Title: *Clinical Study to Evaluate the Safety and Efficacy Performance of the Profound System Using the Dermal and SubQ Cartridges for the Treatment of Cellulite*

Protocol Number: DHF21711

Study Type: Prospective Clinical Study

Date: November 17, 2017

Study Devices: Profound

Sponsor: Syneron Medical Ltd.
Industrial Zone, Tavor Building
P.O.B. 160 Yokneam Illit,
20692 Israel

Project Lead: Ruthie Amir MD
Global Vice President of Clinical & Regulatory Affairs
ruthiea@syneron.com
+ 972-73-244-2349

This document contains confidential information.

This study will be performed in accordance with applicable regulatory requirements and Good Clinical Practice (GCP). This clinical investigation will follow the principles outlined by the International Conference on Harmonization (ICH).

Principal Investigator and study site:

Site:

Principal Investigator's Signature

I, _____ have carefully read the foregoing protocol # DHF21711: *"Clinical Study to Evaluate the Safety and Efficacy Performance of the Profound System Using the Dermal and SubQ Cartridges for the Treatment of Cellulite"* and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, Good Clinical Practices, and local regulatory guidelines, and will attempt to complete the study within the time designated. I will provide copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted by the Sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the study product and conduct of the study. I agree to keep records on all subject information (case report forms, shipment and product return forms and all other information collected during the study) in accordance with GCP and Health Canada regulations.

ACCEPTED AND AGREED:

_____ _____

Investigator's Signature Date

_____ _____

Ruthie Amir, M.D. Date

Table of Contents

GLOSSARY

ADE	Adverse Device Effect
AE	Adverse Event
BMI	Body Mass Index
CFR	Code of Federal Regulations
Cm	Centimeter
CRF	Case Report Form
FDA	Food & Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
ICF	Informed Consent Form
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
Kg	Kilogram
Min	Minute
wk	Weeks
PI	Principal Investigator
USAE	Unanticipated, serious adverse event
USADE	Unanticipated, serious adverse device effect
SAE	Serious Adverse Event
Tx	Treatment

TABLE 1- STUDY SYNOPSIS

Proprietary Name	Profound device utilizing the Dermal and SubQ Cartridges
Design	Prospective, open-label, baseline-controlled, clinical study to evaluate the Profound device using the Dermal and SubQ Cartridges for minimally-invasive treatment of cellulite appearance, skin laxity and subcutaneous fat deposits in the upper arms, above the knees and bra bulges. Eligible subjects will undergo a single treatment with the Profound device using the Dermal and/or SubQ cartridges, based on treating physician discretion.
Study Population	Up to 60 healthy female volunteers, seeking cellulite treatment, 18 to 60 years of age from 2 investigational sites.
Treatment and Duration	Eligible subjects will undergo a single treatment with the Profound device, using the Dermal and/or SubQ cartridges, based on treating physician's discretion. Each subject will be treated on both left and right body sides of one of the treatment areas: upper arms, above the knees or the bra bulge area. Treatment areas will be assessed at the next visits: 1. One-week post treatment follow-up (1wk FU) – safety only 2. One-month post treatment follow-up (1M FU) 3. Three-month post treatment follow-up (3M FU) 4. Six-month post treatment follow-up (6M FU) Total expected study duration is up to 7 months.
Objective	The objective of this trial is to evaluate the safety and efficacy of the Profound device utilizing the Dermal and SubQ Cartridges for minimally-invasive treatment of the upper arms, above the knees and bra bulges to improve the appearance of cellulite, skin laxity and subcutaneous fat deposits.
Primary Objective	Statistically significant improvement in global aesthetic appearance of cellulite, skin laxity and subcutaneous fat deposits of the upper arms, above the knees and bra bulges, following dermal and/or subcutaneous Profound treatment, as assessed by blinded evaluators at 3M post last treatment (3M FU) versus baseline.

Primary Safety Objective	1. Evaluate the safety of cellulite treatment with the Profound device utilizing the Dermal and/or SubQ Cartridges for entire duration of study (1wk Post first treatment, 1 month, 3 month and 6 month post last treatment) 2. Comfort level during treatment: Comfort assessment will be performed independently by the subject using NSR scale. Subjects will be asked to fill out a questionnaire after treatment
Secondary Objectives	1. Statistically significant improvement in global aesthetic appearance of cellulite, skin laxity and subcutaneous fat deposits of the upper arms, above the knees and bra bulges, following dermal and/or subcutaneous Profound treatment, as assessed by study investigator at all post treatment visits, except the 1-week safety evaluation (1M FU, 3M FU & 6M FU) versus baseline. 2. Investigator satisfaction: Satisfaction assessment will be performed by study investigator using a pre-defined scale questionnaire. The investigator will fill out questionnaire at each post treatment follow-up visit (1M FU, 3M FU & 6M FU). 3. Subject improvement and satisfaction: Improvement and satisfaction assessment will be performed independently by the subject using a pre-defined scale questionnaire. Subjects will fill out questionnaires at each follow-up visit (1M FU, 3M FU & 6M FU).
Efficacy Endpoints	Primary and secondary objectives will be assessed for treated areas, using the following efficacy endpoints: 1. Global aesthetic improvement, using a using a 5-point grading scale (0=No change, 1=1%-24%%, 2=25%–49%, 3=50%-74% improvement, and 4=75%-100%) (**Error! Reference source not found.** – Table 6) 2. Skin tightening improvement (Appendix III – Table 7) 3. Investigator satisfaction using a pre-defined scale (Appendix III – Table 8) 4. Subject assessments (Appendix III – Tables 7-10)
Safety Endpoints	1. Number, severity and type of any adverse event recorded throughout the study and post treatment (immediate and delayed response) 2. Pain assessment using NSR scale

	3. Investigator assessment of immediate response 4. Subject 1-week post first treatment follow-up visit (1wk Post Tx.1 FU) - discomfort assessment and duration of side-effect will be conducted
Statistical Methods	Descriptive statistics will be used to present changes in assessments along the study course. Global aesthetic improvement assessments, subject assessments and investigator satisfaction data will be analyzed using two-tailed Wilcoxon Signed Rank test and/or paired t-test (alpha=0.05) to analyze the data difference from baseline and longitudinal change.

INTRODUCTION AND RATIONALE

Background

This is a prospective clinical study to determine the efficacy of *Profound* device for treatment of cellulite in the upper arms, above the knees and the bra bulge area. The *Profound* system received FDA 510(k) clearance in 2009 under K082391, and is intended for use in dermatologic and general surgical procedures for hemostasis and electrocoagulation and the percutaneous treatment of facial wrinkles. In addition, the *Profound* device received FDA 510(K) clearance in 2016 under K161043, and is intended for use in dermatologic and general surgical procedures for electrocoagulation and hemostasis, percutaneous treatment of facial wrinkles, and improvement in the appearance of cellulite (supported by long-term clinical data - 6 months).

Cellulite is an aesthetically unacceptable cosmetic problem for many post-adolescent women. It is largely observed in the gluteal-femoral regions with an "orange-peel" or "cottage cheese" appearance [1]. The condition is not specific to overweight issues although increased adiposity will exacerbate the cosmetic issue.

Recent research papers on cellulite anatomical features have shown specific features in the dermal and subcutaneous layers of the skin which are characteristic of cellulite presence [1-5]. First, superficial fat lobules called *papillae adiposae* were shown to be protruding within the dermal layer in the form of intrusion pockets. **Figure 1** - Fat indentation invading the dermal layer shows a gross histology of the dermis/subcutis transition where the fat pockets are present.

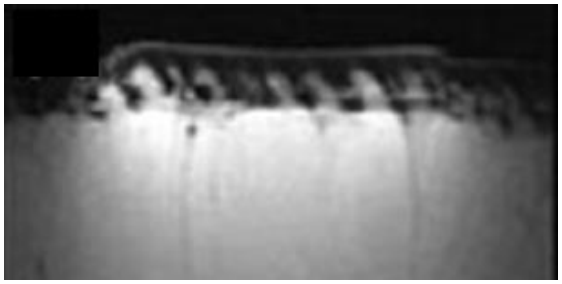

Figure 1 - Fat indentation invading the dermal layer

Second, tissue observations from autopsy on female subjects with cellulite have suggested a higher percentage of fibrous septae oriented perpendicular to the skin surface as opposed to males who tend to have the septae organized in a criss-cross fashion. The arrangement of fibrous septae perpendicular to the skin surface in a female is shown in **Figure 2** - Fibrous septae in subcutis perpendicular to the skin surface.

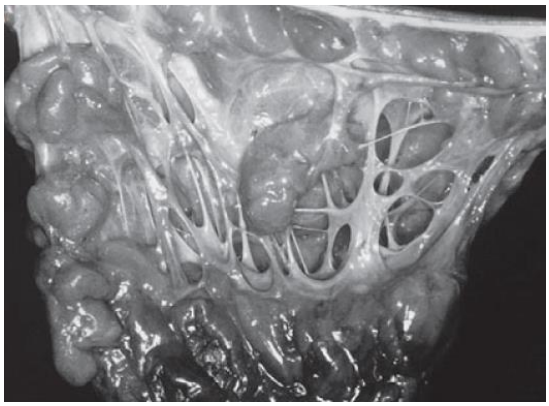

Figure 2 - Fibrous septae in subcutis perpendicular to the skin surface

This subcutaneous fibrous strand organization tends to create uneven appearance of the skin surface, which is characteristic of cellulite. Therefore, it is thought that treatments targeting the dermis and subcutaneous layers of the skin could have beneficial effects on the appearance of cellulite. Indeed, a treatment which would increase the dermal thickness would create a condition where the hypodermal fibrous strand organization described above would have fewer tendencies to deform the skin surface and improve the appearance of cellulite. Furthermore, a remodeling of the subcutaneous fibrous band organization following fractional thermal injuries, in conjunction with a volumetric reduction of the fat lobules would decrease the local tension forces responsible for the presence of cellulite.

This study presents a one arm investigation aimed at using fractional energy delivery targeting the dermal and subcutaneous tissue together.

Device Description: *Profound*

The main intent of the System is to utilize a minimally-invasive approach to directly deliver RF energy into tissue through pairs of micro-electrode needles and use temperature sensors within the needles to reliably create fractional thermal injuries within the skin. The System, shown in **Figure 3** – Cartridge, Handpiece, and Console, consists of:

- Console to allow physician to set treatment parameters and delivers RF energy to a re-useable Handpiece and Cartridge;
- Two types of re-useable Handpieces (**SubQ Handpiece** and **Dermal Handpiece)** to enable subject treatment by making the link between the Console and a single-use sterile Cartridge; and
- Two types of single-use sterile Cartridges to deliver RF energy:

- **SubQ Cartridge (75°)** delivers RF energy to the subcutaneous through the dermal layer of the skin, which creates fractional thermal injuries to ablate the targets – the dermal and subcutaneous layers.
- **Dermal Cartridge (25°)** delivers RF energy to the dermal layer of the skin, which creates fractional thermal injuries to ablate dermal targets.

Figure 3 – Cartridge, Handpiece, and Console

The Console includes a color touch screen with a Graphical User Interface (GUI) which is mainly used to select two treatment parameters – the target temperature and the application time, communicate messages to the user, and setup preferences.

Principles of operation

The System uses a minimally invasive approach to deliver bipolar non-ablative radiofrequency (RF) energy to the dermal layers of the skin. The physician first selects two treatment parameters, target tissue temperature and application time, by interacting with the GUI of the Console. Using the Handpiece and Cartridge connected to the Console, the physician then inserts the array of micro-needle electrode pairs into the dermal layer of the skin. Within each pair, a temperature sensor is located at the distal tip of the electrode to provide real-time feedback of target tissue temperature from within the forming thermal injury. This temperature feedback information allows the console to deliver RF energy to the needles to reach and maintain the physician-selected target temperature. The system allows it to precisely, predictably, and reliably reach and maintain tissue temperature regardless of skin impedance, as shown in peer-reviewed publications [6-11].

STUDY DESIGN OVERVIEW

This study is a prospective, open-label, baseline-controlled, clinical study, to evaluate cellulite appearance, skin laxity and subcutaneous fat following *Profound* treatment, using the Dermal and/or SubQ Cartridges for minimally-invasive treatment targeted to both dermal and subcutaneous layer of the skin in the upper arms, above the knees and bra bulges [area between the armpits and chest].

Up to 60 Healthy subjects at 2 investigational sites will be enrolled in this study. All subjects will undergo an assessment of their general health. Treatment areas will undergo a single Dermal and/or SubQ treatment, depending on the body location, thickness of fat in the treatment area and proximity to bone. The treatment will be according to physician discretion, as both treating physicians are highly experienced Profound users. Global aesthetic improvement (GAI) will be assessed at each follow-up visit starting from the 1-month follow-up.

Before treatment (15-20 minutes) the tissue to be treated will be injected with tumescence solution.

All treatment areas will undergo a single treatment with the *Profound* device, utilizing the Dermal and/or SubQ Cartridges.

During the follow-up period, 4 visits will be conducted as follows: one-week post first treatment safety follow-up visit (1wk FU post Tx.1) and efficacy and safety follow-up visits at the 1-month (1M FU), 3-month (3M FU) and 6-month (6M FU) post treatment visits.

Improvement in cellulite appearance will be assessed at each post baseline visit. Additionally, investigator and subject questionnaires will be completed. Finally, photography will be performed under visible light conditions of the front, right, left and back view. Most assessments will be performed at all study visits.

STUDY OBJECTIVE

The objective of this trial is to evaluate the safety and efficacy of the *Profound* device utilizing the Dermal and SubQ Cartridges for minimally-invasive cellulite treatment in the upper arms, above the knees and bra bulge areas.

Primary Objective

The objective of this trial is to evaluate the efficacy of the *Profound* device for improving the global aesthetic appearance (GAI) of cellulite, skin laxity and subcutaneous fat deposits of the upper arms, above the knees and bra bulges, following dermal and/or subcutaneous Profound treatment, as assessed by blinded evaluators at 3M post last treatment (3M FU) versus baseline. Evaluation by blinded evaluators will be based on a 5-point grading scale (0=No change, 1=1%–24%, 2=25%–49%, 3=50%-74% and 4=75%-100%) (Appendix III – Table 6):

Primary Safety Objective

1. Evaluate the safety of cellulite treatment with the *Profound* device utilizing the Dermal and SubQ Cartridges during all study
2. Comfort level during treatment:
   Comfort assessment will be performed independently by the subject using NSR scale. Subjects will be asked to fill out a questionnaire after the treatment/s (Tx.1/ Tx.2)

Secondary Objectives

1. Statistically significant improvement in appearance of cellulite, skin laxity and subcutaneous fat deposits (Appendix III – Tables 6 and 7) of the upper arms, above the knees and bra bulges, following dermal and/or subcutaneous Profound treatment, as assessed by study investigator at all post treatment visits (1M FU, 3M FU & 6M FU) versus baseline.
2. Investigator satisfaction:
   Satisfaction assessment will be performed by the study investigator using a pre-defined scale questionnaire (Appendix III – Table 8). The investigator will fill out the questionnaire at each post treatment follow-up visit (1M FU, 3M FU & 6M FU).
3. Subject improvement and satisfaction:
   Subject assessments will be performed independently by the subject using a pre-defined scale questionnaire (Appendix III – Tables 7-10). Subjects will fill out the questionnaire at each follow-up visit (1M FU, 3M FU & 6M FU).

Primary Efficacy Endpoint

Blinded evaluation of global aesthetic improvement (GAI) in the appearance of cellulite, skin laxity and subcutaneous fat deposits of the upper arms, above the knees and bra bulges, using a 5-point grading scale (Appendix III – Table 6). Efficacy is assessed by correctly identifying the correct pre- and post-treatment photos of the same subject, and having at least 50% or greater (Grade of 3 or 4) global aesthetic improvement at the 3-month follow-up visit relative to baseline photos. Improvement reflects improvement in cellulite appearance, skin laxity or visible reduction in localized fat deposits in the treated areas. There will be two blinded evaluators to assess the photos.

The study primary endpoint is achieved when 80% subjects show at least 50% improvement at the 3-month follow-up visit relative to baseline photos.

Secondary Efficacy Endpoint

Secondary objectives will be assessed using the next efficacy endpoints:

1. Investigator Assessment of global aesthetic improvement (Appendix III – Table 6) and skin laxity scale (Appendix III – Table 7), using before and after photographs.
2. Investigator satisfaction using a pre-defined scale (Appendix III – Table 8).
3. Subject assessments, using a pre-defined scale questionnaire (Tables 7-10).

Primary Safety Endpoint

1. The number, severity and type of any adverse event recorded throughout the study and post treatment (discomfort (pain), immediate and delayed response).
2. Occurrence of expected post treatment immediate response during all study period based on predefined scale (Appendix III; Table 4).
3. Discomfort (pain) level using a 10-point visual analog scale will also be recorded after each benign pigmented lesion clearance treatment– by Numerical Scale Response (NSR), according to Appendix IV - Pain assessment.
4. Subjects 1-week post treatment follow-up visit (1wk FU) - discomfort assessment and side-effect duration will be conducted.

STUDY POPULATION

Number of Subjects

This study will be comprised of up to 60 female subjects at two (2) investigational sites. Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled.

Subject Withdrawal and Replacement

Subjects enrolled in the study can discontinue their participation at any time for any reason without prejudice or reduction in the quality of their medical care. The investigators or sponsor can terminate a subject's participation in this study to protect the subject's health or if the subject fails to follow directions resulting in noncompliance to study procedures. Subjects who withdraw or are terminated from the study may be replaced to ensure at least 60 subjects have completed the study. Subjects who fail to complete the treatment will be replaced and will not be evaluable.

Inclusion Criteria

A subject is eligible to participate in the study if he/she meets all the following inclusion criteria:

1. Signed informed consent to participate in the study.
2. Healthy male or female subjects, $\geq$ 18 and $\leq$ 60 years of age at the time of enrollment.
3. Fitzpatrick Skin Type I to VI.
4. Subjects seeking treatment of cellulite/skin tightening in the upper arms, above the knees or bra bulge area.

5. Clinically appreciable cellulite, skin laxity or subcutaneous fat deposits in the treatment areas, as determined by the study investigator.
6. Not pregnant, lactating and must be either post-menopausal, surgically sterilized, or using a medically acceptable form of birth control at least 3 months prior to enrollment (i.e., oral contraceptives, contraceptive implant, barrier methods with spermicide or abstinence).
7. Negative urine pregnancy test as tested prior to each treatment and at the last visit for women of child bearing potential (e.g. not menopause).
8. General good health confirmed by medical history and skin examination of the treated area.
9. Willing to receive the proposed *Profound* treatment.
10. Willing to follow the treatment and follow-up schedule and post-treatment care instructions.
11. Willing to have photographs and images taken of the treated areas to be used de-identified in evaluations, publications and presentations.

Exclusion Criteria

A subject is not eligible for participation in this study if he/she meets any of the following exclusion criteria:

1. Subject had surgery or any other procedure for cellulite in the last 6 months.
2. Pregnant or planning to become pregnant, having given birth less than 3 months ago, and/or breast feeding.
3. Known allergy to lidocaine or epinephrine or antibiotics.
4. Active malignancy or history of malignancy in the treatment area in the past 5 years.
5. Having any active electrical implant anywhere in the body, such as a pacemaker or an internal defibrillator.
6. Suffering from significant concurrent illness, such as cardiac disorders, diabetes (type I or II), lupus, porphyria, or pertinent neurological disorders (i.e. any disease state that in the opinion of the Physician would interfere with the anesthesia, treatment, or healing process).
7. Having a known anti-coagulative or thromboembolic condition or taking anticoagulation medications one week prior to and during the treatment course (to allow inclusion, temporary cessation of use as per the subject's physician discretion).
8. History of immunosuppression/immune deficiency disorders (including HIV infection or AIDS) or currently using immunosuppressive medications.
9. Suffering from hormonal imbalance, whether related to thyroid, pituitary, or androgen.
10. History of significant lymphatic drainage problems.

11. History of cancer which required lymph node biopsy or dissection.
12. Suffering from significant skin conditions in treatment areas or inflammatory skin conditions, including, but not limited to, open lacerations or abrasions, hidradenitis, or dermatitis of the treatment area prior to treatment (duration of resolution as per the Investigator's discretion) or during the treatment course.
13. History of keloid scarring, abnormal wound healing and / or prone to bruising.
14. History of epidermal or dermal disorders (particularly if involving collagen or microvascularity), including collagen vascular disease or vasculitic disorders.
15. Use of isotretinoin (Accutane®) within 6 months of treatment or during the study.
16. Subject on systemic corticosteroid therapy 6 months prior to and throughout the course of the study.
17. Dysplastic nevi in the area to be treated.
18. Participation in a study of another device or drug within 3 months prior to enrollment or during this study.
19. Subject has palpable lymphadenopathy at any visit. Standard palpation techniques will be used.
20. Subjects with history of severe edema.
21. As per the Investigator's discretion, any physical or mental condition that might make it unsafe for subject to participate in this study.

STUDY PROCEDURES

Enrollment and Screening

During the first visit, the investigator/ research staff will screen the subject for eligibility to participate. The inclusion/exclusion criteria will be reviewed, the subject's medical history, an examination of the subject's skin in the treatment areas will be conducted.

The subject will review the informed consent form and the study will be explained to the subject including all risks, potential benefits, procedures, visit requirements, and other alternative treatment options. If the subject qualifies and wishes to participate they will complete the ICF with a signature and date. The original will be retained with subject's records and a copy will be provided to the subject.

The following measurements will be performed and recorded at the specified times throughout the study.

Table 2 – Clinical Evaluation Measurements and Tools

Claim/ Task	When to conduct	Method
ICF process, eligibility screening and medical history	Screening/ Baseline	Physician or staff will complete the form with the study subject
Weight	Screening/ Baseline, prior to treatment Tx.1, and at all follow-up visits (1wk FU, 1M FU, 3M FU and 6M FU)	Scale
Photographs		Standardized digital photographs
Global aesthetic improvement & Skin laxity	At all post treatment follow-up visits, except 1-week FU (1M FU, 3M FU and 6M FU)	Physician will assess treated areas, using the scales in Appendix III – Tables 6 & 7
Antibiotic prescription for subject	Evening prior to treatment procedure for seven days post procedure	Physician may prescribe antibiotic for the subject. Antibiotic will be taken for total of 8 days (optional).
Urine pregnancy test	Baseline, prior to treatment Tx.1, and at the last follow-up visit (6M FU)	Urine pregnancy test
Treatment-associated pain	Immediately post treatment:	Subject will be asked to rank/ assess pain level during treatment based on the Numerical Scale Response (NSR scale - Appendix IV - Pain assessment)
Daily diary	Post treatment, for 1-week period	Subjects will be requested to fill daily diary with data regarding their comfort, AE, and activity (7 days of follow-up post treatment) - Post Treatment Side Effect Severity Scale (Table 4 - Post Treatment Side Effect Severity Scale)
Compression Garment wear	Immediately post treatment, for 1-week period	Subject may wear Compression Garment wear for 1-week period after treatment/s (except from bath time) - optional.
Investigator satisfaction	At all post treatment follow-up visits, except 1-week FU (1M FU, 3M FU and 6M FU)	Satisfaction Questionnaire (**Error! Reference source not found.**)
Subject assessments		Subject questionnaire (Tables 7-10).
Safety	Throughout the study.	Skin examination in treated areas, subject interview, Adverse Events form, occurrence of adverse events and severity ratings: as well as relation to treatment, action taken and outcome

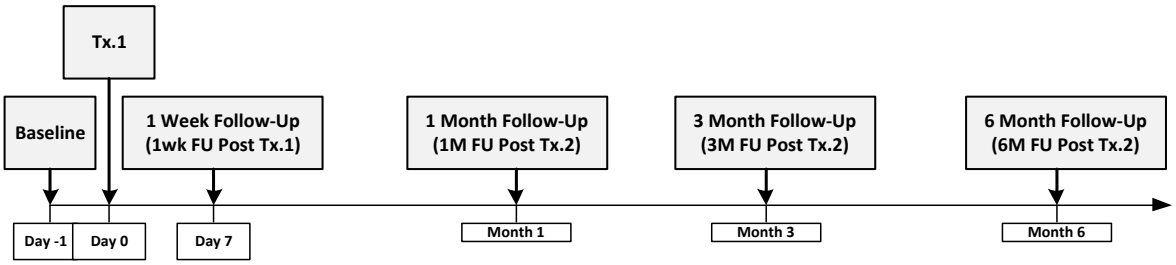

Figure 4: Study Flow-Chart (Visits at the Clinic)

Pre-Treatment Procedures

Screening and Baseline procedures can be conducted at the same visit day, and at least one day prior to the first treatment. It is expected that screening and baseline procedures are conducted during the same visit, while the first treatment visit will occur one day or up to 14 days post baseline.

Screening

1. ICF – should be obtained prior to any study procedures. When subject fully understands all potential risks and benefits of the study, subject will be asked to sign and date the consent form. The subject will be given a copy of the signed ICF.
2. Subject ID - subjects will be assigned a study subject ID number.
3. Medical History - A medical history will be obtained to determine if the subject meets study criteria, including a list of all prescribed and over the counter medications taken within the previous 6 months will be recorded.
4. Weight measurements will be taken.
5. Pregnancy Screen - Subjects who are capable of becoming pregnant will undergo a urine pregnancy test. This will be repeated prior to all treatments and at the end of the study (last FU visit/ 6M FU).
6. Skin Exam - The subject will undergo a routine skin examination to determine study eligibility including the presence of clinically appreciable cellulite, skin laxity or subcutaneous fat deposits in the treatment areas.
7. Scheduling: Subjects will be scheduled to return for the baseline and treatments visit within 14 days following the screening visit. It is preferable the baseline procedures are conducted at the day of screening, while Tx.1 will be conducted one day after the Screening visit.

8. Subjects may be prescribed Antibiotics (type and dosing will be determined by study investigator) for 1 week, starting in the evening prior to treatment until 7 days post procedure (optional).

Baseline

1. Unwanted hair should be removed from the treated area by study staff prior to treatment at the clinic.
2. Photography – Baseline photographs will be obtained using consistent camera and subject placement settings (Appendix II – Photography Guideline).

Treatment/s Procedure

In accordance with the *Profound* User's Manual:

1. Both upper arms or knees or bra bulges will be treated (right and left).
2. Subjects should wear disposable underwear.
3. Subject weight will be taken.
4. Clean with two passes of iodine-based skin sterilizing solution such as Betadyne. Allow to dry completely, without wiping off.
5. Local infiltration of tumescence solution which consists of 1% lidocaine with 1:100,000 epinephrine diluted in a 1:3 sterile normal saline to a final concentration of 0.25% lidocaine with 1:400,000 epinephrine, will be performed throughout the treatment area to manage pain and bleeding/bruising. This will be performed 15-20 minutes prior to the start of treatment to allow vasoconstriction.
6. Tumescence amount for adequate pain control will be administered at the discretion of the Investigator throughout the treatment process.
7. Profound thermal settings of 67°C, 4 sec will be used for all subjects.
8. Cold air will be used to cool down the treated skin for increased comfort - optional.
9. Spacing between adjacent *Profound* needle insertions will be between 3-4mm.
10. Connect the Dermal/ SubQ Cartridge targeted dermal/ subcutaneous layer of the skin, respectively, according to investigator discretion.

Post Treatment Procedures

1. Pain assessment – immediately after each treatment subjects will be asked to rank pain sensation experienced during treatment using Numerical Scale Response (NSR; see Appendix IV - Pain assessment) for the *Profound* procedure
2. Safety aspect will be assessed before and after each treatment:

i. Clinical effects - All visible and palpable immediate response will be recorded for the entire treatment area using a 4-point severity scale (Table 4 - Post Treatment Side Effect Severity Scale).
ii. Adverse Events – Record the number, severity and type of any adverse event occurred before, through and after treatments.

3. If prescribed, subject should continue taking the antibiotics prescribed by investigator, starting from the evening prior the treatment till 7 days post treatment (optional).
4. If suggested by investigator, subjects should apply a thin coat of Vaseline Petroleum Jelly with Bactroban (mupirocin) antibiotic to the treated area per standard medical procedure.
5. Subjects will receive daily diary post first treatment which they will be requested to fill out with data regarding their comfort, adverse events, and daily activities (7 days of follow-up post treatment).
6. Subject may be instructed to wear Compression Garment covering the treated area (supplied by the study sponsor) for 1 week, starting immediately post treatment (optional). The Garment should be worn 24 hours a day, seven days a week and removed only for bath (optional).
7. Subjects should be advised to contact their study physician if they have any concerns about how their treatment areas are responding to treatment or how they are healing.

Follow-Up and Return Visits

1. All subjects will be requested to return to the clinic at the following time-points during the study in order to assess the clinical performance (safety & efficacy) of the device:
   i. FU1 – 1 week (±2 days) post treatment (1wk FU) -Safety only.
   ii. FU2 – 1 month (±7 days) post treatment (1M FU).
   iii. FU3 – 3 month (±14 days) post treatment (3M FU).
   iv. FU4 – 6 month (±14 days) post treatment (6M FU).
2. At 1wk FU visit the following tasks will be conducted and data recorded:
   i. Review changes in medication, medical history, and AE, if applicable from last visit.
   ii. If taken, verify subject completed the course of antibiotic.
   iii. If used, verify subject removed the Compression Garment.
   iv. Photographs of treated area.
   v. Subject's weight will be recorded.
   vi. Completion of subject safety assessment questionnaire (daily dairy) according to pre-defined scale (Table 4 - Post Treatment Side Effect Severity Scale & Table 5 -

Post Treatment Side Effect Duration). Relevant forms should be filled out as necessary.

3. At post-treatment follow-up visits (FU2, FU3 and FU4) the following tasks will be conducted and data recorded:
    i. Review changes in medication, medical history, and AE, if applicable from last visit.
    ii. Photographs of treated area (as needed, un-wanted hair will be removed from the treated area by study staff at the clinic).
    iii. Subject's weight will be recorded.
    iv. Global Aesthetic Improvement (GAI) scale and Skin Tightening scales – will be completed (Appendix III – Tables 6 & 7).
    v. Completion of Physician satisfaction rating (Table 8).
    vi. Completion of Subject assessments (Table 6 –Global Aesthetic Improvement (GAI) Scale).
    vii. At the final visit (6M FU) a urine pregnancy test will be performed for women of childbearing potential.

DATA ANALYSIS

Recording

All data will be recorded in source documents and transcribed onto Case Report Forms (CRFs). Site will be monitored by Syneron staff or designees to assure adherence to the clinical trial requirements, subject safety, protocol procedures, and for data accuracy. The Case Report Forms and images will be reviewed and retrieved during the monitoring visit. All source documentation will remain in the subject's files at the site.

Review and Analysis of all data collected will be conducted by the Sponsor or designee as described for this protocol with the following data:

Demography and Baseline Measurements

Demographic and baseline/screening measurements (e.g., age, weight, cellulite assessment, and digital images) will be collected and descriptively presented.

Treatment Visit

Skin assessment by the PI, photographs of the treated region, and pain scores will be collected used to document any adverse events to assess the device performance.

Follow-up Visit Measurements

Follow-up measurements (e.g.: weight), assessment (e.g.: global aesthetic improvement) and digital images will be used for comparative measurements with their respective measurement at baseline. Primary endpoints will be evaluated at the 3-month follow-up after the Profound treatment. Secondary endpoints may be evaluated at all visits.

Safety

Safety of device procedure will be evaluated through skin assessments by the PI and research staff. The occurrence and severity of all complications from the start of the study will be documented.

Protocol Revisions and/or Deviations

With the exception of emergency situations, no changes or deviations in the conduct of this protocol will be permitted without the prior approval of the sponsor.

The IRB/IEC that granted original approval for the study must be notified of all changes in the protocol, and will approve any change or deviation that may increase risk to the subject, and/or that may adversely affect the rights of the subject or validity of the investigation.

In the event of an emergency, the Investigator will institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the sponsor and the IRB/IEC.

ADVERSE EVENTS (AE)

An adverse event (AE) is any adverse change in health or side effect that occurs in a study participant during their participation in the study.

Anticipated Adverse Effects

Following treatment with the *Profound* the following local adverse effects could occur (anticipated):

- Ecchymosis
- Hyperpigmentation
- Hypopigmentation
- Bruising
- Swelling
- Twinge (pain)
- Loss of sensation
- Numbness
- Infection
- Itching
- Scarring
- First degree burns
- Second degree burns
- Nerve damage

An adverse event (AE) is any undesired clinical occurrence in a study subject as indicated by signs, symptoms, illnesses, events that develop or worsen in severity in association with the study when deemed by the Investigator to be related to use of the device or study procedures. The Investigator will document all adverse signs and symptoms regardless of severity or frequency that are either volunteered by subjects or observed during the course of the study that are related to the device. The Investigator will also record adverse experiences of subjects resulting from concurrent illnesses, reactions to concurrent medications, or progression of disease states that the Investigator deems related to the device. Included in the description will be the nature of the sign or symptom, the date of onset, whether the event was serious, the severity, the relationship to study procedures or investigational device, the action taken, the date of resolution, and the outcome. The Principal Investigator will determine the relationship of the adverse device effect to the investigational device.

Anticipated effects from the injected local or tumescent anesthetic if used may be allergic reaction, feeling anxious, shaky, dizzy, restless, or depressed; drowsiness, vomiting, ringing in the ears, blurred vision; confusion, twitching, seizure (convulsions); fast heart rate, rapid breathing, feeling hot or cold; weak or shallow breathing, slow heart rate, weak pulse; or feeling like passing out. Less serious side effects include: mild bruising, redness, local scars, itching, or swelling where the medication was injected; mild dizziness; nausea.

Unanticipated Adverse Device Effects

For device studies, part 21 CRF 812.3(s) uses the term unanticipated adverse device effect which is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with the device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Significant device failure may constitute an adverse event if an undesirable experience occurs. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device, or any event that is a result of a user error.

All unanticipated adverse effects will be graded as follows:

Mild: Sign or symptom, usually transient, non-life-threatening requiring no special treatment and generally not interfering with usual activities.

Moderate: Sign or symptom, non-life-threatening which may be ameliorated by simple therapeutic measures, and may interfere with usual activity.

Major: Sign or symptom that is intense or debilitating but non-life-threatening and that interferes with usual activities. Recovery is usually aided by therapeutic measures and the discontinuation of the study device may be required.

Severe: Any untoward medical occurrence that at any time results in death or life-threatening illness, resulting in persistent or significant disability/incapacity.

The relationship of the adverse effect to the study is defined as follows:

Probable: An adverse event has a strong temporal relationship to study device, and another etiology is unlikely or significantly less likely.

Possible: An adverse event has a strong temporal relationship to the study device, and an alternative etiology is equally or less likely compared to the potential relationship to study device.

Probably not: An adverse event has little or no temporal relationship to the study device and/or a more likely alternative etiology exists.

Not related: An adverse event has no temporal relationship to study device or has a much more likely alternative etiology.

Reporting Adverse Events (AE) and Serious Adverse Events (SAE)

Anticipated Adverse Events: Anticipated adverse events in this study include ecchymosis, hyperpigmentation, hypopigmentation, bruising, swelling, twinge (pain), numbness, infection, itching, scarring, burns, nerve damage, and/or loss of sensation. If an unanticipated adverse event occurs at any time during or after the use of the *Profound* device, the Investigator must report it to Syneron.

The Investigator must report all unanticipated adverse device effects that are serious in nature to the clinical study monitor immediately or within twenty-four hours by telephone (see below). If such an unanticipated adverse device effect is reported after normal working hours, the Investigator will leave a voice message at the monitor's telephone number with accompanying report of the unanticipated adverse device effect faxed or sent to the fax number/e-mail address below:

Ruthie Amir, MD, Global VP of Clinical Affairs
Telephone/Fax No.: From the U.S. 011 (972) 73-244-2349
011 (972) 54-300-3164 (cell)
E-mail: ruthiea@syneron.com

A written report prepared by the Principal Investigator must follow within five working days to both the IRB and to Syneron and should include a full description of the event and sequence.

Measures taken to protect the rights and welfare of subject

Research records will be available to study personnel, the sponsor, Ethics Review Committee and regulatory agencies as required. Research records may be used for purposes of medical education, after removal of subject names or other identifying information. In the ICF the subjects will be informed that the photographs and video taken of them during the study may be made available to the sponsor for marketing and instructional purposes, after removal of identifying information. All images collected will be stored without personal subject identifiers at the site and at Syneron.

RISK/BENEFIT ANALYSIS

Risks

Syneron has determined that the *Profound* is non-significant risk device for the treatment of cellulite. As indicated in the AE section, the risks associated with the device are:

- Ecchymosis
- Erythema
- Edema
- Scaring
- Infection
- Pain

Anticipated adverse events in this study include:

- Bruising
- Hyperpigmentation
- Hypopigmentation
- Swelling
- Twinge (pain)
- Loss of sensation
- Numbness
- Infection
- Itching
- First degree burns
- Second degree burns
- Nerve damage

Subjects worldwide participated in clinical research and underwent treatment with the *profound* device. The *Profound* device will be used in this study was previously used in study and emitted the same energy. To date, no serious adverse events or unanticipated AEs have been reported. The reported AEs relate to dermal and subcutaneous tissue, confined to the treatment area and were all mild in nature and resolved within the study period.

Potential benefits to participating individuals and to society

Subjects may or may not benefit from improvement in cellulite appearance on the treated area via a minimal-invasive technique. All subjects in the treatment groups are expected to have some benefit from the treatment procedures as would be expected for the commercial I device. Subject will receive treatment/s procedures at no cost. This study will benefit the advancement of medicine by generating data on safety and efficacy that will aid in the development of an alternative treatment options to procedures with higher potential risks subjects. The results of this study will help to determine whether this device is safe and effective for improvement of cellulite appearance.

Conclusion:

In light of the potential benefits of minimal-invasive cellulite appearance relative to its risks, the potential benefits associated with the use of the *Profound* System outweigh its risks, supporting study initiation.

Payment for Participation

Subjects will be paid a total of $200 for all study visits and evaluations. Payments will be issued at the last FU visit. Subjects will not pay for office visits, examinations or procedures that are part of this clinical study. After treatment, subjects who do not complete all study-related procedures and requirements will not be paid nor will they receive partial payments for completed visits.

ETHICS AND GOOD CLINICAL PRACTICE

This study will be carried out in compliance with the following:

- Syneron Standard Operating Procedures.
- Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo, 1975, Venice 1983, and Hong Kong 1989).
- US Code of Federal Regulations (Title 21CFR including parts 50, 56 and 812 governing informed consent and IRB regulations).
- International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP), 1996.

QUALITY ASSURANCE AND STUDY MONITORING

Study Monitoring/Auditing/Inspection

The Study Monitor will be responsible for monitoring the study sites to review the data being collected. The sponsor shall implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) to ensure that the trial is being conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements. Visits will be made prior to the initiation of the study, at scheduled intervals throughout the study, and at termination of the study.

Once enrollment and treatments have begun, monitoring visits will take place more frequently pending enrollment and study activities.

The sponsor and site will maintain regular phone and e-mail correspondence throughout the study to confirm compliance of study procedures.

The investigator/institution agrees to allow the monitor and other authorized personnel direct access to source data/ documents for trial related monitoring, the clinical supplies storage/ dispensing area and to provide all documents in the Investigator Regulatory Binder for review, and to assist site auditors in their activities if requested. Requests by the Health Canada or regulatory agencies of other countries to inspect the study site may be made after adequate notification. The investigator may be required to assist the regulatory inspectors in their duties, if requested.

ADMINISTRATIVE PROCEDURES

Supply and Disposition of Study Device

The *Profound* Dermal and SubQ handpieces and/or cartridges will be supplied to the participating clinics.

Control & Disposition of the Investigational Device

The *Profound* device will be used according to the instructions of the Sponsor and manufacturer, Syneron Medical.

Informed Consent

Study Personnel will obtain written Informed Consent prior to the subject's participation in any study procedures. The Study Personnel will inform the subjects of the experimental procedure to be utilized and assure the subjects that their decision regarding participation in the study will have no bearing on the quality of medical care received and that their decision whether to participate in the study is strictly voluntary.

During the initial interview, the subject will be assured that they are free to change their mind and will be allowed to participate in the study or withdraw from the study with no adverse effect on their standard medical care.

Monitoring Plan

At least 3 monitoring visits are projected during the whole study. The frequency of which will be based on enrolment, study activities and the study visit scheduled. The first visit is scheduled at the initiation of the study prior to the first subject treatment in the study. The second visit is scheduled after enrolment and treatment has been initiated and a third visit will be for a close-out visit for the study. Interim visits may be conducted as needed to assure compliance to the study protocol and regulatory requirements. The number and frequency of monitoring visits may also be increased per the sponsor decision to collect data and images post treatment.

Case Report Forms

Paper case report forms will be used in this trial. All protocol-required information collected during the study must be entered in the appropriate field of the case report form (CRF). The investigator, or designated representative, should complete the appropriate CRF fields as soon as possible after information is collected. The information must match the information that exists as source documents in the clinic chart, hospital chart, and/or investigator's files. An explanation should be given for all missing data.

It is the investigator's responsibility to assure the accurate completion, review, and approval of all CRFs and the timely completion and submission of all adverse event forms.

Record Maintenance

The investigator shall retain a copy of all study documents in accordance with the FDA regulations which specify that records should be kept for a period of two years: 1) following the date a marketing application either is approved or disapproved for the use, or 2) following notification to FDA that no application is being filed and/or that the study has been discontinued.

If an investigator leaves the study site before record retention obligations have expired, the sponsor should be notified in writing of the person designated to retain the study documents during and after the study.

Handling of clinical data. The data are entered into a secure database that only the sponsor has access to. Admission to the database requires access to a password-protected network secured by the Sponsor. This database is maintained by Syneron that performs backups, data verification, and application upgrades. All equipment housing the clinical data is located in locked rooms or a secure computer network. The only individuals, who view, extract and analyze data for protocol reports and publications are physicians and nurses who are members of the study team or Sponsors. Only authorized personnel of the Sponsors have access to databases.

Any paper copies of subject medical records or research records are stored in secure cabinets at the study site.

PUBLICATION POLICY

The investigator will not publish the study results and will not disclose confidential information received from Syneron without prior written agreement from Syneron. Such confidential information shall include any and all information relating to this study as described in the Clinical Trial Agreement. In the event that Syneron consents to the publication of data from this study, the investigator will provide Syneron manuscripts for review thirty days before submission for publication. Syneron will have no editorial rights over manuscripts. The investigator will also provide Syneron with advance notice of at least (30) days, of any presentation, lecture, abstract session, etc., in which any results from the study will be disclosed.

BIBLIOGRAPHY

[1] Rawlings AV. Cellulite and its treatment. Intl J of Cosmetic Science, 2006; 28: 175-190.

[2] Rossi AB, Vergnanini AL. Cellulite: a review. JEADV 2000; 14: 251-262.

[3] Perin F, Perrier C, Pittet JC, et al. Assessment of skin improvement treatment efficacy using the photograding of mechanically-accentuated macrorelief of thigh skin. Int J of Cosmetic Science, 2000; 22: 147-156.

[4] DiBernardo B. Treatment of cellulite using a 1440-nm pulsed laser with one-year follow-up. Aesthetic Surg J; 31(3): 328-341.

[5] Hexsel DM, Dal'Forno T, Hexsel CL. A validated photonumeric cellulite severity scale. JEADV 2009 May;23(5):523-8.

[6] Hantash BM, Renton B, Berkowitz RL, et al. Pilot clinical study of a novel minimally invasive bipolar microneedle radiofrequency device. Lasers Surg Med 2009;41:87–95.

[7] Hantash BM, Ubeid AA, Chang H, et al. Bipolar fractional radiofrequency treatment induces neoelastogenesis and neocollagenesis. Lasers Surg Med 2009;41:1–9.

[8] Berube D, Renton B, Hantash BM. A predictive model of minimally invasive bipolar fractional radiofrequency skin treatment. Lasers Surg Med. 2009;41:473–8.

[9] Willey A, Kilmer S, Newman J, et al. Elastometry and clinical results after bipolar radiofrequency treatment of skin" Dermatol Surg. 2010;36:877–84.

[10] Alexiades M, Rosenberg D, Renton B, et al. Blinded, randomized, quantitative grading comparison of minimally Invasive, fractional radiofrequency and surgical face-lift to treat skin laxity, Arch dermatol. 2010; 146(4):396-405.

[11] Alexiades-Armanakas M, Newman J, Willey A. Prospective Multicenter Clinical Trial of a Minimally Invasive Temperature-Controlled Bipolar Fractional Radiofrequency System for Rhytid and Laxity Treatment. Dermatol Surg 2013;1–11.

APPENDIX I – STUDY SUMMARY

Table 3 - Study Schematics

Task / **Visit** (Interval)	**Screening/ Baseline**	**Tx.1** [1] 1 day ±14 days post baseline	**1 Week FU** 1 week post Tx.1 ±2 days	**1 Month FU** 1 month post Tx.1 ±7 days	**3 Month FU** 2 month post Tx.1. ±14 days	**6 Month FU** 3 month post Tx.1. ±14 days
Informed Consent Process	X					
Eligibility Screening	X					
Medical History & Change in Medical History	X	X	X	X	X	X
Global aesthetic improvement & Skin Tightening Improvement (**Error! Reference source not found.**)				X	X	X
Photographs (Appendix II – Photography Guideline)	X	X		X	X	X
Weight	X	X	X	X	X	X
Antibiotic prescription for subject (optional)	X[2]		X[2]			
Treatment		X				
Urine Pregnancy tests	X	X				X
Subject Pain Assessment (**Error! Reference source not found.**)		X				

[1] The screening and baseline visit should preferably occur together and one day prior to 1st treatment visit or within 14 days.

[2] Physician may prescribe antibiotic for the subjects starting from the evening prior treatment, until 7 days post treatment (optional).

[3] Subject may start Compression Garment wear immediately post treatment for 1-week period (the Garment can be removed for bath only) - optional.

[4] If worn, subject will stop wearing the Compression Garment wear at 1wk FU post treatment.

Task / **Visit** (Interval)	**Screening/ Baseline**	**Tx.1** [1] 1 day ±14 days post baseline	**1 Week FU** 1 week post Tx.1 ±2 days	**1 Month FU** 1 month post Tx.1. ±7 days	**3 Month FU** 2 month post Tx.1 ±14 days	**6 Month FU** 3 month post Tx.1 ±14 days
Daily diary for comfort, AE and activity FU post treatment		X	X			
Compression Garment wear (optional)		X[3]	X[4]			
Subject Safety Assessment (**Error! Reference source not found.** and Table 5 - Post Treatment Side Effect Duration)			X			
Subject Assessments (**Error! Reference source not found.**)				X	X	X
Investigator Satisfaction Rating (**Error! Reference source not found.**)				X	X	X
Adverse Events and Serious Adverse Events	X	X	X	X	X	X
End of participation (Termination)						X

[1] The screening and baseline visit should preferably occur together and one day prior to 1st treatment visit or within 14 days.

[2] Physician may prescribe antibiotic for the subjects starting from the evening prior treatment, until 7 days post treatment (optional).

[3] Subject may start Compression Garment wear immediately post treatment for - week period (the Garment can be removed for bath only) - optional.

[4] If worn, subject will stop wearing the Compression Garment wear at 1wk FU post treatment.

APPENDIX II – PHOTOGRAPHY GUIDELINES

At each time point (before the treatments and at the follow-up visits); photographs of the treated areas should be taken in a standardized manner.

- Photographs should be taken in a private room or area of the clinic under controlled conditions, including the distance from the camera to the subject, height of the camera, background, camera positioning, subject's positioning and lighting in order to achieve high quality before & after sets.
- Subject's hair should be removed at all photographs at all-time points. Unwanted hair at the treated area will be shaved by study staff at the clinic.
- For consistency purposes, the same person should ideally take all study photographs, especially per subject.
- The digital files should follow a consistent standard naming scheme (including: date, subject study ID, subject initials, for example: 001TS_Tx.1_Mar 21 2015, etc.)

Specific photography details for treatment area:

- Front
- Back
- 90º from the right side and left side
- 45º from the right side and left side

APPENDIX III – ASSESSMENT SCALES

Table 4 - Post Treatment Side Effect Severity Scale

(0) Absent / None	❑
(1) Mild	❑
(2) Moderate	❑
(3) Severe	❑

Table 5 - Post Treatment Side Effect Duration

(0) None – Side effect not observed	❑
(0.5) Day of Treatment	❑
(1) 1 day after Treatment	❑
(2) 2 days after Treatment	❑
(3) 3 days after Treatment	❑
(4) 4 days after Treatment	❑
(5) 5-7 days after Treatment	❑

Table 6 –Global Aesthetic Improvement (GAI) Scale

(0) No change	❑
(1) 1%-24%	❑
(2) 25%-49%	❑
(3) 50%-74%	❑
(4) 75%-100%	❑

Table 7 – Skin Laxity/Tightening Improvement Scale

(0) No tightening/firmness	❑
(1) Slightly visible tightening/firmness	❑
(2) Visible tightening/firmness	❑
(3) Very visible tightening/firmness	❑

Table 8–Satisfaction Scale

(2) Very satisfied	❑
(1) Satisfied	❑
(0) No opinion	❑
(-1) Dissatisfied	❑
(-2) Very dissatisfied	❑

Table 9–Subject Overall Aesthetic Improvement Scale

(0) No change	❑
(1) Minimal improvement	❑
(2) Moderate improvement	❑
(3) Good improvement	❑
(4) Excellent improvement	❑

Table 10–Subject Recommendation of Treatment Scale

(2) Highly recommended procedure	❑
(1) Recommended procedure	❑
(0) Neutral	❑
(-1) Not recommended procedure	❑
(-2) Very not recommended procedure	❑

APPENDIX IV - PAIN ASSESSMENT

Immediately after treatment the subject will be asked to rate treatment related pain. Pain will be assessed post treatment based on the Numerical Scale Response (NSR). The subject will be presented a scale (below) with words along a horizontal line and asked to make a mark along the scale to rate their pain from no pain to worst possible pain. A number will be derived by the research staff by measuring up to the point the subject has indicated versus the entire line.