Title: *Clinical Study to Evaluate the Safety and Efficacy of the UltraShape Power Device Using the U-Sculpt Power Transducer for Abdominal Fat and Circumference Reduction*

Protocol Number: DHF21621

Study Type: Prospective Clinical Study

Date: April 05, 2016

Study Devices: UltraShape Power

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 1:

Site 2:

Site 3:

Site 4:

Site 5:

Site 6:

Site 7:

Site 8:

Site 9:

Site 10:

Principal Investigator's Signature

I, _____ have carefully read the foregoing protocol # DHF21621: *"Clinical Study to Evaluate the Safety and Efficacy of the UltraShape Power Device Using the U-Sculpt Power Transducer for Abdominal Fat and Circumference Reduction"* 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
US	Ultrasound
W	Watt (Output Electric Power)

TABLE 1- STUDY SYNOPSIS

Proprietary Name	UltraShape Power device utilizing the U-Sculpt Power Transducer
Design	Prospective, one arm, baseline-controlled, clinical study for the evaluation of the UltraShape Power treatment using the U-Sculpt Power Transducer for non-invasive abdominal fat and circumference reduction. Study subjects will undergo UltraShape Power treatments on the abdominal area
Study Population	Up to 120 healthy adult volunteers, seeking for noninvasive abdominal fat and circumference reduction, male and females, 18 to 60 years of age from up to 10 investigational sites.
Treatment and Duration	Eligible subjects will receive 3 bi-weekly treatments (2 weeks interval) with the UltraShape Power device utilizing the U-Sculpt Power Transducer according to the study protocol. The subject will return for 3 follow up visits: four weeks (4wk FU), eight weeks (8wk FU) and 12 weeks (12wk FU) after the last treatment (Third Treatment). Each subject will be enrolled for total expected study duration of 16 weeks.
Objective	The objective of this trial is to evaluate the safety and efficacy of the UltraShape Power device utilizing the U-Sculpt Power Transducer for abdominal non-invasive fat and circumference reduction
Primary Objective	Statistically significant abdominal fat reduction post UltraShape Power treatments at 12 weeks follow-up (12wk FU) versus baseline
Primary Safety Objective	1. Evaluate the safety of the treatment with the UltraShape Power device utilizing the U-Sculpt Power Transducer during all study 2. Comfort level during treatment: Comfort assessment will be performed independently by the subject himself using NSR scale. The subjects will answer this questionnaire after each treatment (Tx.1, Tx.2 and Tx.3)
Secondary Objectives	3. Statistically significant abdominal fat reduction post UltraShape Power treatments as measured by Ultrasound device at Pre Tx.3, 4 weeks, and 8 weeks follow-up (4wk FU and 8wk FU) versus baseline 4. Statistically significant abdominal fat reduction post UltraShape Power treatments as measured by calibrated Caliper at Pre Tx.2, Pre Tx.3, 4 weeks, 8 weeks and 12 weeks follow-up (4wk FU, 8wk FU and 12wk FU) versus baseline 5. Statistically significant abdominal circumference reduction post UltraShape Power treatment/s at Pre Tx.2, Pre Tx.3, 4 weeks, 8 weeks and 12 weeks follow-up (4wk FU, 8wk FU and 12wk FU) versus baseline 6. Investigator satisfaction: Satisfaction assessment will be performed by the study investigator using a pre-defined scale questionnaire. The investigator will answer this questionnaire at each follow-up visit (4wk FU, 8wk FU and 12wk FU)

	7. Subject improvement and satisfaction: Improvement and satisfaction assessment will be performed independently by the subject himself using a pre-defined scale questionnaire. The subjects will answer this questionnaire at each follow-up visit (4wk FU, 8wk FU and 12wk FU)
Efficacy Endpoints	Primary and secondary objectives will be measured using the next efficacy endpoints: 1. Fat thickness measurements using Ultrasound device 2. Fat thickness measurements using calibrated Caliper 3. Circumference measurements of the abdominal area using Measuring Tape 4. Investigator satisfaction using a pre-defined scale 5. Subject improvement and satisfaction using a pre-defined scale 6. Photography
Safety Endpoints	1. The 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
Statistical Methods	Descriptive statistics will be used to present changes in the assessments along the study course. Circumference measurements and subject assessments' and 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

Adipose tissue is a loose type of connective tissue specialized to store lipids. The majority of lipids stored in adipose cells are triglycerides formed from imported free fatty acids and glycerol. It is not uniformly distributed in the body. The major adipose depot is subcutaneous (about 80% of all body fat).[1] In men it normally represents 15-20% of body weight and in women, 20-25% of body weight. A certain amount of body fat is necessary for normal female reproduction and health. Subcutaneous adipose tissue helps to shape, cushion and insulate the body and provides padding to some organs.

Liposuction is a procedure that can help sculpt the body by removing unwanted fat from specific areas.[2,3,4] The increasing popularity of this procedure is associated with the evolution of techniques and equipment for fat removal, body reshaping and cellulite treatments. Besides the traditional suction-assisted lipoplasty, other options include ultrasound-assisted and external

ultrasound-assisted liposuction, power-assisted liposuction, laser lipolysis as well as low-level laser-assisted liposculpture.[5]

The efforts in the search for alternative non-invasive or minimally invasive techniques and new tools aim mainly at reducing downtime, and facilitating treatment for reduction of the localized fatty tissue areas. New minimally invasive technologies include subcutaneous injection of phosphatidylcholine. This drug was initially used in emergencies and in the treatment of atheroma plaques in cardiac diseases. Recently, it has also been used in the treatment of localized fat deposits, with mixed reviews.[6]

The UltraShape® Contour I VER 3.1 is a device cleared by the Food and Drug Administration (FDA – K133238) and Health Canada (HC). The UltraShape, the next generation of Contour I VER 3.1, is a commercial device cleared by the CE, Health Canada and by the Food and Drug Administration (FDA – K141708) which uses focused ultrasound to produce localized mechanical motion within fat tissues and cells for the purpose of producing mechanical cellular membrane disruption. It is intended for reduction in abdominal circumference.

The UltraShape Power System delivers focused ultrasound energy that can disrupt subcutaneous adipose tissue (SAT) to provide a non-invasive approach to achieve a desired aesthetic effect. It is intended for non-invasive reduction in abdominal circumference. This study intends to assess UltraShape Power device utilizing the U-Sculpt Power transducer performance.

Device Descriptions

Syneron UltraShape Power Device

General: Tissue selectivity is achieved by a proprietary knowledge of ultrasound parameters ensuring specific destruction of the fat cells only within the target area. All other types of tissue, such as blood vessels, muscles and peripheral nerves remain intact. There are no thermal effects. Fat cell destruction is achieved by ultrasound-induced mechanical effects during a very short exposure time.

The UltraShape Power system comprised of two main parts:

- The Main console
- Transducer

Main Console

The Pulser

The main console contains: the Pulser, Touch Screen, PC, Cooling System, Power supply Module and Video Camera. The main console hardware and software enable operation of the Transducer Unit.

The Pulser is responsible for producing high power electrical signals for feeding the Transducer Unit, with the ability to control operating frequencies, burst length, duty cycle and on-line output power. The Pulser has communication interfaces with the PC, the Power Supply Module (PSM), the Distributer Board (DSB), the Transducer and the cooling system. The Pulser is comprised of a CPU unit and Pulse generator. The Pulser uses transducer-unique parameters and "Power Level" (high \ medium \ low) selected by the user to send the relevant electric signal to the transducer.

Touch Screen and PC

The operator interfaces with the UltraShape Power system using its Touch Screen.

The Touch Screen interface allows the user to command and control the system using dedicated software. The Touch Screen interfaces with the Pulser, the camera and external USB. The Touch Screen operates the system's tracking system that uses a video camera in order to monitor the position of the transducer over the patient's body. The System database is managed by the Touch Screen.

Cooling system

Inside the Transducer there is a cooling element (TEC). The cooling system evacuates heat from the hot side of the TEC, by circulating water into the system's radiator.

Power Supply Module

The Power Supply Module (PMS) provides the input power to the system sub-units. The Power Supply Module receives external AC voltage and converts it into DC: Low Voltage and High Voltage. The PSM is controlled by the Pulser and the DSB.

Video Camera

The system includes a video camera as a part of its tracking system. The camera captures the image of the treatment area, enabling the operator to monitor the procedure and track the treated area and transducer position.

Distributor Board (DSB)

The Distributor Board is responsible for distribution of DC voltages to the system's sub-units.

The DSB is controlled by the Pulser. The DSB gathers feedback signals from the Cooling system and returns it to the Pulser.

Transducer

The transducers are electro-mechanical devices that convert electrical signals into mechanical (acoustical) energy. Functionality of the transducer is based on piezoelectric ceramics, whose characteristics are to change their physical dimensions when electrical voltage is applied. When an alternating voltage, with a certain frequency, is applied across the piezoelectric element, it causes it to oscillate with the same frequency, thus producing ultrasound waves. The spherical shape of the piezoelectric element enables focusing of the ultrasonic wave, which enables the ultrasound waves to be focused into a narrow focal region (which is actually the target region). The UltraShape Power system supports use of the "U-Sculpt Power" (Isppa 660 W/cm^2) and the "VDF Power" (Isppa 550 W/cm^2) Transducers.

Figure 1: UltraShape Power System

<u>Accessories needed for the UltraShape Power Treatment</u>

Reusable Straps

Gather skin and fat at the area to be treated. Straps are supplied at 3 sizes.

Parker Gel

Used as a coupler agent between skin surface and the ultrasonic transducer

Ultrasound Device

Measure fat thickness at treatment area prior starting the treatment.

Calibrated Caliper

Assess fat thickness at treatment area prior starting the treatment.

Circumference measuring tape

Assess circumference reduction

Height Measuring Device(Seca)

Measure circumference at the same height in the subsequent visits

A3 Transpaernt Paper (B ledger size)

Assure repeatable marking of treatment area at each treatment visit

STUDY DESIGN OVERVIEW

This study is a prospective, baseline controlled, multi-center, one arm clinical study showing the performance and safety of the UltraShape Power treatment for abdominal non-invasive fat and circumference reduction.

Up to 120 Healthy subjects in up to 10 investigational sites will be enrolled in this study. All subjects will undergo an assessment of their general health. During the treatment period, subject's fat thickness and circumference will be measured and three successive bi-weekly (two weeks interval) treatments will be performed.

The study subjects will undergo treatments with UltraShape Power device utilizing the U-Sculpt Power Transducer.

During the follow-up period visit will be conducted as follow: 4 weeks (4wk FU), 8 weeks (8wk FU) and 12 weeks (12wk FU) post last treatment (Tx.3). Subject's fat thickness will be measured in two different methods (Caliper & Ultrasound) and fat reduction will be assessed at each post baseline visit. Circumference will be measured in 3 measurements heights and circumference reduction 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 of the assessments will occur at each of the visits to the clinic.

SUTDY OBJECTIVE

The objective of this trial is to evaluate the safety and efficacy of the UltraShape Power device utilizing the U-Sculpt Power Transducer for abdominal non-invasive fat and circumference reduction

Primary Objective

Statistically significant abdominal fat reduction as measured by Ultrasound device post UltraShape Power treatments at 12 weeks follow-up (12wk FU) versus baseline.

Primary Safety Objective

1. Evaluate the safety of the treatment with the UltraShape Power device utilizing the U-Sculpt Power Transducer during all study.
2. Comfort level during treatment:
   Comfort assessment will be performed independently by the subject himself using NSR scale; the subjects will answer this questionnaire after each treatment (Tx.1, Tx.2 and Tx.3).

Secondary Objectives

1. Statistically significant abdominal fat reduction post UltraShape Power treatments as measured by Ultrasound device at Pre Tx.3, 4 weeks, and 8 weeks follow-up (4wk FU and 8wk FU) versus baseline.
2. Statistically significant abdominal fat reduction post UltraShape Power treatments as measured by calibrated Caliper at Pre Tx.2, Pre Tx.3, 4 weeks, 8 weeks and 12 weeks follow-up (4wk FU, 8wk FU and 12wk FU) versus baseline.
3. Statistically significant abdominal circumference reduction post UltraShape Power treatment/s at Pre Tx.2, Pre Tx.3, 4 weeks, 8 weeks and 12 weeks follow-up (4wk FU, 8wk FU and 12wk FU) versus baseline.
4. Investigator satisfaction:
   Satisfaction assessment will be performed by the study investigator using a pre-defined scale questionnaire. The investigator will answer this questionnaire at each follow-up visit (4wk FU, 8wk FU and 12wk FU).
5. Subject improvement and satisfaction:
   Improvement and satisfaction assessment will be performed independently by the subject himself using a pre-defined scale questionnaire. The subjects will answer this questionnaire at each follow-up visit (4wk FU, 8wk FU and 12wk FU).

Primary and Secondary Efficacy Endpoint

Primary and secondary objectives will be measured using the next efficacy endpoints:

1. Fat thickness measurements using Ultrasound device
2. Fat thickness measurements using calibrated Caliper
3. Circumference measurements of the abdominal area using Measuring Tape
4. Investigator satisfaction using a pre-defined scale
5. Subject improvement and satisfaction using a pre-defined scale
6. Photography

Primary Safety Endpoint

The number, severity and type of any adverse event recorded throughout the study and post treatment (discomfort (pain), immediate and delayed response).

1. Occurrence of expected post treatment immediate response including erythema and edema and during all study period based on predefined scale (Table 4).
2. Number, severity and type of any adverse event recorded throughout the course of the study.
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 IIIAppendix III - Pain assessment.

STUDY POPULATION

Number of Subjects

This study will be comprised of up to 120 subjects in up to ten (10) investigational sites. Subjects who meet all the inclusion and none of the exclusion criteria will be enroll.

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 120 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. Female and male subjects, $\geq$ 18 and $\leq$ 60 years of age at the time of enrolment
3. Fitzpatrick Skin Type I to VI.
4. Abdominal fat thickness of at least 1.5 cm (measured by calibrated caliper).
5. BMI interval: 22 ≤ BMI ≤ 30 (normal to overweight, but not obese).
6. If female, 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. In addition, negative urine pregnancy test as tested before each treatment and at the last visit for women with bearing potential (e.g. not menopause).
8. General good health confirmed by medical history and skin examination of the treated area.
9. Willing to follow the treatment and follow-up schedule and post-treatment care instructions.
10. Willingness to refrain from a change in diet/ exercise/medication regimen for the entire course of the study.
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. History of hypertension, ischemic heart disease, valvular heart disease, congestive heart failure, pacemaker/defibrillator, abdominal aortic aneurism
2. Current hyperlipidemia, diabetes mellitus, hepatitis, liver disease, HIV positive status, blood coagulopathy or excessive bleeding, autoimmune or connective tissue disease
3. Having or undergoing any form of treatment for active cancer, or having a history of skin cancer or any other cancer in the areas to be treated, including presence of malignant or pre-malignant pigmented lesions
4. Having any active electrical implant anywhere in the body, such as a pacemaker or an internal defibrillator
5. Having a permanent implant in the treated area, such as metal plates or an injected chemical substance such as silicone
6. Having undergone any other surgery in the treated areas within 12 months of treatment or during the study, including liposuction
7. Previous body contouring procedures in the treatment area within 12 months
8. History of skin disease in the treatment area, known tendency to form keloids or poor wound healing
9. Suffering from significant skin conditions in the treated areas or inflammatory skin conditions, including, but not limited to, open lacerations or abrasions and active cold sores or herpes sores prior to treatment (duration of resolution as per the Investigator's discretion) or during the treatment course
10. Skin lesions in the treatment area other than simple nevi on physical examination (e.g., atypical nevus, tattoo, abrasions) including depressed scars in the treatment area

11. Very poor skin quality (i.e., severe laxity)
12. Abdominal wall diastasis or hernia on physical examination
13. Abnormal kidney, liver or coagulation functions, abnormal lipid profile or blood count within the last 3 months
14. Obesity (BMI > 30)
15. Childbirth within the last 12 months or breastfeeding women. Any acute or chronic condition which, in the opinion of the investigator, could interfere with the conduct of the study
16. Unstable weight within the last 6 months (i.e., ± 3% weight change in the prior six months)
17. Inability to comply with circumference measurement procedure (e.g., inability to hold breath for the required duration).
18. Abdominal fat thickness lower than 2.5 cm after strapping.
19. Participation in another clinical study involving same anatomical areas within the last 6 months (or 30 days in case different anatomical areas were treated in previous trial/s).
20. As per the Investigator's discretion, any physical or mental condition which might make it unsafe for the subject to participate in this study.

STUDY PROCEDURES

Enrollment and Screening

During the first visit, the 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

Measurement	When to conduct	Method
Height	Baseline	Scale
Weight	Prior to all treatments (Tx.1, Tx.2 & Tx.3), and at all follow-ups visits (4wk FU, 8wk FU & 12wk FU)	Scale
BMI		Calculation
Fat thickness UltraSound measurement	Baseline, Prior to Tx.3, and at all follow-ups visits (4wk FU, 8wk FU & 12wk FU)	Ultrasound device.
Fat thickness Caliper measurement	Prior to all treatments (Tx.1, Tx.2 & Tx.3), and at all follow-ups visits (4wk FU, 8wk FU & 12wk FU).	Caliper
Circumference measurements		Standardized circumference measuring tape
Photographs		Standardized digital photographs
Urine pregnancy test	Prior to all treatments (Tx.1, Tx.2 & Tx.3), and at the last follow-up visit (12wk FU)	Urine pregnancy test
Treatment-associated pain	Immediately after each treatment (Tx.1, Tx.2 & Tx.3)	Subject will be asked to rank/ assess pain level during treatment based on the Numerical Scale Response (NSR scale) - Appendix IIIAppendix III - Pain assessment
Immediate response assessment	Immediately after each treatment (Tx.1, Tx.2 & Tx.3)	Post Treatment Side Effect Severity Scale (Table 4)
Investigator satisfaction	At all follow-up visits (4wk FU, 8wk FU and 12wk FU)	Satisfaction Questionnaire (Table 6)
Subject satisfaction		Satisfaction Questionnaire (Table 6)
Improvement assessment		Improvement Questionnaire (Table 5)
Safety	During treatment and throughout study.	Examination of skin in the treated area, interview subjects, Adverse Events form, Occurrence and Severity Ratings, as well as relation to treatment, action taken and outcome

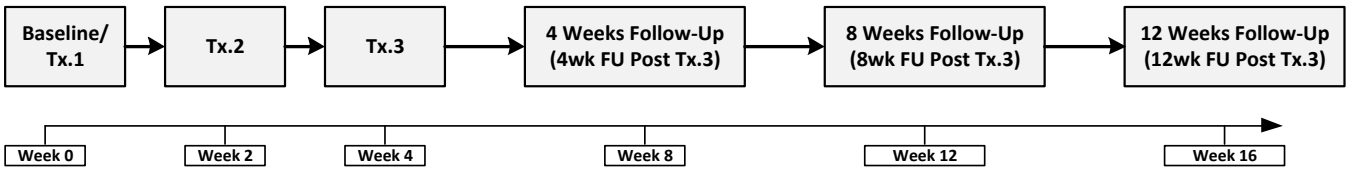


Figure 2: Study Flow-Chart (Visits at the Clinic)

Pre-Treatment Procedures

Screening and Baseline procedures may be conducted on the same visit day as the treatment, prior to the treatment. It is expected that the screening and baseline procedures will be conducted during the same visit and the treatment visit procedures will take up to 2 hours.

Screening

1. ICF - Prior to any study procedures, informed consent will be obtained. When the subject fully understands the possible benefits and risks of the study, the subject will be asked to sign and date the informed consent form (ICF). 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 the study criteria, including a list of all prescribed and over the counter medications taken within the previous 6 months will be recorded.
4. Skin Exam - The subject will undergo a routine skin exam to determine if they meet the study criteria including the presence of fatty tissue deposits in the treatment area.
5. BMI – the volunteers' height and weight will be taken for calculation of BMI.
6. Pregnancy Screen - Subjects who are capable of becoming pregnant will undergo a urine pregnancy test. This will be repeated at visits 2 and 3 (prior to all treatments) and at the end of the study (last FU visit/ 12wk FU). If the Screening and Treatment procedures are not conducted on the same day, the urine pregnancy test will be repeated on the treatment day.
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 and Tx.1 will be conducted immediately after the Screening visit.

Baseline

1. Photography – Baseline photographs will be obtained using a consistent camera and subject placement settings with a digital imaging system.
2. BMI – the subject weight and height will be taken if baseline visit is a different day than the screening visit.

Measurements

Measure the Fat Thickness at the Treated Area – Calibrated Caliper

The procedure can be performed only in areas where the fat thickness is ≥1.5 cm as measured by a skin fold caliper (or ≥3.0 cm as measured by a pinch test), and ≥2.5 cm as measured by a skin fold caliper after strapping.

Marking Area for Treatment and Sequence of Treatments

The mark of area to be treated should be copied to a transparent template (at size of A3 paper) to ensure consistent marking of the same area for same patient during the subsequent visits.
During copying the treatment area to the transparent template, the following signs will be marked on transparency (Figure 3)

a) Margins of area to be treated (A in Figure 3)
b) Subject's identification code (B in Figure 3)
c) Location of navel (C in Figure 3)
d) Sides of right and left (D in Figure 3)

At the subsequent treatment sessions, this transparent template will be placed according to these signs on the abdomen, and the line of treatment area will be re-marked.

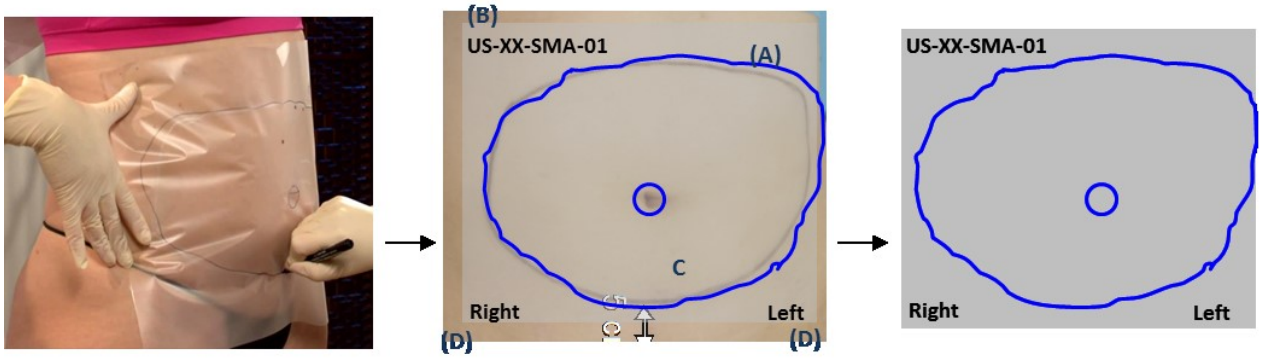


Figure 3: Marked area of treatment is copied to transparent template, which includes: (A) margin of area to be treated (B) Subject's code (C) location of navel (blue central circle) (D) right and left side. The left picture demonstrates the procedure on patient.

Measure the Fat Thickness at the Treated Area – Ultrasound Imaging Device

Ultrasound Imaging (USI) provides a valid way for measuring fat thickness using known interfaces observed in any individual. USI is relies on the ability to recognize different sub-skin interfaces and correctly identifying them, such as the **dermis** and the **subcutaneous fat layer** interfaces.

a) Divide the treatment area into 4 sub areas:
   1. Right Upper
   2. Right Lower
   3. Left Upper
   4. Left Lower

b) Locate each sub area mid-point and measure

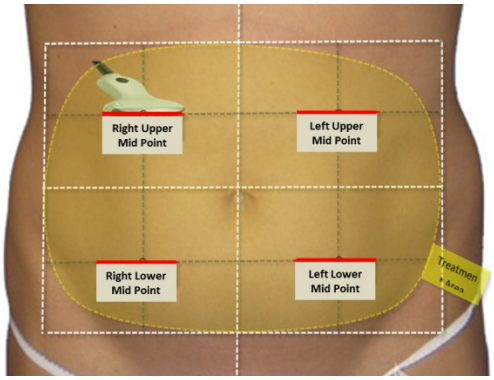


Figure 4: Ultrasound Measurements Points

c) Mark the measurements points on the transparency (made while marking the treatment area), to measure the same point in each subsequent visit.
d) Place the applicator on the skin surface at angle of 90^{o} (located the applicator under the measurement point line for consistency).
e) Measurement should include all the area between the dermis and end of the fat tissue fascia.

Marking height of circumference measurement

The abdominal midsection for circumference (=Midline) measurement will be marked at the widest region within the defined area for treatment (see Figure 5). Patient should stand up straight when arms are placed at the rear of neck and head is positioned towards the horizon (Figure 6). Elbows will be positioned in front of the body (Figure 6).

The height for the circumference measurement will be marked at the anterior abdomen, at the back and at each lateral side of the body (Figure 7). Additional measurements will be taken at 2 cm above midsection (=2cm above Midline) measurement and 2 cm below midsection (=2cm below Midline) measurement.

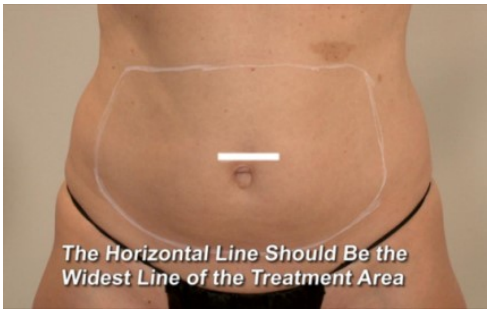


Figure 5: Circumference measurement will be done at the widest region within the defined area for treatment (white arrow)

Figure 6: Body poisoning during marking height for circumference measurement

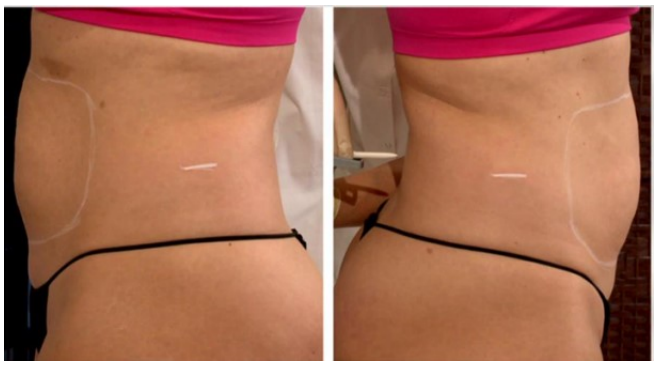


Figure 7: Height of circumference measurement will be marked at the anterior abdomen, at the back and at each lateral side of the body.

The height of midsection will be measured using the height measuring device (supplied by Syneron Medical) (Figure 8). The marking pencil will be placed horizontally at the stage of the measurement device (Figure 8) during the marking procedure.

Height of midsection area and circumference results will be recorded in the CRF (will used as reference for the next visits measurements).

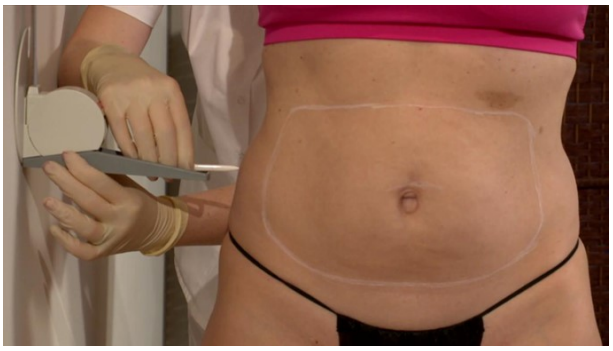


Figure 8: Mark pencil will be placed horizontally at the stage of measurement device

Measuring Circumference

Abdominal circumference is measured to quantify the treatment effect. This procedure will be performed and recorded every visit at the clinic, immediately following the measurement of height marking.

In order to achieve reproducible measurement results, the following requirements should be fulfilled:

1. Patient should be wearing underwear and barefoot during circumference measurement.
2. Patient should stand up straight when arms are placed at the rear of neck and head is positioned towards the horizon. Elbows will be positioned in front of the body (see Figure 9A).
3. The measurement tape (supplied by Syneron Medical) should be in parallel to the floor during the measurement (see Figure 9B).
4. The circumference measurement tape should be placed under the marked reference points, in order to maintain repetitive height of the measurement.
5. Midline measurement should be taken at the level of the widest part within the defined area for treatment (Figure 5) – horizontal midsection. This height level should be recorded for follow up assessments. Additional two measurements at 2 cm above and 2 cm below the horizontal midsection (=Midline) will be taken.
6. Consecutive measurements should be performed at the same height recorded at baseline. In order to assure that the measuring tape is parallel to the floor, several reference points should be marked around the treatment area and the measuring tape should be placed such that it is aligned with them.

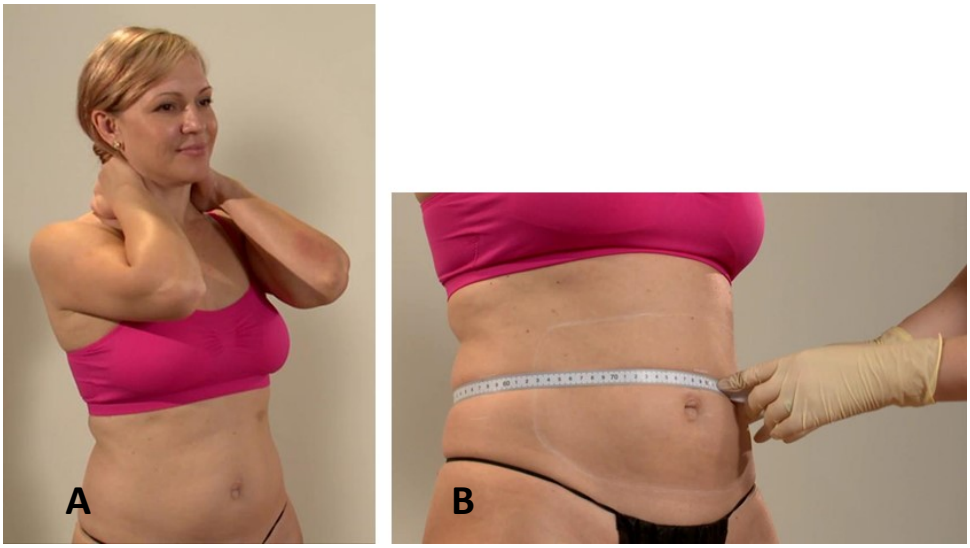


Figure 9: Patient positioning during circumference measurements (A) and measuring device position around the abdomen (B)

7. The measurement device should be activated at a constant tension to achieve an exact measurement of the circumference (use measurement device supplied by Syneron only).
8. In order to minimize measurement inaccuracies originating from human error, it is recommended that, whenever possible, the same operator re-measures the patient at approximately at the same hour of day (± 3 hours).
9. Patients should be under fasting for at least 3 hours prior to circumference measurement.

Treatment Procedure

Subjects will receive treatments with UltraShape Power device utilizing the U-Sculpt Power Transducer on the anterior abdomen.

Prior to each treatment measurements of weight, fat thickness (both by Ultrasound and Caliper), and abdominal circumference will be done according to the references from the enrollment visit (Baseline/ prior to Tx.1). Only patients who are eligible for treatment will be allowed to undergo the UltraShape Power procedure.

Enrolled subjects will undergo 3 successive bi-weekly (2 weeks interval) treatments (Tx.1, Tx.2 and Tx.3). Additional three (3) visits in the clinic will be occurred to follow-up the abdominal fat and circumference reduction at visits 4, 5 and 6 (4 weeks, 8 weeks and 12 weeks following last treatment).

UltraShape Power Treatment Procedure

The subject abdomen will be gathered using reusable straps (supplied by Syneron Medical), to gather the fat area for treatment according to the instruction written in the User Manual.

According to size of the treatment area, the UltraShape Power device will determine the total number of FTZs to be delivered during treatment. While the recommended minimal number of ultrasound FTZs to be delivered per subject at a whole single treatment will be defined / determined by the system according to the subject physical characteristic and treated area size.

Prior to admitting the FTZs (pulses) Parker acoustic gel will be applied and on the treated area and used as a coupler agent between the ultrasonic U-Sculpt Power Transducer and the skin surface.

Perform the UltraShape Power utilizing the U-Sculpt Power Transducer treatment according to the instruction in the User Manual.

Expected post treatment side effects are limited to Erythema (blanchable/non-blanchable), Edema, Heat sensation and pain sensation.

Post Treatment Procedures

1. Pain assessment – immediately after each treatment the subjects will be asked to rank the pain sensation during treatment using Numerical Scale Response (NSR; see Appendix III) for the UltraShape Power procedure
2. Safety aspect will be assessed before and after each treatment:
    a. Clinical effects - All visible and palpable immediate response will be recorded for the entire treatment area using a 4-point severity scale (Table 4)
    b. Adverse Events – Record the number, severity and type of any adverse event occurred before, through and after treatments.

Return Visits

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 of the device:

- Visit 4: FU1 – 4 weeks (±7 days) post last treatment.
- Visit 5: FU2 – 8 weeks (±7 days) post last treatment.
- Visit 6: FU3 – 12 weeks (±7 days) post last treatment.

At each return visit the following procedures will be conducted and data recorded:

- Weight.
- Ultrasound fat-thickness measurements.
- Caliper fat-thickness measurements.
- Circumference measurements.

- Skin assessment for clinical effects due the procedures:
    - Post treatment response and adverse events.
- Photographs as conducted at baseline.
- Satisfaction questionnaire performed by the investigator using the Global Aesthetic Improvement (GAI).
- Completion of the Subject Follow Up questionnaire:
    - Subjective Improvement and satisfaction performed by the subject using the Global Aesthetic Improvement (GAI).
- At the final visit a urine pregnancy test will be performed for women with bearing potential.

DATA ANALYSIS

Recording

All data will be recorded on site source documents and transcribed onto Case Report Forms (CRFs). The 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., weight, height 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 for weight, circumference and digital images will be used for comparative measurements with their respective measurement at baseline. Primary endpoints will be evaluated 12 weeks post last treatment (Tx.3). 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 recoded.

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 *UltraShape Power* the following local adverse effects could occur (anticipated):

- Purpura
- Blister
- Bruising
- Bullae
- Erosion
- soreness
- First degree burn
- Second degree burn

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.

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 Purpura, blistering, bruising, bullae, erosion, soreness and burn. If an unanticipated adverse event occurs at any time during or after the use of the UltraShape Power 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 *UltraShape Power* system is non-significant risk device. As indicated in the AE section, the anticipated risks associated with the use of both of the systems are:

- Purpura
- Blister
- Bruising
- Erosion
- soreness
- First degree burn

- Bullae
- Second degree burn

Over 1000 subjects worldwide participated in clinical research and underwent treatment with the different *UltraShape* devices. The *UltraShape Power* device will be used in this study was previously used in studies and emitted the same acoustic energy. To date, no serious adverse events or unanticipated AEs have been reported. The reported AEs relate to skin 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 reduction of subcutaneous fatty tissue on the treated area via a non-invasive technique resulting in body contouring improvement. All subjects in the treatment groups are expected to have some benefit from the treatment procedures as would be expected for the commercial devices (*UltraShape Power*). Subject will receive all treatment 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, such as liposuction. The results of this study will help to determine whether this device is safe and effective for improvement of localized subcutaneous fat.

Conclusion:

In light of the potential benefits of non-invasive body contouring relative to its risks, the potential benefits associated with the use of the UltraShape Power System outweigh its risks, supporting study initiation.

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 *UltraShape Power* device and Parker Gel (coupler agents) will be supplied to the participating clinic. The device will be maintained by the Sponsor, as needed. Unused equipment or coupler agents will be returned to the sponsor at the end of the study. At the end of all planned treatment sessions the devices will be returned to Syneron.

Control & Disposition of the Investigational Device

The *UltraShape Power* device will be used according to the instructions of the Sponsor and manufacturer, Syneron Medical. At the end of this study, any materials provided specifically for use in this study may be returned to the Sponsor, as described in the Clinical Trial Agreement and study budget.

Informed Consent

The 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. Arner P. *OBESITY AND THE ADIPOCYTE, Regional adipocity in man*. Journal of Endocrinology (1997) 155, 191–192
2. Illouz YG, de Villiers YT. *Body Sculpturing by Lipoplasty.* Edinburgh: Churchill Livingstone, 1989.
3. Gasparotti M. *Superficial liposuction: a new application of the technique for aged and flaccid skin*. Aesthet Plast Surg (1992) 16, 141–53
4. Adamo C, Mazzocchi M, Rossi A and Scuderi N. *Ultrasonic liposculpturing. extrapolations from the analysis of in vivo sonicated adipose tissue*. Plast Reconstr Surg (1997) 100, 220–6
5. Goldman A. *Submental Nd:YAG Laser-Assisted Liposuction.* Lasers in Surgery and Medicine 38:181–184 (2006).
6. Hexsel D, Serra M, Mazzuco R, Dal'Forno T, Zechmeister D. *Phosphatidylcholine in the treatment of localized fat.* J. Drugs Dermatol. 2003 Oct;2(5):511-8.

APPENDIX I – STUDY SUMMERY

Table 3 - Study Schematics

		Screen / Baseline* Tx.1	Tx.2 ±5 days	Tx.3 ±5 days	4 weeks Follow-Up (4wk FU) ±7 days	8 weeks Follow-Up (8wk FU) ±7 days	12 weeks Follow-Up (12wk FU) ±7 days
Informed Consent Process		X					
Eligibility Screening & Medical History		X					
PERFORM BEFORE TREATMENT	**Photography**	X	X	X	X	X	X
	Height	X					
	Weight (BMI calculation)	X	X	X	X	X	X
	Marking of the Treatment Areas	X	X	X			
	Transplant Preparation	X					
	Fat Thickness Ultrasound Measurement (Prior Strapping)	X		X	X	X	X
	Fat Thickness Caliper Measurement (Prior Strapping)	X	X	X	X	X	X
	Fat Thickness Caliper Measurement (Prior Strapping)	X	X	X			
	Circumference Measurements	X	X	X	X	X	X
Treatment		X	X	X			
Subject Pain Assessment		X	X	X			
Safety Monitoring		X	X	X	X	X	X
Subject Questionnaire					X	X	X
Investigator Questionnaire					X	X	X
Urine Pregnancy Test		X	X	X			X
End of Participation (Termination)							X

APPENDIX II - SCALES

Table 4 - Post Treatment Side Effect Severity Scale

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

Table 5 – Global Aesthetic Improvement (GAI) Scale

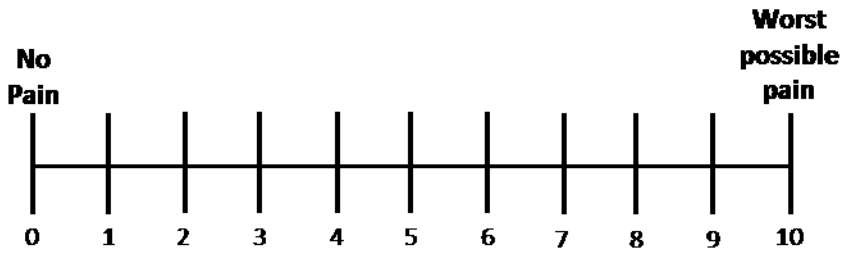
(0) No change	❑
(1) Slight improvement	❑
(2) Moderate improvement	❑
(3) Significant improvement	❑

Table 6 – Satisfaction Scale

(0) Dissatisfied	❑
(1) No Opinion	❑
(2) Satisfied	❑
(3) Very Satisfied	❑

APPENDIX III - 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.



APPENDIX IV - PHOTOGRAPHY

At each of the specified time points; photographs of the treated areas should be taken by investigator or their designee.

- 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.
- Consistent lighting- Lighting should be projected from about 45º angle in order to emphasize the body appearance.
- It is important to keep a constant distance between the subject's feet (use "sticky feet" or another way of marking) in order to properly present the effect of the treatment. The recommended distance between the feet is ~20 cm, but the main point is not to make this distance too small, so the thighs touch each other, or too large.
- The disposable underwear should be used for all photographs of all of the anatomical areas at all time points.
- For consistency purposes, the same person should ideally take all study photographs, especially per area and subject.
- The digital files should follow a consistent standard naming scheme containing subject initials and study ID #, visit or visit date.

Specific photography details:

Abdomen:

Three photographs should be taken at each specified time point

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

The subject's arms should remain out of the way; it is best to either cross them over each other in front of the chest or hold them up at a 90° angle to the body, ensuring that they do not rest on the chest or touch the body and that they do not cast a shadow in the photograph.

APPENDIX V - CLINICAL TRIAL ACKNOWLEDGEMENT

I have read and understood the foregoing protocol, and agree to conduct this clinical study as outlined herein and in accordance with Good Clinical Practices, as well as with local and universal regulations pertaining to clinical trials.

Investigator's Signature

Date

Name

Clinic

Street Address

City, State & Zip Code

Country

Phone #

Fax #

E-mail Address