Events Schedule

TABLE 1

	Baseline Screening	Treatment 1	Treatment 2	12 Week Follow up	26 Week Follow Up	52 Week Follow Up
Timeline	Day -30 to 0	Day 0	See Below	12 Wk Follow Up Post Final Treatment	Wk 26 Follow Up Post Final Treatment	Wk 52 Follow Up Post Final Treatment
2TX Up to 60 Participants	Visit 1	Visit 2	Visit 3 WK 4 (±14 Days)	Visit 4 Wk 16 (±14 Days)	Visit 5 Wk 30 (±14 Days)	Visit 6 Wk 56 (±14 Days)
Actions						
Informed Consent	X					
Inclusion/Exclusion	X					
Limited Physical Exam	X	X				
Medical History	X					
Con Meds	X	X	X	X	X	X
Urine Pregnancy Test	X	X	X			
Cellulite Dimple – At Rest Scale -for inclusion	X					
Fitzpatrick Skin Type Scale	X					
Weight	X			X	X	X
Height	X					
Skin Ultrasound (Optional)	X		X	X	X	X
Photos 2D	X	X	X	X	X	X
Photos 3D (Optional)	X	X	X	X	X	X
Mark sites to be treated		X	X			
RAP Treatment		X	X			
Patient Tolerability Questionnaire		X	X			
AE Assessment (#Before TX) (=After TX)		X=	X#/=	X	X	X
Body Q Surveys X 3	X		X	X	X	X
Particpant Diary (*Provide) (+Collect)		X*	X*/+	X+		
Pre and Post Treatment Instructions Reviewed	X	X	X	X	X	
PI GAIS			X	X	X	X
Participant Satisfaction Survey			X	X	X	X

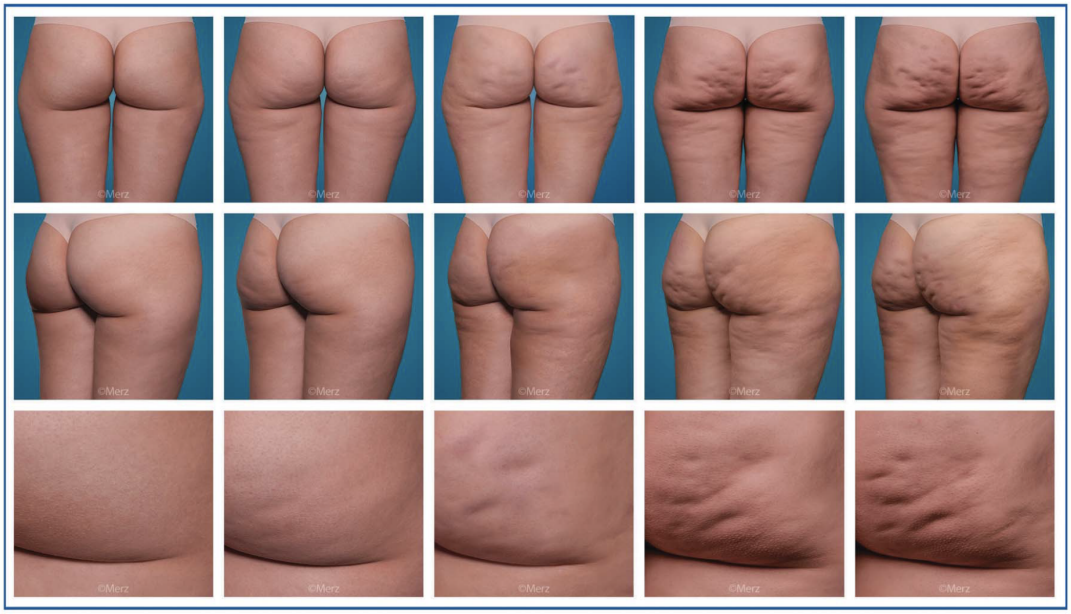
Note: Visits 1 and 2 may be combined if feasible at time of screening and enrollment.

Participants may be invited to attend post-study follow-up visits, at a future date/s, to assess the treatment area.

STUDY SCALES AND ASSESSMENTS

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

Scale 1: Cellulite Dimple – At Rest Scale - Investigator to establish participant eligibility for study by using the 5-point Cellulite Dimple – At Rest Scale. For inclusion in this study, participant must have a grade of 2 or 3 on both thighs and/or buttocks on right and left side based on review of Baseline **photos** by the PI.



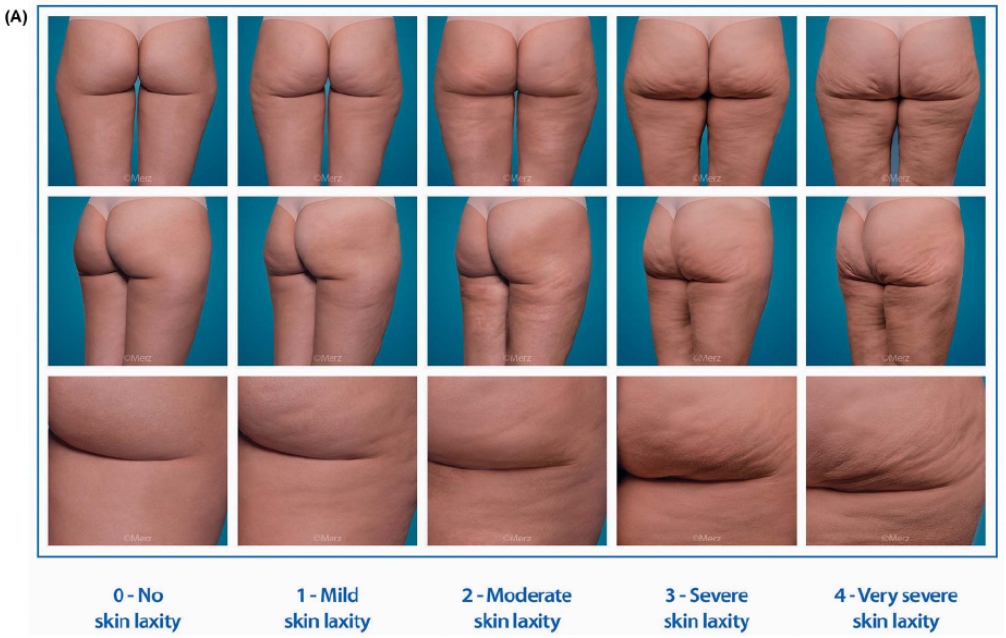
0 - No cellulite dimples	1 - Mild cellulite dimples	2 - Moderate cellulite dimples	3 - Severe cellulite dimples	4 - Very severe cellulite dimples
(no depressions)	(≤ 6 depressions)	(7-11 depressions)	(12-16 depressions)	(≥ 17 depressions)

Source: Hexsel D, et al, Validated Assessment Scales for Cellulite Dimples on the Buttocks and Thighs in Female Patients. Dermatol Surg. 2019 Aug;45 Suppl 1:S2-S11. doi: 10.1097/DSS.0000000000001993. PMID: 31246867.

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

Scale 3: At Rest Skin Laxity Scale, Buttocks and Posterior Thigh - Independent Physician Reviewers will assess the baseline and post-treatment level of skin laxity in the buttock and posterior thigh using the five-category scale (0-4); Skin Laxity Scale.



Source: Kaminer, Michael S. MD*; et al, Validated Assessment Scales for Skin Laxity on the Posterior Thighs, Buttocks, Anterior Thighs, and Knees in Female Patients, Dermatologic Surgery: August 2019 - Volume 45 - Issue - p S12-S21 doi: 10.1097/DSS.0000000000001994

Assessment 1: Procedure Tolerability Questionnaire - Questions to be asked by the Investigator or designee after the participant's RAP treatment of the entire thigh and/or buttock treatment area is completed. Participant to refer to **Assessment 2** Numeric Pain Scale below, when answering Question 2.

PARTICIPANT'S **LEFT** SIDE

1. Was the RAP treatment procedure tolerable? (Yes or No)
2. Using 1-10 pain scale with 0 being 'no pain', 5 being 'moderate pain' and 10 being the 'worst possible pain', how would you rate the tolerability for:
    - The MAJORITY of the RAP Doses? _____ (0-10 pain score)
    - The MAXIMUM pain score for all the RAP Doses? _____ (0-10 pain score)
    - The OVERALL pain score DURING the procedure? _____ (0 -10 pain

score)

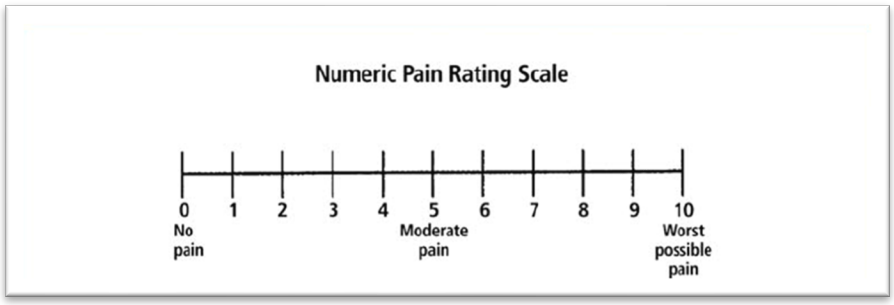
- The OVERALL pain score AFTER the procedure? _____ (0-10 pain score)

3. Have you had previous cellulite laser or RF cosmetic procedures? _____ (Laser, RF, Both or None)
    - If you had a cellulite laser procedure-- How was the <u>overall</u> pain from the RAP procedure in comparison? _____ (More tolerable; less tolerable; the same; or "NA")
    - If you had a cellulite RF procedure, how was the <u>overall</u> pain from the RAP procedure in comparison? _____ (More tolerable; less tolerable; the same; or "NA")

<u>PARTICIPANT'S **RIGHT** SIDE</u>

4. Was the RAP treatment procedure tolerable? (Yes or No)
5. Using 1-10 pain scale with 0 being 'no pain', 5 being 'moderate pain' and 10 being the 'worst possible pain', how would you rate the tolerability for:
    - The MAJORITY of the RAP Doses? _____ (0-10 pain score)
    - The MAXIMUM pain score for all the RAP Doses? _____ (0-10 pain score)
    - The OVERALL pain score DURING the procedure? _____ (0 -10 pain score)
    - The OVERALL pain score AFTER the procedure? _____ (0-10 pain score)
6. Have you had previous cellulite laser or RF cosmetic procedures? _____ (Laser, RF, Both or None)
    - If you had a cellulite laser procedure-- How was the <u>overall</u> pain from the RAP procedure in comparison? _____ (More tolerable; less tolerable; the same; or "NA")
    - If you had a cellulite RF procedure, how was the <u>overall</u> pain from the RAP procedure in comparison? _____ (More tolerable; less tolerable; the same; or "NA")

Assessment 2: Numeric Pain Scale - The Investigator or designee will ask the participant to rate the average discomfort/pain during and immediately post treatment using the Numeric Pain Scale once the participant's RAP treatment of the entire thigh and/or buttock treatment area is completed. The scale measures from 0 =No Pain to 10 = Worst Possible Pain.

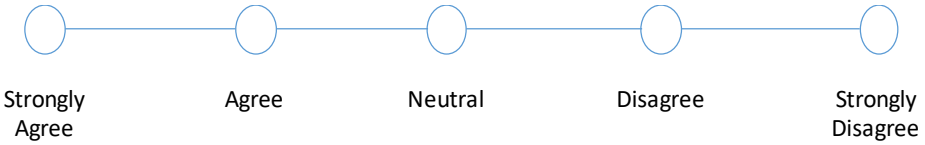


[6]

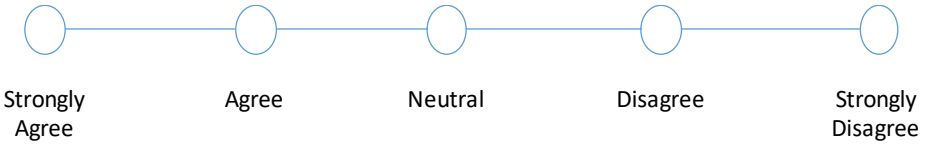
Assessment 3: Participant Satisfaction Survey - The participants in the study will asked by the Investigator or designee to grade the overall improvement of the treatment areas as indicated by the Participant Satisfaction Survey when comparing baseline photos to 4-, 12-, 26-, and 52-weeks post last treatment photos.

PARTICIPANT'S **LEFT** SIDE

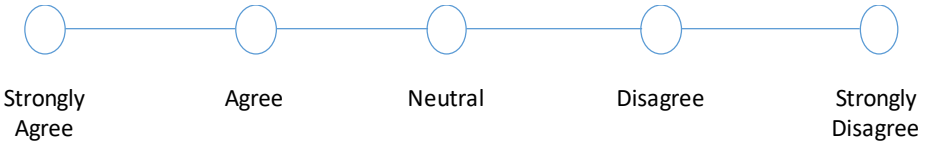
1. In comparison to the pre-treatment photo, the final photograph of the treatment area appears improved.



2. I feel there is good improvement in the appearance of my cellulite.

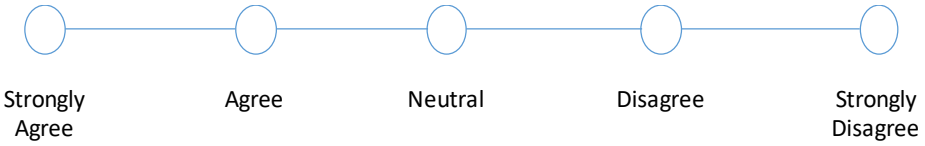


3.The RAP treatment was relatively pain-free.

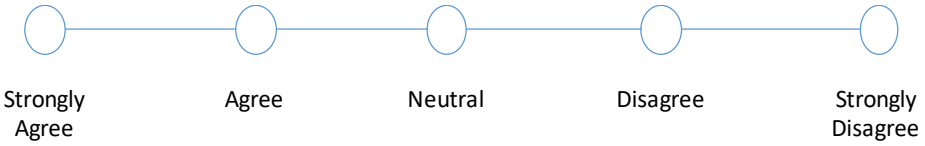


PARTICIPANT'S **RIGHT** SIDE

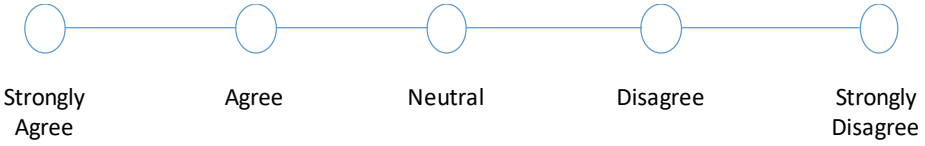
4. In comparison to the pre-treatment photo, the final photograph of the treatment area appears improved.



5. I feel there is good improvement in the appearance of my cellulite.



6.The RAP treatment was relatively pain-free.



Assessment 4: Body Q Surveys - The participants in the study will be asked to complete the Appraisal of Cellulite, Satisfaction with Buttocks and Satisfaction with Hip and Outer Thigh Surveys at Baseline, 4-, 12-, 26-, and 52-weeks post last treatment visits.

BODY-Q™ - APPRAISAL OF CELLULITE

These questions ask about CELLULITE. Cellulite is a condition in which the skin appears to have areas with underlying fat deposits, giving it a dimpled, lumpy appearance.

If you have cellulite on more than one area of your body, answer these questions thinking of the area with cellulite that you are most bothered by.

With your cellulite in mind, in the past week, how much have you been bothered by:

	Extremely bothered	Moderately bothered	A little bothered	Not at all bothered
1. How deep the dimpling in your cellulite looks?	1	2	3	4
2. Having to dress in a way to hide your cellulite?	1	2	3	4
3. Not being able to wear certain clothes because of your cellulite?	1	2	3	4
4. How lumpy your cellulite looks?	1	2	3	4
5. How noticeable your cellulite is?	1	2	3	4
6. The amount of dimpling in your cellulite?	1	2	3	4
7. The amount of cellulite you have?	1	2	3	4
8. How the skin where you have cellulite looks (not as smooth as you would like)?	1	2	3	4
9. People seeing your cellulite?	1	2	3	4
10. How your cellulite looks up close?	1	2	3	4
11. How your cellulite looks when you are naked?	1	2	3	4

Note to Investigators: This scale can be used independently of the other scales.

BODY-Q™ - SATISFACTION WITH BUTTOCKS

For each question, circle only one answer. With your buttocks (i.e., bum) in mind, in the past week, how dissatisfied or satisfied have you been with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
1. The size of your buttocks?	1	2	3	4
2. How your buttocks look from the side (i.e., profile view)?	1	2	3	4
3. The shape of your buttocks?	1	2	3	4
4. How smooth your buttocks look?	1	2	3	4
5. How the skin on your buttocks looks?	1	2	3	4

Note to Investigators: This scale can be used independently of the other scales.

BODY-Q™ - SATISFACTION WITH HIPS AND OUTER THIGHS

For each question, circle only one answer. With your hips and outer thighs in mind, in the past week, how dissatisfied or satisfied have you been with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
1. The size of your hips and outer thighs?	1	2	3	4
2. The shape of your hips and outer thighs?	1	2	3	4
3. How the skin on your hips and outer thighs looks?	1	2	3	4
4. How smooth your hips and outer thighs look?	1	2	3	4
5. How your hips and outer thighs look from behind?	1	2	3	4

Note to Investigators: This scale can be used independently of the other scales.

Assessment 5: GAIS - The Investigator will grade the overall improvement of each treatment area (thigh/buttock) by comparing baseline photos to post treatment photos at 4-, 12-, 26-, and 52-weeks post last treatment visits.

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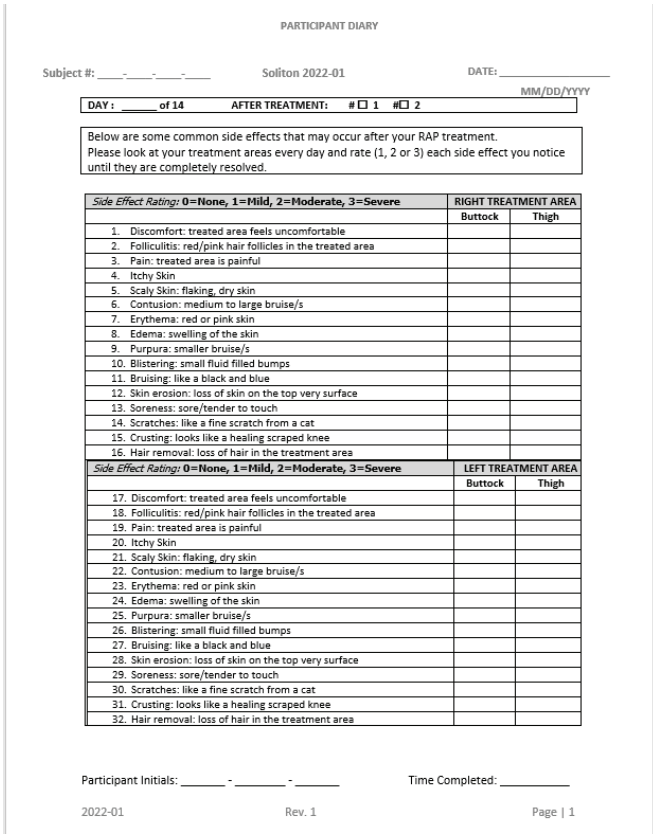
Grade	Level	Description
1	Very much improved	Optimal cosmetic result in the treated areas for this participant
2	Much improved	Marked or significant improvement in appearance of the treated areas from the initial condition
3	Improved	Noticeable improvement in appearance of the treated areas from the initial condition but more subtle in magnitude
4	No Change	The appearance of the treated areas is essentially the same as the original condition
5	Worse	The appearance of the treated areas is worse the original condition

Assessment 6: Participant Diary - The participant will complete a 14-day diary after each treatment.

Sample:



PARTICIPANT DIARY

Subject #: ____-____-____-____ Soliton 2022-01 DATE: _____
MM/DD/YYYY

DAY : _____ of 14 AFTER TREATMENT: # ☐ 1 #☐ 2

Below are some common side effects that may occur after your RAP treatment.
Please look at your treatment areas every day and rate (1, 2 or 3) each side effect you notice until they are completely resolved.

Side Effect Rating: **0=None, 1=Mild, 2=Moderate, 3=Severe**	RIGHT TREATMENT AREA	
	Buttock	Thigh
1. Discomfort: treated area feels uncomfortable		
2. Folliculitis: red/pink hair follicles in the treated area		
3. Pain: treated area is painful		
4. Itchy Skin		
5. Scaly Skin: flaking, dry skin		
6. Contusion: medium to large bruise/s		
7. Erythema: red or pink skin		
8. Edema: swelling of the skin		
9. Purpura: smaller bruise/s		
10. Blistering: small fluid filled bumps		
11. Bruising: like a black and blue		
12. Skin erosion: loss of skin on the top very surface		
13. Soreness: sore/tender to touch		
14. Scratches: like a fine scratch from a cat		
15. Crusting: looks like a healing scraped knee		
16. Hair removal: loss of hair in the treatment area		
Side Effect Rating: **0=None, 1=Mild, 2=Moderate, 3=Severe**	LEFT TREATMENT AREA	
	Buttock	Thigh
17. Discomfort: treated area feels uncomfortable		
18. Folliculitis: red/pink hair follicles in the treated area		
19. Pain: treated area is painful		
20. Itchy Skin		
21. Scaly Skin: flaking, dry skin		
22. Contusion: medium to large bruise/s		
23. Erythema: red or pink skin		
24. Edema: swelling of the skin		
25. Purpura: smaller bruise/s		
26. Blistering: small fluid filled bumps		
27. Bruising: like a black and blue		
28. Skin erosion: loss of skin on the top very surface		
29. Soreness: sore/tender to touch		
30. Scratches: like a fine scratch from a cat		
31. Crusting: looks like a healing scraped knee		
32. Hair removal: loss of hair in the treatment area		

Participant Initials: _____ - _____ - _____ Time Completed: _____

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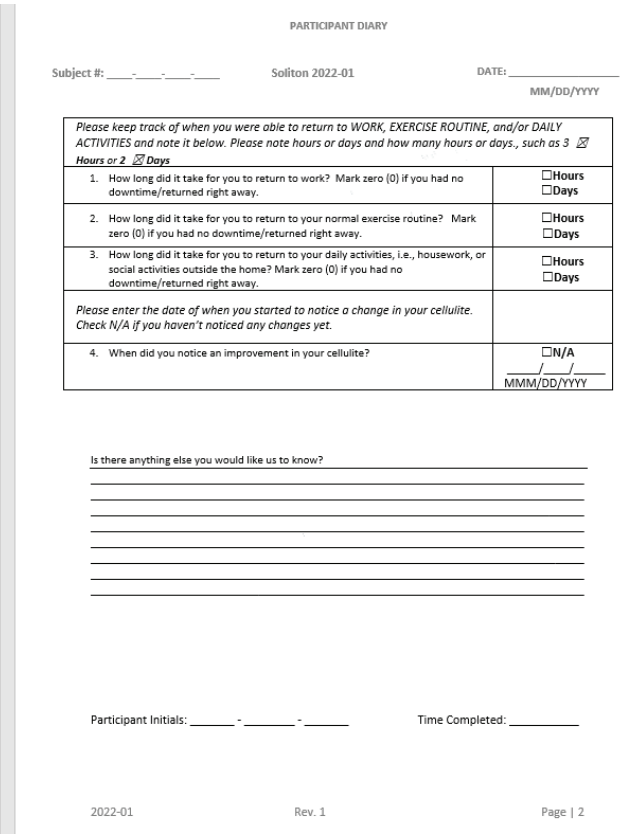

PARTICIPANT DIARY

Subject #: ____-____-____-____ Soliton 2022-01 DATE: _____
MM/DD/YYYY

*Please keep track of when you were able to return to WORK, EXERCISE ROUTINE, and/or DAILY ACTIVITIES and note it below. Please note hours or days and how many hours or days., such as 3 ☒ **Hours** or **2 ☒ Days***

1. How long did it take for you to return to work? Mark zero (0) if you had no downtime/returned right away.	☐**Hours** ☐**Days**
2. How long did it take for you to return to your normal exercise routine? Mark zero (0) if you had no downtime/returned right away.	☐**Hours** ☐**Days**
3. How long did it take for you to return to your daily activities, i.e., housework, or social activities outside the home? Mark zero (0) if you had no downtime/returned right away.	☐**Hours** ☐**Days**
Please enter the date of when you started to notice a change in your cellulite. Check N/A if you haven't noticed any changes yet.	
4. When did you notice an improvement in your cellulite?	☐**N/A** ____/____/____ MMM/DD/YYYY

Is there anything else you would like us to know?

Participant Initials: _____ - _____ - _____ Time Completed: _____

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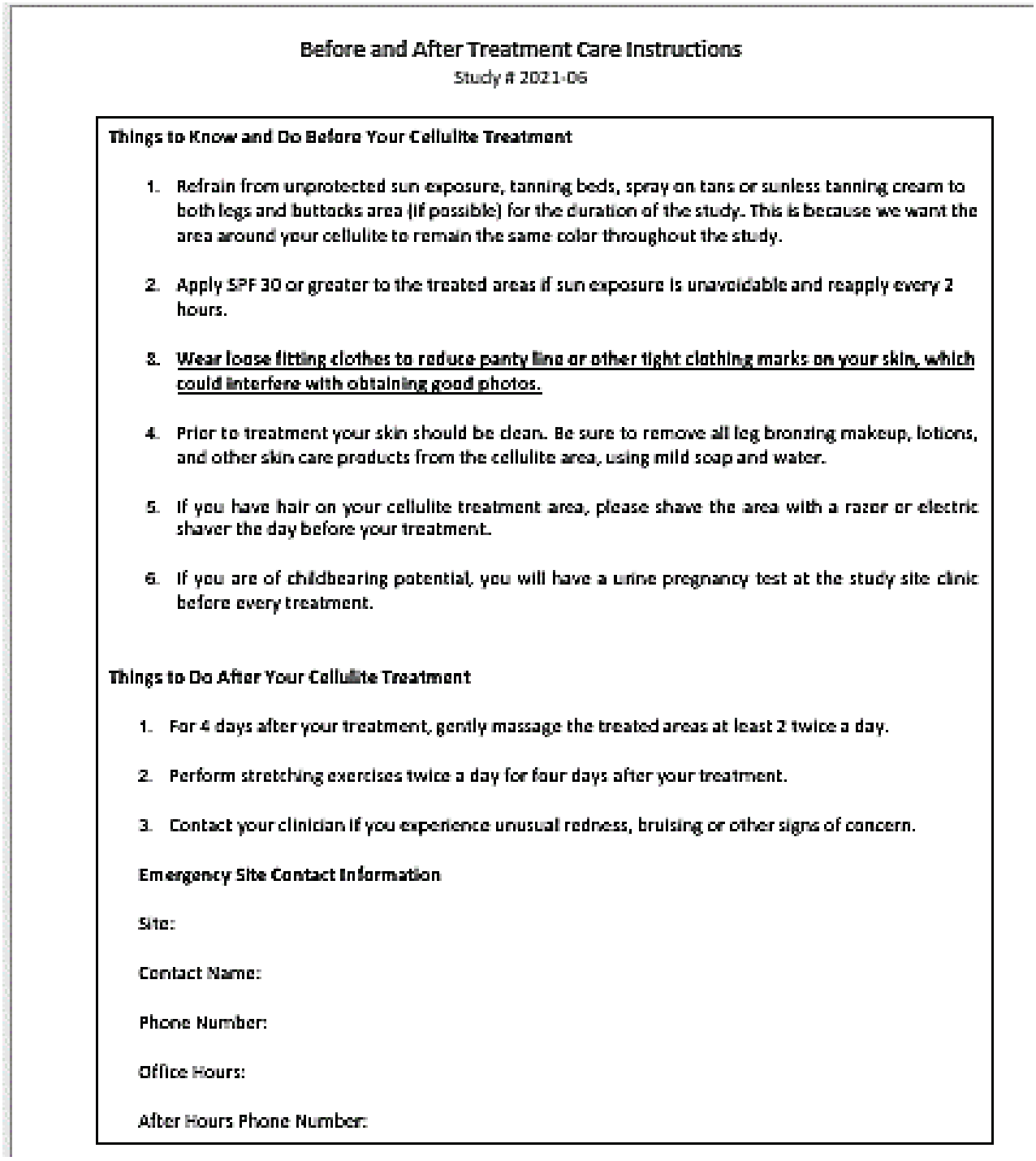
Instructions 1: Participant Pre and Post Treatment Instructions – the participant will receive a copy of the instructions before and after treatment.

Sample:



Before and After Treatment Care Instructions

Study # 2021-06

Things to Know and Do Before Your Cellulite Treatment

1. Refrain from unprotected sun exposure, tanning beds, spray on tans or sunless tanning cream to both legs and buttocks area (if possible) for the duration of the study. This is because we want the area around your cellulite to remain the same color throughout the study.
2. Apply SPF 30 or greater to the treated areas if sun exposure is unavoidable and reapply every 2 hours.
3. Wear loose fitting clothes to reduce panty line or other tight clothing marks on your skin, which could interfere with obtaining good photos.
4. Prior to treatment your skin should be clean. Be sure to remove all leg bronzing makeup, lotions, and other skin care products from the cellulite area, using mild soap and water.
5. If you have hair on your cellulite treatment area, please shave the area with a razor or electric shaver the day before your treatment.
6. If you are of childbearing potential, you will have a urine pregnancy test at the study site clinic before every treatment.

Things to Do After Your Cellulite Treatment

1. For 4 days after your treatment, gently massage the treated areas at least 2 twice a day.
2. Perform stretching exercises twice a day for four days after your treatment.
3. Contact your clinician if you experience unusual redness, bruising or other signs of concern.

Emergency Site Contact Information

Site:

Contact Name:

Phone Number:

Office Hours:

After Hours Phone Number: