Clinical Evaluation of the Safety and Performance of Fractional RF for the Treatment of Surgical Scars Following Breast Augmentation, Abdominoplasty or Face Lift

Protocol Identifying Number: CS0717

Principal Investigator: Dr. Kai O. Kaye

Funded by: Venus Concept

Version Number: 2.0

07 February 2018

Sponsor Contact

[redacted]

[redacted] 02/15/19

Signature of Sponsor Representative **Date: (DD/MMM/YYYY)**

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CRF	Case Report Form
EC	Ethics Committee
GAIS	Global Aesthetic Improvement Scale
MSS	Manchester Scar Scale
GCP	Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISO 14155:2011	International Organization for Standardization Good Clinical Practices for Clinical Investigations of Medical Devices
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
POSAS	Patient and Observer Scar Assessment Scale
QC	Quality Control
EC	Ethics Committee
RF	Radio Frequency
SAE	Serious Adverse Event
SAP	Statistical and Analytical Plan
VAS	Visual Analog Scale

STATEMENT OF COMPLIANCE

This clinical study will be conducted in compliance with the latest version of the Declaration of Helsinki (2013), ISO 14155:2011 (Clinical investigation of medical devices for human subjects - Good clinical practice), Medical Devices Directive 93/42/EEC, MEDDEV 2.7/3 and any of the applicable regional or national regulations pertaining to conduct of a clinical investigation of a medical device.

The clinical investigation shall not begin until the required approval or favorable opinion from the ethics committee (EC) has been obtained and, if applicable, any local or national regulatory authority approvals or notifications have been obtained.

Any additional requirements imposed by the EC or applicable regulatory authority shall be followed in the conduct of this clinical investigation.

The Sponsor has obtained clinical investigation insurance that will cover expenses in the event of any physical injury resulting from research procedures.

INVESTIGATOR SIGNATURE PAGE

Protocol #:	CS0717
Protocol Title:	Clinical Evaluation of the Safety and Performance of Fractional RF for the Treatment of Surgical Scars Following Breast Augmentation, Abdominoplasty or Face Lift
Protocol Version:	2
Protocol Date:	07 February, 2018

I have read this clinical investigation plan and appendices and agree to adhere to the requirements. I will provide copies of this clinical investigation plan and all pertinent information to the trial personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the device and the conduct of the trial.

I will conduct the trial in accordance with the clinical investigation plan, Good Clinical Practice guidelines, ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice), as well as local regulations. I also accept respective revisions to the clinical investigation plan approved by authorized personnel of the Sponsor and by regulatory authorities.

Institution:

Dr. KAI KATE

Principal Investigator (Printed name)

Principal Investigator (Signature)

22/2/18

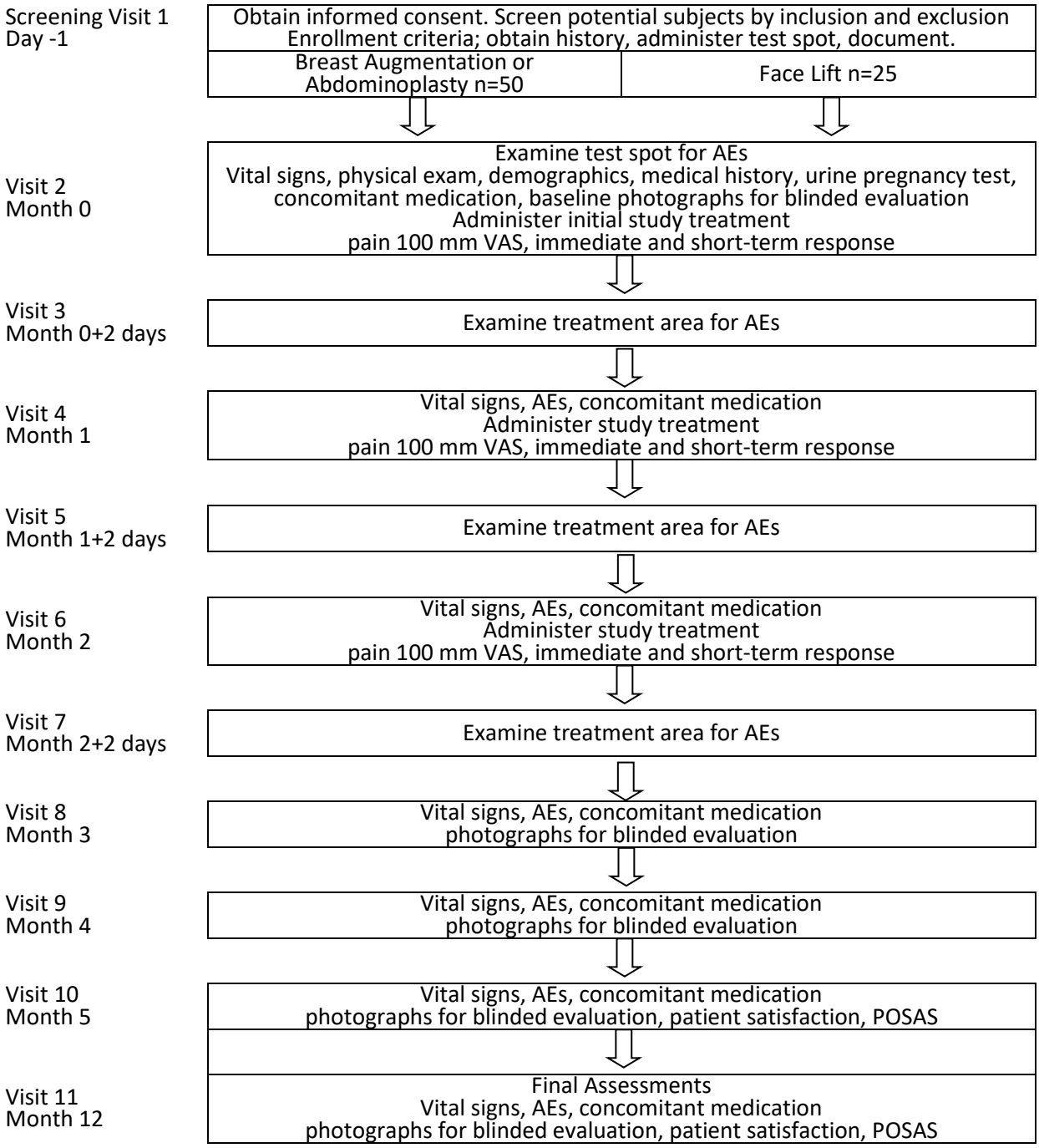
Date

PROTOCOL SUMMARY

TITLE	Clinical Evaluation of the Safety and Performance of Fractional RF for the Treatment of Surgical Scars Following Breast Augmentation, Abdominoplasty or Face Lift
SUMMARY	Split-body/face evaluator-blind study of the safety and performance of fractional RF for the treatment of surgical scars following breast augmentation, abdominoplasty or face lift. The study will enroll up to 50 female subjects requesting treatment of surgical scars following breast augmentation or abdominoplasty and up to 25 male and female subjects requesting treatment of surgical scars following face lift surgery. Subjects will receive a total of three treatments of their surgical scars at one-month intervals on one side of the body or facial incision only. Subjects will be followed up at one, two, three and ten months after their last treatment. Analysis will be performed on all subjects who receive at least one treatment. Outcomes will be compared to the non-treated side.
OBJECTIVES	The objective of this clinical study is to evaluate the safety and performance of fractional RF for the treatment of surgical scars following breast augmentation, abdominoplasty or face lift.
ENDPOINT	Primary performance endpoints • Improvement of surgical scars at 3 months post-treatment as evaluated by independent blinded reviewer using the General Aesthetic Improvement Scale (GAIS) and Manchester Scar Scale (MSS). • Improvement of surgical scars at 10 months post-treatment as evaluated by independent blinded reviewer using the General Aesthetic Improvement Scale (GAIS) and Manchester Scar Scale (MSS). Secondary performance endpoints • Improvement of surgical scars at 1 and 2 months post-treatment as evaluated by independent blinded reviewer using the General Aesthetic Improvement Scale (GAIS) and Manchester Scar Scale (MSS). • Assessment of surgical scars at 3 and 10 months post-treatment as evaluated by independent blinded reviewer using the Patient and Observer Scar Assessment Scale. • Assessment of surgical scars at 3 and 10 months post-treatment as evaluated by the subject using the Patient and Observer Scar Assessment Scale. • Subjects' assessment of satisfaction with the treatment at 3 and 10 months post-treatment. Safety endpoints • Subject's assessment of discomfort and pain after treatment as measured by a 10 cm visual analog scale (VAS). • Subjects experiencing a treatment-related adverse event (AE) by 10 months post-treatment.
POPULATION	The study will enroll up to 50 female subjects requesting treatment of surgical scars following breast augmentation or abdominoplasty and up to 25 male and female subjects requesting treatment of surgical scars following face lift surgery.

PHASE	Post-marketing
NUMBER OF SITES	One site
DESCRIPTION OF DEVICE	The Venus Viva™ fractional RF device has been shown in clinical studies to improve various skin conditions related to aging and alter collagen structures such as wrinkles, rhytids and scars. The device utilizes a 160 pin tip to deliver fractional RF energy to the skin.
STUDY DURATION	Approximately fifteen months
PARTICIPANT DURATION	Twelve months

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

[redacted]

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Skin laxity, facial texture irregularities such as post acne scars, and facial wrinkles, clinically referred to as rhytides, are common skin conditions in both men and women. The appearance of these types of facial irregularities can result in distress for people of all ages, causing them to turn to cosmetic treatments such as surgical procedures (e.g., face lifts) as well as non-surgical procedures including chemical or laser peels, non-ablative laser resurfacing, or dermabrasion.[1] These procedures are usually associated with prolonged recovery times as well as arduous side effects. To circumvent these issues, the use of non-invasive, nonsurgical approaches that do not require downtime are becoming the preferred method of choice for patients seeking cosmetic improvements. An innovative technique that was introduced to reduce facial wrinkles and rhytides is known as radiofrequency (RF).

One of the earliest procedures entailed using mono-polar RF[2], although bipolar and multi-polar RF devices have also been developed. The premise behind RF technology is dermal heating, which initiates the denaturation of collagen and the stimulation of neocollagenesis through the induction of inflammation that leads to the production of fibroblasts at the heated area and the subsequent development of new collagen.[3,4] RF energy produces an oscillating electrical current that can penetrate the dermis and hypodermal tissues without disturbing the epidermal-dermal barrier. The generation of the heat energy is the result of the natural resistance that dermal tissue has to the movement of ions with an electromagnetic field. Accordingly, the oscillating electrical current causes collisions between charged ions that are transformed into heat energy.[3,5] The production of heat energy through RF typically results in ablation, coagulation, and skin resurfacing.

Mono-polar RF devices were used initially for facial treatments, and although the results appeared to be promising, this approach was associated with serious pain as well as the high incidence of adverse events including second-degree burns that are caused by the deeply penetrating heat production of the single electrode.[6] Bipolar and multi-polar RF devices allow the heat energy to be distributed more evenly with less depth-penetration, thereby resulting in less pain and improved safety profiles[7,8] but concerns remained regarding the ability to precisely control the degree of ablation and coagulation that is required depending on a patient's skin type. Moreover, a randomized, blinded, split-face study comparing the use of mono-polar and bipolar RF devices for the treatment of skin laxity and wrinkles indicated that there was no difference in pain, side effects, or efficacy between mono-polar and bipolar devices.[9] Therefore, RF techniques that improve the ability to control the ablation and coagulation of

the skin can result in treatment consistency that will provide more flexibility to treat a wider variety of skin conditions.

2.2 RATIONALE

Fractional RF technology has been shown in clinical studies to improve skin laxity, and to treat various skin conditions related to aging and alternate collagen structures such as wrinkles, rhytids and scars.

The objective of this clinical study is to evaluate the safety and performance of fractional RF for the treatment of surgical scars following breast augmentation, abdominoplasty or face lift.

The use of the Venus Viva™ has been determined to present non-significant risk in accordance with 21 CFR 812.3 for the intended use in this study, because the device is not:

- Intended as an implant;
- Purported or represented to be for use supporting or sustaining human life;
- Substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health
- Otherwise presenting a potential for serious risk to the health, safety, or welfare of a subject.

This study will be conducted in compliance with the protocol and according to Good Clinical Practice (GCP) standards.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

The potential risks for adverse events of the treatment procedure include but are not limited to discomfort or significant pain post-treatment, excessive skin redness (erythema) and/or swelling (edema), in-grown hairs, damage to natural skin texture (crust, blister, burn), change of pigmentation (hyper- and hypo-pigmentation) and scarring. Treatment of hair-bearing areas in male patients may result in some damage to the follicles and subsequent loss of hair. Avoid the beard area and other hair-growing zones if the patient does not wish to experience hair growth reduction.

Further information about residual risks associated with the device and with participation in the clinical investigation are reported in the device User Manual.

Residual risks will be mitigated as follows:

- Selection of Investigator with experience in the therapeutic area of the clinical investigation
- Investigator will undergo training prior to patients' enrollment
- For the first procedure of each site, an experienced person with the use of the device, representing the sponsor, will attend.
- Patients will be rigorously screened prior to their enrollment
- Patients will be rigorously followed over the course of the study

2.3.2 KNOWN POTENTIAL BENEFITS

If the subject agrees to participate in this study, he/she will be contributing to the understanding of the device's impact and the biological processes that are occurring regarding surgical scar tissue. This

understanding may lead to optimization of the treatment with this device for these indications. In addition, the subject may benefit from improvement in surgical scar tissue in the treated areas.

3 OBJECTIVES AND PURPOSE

The study is being conducted to evaluate the safety and performance of fractional RF for the treatment of surgical scars following breast augmentation, abdominoplasty or face lift. Total expected duration of the clinical investigation is fifteen months (enrolment period of 3 months, follow-up period of 12 months), while individual subject participation will take 12 months.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a split-body/face evaluator-blind study of the safety and performance of fractional RF for the treatment of surgical scars following breast augmentation, abdominoplasty or face lift.

4.2.1 PRIMARY ENDPOINT

- The primary endpoints were chosen since it clearly links to the overall objectives of the study, that is, treating surgical scar tissue to improve appearance as evaluated by an independent blinded reviewer using the General Aesthetic Improvement Scale (GAIS) and Manchester Scar Scale (MSS) at 3 and 10 months post-treatment.

4.2.2 SECONDARY PERFORMANCE ENDPOINTS

- Improvement in appearance of surgical scars at 1 and 2 months post-treatment as evaluated by independent blinded reviewer using the General Aesthetic Improvement Scale (GAIS) and Manchester Scar Scale (MSS).
- Assessment of surgical scars at 3 and 10 months post-treatment as evaluated by independent blinded reviewer using the Patient and Observer Scar Assessment Scale (POSAS).
- Assessment of surgical scars at 3 and 10 months post-treatment as evaluated by the subject using the Patient and Observer Scar Assessment Scale (POSAS).
- Subjects' assessment of satisfaction (5-point Likert Scale) with the treatment at 3 and 10 months post-treatment.

Safety endpoints:

- Subject's assessment of discomfort and pain after treatment as measured by a 10 cm visual analog scale (VAS).
- Subjects experiencing a treatment-related adverse event (AE) by 10 months post-treatment.

4.2.3 EXPLORATORY ENDPOINTS

None

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 STUDY POPULATION

The study will enroll up to 50 female subjects requesting treatment of surgical scars following breast augmentation or abdominoplasty and up to 25 male and female subjects requesting treatment of surgical scars following face lift surgery.

5.2 PARTICIPANT INCLUSION CRITERIA

1. Healthy, female, subjects 20-60 years of age who are seeking treatment for their breast augmentation or abdominoplasty surgical scars or male and female patients 40-75 years of age who are seeking treatment for their face lift surgical scars.
2. A minimum of four weeks since surgery.
3. Able to read, understand and voluntarily provide written Informed Consent.
4. Able and willing to comply with the treatment/follow-up schedule and requirements.
5. Willing to avoid direct sunlight for the duration of the study.
6. Women of child-bearing age are required to be using a reliable method of birth control at least 3 months prior to study enrollment and for the duration of the study, and have a negative Urine Pregnancy test at baseline.

5.3 PARTICIPANT EXCLUSION CRITERIA

1. Fitzpatrick skin types 5-6.
2. Implantable defibrillators, cardiac pacemakers, and other metal implants
3. Subjects with any implantable metal device in the treatment area
4. Pacemaker or internal defibrillator, or any other active electrical implant anywhere in the body (e.g. cochlear implant).
5. Permanent implant in the treated area, such as metal plates and screws, or an injected chemical substance.
6. Current or history of any kind of cancer, or pre-malignant moles.
7. Severe concurrent conditions, such as cardiac disorders.
8. Pregnancy or intending to become pregnant during the study and nursing.
9. Impaired immune system due to immunosuppressive diseases, such as AIDS and HIV, or use of immunosuppressive medications.
10. History of diseases stimulated by heat, such as recurrent herpes simplex in the treatment area; may be enrolled only following a prophylactic regime.
11. Poorly controlled endocrine disorders, such as diabetes.
12. Any active condition in the treatment area, such as sores, psoriasis, eczema, and rash.
13. History of skin disorders, such as keloids, abnormal wound healing, as well as very dry and fragile skin.
14. History of bleeding coagulopathies, or use of anticoagulants.
15. Use of isotretinoin (Accutane®) within six months prior to treatment.
16. Treating over tattoo or permanent makeup.
17. Excessively tanned skin from sun, tanning beds or tanning creams within the last two weeks.
18. As per the practitioner's discretion, refrain from treating any condition which might make it unsafe for the patient.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Up to 50 female subjects with surgical scars due to breast augmentation or abdominoplasty and 25 male and female subjects with surgical scars due to face lift surgery will be enrolled at the single investigative site. It is anticipated that it will take up to fifteen months to complete the study. A qualified dermatologist or plastic surgeon will be the recruited to participate as an investigator. Subjects will be primarily be recruited primarily from the investigator's practice. Any advertising campaigns and materials will be reviewed and approved by an Ethics Committee or Institutional Review Board (EC or IRB) before implementation. Due to the long duration of the study, subjects will be contacted by the investigative site on a regular basis in order to enhance retention.

5.5 PARTICIPANT WITHDRAWAL OR TERMINATION

5.5.1 REASONS FOR WITHDRAWAL OR TERMINATION

Subjects are free to withdraw from participation in the study without prejudice at any time upon request. In the event that a subject drops out of the study or is withdrawn from the study, the End of Study/Early Discontinuation CRF form should be completed. On the discontinuation page, the Investigator should record the date of the withdrawal and the reason for withdrawal.

Reasonable effort should be made to contact any subject lost to follow up during the course of the study in order to complete assessments and retrieve any outstanding data. The records of subjects who terminate prior to completing the study will be retained and the reason for termination will be documented.

The investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.5.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Every effort will be made to continue follow-up of withdrawn or terminated subjects or subjects who discontinue the intervention but remain in the study for follow-up, especially for safety and performance study endpoints. Every effort will be made to conduct an exit visit (final study visit, see section 7.3.5) to withdrawn patients, and to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs) and device deficiencies.

5.6 PREMATURE TERMINATION OR SUSPENSION OF STUDY

The sponsor may suspend or prematurely terminate this study at the investigation site for significant and documented reasons.

The principal investigator, EC/IRB, or regulatory authority may suspend or prematurely terminate participation in the study at the investigation site for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the study, or when so instructed by the EC/IRB or regulatory authorities, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the study if an unacceptable risk is confirmed.

The sponsor shall consider terminating or suspending the participation of the investigation site or investigator in the study if monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The principal investigator and sponsor shall keep each other informed of any communication received from either the EC/IRB or the regulatory authority.

If, for any reason, the sponsor suspends or prematurely terminates the study at the investigation site, the sponsor shall inform the responsible regulatory authority as appropriate and ensure that the EC/IRB is notified, either by the principal investigator or by the sponsor. If the suspension or premature termination was in the interest of safety, the sponsor shall inform all other principal investigators.

If suspension or premature termination occurs,

a) the sponsor shall remain responsible for providing resources to fulfil the obligations from the clinical investigative plan and existing agreements for following up the subjects enrolled in the study, and
b) the principal investigator or authorized designee shall promptly inform the enrolled subjects at the investigation site, if appropriate

In case of early termination, final study activities according to the protocol, including the follow up visits and procedures to assess the safety and efficacy of the device will be conducted, regardless of the sponsor's interest in the study. Follow-up activities will be conducted so that device deficiencies can be identified and appropriate safety measures can be implemented.

At the completion or termination of the study, the Investigator will return all remaining clinical supplies to Sponsor along with a copy of the device supply and inventory records.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants (examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events – refer to section 8.5 STUDY HALTING RULES.
- Demonstration of performance that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, EC / IRB and/or regulatory authorities.

6 INVESTIGATIONAL DEVICE

6.1 INVESTIGATIONAL DEVICE AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

If the investigative site does not own a Venus Viva™, a device will be provided by the sponsor. An activation code will be required to activate the device (not applicable if the site owns the device). This code will not be provided to the investigative site until all regulatory and EC or IRB approvals are in place and the site has received training for both the device and the study (if applicable).

6.1.2 DEVICE SPECIFIC CONSIDERATIONS

- Device model(s) - Venus Viva™
- Device settings and programming – 240-280 volts, 15-20 ms pulse duration
- Duration of exposure and frequency – single pass, monthly for 3 months

The Venus Viva™ is a non-invasive medical aesthetic device, intended for use in dermatologic and general surgical procedures, requiring ablation and resurfacing of the skin, using the Viva applicator.

The system consists of a handheld applicator with disposable tips. The tip consists of 160 pins, 8x20 mm in size, that that delivers the Multi Polar Radiofrequency (RF) to the skin. Further details about the Venus Viva™ can be found in the device User Manual.

6.2 INVESTIGATIONAL DEVICE ACCOUNTABILITY PROCEDURES

If the device is supplied by the sponsor, traceability shall be achieved during and after the clinical investigation by assignment of serial numbers to device and applicators. Disposal tips will be provided by the sponsor.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

The following procedures and evaluations will be done as part of the study:

Demographics
Medical /surgical history (obtained by interview and/or medical records)
Physical examination
Assessment of eligibility
Vital signs [weight, temperature, respiratory rate, heart rate and blood pressure]
Photographs
Blinded assessment
Administration of questionnaires and scales for blinded reviewer and patient-reported outcomes
Adverse event recording
Concomitant medications

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Urine pregnancy test to be performed within 24 hours of study intervention with results available prior to administration of treatment.

7.2.2 OTHER ASSAYS OR PROCEDURES

None.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Visit 1, Day -1 (Skin Types I-III) or Day -5 (Skin Type IV)

Point of enrollment
Point of enrollment is defined as the point where the patient, after having signed the informed consent form, is confirmed to fulfill all criteria for eligibility.

Following the point of enrollment, each subject will receive study treatment and study questionnaires.

Screening Visit
If the subject meets the preliminary study criteria, the study doctor, and/or his/her designee, will obtain an informed consent from the subject prior to any study procedure, clearly indicating his/her understanding of the requirements and possible risks associated with study participation and other applicable treatment options.

During the first visit, the study investigator, and/or his/her designee, will screen the subject for eligibility to participate in the clinical study using the inclusion/exclusion criteria. A urine sample for the pregnancy test will be obtained (in patients of child-bearing potential). During screening, the study doctor will review the subject's medical/surgical history and examine the subject's targeted area to ensure that it meets the study criteria. The subject will complete screening and the treatment will be scheduled.

During the first visit, the investigator will ask women of child-bearing potential for the date of their last period, if not applicable the investigator shall inquire about the form of contraceptive they use to confirm they meet the inclusion criteria.

<u>Test Spots</u>

A small test spot will be performed in a non-conspicuous area of the treatment site, prior to the first complete session. Test spots are performed to establish the following requirements:

- Confirm the patient's suitability for treatment: For skin types I-III wait 24-48 hours before assessing the skin response and 5-7 days for skin type IV.

- Establish and confirm treatment parameters: If the desired endpoint of erythema and edema – in a tip-shaped pattern – has not been achieved within 10-15 minutes, increase the RF indicator level and perform another test spot. If the response is excessive, decrease the parameters and perform another test spot.

Test spot results will indicate if the patient can tolerate the treatment without developing adverse effects. According to patient tolerance to the test spot, you may determine treatment parameters and whether anesthesia is needed. In addition, it is advisable to perform a test spot whenever changing parameters.

Treatment

Shave any hair in the treatment area. Ensure that the skin is completely dry during the entire treatment. If the skin moistens during treatment (i.e. perspiration, etc.) re-wipe the skin with an alcohol pad and ensure that the skin is completely dry before continuing the treatment.

Set the treatment parameters (Voltage 240-280, 15-20 ms pulse duration). Set the desired energy level according to the skin type, severity of the treated condition, treatment area, bone proximity, etc. Set conservative parameters from a test spot for the first treatment, and then gradually increase during treatment or in subsequent treatments according to the desired impact and test spot results.

Select the desired tip pattern to Full or Half if the tip extends beyond the boundary of the scar tissue in order to restrict treatment to the scar tissue. Treatment consists of a single pass over the treatment area, however, the test spot will consist of a single pulse. Adjust the treatment parameters according to the test spot response. To perform the treatment, place the tip on the target zone, perpendicular to the skin surface and with full contact with the skin. Emit a pulse by pressing the applicator's trigger; this will create a tip-shaped pattern on the patient's skin that will appear 1-2 minutes later. Move the applicator to an adjacent spot on the skin overlapping by 10% and emit another pulse (not applicable to the test spot). There should be no untreated gaps between the pulses.

Examine the treated area. The immediate responses, indicative of the desired effect, are erythema and edema in the immediate area of the tip-shaped pattern and possibly also around it. The edema usually appears 1-2 minutes after pulsing and reaches its peak (of up to moderate edema) within 30 minutes. It should be noted that erythema is not easily noticeable – if at all – in darker skin types. Therefore, the edema will be more prominent in these patients. After completing a full pass on the entire treatment area, if untreated patches of skin are apparent, re-treat these patches as per the following procedure:

i. Wipe the untreated patch of skin with a dry gauze pad.
ii. Treat the untreated patches of skin as normally.

Fine-tuning of the parameters should be done before proceeding to treatment of the entire sub-area with the selected parameters. Treatment consists of a single pass over the designated area. The applicator tip should be placed on the skin, a pulse emitted, then lifted and moved to an adjacent spot of the skin. The emitted pulses should create tip-shaped patterns. Leave, no untreated gaps between the pattern marks, while also being careful not to overlap the treated zones. The parameters can be modified during subsequent visits, as per the practitioner's discretion.

Post-Treatment Care

Post-treatment cooling is not necessary. In the event of post-treatment discomfort, it is recommended to cool the treated area immediately with air cooling. Cold (not frozen) packs may also be used.

Blistered or ulcerated skin can be treated with a prescribed cream. Tiny scabs of less than 1 mm diameter will usually form 24-72 hours post-treatment and may remain for several days. The scabs should not be touched or scratched even if they itch, and should be allowed to shed off naturally. Blistered or ulcerated skin can be treated with a prescribed antibiotic ointment or burn treatment cream as per physician's discretion. During the first two days following treatment, care should be taken to prevent trauma to the treated site. Hot baths, massage, etc. should be avoided. The skin should be kept clean to avoid contamination or infection. Any mechanical or thermal damage to the area must be avoided. Moisturizer may be applied only 24 hours after each treatment, and then should be applied regularly throughout the course of the treatment. Make-up may be applied only 24 hours after each treatment if desired, unless an unwanted reaction occurs in the area. Generally, 24 hours after treatment, patients may use regular soaps, but not scrub soaps or exfoliants. The patient should use a high-factor sunscreen (at least 30 SPF) and protect the treated area from sunlight for at least one month after the treatment. Tanning of any sort (sun exposure, tanning beds, and artificial sunless tanning lotions) is not allowed in the treated areas during the entire course of the treatment. Tanning after treatment may cause hyperpigmentation.

The patient should return 1-2 days for skin types I-III or 5-7 days for skin type IV after the test spot treatment to ensure that no adverse events have occurred.

7.3.2 ENROLLMENT/BASELINE

Enrollment/Baseline Visit (Visit 2, Day 0)

Once a subject has been confirmed that they continue to meet inclusion/exclusion criteria, they will receive a unique identifying number that will be composed of a two-digit site number and a two-digit subject number in sequence. This unique identifier will be used throughout the entire study and will be entered in the subject's case report form (CRF). The investigator will confirm that the subject still meets the inclusion/exclusion criteria. Vital signs and demographics will be collected and a physical exam will be performed. The subject will complete the POSAS.

Photography

Photographs will be taken prior to first treatment and throughout the study according to specified time points detailed in the Schedule of Events Table (section 7.3.7), utilizing standard scientific equipment. Two sets of photographs will be required, one set for the treated side of the body/face and a second set for the untreated side of the body/face.

The photos should be taken in a private room or area of the clinic under controlled conditions, including the distance, angle, background and lighting in order to achieve high-quality sets of photographs. Direct illumination will not be used. The subject should be placed in the same position each time. As each photograph is taken, it should be viewed to ensure that it is in focus and is similar to its baseline counterpart in all technical aspects, including lighting, distance and angle.

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.

Treatment

Subjects will receive treatment as described in section 7.3.1. Only one side of the body/face will be treated. The same side will be treated for the duration of the study. Only half of a scar will be treated

and remaining half will serve as the control. Following treatment, the investigator will examine the treated area and report immediate and short term response. Subjects will complete the 10 cm discomfort/pain VAS immediately after treatment. A new disposal tip will be used for each patient treatment.

Treatment procedure should include positioning of the patient in a manner that enables comfortable access to the treated anatomical site.

Assessment

The investigator will examine the treated areas and report immediate and short term response (30 minutes post-treatment) (pain during treatment, hemorrhage, burn, erythema, edema, purpura) using a 5-point scale: 1=none; 2=trace; 3=moderate; 4=marked; 5=severe.

The assessment of discomfort/pain based on the subject's completion of the 10 cm VAS should also be documented immediately after each treatment.

The normal response to these treatments is transient erythema and edema. If any other side effects occur, as indicated in the protocol, they must be recorded.

Subjects will be discharged from the clinic and will be instructed to return in 2-3 days in order to be examined for adverse events.

7.3.3 FOLLOW-UP

Visit 3, Day 0+2 days

Subjects will be examined 2-3 days after treatment for the occurrence of adverse events. Vital signs and any changes in concomitant medication will be recorded. Subjects will be discharged from the clinic and will be instructed to return for the Month 1 assessment and treatment.

Visit 4, Month 1 (± 7 days)

Subjects will return to the clinic one month after the first treatment. Adverse events, vital signs and any changes to concomitant medications will be recorded.

Subjects will receive treatment as described in section 7.3.1. Following treatment, the investigator will examine the treated area and report immediate and short term response. Subjects will complete the 10 cm discomfort/pain VAS immediately after treatment.

Subjects will be discharged from the clinic and will be instructed to return in 2-3 days in order to be examined for adverse events.

Visit 5, Month 1+2 days

Subjects will be examined 2-3 days after treatment for the occurrence of adverse events. Vital signs and any changes in concomitant medication will be recorded. Subjects will be discharged from the clinic and will be instructed to return for the Month 2 assessment and treatment.

Visit 6, Month 2 (± 7 days)

Subjects will return to the clinic one month after the second treatment. Adverse events, vital signs and any changes to concomitant medications will be recorded.

Subjects will receive treatment as described in section 7.3.1. Following treatment, the investigator will examine the treated area and report immediate and short term response. Subjects will complete the 10 cm discomfort/pain VAS immediately after treatment.

Subjects will be discharged from the clinic and will be instructed to return in 2-3 days in order to be examined for adverse events.

Visit 7, Month 2+2 days

Subjects will be examined 2-3 days after treatment for the occurrence of adverse events. Vital signs and any changes in concomitant medication will be recorded. Subjects will be discharged from the clinic and will be instructed to return for the Month 3 assessment.

Visit 8, Month 3 (± 7 days)

Subjects will return to the clinic one month after the third treatment. Adverse events, vital signs and any changes to concomitant medications will be recorded.

Photographs of the treated area will be taken as described in section 7.3.1. Subjects will be discharged from the clinic and will be instructed to return for the Month 4 assessment.

Visit 9, Month 4 (± 7 days)

Subjects will return to the clinic one month after the last assessment. Adverse events, vital signs and any changes to concomitant medications will be recorded.

Photographs of the treated area will be taken as described in section 7.3.1. Subjects will be discharged from the clinic and will be instructed to return for the Month 5 assessment.

Visit 10, Month 5 (± 7 days)

Subjects will return to the clinic one month after the last assessment. Adverse events, vital signs and any changes to concomitant medications will be recorded. Subjects will complete a 5-point Likert satisfaction questionnaire and the POSAS.

Photographs of the treated area will be taken as described in section 7.3.1. Subjects will be discharged from the clinic and will be instructed to return for the final Month 12 assessment.

7.3.4 FINAL STUDY VISIT

Visit 11, Month 12 (± 14 days)

Subjects will return to the clinic seven months after the last assessment. Adverse events, vital signs and any changes to concomitant medications will be recorded. Subjects will complete a 5-point Likert satisfaction questionnaire and the POSAS.

Photographs of the treated area will be taken as described in section 7.3.1. The photographs will be sent to the blinded independent reviewer for assessment (GAIS, MSS and POSAS). The termination form will be completed and subjects will be discharged from the clinic and terminated from the study. The PI will

record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation.

After the study is completed, subjects will be offered treatment on their untreated side (body/face).

7.3.5 EARLY TERMINATION VISIT

Subjects who terminate the study early for whatever reason, will be asked to return to the clinic, if they are willing, to complete the final visit (Visit 11). Adverse events and the reason for early termination will be recorded.

7.3.6 UNSCHEDULED VISIT

If an unscheduled visit occurs, the reason for the unscheduled visit will be documented. If the unscheduled visit is the result of an adverse event, the event will be recorded on the adverse event CRF.

7.3.7 SCHEDULE OF EVENTS TABLE

Procedures	Screening/Baseline (Visit 1, Day -1	Enrollment/Treatment (Visit 2, Day 0)	Follow-up (Visit 3, Day 0+2 days	Treatment & Follow-up (Visit 4, Month 1 (±7 days)	Follow-up (Visit 5, Month 1+2 days	Treatment & Follow-up (Visit 6, Month 2 (±7 days)	Follow-up (Visit 7, Month 2+2 days	Follow-up (Visit 8, Month 3 (±7 days)	Follow-up (Visit 9, Month 4 (±7 days)	Follow-up (Visit 10, Month 5 (±7 days)	Final Study Visit (Visit 11, Month 12 (±14 days)
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demographics	X										
Medical history	X										
Physical exam	X										
Vital signs		X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[a]	X										
Test Spot	X										
Photographs		X						X	X	X	X
Administer Treatment		X		X		X					
Discomfort/Pain VAS		X		X		X					
PI immediate & short-term response		X		X		X					
Blinded reviewer GAIS		X						X	X	X	X
Blinded reviewer MSS		X						X	X	X	X
Blinded reviewer POSAS		X								X	X
Subject POSAS		X								X	X
Subject satisfaction questionnaire										X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Adverse event evaluation		X	X	X	X	X	X	X	X	X	X

Procedures	Screening/Baseline (Visit 1, Day -1	Enrollment/Treatment (Visit 2, Day 0)	Follow-up (Visit 3, Day 0+2 days	Treatment & Follow-up (Visit 4, Month 1 (±7 days)	Follow-up (Visit 5, Month 1+2 days	Treatment & Follow-up (Visit 6, Month 2 (±7 days)	Follow-up (Visit 7, Month 2+2 days	Follow-up (Visit 8, Month 3 (±7 days)	Follow-up (Visit 9, Month 4 (±7 days)	Follow-up (Visit 10, Month 5 (±7 days)	Final Study Visit (Visit 11, Month 12 (±14 days)
[a] For women of child-bearing potential.											

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

This is a non-life-threatening aesthetic treatment with a low potential for serious adverse events.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Other medications to be reported in the CRF are concomitant over-the-counter medications, non-prescription medications and herbal/naturopathic preparations.

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Use of immunosuppressive medications, anticoagulants, isotretinoin and non-steroidal anti-inflammatory drugs is prohibited.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

None

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

In the event that the subject experiences pain, the principal investigator may prescribe any analgesic deemed appropriate to the level of pain. If a subject experiences any first, second or third degree burn or pain beyond narcotics, then the following procedure will be implemented:

- Immediate triage and treatment of the patient shall be determined by the treating physician and based upon severity and type of burn identified.
- The event will be reported to the sponsor study Director within 24 hours of occurrence. If the event meets the criteria of a SAE, then it must be reported on the SAE form.
- An anonymized copy of the patient chart and treatment parameters are to be forwarded to the sponsor study Director within 24 hours.

The sponsor study Director will be responsible for issuing a written report to the company and the EC or IRB Chairman no later than 7 days from the event

Long term follow up and care shall continue at the discretion of the treating physician.

All patients experiencing a complication of the device will be followed a minimum of 2 years following the initial injury. Longer care and observation will be at the discretion of the treating physician.

All minor complications such as appearance or altered sensation, except for pain, can be reported within 30 days of patient complaint. Both chart and treatment parameters are to be provided to the study Director and shared with the company and EC or IRB chairman.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

In addition to spontaneous reports of adverse events, subjects will complete a 10 cm discomfort/pain VAS and the principal investigator will examine the treated area and report immediate and short term response.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE) AND ADVERSE DEVICE EFFECT (ADE)

Adverse event means any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or the comparator. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices (ISO 14155:2011).

Adverse device effect means any adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device (ISO 14155:2011).

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

NOTE: The term serious is not synonymous with severity, which may be used to describe the intensity of an event experienced by the subject). An AE that does not meet any of the below criteria will be classified as non-serious.

A serious AE is any adverse event that:

- led to death,
- led to serious deterioration in the health of the subject, that either resulted in
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or

- in-patient or prolonged hospitalization, or
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- led to fetal distress, fetal death or a congenital abnormality or birth defect

Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event (ISO 14155:2011).

8.1.3 DEFINITION OF SERIOUS ADVERSE DEVICE EFFECT (SADE)

This definition includes any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. Unanticipated serious adverse device effect (USADE) is any serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report (ISO14155:2011).

8.1.4 DEFINITION OF DEVICE DEFICIENCY

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling (ISO 14155:2011).

Any Investigational Medical Device Deficiency that might have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is subject to the same reporting requirement of SAEs (MEDDEV 2.7/3 revision 3).

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 RELATIONSHIP TO INVESTIGATIONAL DEVICE

The clinician's assessment of an AE's relationship to the investigational device is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to investigational device assessed. In a clinical trial, the study product must always be suspect. To help assessment, the following guidelines are used.

- **Not Related** – relation to the device or procedure can be excluded when:
  - The event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
  - the event has no temporal relationship with the use of the investigational device or the procedures;
  - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible
  - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
  - the event involves a body-site or an organ not expected to be affected by the device or procedure;
  - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors).
- **Unlikely**: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- **Possible**: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- **Probable**: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
- **Causal relationship**: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
  - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
  - the event has a temporal relationship with investigational device use/application or procedures;
  - the event involves a body-site or organ that the investigational device or procedures are applied to or the investigational device or procedures have an effect on;
  - the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
  - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
  - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
  - harm to the subject is due to error in use;

8.2.3 EXPECTEDNESS

Expected (anticipated) adverse reactions are AEs that are common and known to occur for the investigational device being studied. Expected adverse events in this study include discomfort or significant pain post-treatment, excessive skin redness (erythema) and/or swelling (edema), in-grown hairs, damage to natural skin texture (crust, blister, burn), change of pigmentation (hyper- and hypo-pigmentation), scarring. Treatment of hair-bearing areas in males may result in some damage to the follicles and subsequent loss of hair.

An AE or suspected adverse reaction is considered "unexpected" (unanticipated) if it is not known to occur for the investigational device being studied and at the specificity or severity that has been observed (AE not described into the Clinical protocol or User Manual).

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to investigational device and study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all adverse events with start dates occurring any time after informed consent is obtained. At each study visit, the investigator will inquire study subjects about the occurrence of AE/SAEs since the last visit. All adverse events need to be followed until resolution or until study end, whichever occurs first.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

All AEs will be recorded on the appropriate CRF and will include information about the start and stop dates, severity and relatedness. There should be an attempt to report a "diagnosis" rather than the individual signs, symptoms and abnormal laboratory values associated with the diagnosis. However, a diagnosis should be reported only if, in the Investigator's judgment, it is relatively certain (i.e., definite or possible). Otherwise individual signs, symptoms and abnormal laboratory values should be reported as distinct adverse events.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

All serious AE, whether or not deemed procedure or device related, must be reported to the sponsor's clinical research department immediately or within 24 hours by telephone or by email (see contact details below).

[redacted]

A written report prepared by the Principal Investigator (or designate) must follow within seven working days to the clinical monitor and should include a full description of the event and sequence.

The study investigator shall complete a Serious Adverse Event / Serious Adverse Device Effect Form and submit to the study sponsor as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

In accordance with the requirements of Directive 93/42/EEC, and with MEDDEV 2.7/3, the following events are considered reportable events:

1. any SAE (whether or not study procedure or device related),
2. any Investigational Medical Device Deficiency that might have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate,
3. new findings/updates in relation to already reported events.

The sponsor will report the above-mentioned events to the Competent Authorities of all countries where the study is being conducted, within the following timelines:

- Any SAE which indicates an imminent risk of death, serious injury, or serious illness AND that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.
- Any other reportable event or a new finding / update to it: immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

Reporting of the events listed above (under bullets 1-3) to the ECs of the participating sites and to the other investigators will be performed according to country and/or site-specific requirements.

8.4.4 REPORTING OF PREGNANCY

If a subject becomes pregnant during the course of the study, the subject will be terminated from the study. The pregnancy will be immediately reported to the sponsor on the Notification of Subject or Partner Pregnancy form using the same reporting timelines as a SAE. The investigator will follow the pregnancy until completion and will report the outcome of the pregnancy to the sponsor on the Notification of Subject or Partner Pregnancy Outcome form within 10 business days.

8.5 STUDY HALTING RULES

The study may be halted at any time by the sponsor, the EC / IRB, Competent Authorities due to safety concerns. Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events. If the study is halted, the sponsor will immediately notify all investigational sites, the EC / IRB(s), the Competent Authorities of all countries where the study is being conducted.

8.6 SAFETY OVERSIGHT

Independent oversight is an important component to ensure human subjects' protection. Safety oversight will be under the direction of the sponsor and a medical monitor.

8.7 TRAINING REQUIREMENTS

Prior to patients' enrollment, the Sponsor will provide training relevant and pertinent to the involvement of personnel conducting study activities. Training for investigators and staff will include study-specific protocol and CRF completion training by the sponsor or designate and on-site training on the use of the investigational device by the sponsor. Evidence of training will be documented during the site initiation visit and by the issuance of a device training certificate.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the sponsor or designate.
- On-site monitoring will occur within 4 weeks of first enrolled subject and will occur at a frequency described in the Monitoring Plan.
- Variables to be monitored will be described in the Monitoring Plan.
- The Study Director or designate will be provided copies of monitoring reports within 15 business days of visit.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

The Statistical and Analytical Plan (SAP) may be revised during the study to accommodate Clinical Trial Protocol Amendments and to make changes to adapt to unexpected issues in study execution and data that affect planned analyses. If revised, a formal Statistical and Analytical Plans (SAP) will be completed and issued prior to database lock and unblinding of the study data if applicable.

10.2 STATISTICAL HYPOTHESES

The null and alternative hypotheses for the study's primary, key secondary and safety endpoints are;

- Primary Performance Endpoint:
  - **Null Hypothesis** ***(H_o: $\mu_d = \mu_{post} - \mu_{pre} = 0$)*** – There is no improvement of surgical scars at 3 months post-treatment review compared to baseline.
    Alternative Hypothesis ***(H_a: $\mu_d = \mu_{post} - \mu_{pre} \neq 0$)*** – There is improvement of surgical scars at 3 months post-treatment review compared to baseline. The improvement of surgical scars will be defined by General Aesthetic Improvement Scale (GAIS) and Manchester Scar Scale (MSS) scores evaluated by independent blinded reviewer. Expected mean improvement difference is not less than one (1) GAIS and MSS score higher than baseline.

  - **Null Hypothesis** ***(H_o: $\mu_d = \mu_{post} - \mu_{pre} = 0$)*** – There is no improvement of surgical scars at 10 months post-treatment review compared to baseline.

Alternative Hypothesis ***(H_a: $\mu_d = \mu_{post} - \mu_{pre} \neq 0$)*** – There is improvement of surgical scars at 10 months post-treatment review compared to baseline. The improvement of surgical scars will be defined using General Aesthetic Improvement Scale (GAIS) and Manchester Scar Scale (MSS) scores evaluated by independent blinded reviewer. Expected mean improvement difference is not less than one (1) GAIS and MSS score higher than baseline.

- Secondary Performance Endpoint(s):
  - **Null Hypothesis** ***(H_o: $\mu_d = \mu_{post} - \mu_{pre} = 0$)*** – There is no improvement of surgical scars at 1 and 2 months post-treatment review compared to baseline.
    Alternative Hypothesis ***(H_a: $\mu_d = \mu_{post} - \mu_{pre} \neq 0$)*** – There is improvement of surgical scars at 1 and 2 months post-treatment review compared to baseline. The improvement of surgical scars will be defined using General Aesthetic Improvement Scale (GAIS) and Manchester Scar Scale scores evaluated by independent blinded reviewer.

  - **Null Hypothesis** ***(H_o: $\mu_d = \mu_{post} - \mu_{pre} = 0$)*** – There is no improvement of surgical scars at 3 and 10 months post-treatment review compared to baseline.
    Alternative Hypothesis ***(H_a: $\mu_d = \mu_{post} - \mu_{pre} \neq 0$)*** – There is improvement of surgical scars at 3 and 10 months post-treatment review compared to baseline. The improvement of surgical scars will be defined using Patient and Observer Scar Assessment Scale (POSAS) scores evaluated by independent blinded reviewer.

  - **Null Hypothesis** ***(H_o: $\mu_d = \mu_{post} - \mu_{pre} = 0$)*** – There is no improvement of surgical scars at 3 and 10 months post-treatment review compared to baseline.
    Alternative Hypothesis ***(H_a: $\mu_d = \mu_{post} - \mu_{pre} \neq 0$)*** – There is improvement of surgical scars at 3 and 10 months post-treatment review compared to baseline. The improvement of surgical scars will be defined using Patient and Observer Scar Assessment Scale (POSAS) scores evaluated by the subject.

  - **Null Hypothesis** ***(H_o: $\mu_d = \mu_{post} - \mu_{pre} = 0$)*** – There is no satisfaction with treatment as documented on a 5-point Likert scale at 3 and 10 months compared to baseline.
    Alternative Hypothesis ***(H_a: $\mu_d = \mu_{post} - \mu_{pre} \neq 0$)*** – There is satisfaction with treatment as documented on a 5-point Likert scale at 3 and 10 months compared to baseline. The satisfaction with treatment will be defined by 5-point Likert scale at 3 and 10 months compared to baseline as assessed by the subjects.

- Safety Endpoint:
  - **Null Hypothesis** ***(H_o: $\mu_d = \mu_{post} - \mu_{pre} = 0$)*** – There is no difference in subjects' 10 cm discomfort/pain VAS score experienced after at Visit 6 treatment and that of baseline treatment (Visit 2).
    Alternative Hypothesis ***(H_a: $\mu_d = \mu_{post} - \mu_{pre} \neq 0$)*** – There is a difference in subjects' 10 cm discomfort/pain VAS score experienced after at Visit 6 treatment and that of baseline treatment (Visit 2). Expected mean difference is maximum VAS score $\leq$ 1.

10.3 ANALYSIS DATASETS

Modified Intention-to-Treat Analysis Dataset will be used; performance and safety analyses will be carried out on all subjects who received at least one treatment of Venus Viva™ system and for whom at least one valid post-baseline performance and safety evaluation were obtained.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

[redacted]

All summary tables for quantitative parameters will display mean, standard deviation, median, range (minimum and maximum), percentages as well as number of missing data (if relevant). All summary tables for qualitative parameters will display counts, percentages and number of missing data if relevant. Baseline data are defined as the last measurement performed before the first treatment on Visit 2.

All statistical tests will be two-sided. The level of statistical significance for effectiveness analyses is 5% ($\alpha = 0.05$) for all tests of differences. Where appropriate, Paired t-test and/or Wilcoxon Signed-Ranks Test for Matched Pairs will be used to compare the evaluations at the baseline and post treatment sessions. This test will enable us to accept or reject the null hypotheses. Rejection of null hypotheses will establish that:

- The two-sided 95% confidence interval for the difference between the means excludes zero.
- The two means are statistically significantly different at the 5% level ($P < 0.05$) two-sided.

Upon rejection of null hypotheses, further statistical test tools such as Confidence Interval and/or t-test will be used to determine the performance of Venus Viva™ fractional RF System in the treatment of surgical scars following breast augmentation, abdominoplasty or face lift.

In order to accommodate imbalances of some baseline General Aesthetic Improvement Scale (GAIS) and Manchester Scar Scale (MSS) scores, covariate adjustment analysis may be performed in SAP to estimate adjusted treatment effects for the primary endpoint analysis.

The assumption for the statistical test is that the paired differences of baseline and post treatment data are normally distributed.

10.4.2 ANALYSIS OF THE PRIMARY PERFORMANCE ENDPOINT(S)

The following will be considered for the analysis primary performance endpoint:

Summary table for differences of baseline, 3-month and 10-month post treatment General Aesthetic Improvement Scale (GAIS) and Manchester Scar Scale (MSS) scores will be displayed as mean difference, standard deviation and standard error. The General Aesthetic Improvement Scale (GAIS) scores is a 5-point scale improvement assessment chart while Manchester Scar Scale (MSS) is two scales whose scores are combined - an overall VAS and seven scar parameters.

Bar, pie charts or graphs indicating scores will also be used to analyse performance, where applicable.

All statistical tests will be two-sided. The level of statistical significance for effectiveness analyses is 5% (α = 0.05) for all tests of differences. Where appropriate, Paired t-test and/or Wilcoxon Signed-Ranks Test for Matched Pairs will be used to compare the evaluations of General Aesthetic Improvement Scale (GAIS) scores and Manchester Scar Scale (MSS) scores at 3 and 10 months against baseline. Analysis of Covariance (ANCOVA) may also be used where appropriate.

The Paired t-test and/or Wilcoxon Signed-Ranks Test for Matched Pairs will enable us to accept or reject the null hypotheses. Rejection of null hypotheses will establish that:

- The two-sided 95% confidence interval for the difference between the means excludes zero.
- The two means are statistically significantly different at the 5% level ($P < 0.05$) two-sided.

Upon rejection of null hypotheses, further statistical test tools such as Confidence Interval and/or t-test will be used to test expected primary performance endpoint; that is alternative hypothesis that $H_a \geq 1$. This will be used to determine if the study meets the primary performance endpoint.

General Aesthetic Improvement Scale (GAIS) scores and Manchester Scar Scale (MSS) scores of all subjects who received at least one treatment of Venus Viva™ system for the treatment of surgical scars following breast augmentation, abdominoplasty or face lift and for whom at least one valid post-baseline GAIS and MSS assessment were obtained will be analysed for the primary endpoint. Multiple imputation method or modelling of available data may be used for missing data as appropriate.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For the analysis of GAIS, MSS, POSAS and 5-point Likert scale secondary performance endpoints, the following analysis will be considered:

- Summary tables for differences of 1 and 2 month post treatment GAIS and MSS scores compared to baseline as evaluated by independent blinded reviewer will be displayed as mean difference, standard deviation and standard error. The point level for each of these ordinal scale assessment tools will be put into consideration where applicable.

  Summary tables for differences of 3 and 10 month post treatment POSAS score compared to baseline as evaluated by independent blinded reviewer and the subjects will be displayed as mean difference, standard deviation and standard error. The point level for each of these ordinal scale assessment tools will be put into consideration where applicable.

  Similarly, summary tables of 5-point Likert scale satisfaction scores assessed by the subjects at 3 and 10 month post treatment visits as well as differences between satisfaction scores at 10 months compared to 3-month post treatment visits will be displayed as mean, mean difference, standard deviation and standard error. The point level for each of these ordinal scale assessment tools will be put into consideration where applicable.

- Where applicable, bar charts, pie chart, graphs or any other descriptive statistical displays indicating scores, percentages or proportions of subjects' GAIS, MSS, POSAS and 5-point Likert scale improvement and satisfaction scores will be used to analyse performance.

- All statistical tests that will be two-sided. The level of statistical significance for effectiveness analyses is 5% (α = 0.05) for all tests of differences. Where appropriate, Paired t-test and/or Wilcoxon Signed-Ranks Test for Matched Pairs will be used to compare the evaluation of score differences of GAIS, MSS, POSAS and 5-point Likert scale post treatment assessment. Analysis of Covariance (ANCOVA) may also be used where appropriate.

GAIS, MSS, POSAS and 5-point Likert scale scores of all subjects who received at least one treatment of Venus Viva™ system for the treatment of surgical scars following breast augmentation, abdominoplasty or face lift and for whom at least one valid post-baseline assessment were obtained will be analysed for these secondary endpoints. Multiple imputation method or modelling of available data may be used for missing data as appropriate.

10.4.4 SAFETY ANALYSES

The safety analysis will be done by analyzing spontaneous reports of adverse events (AE), subjects' completed 10 cm discomfort/pain VAS and a response questionnaire as well as analysis of immediate and short term response reports by the principal investigator from his/her observation/examination of the treated area. Appropriate Medical Dictionary for Regulatory Activities (MedDRA) code will be used to describe all spontaneously reported or other study related adverse events.

Summaries of spontaneously reported or other study related adverse events will be presented as:

- Number (%) of subjects with any AE,
- Number (%) of subjects with any serious adverse events (SAE),
- Number (%) of subjects permanently withdrawn from treatment due to AE

Summaries of analysis of immediate and short term response reports by the principal investigator examination will be displayed on a bar or pie chart as;

- the overall frequency of subjects with each event (pain during treatment, hemorrhage, burn, erythema, edema, purpura)
- Frequency of subjects with specific severity/intensity for each event using a 5 points scale: 1=none; 2=trace; 3=moderate; 4=marked; 5=severe
- The overall percentage or proportion of subject observed with marked or severe intensity of any event will be calculated and compared to those with none, trace or moderate severity/intensity with the aid of a bar or pie chart.

The following will be considered for the analysis of 10 cm discomfort/pain VAS scores safety data:

Summary table for differences of baseline post-treatment (Visit 2) and Visit 6 post-treatment 10 cm discomfort/pain VAS scores will be displayed as mean difference, standard deviation and standard error. The 10 cm discomfort/pain VAS is a 11-level (0 to 10) ordinal scale tool for assessing pain.

Bar, pie charts or graphs indicating scores, percentages or proportions of subjects with Visit 6 and baseline (Visit 2) post-treatments VAS scores difference that is < 1 and >1 will be used to analyse subjects' tolerability of this treatment.

All statistical tests will be two-sided. The level of statistical significance for effectiveness analyses is 5% (α = 0.05) for all tests of differences. Where appropriate, Paired t-test and/or Wilcoxon Signed-Ranks Test

for Matched Pairs will be used to compare the difference between Visit 2 and Visit 6 post treatment VAS scores.

The Paired t-test and/or Wilcoxon Signed-Ranks Test for Matched Pairs will enable us to accept or reject the null hypotheses. Rejection of null hypotheses will establish that:

- The two-sided 95% confidence interval for the difference between the means excludes zero.
- The two means are statistically significantly different at the 5% level ($P < 0.05$) two-sided.

Upon rejection of null hypotheses, further statistical test tools such as Confidence Interval and/or t-test will be used to test expected safety endpoint; that is alternative hypothesis, $H_a \leq 1$.

10.4.5 ADHERENCE AND RETENTION ANALYSES

Adherence to the protocol will be assessed by calculating the number (%) subjects' data for each endpoint assessment that is not provided in subjects Case Report Forms. This will be further analyzed as per frequency of each endpoint data that is not available due to loss to follow-up, discontinuation of the intervention or any other reason.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Subjects baseline scores of all endpoints (GAIS, MSS and POSAS) will be compared using descriptive statistics such as mean score, standard deviation, standard error, range and graphical presentations.

10.4.7 PLANNED INTERIM ANALYSES

Not applicable. There will be no interim analysis during this study.

10.4.7.1 SAFETY REVIEW

There will be no interim analysis during this study. However, this study may be suspended or prematurely terminated if there is sufficient reasonable cause as per section 5.5 and 8.5.

10.4.7.2 PERFORMANCE REVIEW

There will be no interim analysis during this study. However, this study may be suspended or prematurely terminated if there is sufficient reasonable cause as per section 5.5 and 8.5.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

Not applicable. Primary or secondary endpoints will not be analyzed based on age, sex, race/ethnicity or other demographic characteristic(s).

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

Not applicable.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

Individual participant data will be listed by measure and time point as appendix to the study report.

10.4.11 EXPLORATORY ANALYSES

Not applicable.

10.5 SAMPLE SIZE

One of the primary performance endpoints outcome measures was used to calculate the study sample size.

Sample size calculation using the subject's improvement of surgical scars at 3 months post-treatment as evaluated by independent blinded reviewer using the General Aesthetic Improvement Scale (GAIS);

- Null and alternate hypotheses:
  - **Null Hypothesis** ***(H_o: $\mu_d = \mu_{post} - \mu_{pre} = 0$)*** – There is no improvement of surgical scars at 3 months post-treatment review compared to baseline.
    Alternative Hypothesis ***(H_a: $\mu_d = \mu_{post} - \mu_{pre} \neq 0$)*** – There is improvement of surgical scars at 3 months post-treatment review compared to baseline. The improvement of surgical scars will be defined by General Aesthetic Improvement Scale (GAIS) scores evaluated by independent blinded reviewer. Expected mean improvement difference is not less than one (1) GAIS score higher than baseline.

- In view of the nature of this study in regard to treatment period of 3 months and up to 10 months follow-up, we make provision for 30% study drop out, withdrawal or loss to follow-up.
- Due to the natures of 3 types of surgical scars that will be treated in this clinical study, the study will be viewed as 3 groups of cohort studies;
  - breast augmentation cohort group
  - abdominoplasty cohort group
  - face lift cohort group

  The study's sample size calculation below is number of subjects required for each group the makes up the study
- 2- Tailed Sample Size calculation formula for Matched Samples was used in the table below:

(1-β), Power	0.9
α, Level of Significance	0.05
μ_d, mean difference; this is the expected improvement (difference) to treatment assessed by GAIS scores under H_a	1.0
σ_d, Standard Deviation of the difference scores (GAIS range ÷ 4) = [4÷4]	1.0
ES, Effect Size [(μ_d/σ_d)	1.0
$Z_{1-\alpha/2}$	1.96
$Z_{1-\beta, (\text{for } 90\%)}$	0.84
Estimated Sample Size	**10.51 ≈ 11**
Estimated Sample Size + 30% drop out	**14.30 ≈ 15**

Conclusion: The estimated sample size for each cohort group obtained from the primary performance endpoint outcome measure calculation plus 30% drop out provision that will be used for this study is 15.

The study will enroll up to 50 female subjects requesting treatment of surgical scars following breast augmentation or abdominoplasty and up to 25 male and female subjects requesting treatment of surgical scars following face lift surgery.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

At screening, once a subject has signed the informed consent, and inclusion/exclusion criteria has been met, a subject number will be assigned. The subject number will consist of a two-digit code corresponding to the site and a three-digit subject code in numerical sequence. (Example: 10-05 corresponds to site #10, subject #5.)

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Only the independent reviewers will be blinded. The treating physician and biostatistician or designated party (who conducts interim analysis) will not be blinded.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Not applicable.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ISO 14155:2011, and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the study sponsor, ethics committee and/or regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aids or evaluation checklists, pharmacy dispensing records, recorded audio tapes of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives (where applicable), microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

It is acceptable to use CRFs as source documents. The following CRFs collected on no carbon required (NCR) paper will be source documents:

- Independent blinded reviewer POSAS
- Subject self-reported POSAS

- Subject self-reported VAS and 5-point Likert satisfaction questionnaire
- Investigator reported immediate (immediately post-treatment) and short term (30 minutes after treatment) safety response

The remainder of the data collected from other sources.

It is not acceptable for the CRF to be the only record of a subject's participation in the study. This is to ensure that anyone who would access the patient medical record has adequate knowledge that the patient is participating in a clinical trial.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Prior to any independent use of the Venus Viva™ device, study personnel, will receive proper training from the sponsor. Site personnel will be trained on the use of the device prior to study initiation at the site. Additional training requirements will be discussed during study initiation and will include site responsibilities, and study documentation. In addition, the sponsor will provide protocol specific training for the site. The site will document which individual has been assigned to a specific task and will ensure that appropriate training has occurred for that task.

Regular monitoring and an independent audit, if conducted, must be performed according to ISO 14155:2011. See also **Section 9, Clinical Monitoring**.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with the latest version of the Declaration of Helsinki (2013), ISO 14155:2011 (Clinical investigation of medical devices for human subjects - Good clinical practice), Ley 14/2007, de 3 de julio, de Investigación Biomédica and any other applicable country's ethical policy statement, whichever provides the higher level of protection to human subjects.

13.2 ETHICS COMMITTEE AND COMPETENT AUTHORITIES

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the EC / IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the EC / IRB before the changes are implemented to the study. All changes to the consent form will be EC / IRB approved; a determination will be made by Sponsor regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Informed consent is required for all subjects in a study. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to ISO 14155:2011 and to the latest version of the Declaration of Helsinki (2013). Prior to the beginning of a trial, the investigator should have the EC / IRB's written approval for the protocol and the written informed consent forms(s) and any other written information to be provided to the participants. Consent forms describing in detail the investigational medical device, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention with investigational medical device.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be EC or IRB approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, potential risks of the study and their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents according to Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the EC / IRB and Competent Authorities or device company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the sponsor, and any applicable regulations (refer to section 14.2 STUDY RECORDS RETENTION).

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the sponsor's office. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by sponsor's research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the sponsor.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

The investigator will store all data according to the local regulatory standards.

13.5 FUTURE USE OF STORED SPECIMENS

Not applicable

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the paper CRF will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the CRF derived from source documents

should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official study record. Self-reported subject data and investigator CRF reported data recorded on the copy CRF page is permitted. The original form will be collected by the sponsor and the copy will remain at the site.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data from paper CRFs will be entered directly onto paper CRFs from the source documents and will be collected by the study sponsor.

14.2 STUDY RECORDS RETENTION

Study documents, including copies of the paper CRFs, signed informed consent forms, photographs (where applicable), laboratory results, medical records, data clarification forms and regulatory documents, should be retained for a minimum period of 5 years after the end of the clinical investigation, or longer if required by local regulation. The investigator should take measures to prevent accidental or early destruction of the study related materials. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any instance(s) of failure to follow, intentionally or unintentionally, the requirements of the Clinical Investigation Plan. Applicable definition follow:

- Major deviation: CIP deviations that can have affected the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation.
- Minor deviation: CIP deviations that do NOT have affected the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation.

The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ISO 14155:2011:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Except in emergency situations, implementation of any clinical investigation plan change that affects patient safety, investigational scope, or the scientific quality of the study will not be permitted until all of the following conditions have been met:

a. The Investigator, the Sponsor and Statistician have approved the protocol amendment and

b. The responsible EC and Competent Authority has reviewed and approved the protocol change.

Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible.

A corrective action will be taken: documenting the deviation (source document, log, CRF as relevant) including its reasons of occurrence and corrective actions to be taken to further avoid reoccurrence of it and properly reporting. The investigator as well as site personnel will be trained in order to avoid any major protocol deviation in the future.

Failure to comply with this clinical investigation plan and/or EC, Competent Authorities, any local requirement will result in corrective actions and could result in the removal of the investigator from the study.

It is the responsibility of the site to use continuous vigilance to identify and report deviations promptly to study sponsor and to EC (if required by local regulation). All deviations must be addressed in study source documents. The site PI/study staff is responsible for knowing and adhering to their EC requirements.

14.4 PUBLICATION AND DATA SHARING POLICY

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. The Declaration of Helsinki current revision (2013) states that every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject (sec.35).

The sponsor or its designee will register the CS0717 study into a publicly accessible database. All data generated from this study are the property of Venus Concept Ltd and shall be held in strict confidence along with all information furnished by Venus Concept Ltd.

Independent analysis and/or publication of these data by the Investigator or any member of his/her staff are not permitted without prior written consent of Venus Concept Ltd. Written permission to the Investigator will be contingent on the review by Venus Concept Ltd of the statistical analysis and manuscript and will provide for nondisclosure of Venus Concept Ltd confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties at least 60 days prior to submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

This policy might be overruled by other signed agreements made between the sponsor and investigators at a later date.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The study will be administered by the sponsor.

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the device industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The sponsor will ensure that all study group members disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

17 LITERATURE REFERENCES

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APPENDIX

Version	Date	Significant Revisions
1.0	27 September 2017	
2.0	07 February, 2018	• Revise sponsor contact information • Correct visit schedule information in section 7.3.4 • Added Manchester Scar Scale as a primary and secondary endpoint in protocol summary • Added Manchester Scar Scale as Primary end point in section 4.2.1

Version	Date	Significant Revisions
		• Added Manchester Scar Scale as secondary performance end point in section 4.2.2 • Added Manchester Scar Scale in schedule of events table in section 7.3.7 • Added Manchester Scar Scale in visit 11, section 7.3.4 • Revised Participant Inclusion criteria to permit female subjects up to 60 years of age requesting breast augmentation or abdominoplasty to participate.