CHANGE IN SKIN ELASTICITY AFTER COMBINED RADIO FREQUENCY AND ELECTROMAGNETIC TREATMENT

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Science
CRF	Case Report Form
FDA	Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
PEMF	Pulsed Electromagnetic Field
PI	Principal Investigator
QC	Quality Control
RF	Radio Frequency
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
UP	Unanticipated Problem
VAS	Visual Analog Scale

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following (use applicable regulations depending on study location and sponsor requirements; examples follow):

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812) or equivalent local regulatory regulations or guidelines
- ICH E6
- ISO 14155:2011

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: Monica Chau Kieu

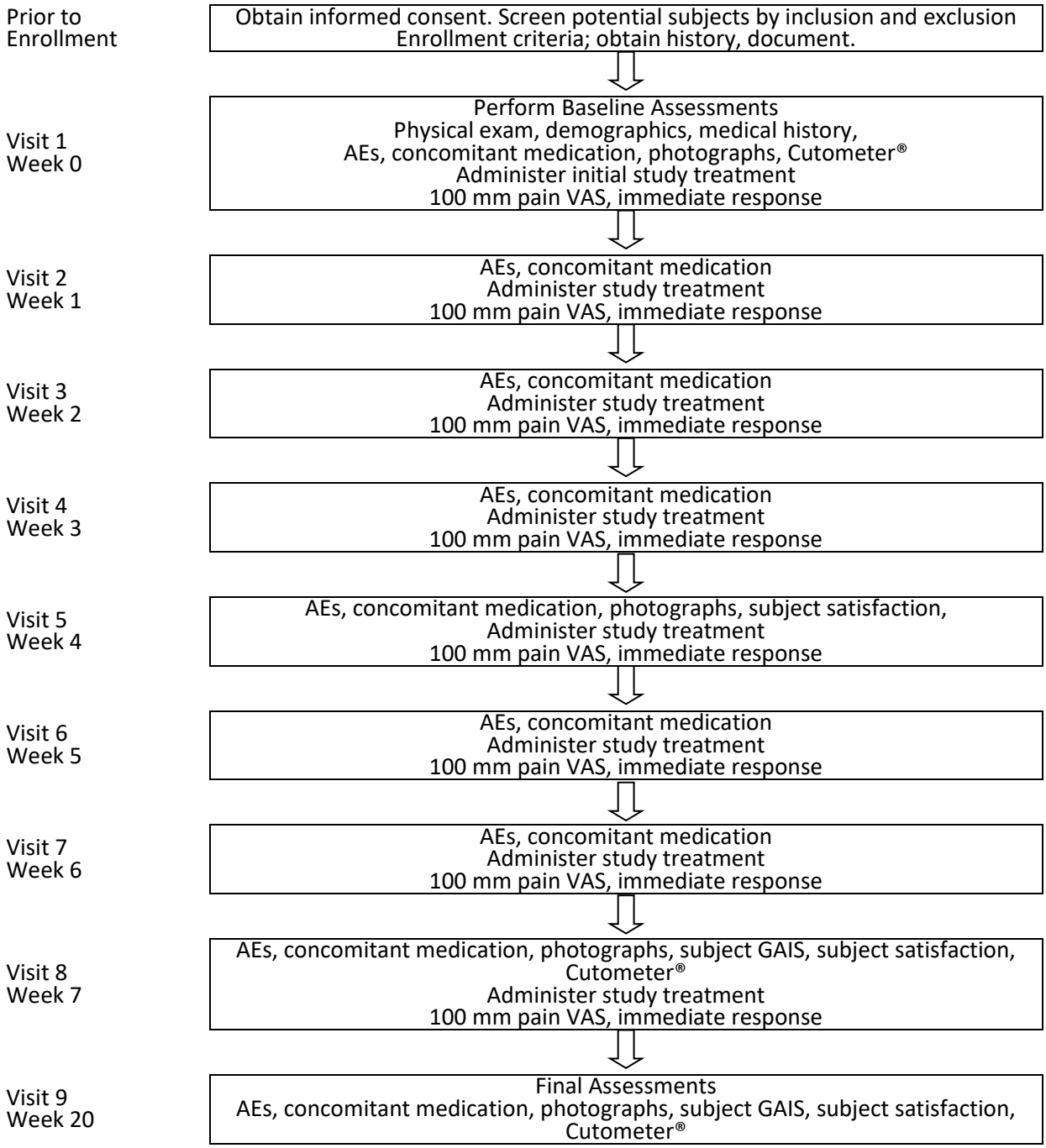
Signed: _____ Date: _____

PROTOCOL SUMMARY

Title:	Change in skin elasticity after combined radio frequency and electromagnetic treatment
Summary:	This study is an open-label, baseline-controlled, single-center study to measure the change in skin elasticity after combined radio frequency (RF) and pulsed electromagnetic field (PEMF) treatment. Forty-five adult females will undergo weekly treatments over a period of 8 weeks. Skin elasticity will be measured by a Cutometer® prior to beginning treatment, week 7 and 3 months after completion of treatment. Photographs will be taken prior to treatment, at week 4, week 7 and 3 months after completion of treatment. Patient discomfort/pain and satisfaction questionnaires will be completed before, during and after treatment.
Objectives:	The objective is to determine the quantitative change in elasticity of facial skin in subjects who have undergone treatment with combined RF and PEMF.
Endpoint	Primary endpoint: • Quantitatively and objectively measure the change in facial skin elasticity following combined radio frequency and electromagnetic treatment. Secondary endpoints: • Improvement in facial skin laxity at 7 and 20 weeks post-intervention compared to baseline as assessed by blinded evaluators by photographic assessment utilizing the Fitzpatrick Wrinkle and Elastosis Scale (FWES) scale. • Improvement in subject appearance at 7 and 20 weeks post-intervention compared to baseline as assessed by the subject utilizing the Global Aesthetic Improvement Scale (GAIS) • Improvement in subject satisfaction with facial skin laxity at 4, 7 and 20 weeks post-intervention compared to baseline as measured by the 5-point Likert Subject Satisfaction questionnaire.
Population:	The study will enroll approximately 45 healthy adult females desiring improvement in facial skin elasticity and tightness.
Phase:	Post-approval
Number of Sites enrolling participants:	One site
Description of Study Agent:	Venus Versa is an FDA approved aesthetic device. The Diamondpolar applicator combining multi-polar RF and PEMF energies will be used in this study. It is approved for non-invasive skin tightening of the face in skin types I - IV.
Study Duration:	8 months

Participant Duration: 5 months

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

The Venus Versa is a multi-application device used in aesthetic and cosmetic procedures, approved by the FDA for over 20 indications. It is comprised of a console and ten detachable applicators. The system can deliver three types of energies using the associated applicators - radiofrequency (RF), pulsed electromagnetic field (PEMF) and intense pulse light (IPL). The Diamondpolar applicator used in this study [combining multi-polar radiofrequency (RF) and pulsed electromagnetic field (PEMF) energies] is approved for non-invasive skin tightening of the face in Fitzpatrick skin types I - IV.

The Cutometer® is a non-invasive measurement device that measures the viscoelastic properties of human skin using the suction method. Negative pressure is created in the device and the skin is drawn into the aperture of the probe. Inside the probe, the penetration depth is determined by a non-contact optical measuring system. This optical measuring system consists of a light source and a light receptor, as well as two prisms facing each other, which project the light from transmitter to receptor. The light intensity varies due to the penetration depth of the skin. The resistance of the skin to be suctioned by the negative pressure (firmness) and its ability to return into its original position (elasticity) are displayed as curves at the end of each measurement.

Ryu et al determined that skin aging of women could be expressed numerically by measuring the skin elasticity using a Cutometer®.[1] A distinct trend in aesthetic medicine is the patient's demand for

efficient, noninvasive treatments with no downtime. These treatments are expected to be as safe and painless as possible. A technique based on a combination of RF and PEMF has shown to be effective in the treatment of facial wrinkles and is virtually pain free.[2] These previous studies focused on the photographic appearance of the skin pre- and post-treatment as judged by blinded raters. To date, there are no studies which use objective parameters to determine treatment efficacy. This study will determine if the Cutometer® can provide objective evidence of treatment efficacy.

2.2 RATIONALE

The combination RF and PEMF technology has already been proven to be safe and effective in the improvement of skin laxity. However, to date, there is no study that quantitatively analyzes the degree of improvement.

The objective of this clinical study is to evaluate the use of the Cutometer® in providing objective evidence of improvement in facial skin elasticity after treatment with combined RF and PEMF technology in adult females seeking treatment for the aesthetic appearance of facial wrinkles.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

The potential risks for adverse effects of the treatment procedure include but are not limited to temporary swelling, redness, pain and burns at treatment site. The following long range risks were also identified as low probability adverse events: scarring, skin breakdown and hyper or hypopigmentation.

Previous studies have shown the immediate risks outlined above are transient and generally well-tolerated by patients. The long-range risks outlined above are theoretical, as there have been no reports of these incidences.

2.3.2 KNOWN POTENTIAL BENEFITS

If the subject agrees to be in this study, she will be contributing to the understanding of the Cutometer®'s ability to quantify the device's impact on the degree of skin rejuvenation, skin tightening and improved appearance of facial rhytids. In addition, the subject may benefit from improvement in skin laxity in the treated areas.

3 OBJECTIVES AND PURPOSE

Primary objective:

Quantitatively and objectively measure the change in facial skin elasticity following combined radio frequency and electromagnetic treatment.

Secondary objectives:

Improvement in skin laxity at 20 weeks post-intervention compared to baseline as assessed by blinded evaluators by photographic assessment utilizing the Fitzpatrick Wrinkle and Elastosis Scale (FWES) scale.

Improvement in subject appearance at 7 and 20 weeks post-intervention compared to baseline as assessed by the subject utilizing the Global Aesthetic Improvement Scale (GAIS).

Improvement in subject satisfaction with skin laxity at 4, 7 and 20 weeks post-intervention compared to baseline as measured by the 5-point Likert Subject Satisfaction questionnaire.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is an open-label, baseline-controlled, single-center study to objectively measure the change in skin elasticity after combined radio frequency and electromagnetic treatment

4.2.1 PRIMARY ENDPOINT

As skin ages, collagen can become disorganized, causing changes in both the mechanical property of the skin and skin appearance. The change in gross elasticity (R2 or Ua/Uf which is a ratio of maximum recovery (Ua) and skin distensibility (Uf)) as measured by a Cutometer® has been found to be one of the most suitable parameters to represent the influence of aging on skin mechanical properties.[i] This is expressed as a percentage, the closer the value is to 1 (100%), the more elastic the skin. Thus, the primary endpoint will be the change in gross elasticity after treatment with combined RF and PEMF. The gross elasticity of facial skin will be measured prior to the start of the treatment regimen (baseline), and 20 weeks after completion of the treatment regimen.

4.2.2 SECONDARY ENDPOINTS

Secondary endpoint #1: Change in photographic appearance of rhytids, as determined by blinded Facial Plastic & Reconstructive surgeons using the Fitzpatrick Wrinkle and Elastosis Scale (FWES) from baseline to week 20. Photographs from weeks 4 and 7 will only be used to track treatment progress, and will not be used by the raters to determine treatment efficacy.

Secondary endpoint #2: To assess clinical efficacy subjectively, the subjects will complete the Global Aesthetic Improvement Scale (GAIS), which is a 7-grade instrument.

Secondary endpoint #3: To assess satisfaction with the treatment, subjects will complete a 5-point Likert Subject Satisfaction scale.

The secondary endpoints serve to augment the findings of the primary endpoint. They help to provide a more complete understanding of treatment efficacy by including evaluations by trained physicians as well as the subjects themselves.

4.2.3 EXPLORATORY ENDPOINTS

None

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Healthy adult female subject at least 18 years of age and older with Fitzpatrick skin types I-IV who are willing to participate.
2. Women requesting treatment for skin laxity of the face.
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. Ability to tolerate the RF/PEMF procedure, and willing to adhere to the treatment regimen.

5.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Having any active electrical implant anywhere in the body, such as a pacemaker or an internal defibrillator.
2. Having a permanent implant in the treated area.
3. Prior use of retinoids in treated area within 2 weeks of initial treatment or during the course of the study.
4. Use of oral Isotretinoin (Accutane®) within 6 months of initial treatment or during the course of the study.
5. Patient on systemic corticosteroid therapy 6 months prior to and during the course of the study.
6. Prior use of collagen, fat injections and /or other methods of skin augmentation (enhancement with injected or implanted material) in treated area within 4-6 weeks of initial treatment or during the course of the study. Treatment may not be performed at all over permanent dermal implants.
7. Prior ablative resurfacing procedure in treated area with laser or other devices within 12 months of initial treatment or during the course of the study.
8. Any other surgery in treated area within 12 months of initial treatment or during the course of the study.
9. History of keloid formation or poor wound healing in a previously injured skin area.
10. History of epidermal or dermal disorders (particularly if involving collagen or micro vascularity).
11. Open laceration or abrasion of any sort on the area to be treated.
12. History of immunosuppression/immune deficiency disorders (including HIV infection or AIDS) or use of immunosuppressive medications.

13. Having any form of active cancer at the time of enrollment and during the course of the study.

14. Significant concurrent illness, such as uncontrolled diabetes i.e. any disease state that in the opinion of the Investigator would interfere with the treatment, or healing process.

15. Participation in a study of another device or drug within 1 month prior to study enrollment or during this study, and as per the Investigator's careful discretion, as long as not contradictory to any of the above criteria.

16. Tattoos in the treatment area.

17. Mentally incompetent, prisoner or evidence of active substance or alcohol abuse.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Approximately 45 subjects will be recruited through the site investigator's outpatient clinic. Potential subjects will be identified through the existing database of over 20,000 patients and a recruitment email with a brief description of the study will be sent. In addition, an ethics-approved flyer will be posted in the patient waiting area of the clinic. It is also anticipated that a substantial number of participants will be recruited through word of mouth.

To enhance participant retention, email and phone calls will be employed to remind patients of treatment and follow up appointments.

No financial incentives will be offered, however the potential for improved aesthetic appearance is a compelling non-financial incentive.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 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 Exit/Termination CRF form should be completed. On the withdrawal page, the Investigator should record the date of the withdrawal, the person who initiated withdrawal and the reason for withdrawal.

Reasonable effort will 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 and study medication/supplies. The records of subjects who terminate prior to completing the study will be retained and the reason for termination will be documented.

An 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 participant.

- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.4.2 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 efficacy study endpoints. Every effort will be made to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs), and unanticipated problems (UPs). Subjects that withdraw will be replaced until a maximum of 60 subjects are randomized with 45 subjects expected to complete the study. Subjects that withdraw or are terminated from the study will still be requested to complete the week 20 follow-up procedure in order to evaluate for possible AEs or unanticipated problems (UPs).

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the principal investigator (PI) and Venus Concept. If the study is prematurely terminated or suspended, the PI will promptly inform the ethics board and will provide the reason(s) for the termination or suspension.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy 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, ethics board and/or regulatory authorities.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

The investigational device will be shipped to the investigative site directly from the sponsor. An activation code will be required to activate the device. This code will not be provided to the investigative site until all regulatory and institutional review board (IRB) approvals are in place and the site has received training for both the device and the study.

6.1.2 DEVICE SPECIFIC CONSIDERATIONS

The Venus Versa $(MP)^2$ by Venus Concept Ltd. is a non-invasive dermatological treatment system based on patented and proprietary $(MP)^2$ technology which combines Multi Polar Radiofrequency (RF) and Pulsed Magnetic Fields. The RF energy penetrates the skin and results in RF-generated tissue heating that has known effect on skin laxity. The magnetic field that is simultaneously induced increases fibroblast collagen production through a non-thermal mechanism and contributes to the clinical effect

of skin laxity improvement. The Diamondpolar applicator used for this study includes electrodes that deliver the Multi Polar Radiofrequency (RF) and Pulsed Magnetic Fields energy.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

The device will be shipped to the site by the sponsor. The device will require an activation code in order to function. The activation code will only be provided once all the ethics and regulatory approvals for the site are in place. The treatments will be administered by a trained technician according to the protocol under direct supervision of the PI. When not in use, the device will be turned off and kept in a locked room. At the end of the study, the device will be returned to the sponsor.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

- Medical history: obtained through interview. History will include age, other medical conditions, and previous invasive or non-invasive cosmetic procedure to the face or neck in the last 6 months.
- Medication history: current medications will be obtained through interview and will include prescription, over the counter, and herbal medications taken 4 weeks prior to study enrollment.
- Physical examination: completed by PI. Focused head and neck skin assessment that will include Fitzpatrick skin type and evidence of scars, infection, or inflammation of the face or neck.
- Imaging assessment: standard photos of the treated area will be taken by the PI using a Nikon D3100 using a 105 mm lens with fixed 2 Nikon flashes using diffuse bounce flash technique that reduces shadows and accentuates the subject's contours.
- Cutometer assessment at baseline, week 7 and at week 20.
- Rater assessment: The FWES will be used to rate the level of skin aging.
- Patient-reported outcomes: subjects will be asked to complete the GAIS questionnaire at weeks 7 and 20, and a 5-point Likert subject satisfaction scale at weeks 4, 7 and 20.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Not applicable

7.2.2 OTHER ASSAYS OR PROCEDURES

Not applicable

7.3 STUDY SCHEDULE

7.3.1 SCREENING

If the subject meets the preliminary study criteria the study doctor, and/or his/her designee, will obtain an informed consent from the subject, clearly indicating her understanding of the requirements and possible risks involved 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. 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.

Enrollment/baseline visit can be conducted on the same day as screening or up to 30 days after screening.

7.3.2 ENROLLMENT/BASELINE

Enrollment/Baseline Visit (Visit 1, Week 0)

Once a subject has been confirmed that they continue to meet inclusion/exclusion criteria, each subject will receive a unique identifying number that will be composed of a two-digit site number and a three-digit subject number in sequence. This unique identifier will be used throughout the entire study and will be entered in the subject's CRF for each treatment.

Baseline Cutometer® measurements of the area to be treated will be obtained.

Subjects will be asked to refrain from using skin products or medications containing ingredients listed in the exclusion criteria, and may have to undergo washout periods for any such substances or medications prior to receiving treatment as part of this study. The Investigator should review the subject’s skin care regimen and suggest appropriate alternatives for the course of the study, as needed.

All subjects will have photographs taken of the area to be treated. All subjects will be asked to remove all jewelry and piercings and wash the area to be photographed with provided cleanser to remove all makeup and skincare products. Subject will then wait 10 minutes for any washing related erythema to subside prior to initiation of photography session. All stray hairs will then be pulled away from the face. If seated photos, the stool height will be adjusted to ensure the subject’s head, neck and spine are aligned and the subject is sitting up straight. Subject will then be positioned so they are centered in the frame using chin and forehead rests as applicable for seated three-point photo capture and if standing, feet are aligned with standardized photo foot marking on the floor standing straight with back flat against the draped back drop (blue, green or white) wall. All photography is to take place within the same room with standardized lighting, no natural light, for the duration of the study.

Standardized photographs will be taken using a high quality digital SLR camera to obtain three photos (frontal 90°, right 45° and left 45°). These photographs will be used as an assessment tool. They may also be used for publication and/or presentation of the study findings and generalized characterization of the disease state. Moreover, they may use the photographs for marketing or other commercial purposes.

The photos will be taken in a private room or area. The investigative site will ensure that digital photography equipment with standardized illumination and background is available for use during this study. Digital photos will be stored on dedicated media. A copy of all study photographs will be transferred to Venus Concept at the end the study or as part of interim analysis. Only the subject code will appear on the records being transferred to the sponsor to ensure anonymity of the subjects.

Study visits that include photography: Baseline, week 4, week 7, week 20.

Standard conditions: The photos should be taken in standardized conditions, including distance, angle, background, and illumination in order to achieve high-quality before & after sets. Do not use direct illumination.

Subject posture: The subject will 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.

Order of photos: the first photograph in each session should be of an identification card that will include subject code and visit details.

File names: The digital files should follow a consistent standard naming scheme, for example: 01-001TS_Tx1_face.

Treatment Procedure (also see user manual)

During each treatment session, subjects will be treated with the Venus Versa system using the Diamondpolar applicator as per standard treatment parameters.

Prior to the treatment, glycerin in gel formulation should be applied thoroughly to the treatment area.

In the initial treatment it is important to adjust the treatment required energy level to best suit the patient's tolerance to the treatment. Tolerance will increase as the patient becomes more familiar with the treatments.

The aim of the procedure is to heat the surface of the skin on the treatment area and raise the temperature up to at least 39°C and maintain it for a minimum of 5 minutes. Always aim for the highest temperature that the subject can tolerate. The treatment should be monitored with an external infrared (IR) thermometer.

During the procedure, the applicator's electrodes will press against the patient's skin, making sure that all electrodes are in contact with the skin as much as possible.

The applicator strokes are long and continuous, and performed in form of "8" figures, circles, ellipses or waves. The applicator will always be in motion, while in contact with the skin surface.

If the measured skin surface temperature (as measured by the IR thermometer) is less than 39^{o}C, treatment is not optimal and the desired results will not be accomplished. The achieved skin temperature depends on the applicator movement speed and energy level. The lower the energy, the slower the movement will be and vice-versa.

In the event that the patient experiences discomfort or pain during the treatment, either the energy percentage will be decreased, more glycerin in gel should be applied or wider and quicker movements should be performed. Treatment may also be halted.

Subject discomfort evaluation

The subject will record their assessment of discomfort/pain on a 100 mm VAS CRF page immediately after each treatment which will be considered to be a source document.

Skin safety – immediate response after procedure

Local (dermal) tolerability examination (only on the face) will be performed immediately following treatment at the time-points given in the Study Visit Table and will include assessments of pain during treatment, hemorrhage, burn, erythema, edema or other reactions. All tolerability assessments must be completed by the same person throughout the study whenever possible. Local tolerability on the face will be rated as none, mild, moderate, or severe.

Subjects should remain in the research setting at least 30 minutes after treatment in order to ensure their well-being.

Subjects will be discharged from the clinic and will be instructed to return for the Visit 2, Week 1 assessment and treatment.

7.3.3 FOLLOW-UP

Visit 2, Week 1

Subjects will return to the clinic one week (±3 days) after the first treatment. Adverse events and any changes to concomitant medications will be recorded.

Subjects will receive treatment of the face as described above in section 7.3.2. Following treatment, the investigator will examine the treated area and report the immediate response.

The assessment of discomfort/pain will be based on the subject's completion of the 100 mm VAS immediately after treatment.

Subjects will be discharged from the clinic and will be instructed to return for the Visit 3, Week 2 assessment and treatment.

Visit 3, Week 2

Subjects will return to the clinic one week (±3 days) after the last treatment. Adverse events and any changes to concomitant medications will be recorded.

Subjects will receive treatment of the face as described above in section 7.3.2. Following treatment, the investigator will examine the treated area and report the immediate response.

The assessment of discomfort/pain will be based on the subject's completion of the 100 mm VAS immediately after treatment.

Subjects will be discharged from the clinic and will be instructed to return for the Visit 4, Week 3 assessment and treatment.

Visit 4, Week 3

Subjects will return to the clinic one week (±3 days) after the last treatment. Adverse events and any changes to concomitant medications will be recorded.

Subjects will receive treatment of the face as described above in section 7.3.2. Following treatment, the investigator will examine the treated area and report immediate response.

The assessment of discomfort/pain will be based on the subject's completion of the 100 mm VAS immediately after treatment.

Subjects will be discharged from the clinic and will be instructed to return for the Visit 5, Week 4 assessment and treatment.

Visit 5, Week 4

Subjects will return to the clinic one week (±3 days) after the last treatment. Adverse events and any changes to concomitant medications will be recorded. Photographs will be taken as described above in section 7.3.2. Subjects will complete a 5-point Likert satisfaction scale.

Subjects will receive treatment of the face as described above in section 7.3.2. Following treatment, the investigator will examine the treated area and report immediate response.

The assessment of discomfort/pain will be based on the subject's completion of the 100 mm VAS immediately after treatment.

Subjects will be discharged from the clinic and will be instructed to return for the Visit 6, Week 5 assessment and treatment.

Visit 6, Week 5

Subjects will return to the clinic one week (±3 days) after the last treatment. Adverse events and any changes to concomitant medications will be recorded.

Subjects will receive treatment of the face as described above in section 7.3.2. Following treatment, the investigator will examine the treated area and report immediate response.

The assessment of discomfort/pain will be based on the subject's completion of the 100 mm VAS immediately after treatment.

Subjects will be discharged from the clinic and will be instructed to return for the Visit 7, Week 6 assessment and treatment.

Visit 7, Week 6

Subjects will return to the clinic one week (±3 days) after the last treatment. Adverse events and any changes to concomitant medications will be recorded.

Subjects will receive treatment of the face as described above in section 7.3.2. Following treatment, the investigator will examine the treated area and report immediate response.

The assessment of discomfort/pain will be based on the subject's completion of the 100 mm VAS immediately after treatment.

Subjects will be discharged from the clinic and will be instructed to return for the Visit 8, Week 7 assessment and treatment.

Visit 8, Week 7

Subjects will return to the clinic one week (±3 days) after the last treatment. Adverse events and any changes to concomitant medications will be recorded. Photographs will be taken as described above in section 7.3.2. Cutometer® measurements of the treated area will be obtained.

Subjects will receive treatment of the face as described above in section 7.3.2. Following treatment, the investigator will examine the treated area and report immediate response.

The assessment of discomfort/pain will be based on the subject's completion of the 100 mm VAS immediately after treatment.

Subjects will complete the GAIS scale and the 5-point Likert satisfaction scale.

Subjects will be discharged from the clinic and will be instructed to return for the final study visit, Visit 9, Week 20 assessment.

7.3.4 FINAL STUDY VISIT

Visit 9, Week 20

Subjects will return to the clinic twelve weeks (±2 weeks) after the last treatment for the final visit. Adverse events and any changes to concomitant medications will be recorded. Photographs will be taken as described above in section 7.3.2. The subject will complete the GAIS scale and the 5-point Likert satisfaction scale. Cutometer® measurements of the treated area will be taken.

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.

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 9). Adverse events and the reason for early termination will be recorded.

7.3.6 UNSCHEDULED VISIT

Participants will be encouraged to contact the PI at any time during the course of the study if they believe they are experiencing an AE or undesirable outcome. If necessary, an unscheduled visit will be made to examine the participant and provide further care as needed. 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 (Visit 1, Week 0)	Baseline (Visit 1, Week 0)	Follow-up (Visit 2, Week 1)	Follow-up (Visit 3, Week 2)	Follow-up (Visit 4, Week 3)	Follow-up (Visit 5, Week 4)	Follow-up (Visit 6, Week 5)	Follow-up (Visit 7, Week 6)	Follow-up (Visit 8, Week 7)	Final Study Visit (Visit 9, Week 20)
Informed Consent	X									
Eligibility assessment	X	X								
Demographics	X									
Medical History	X									
Physical exam	X									
Photographic imaging		X				X			X	X
Cutometer® readings		X							X	X
Administer treatment		X	X	X	X	X	X	X	X	
Immediate response		X	X	X	X	X	X	X	X	
Subject pain VAS		X	X	X	X	X	X	X	X	
Subject GAIS									X	X
Subject satisfaction						X			X	X
Adverse events		X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable

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. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Treatment with any invasive or non-invasive cosmetic procedure to the face and neck (other than the investigative treatment) during the study period will not be permitted.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Medical grade glycerin will be applied to the treated area.

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.
- Event will be reported to the 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.
- Copy of the patient chart and treatment parameters are to be forwarded to the study Director within 24 hours.
- Study Director will be responsible for issuing a written report to the company and the IRB Chairman no later than 7 days from the incident.
- 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 IRB chairman.

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

At study closure, participants will be given a list of providers in the area who can continue treatments to the same area or other body areas if desired. However, subjects will be notified that additional treatments will incur a cost not covered by the study.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

In addition to spontaneous reports of adverse events, subjects will complete a 100 mm pain VAS and the principal investigator will examine the treated area and report immediate response.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

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 STUDY AGENT

The clinician's assessment of an AE's relationship to study agent (drug, biologic, 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 study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

Related – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
Not Related – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

8.2.3 EXPECTEDNESS

Expected adverse reactions are AEs that are common and known to occur for the study agent being studied. Expected adverse events in this study include pain, tenderness, purpura, persistent erythema, edema, burn, blistering, crusting, hyperpigmentation, hypopigmentation, scarring and potential for damage to hair follicles within the treatment area and subsequent loss of hair within the treatment area.

An AE or suspected adverse reaction is considered "unexpected" if it is not known to occur for the study agent being studied and at the specificity or severity that has been observed.

The sub-investigator (SI) will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

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 study product (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. UPs will be recorded in the data collection system throughout the study.

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 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. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

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 expected or device related, must be reported to the sponsor’s clinical research department immediately or within 24 hours by telephone (see contact details below).

Name: Joseph Reiz, Director of Clinical Research

Phone: 888-907-0115 ext. 563

Email: jreiz@venusconcept.com

Address: 255 Consumers Road, #110, Toronto, Ontario, Canada, M2J 1R4

A written report prepared by the Principal Investigator using the Serious Adverse Event or Serious Adverse Device Effect Report 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 an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor contact information is provided in Section 1, Key Roles. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to FDA, any other country regulatory authority and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as the applicable regulatory authority requests.

8.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the study sponsor. The UP report will include the following information:

Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the applicable regulatory authority and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as the applicable regulatory authority requests.

8.4.4 REPORTING OF PREGNANCY

Not applicable

8.5 STUDY HALTING RULES

The study may be halted at any time by the sponsor, the IRB, Health Canada or the FDA 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 IRB(s) and the applicable regulatory authority.

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.

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.
- The sub-investigator will provide on-site monitoring weekly during the study period to ensure patient safety and verify accurate data collection.
- The clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

An initial statistical analysis plan has been developed and will be finalized once all data collection is complete.

10.2 STATISTICAL HYPOTHESES

Statistical null hypothesis for primary endpoint: there will be no statistical change in gross elasticity as measured by the Cutometer® after treatment with combined RF/PEMF compared to before treatment.

Statistical null hypothesis for secondary endpoint #1: there will be no statistical change in the FWES as rated by blinded clinicians after treatment with combined RF/PEMF compared to before treatment.

Statistical null hypothesis for secondary endpoint #2: there will be no statistical change in the GAIS as rated by the subjects after treatment with combined RF/PEMF compared to before treatment.

Statistical null hypothesis for secondary endpoint #3: there will be no statistical change in the subject satisfaction score after treatment with combined RF/PEMF compared to before treatment.

10.3 ANALYSIS DATASETS

There will be one analysis dataset, which will only include subjects who completed the entire treatment and follow up protocol.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

After data set compilation and cleaning, a series of descriptive statistics will first be generated to examine the data set for distributional/potential missing data patterns and sample characteristics. The study team will conduct a series of pooled time series analyses with generalized estimating equations regression (GEE) models.[3] These types of non-parametric (i.e., not based on normal distribution assumptions) predictive modeling procedures are capable of using both robust and standard estimating functions to more fully evaluate the influence RF/PEMF treatments and other factors/covariates on serial face gross elasticity measurements. These types of procedures will also enable the study team to examine the potential effects of both *within group* (e.g., face gross elasticity measurements for Patient X at three measurement points) and *between group* (e.g., face gross elasticity measurement changes of younger women versus older women) model variables. A *P*-value of <0.05 will be considered statistically significant.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Gross elasticity as measured by the Cutometer® is a ratio expressed as a percentage. Baseline and post-treatment measurements will be taken and analyzed using analysis of variance (ANOVA).

Results will be reported as baseline means with standard deviation, post-treatment means with standard deviation, and individual change for each subject.

Subjects with missing data, non-adherence, or lost to follow-up will not be included in the final analysis dataset.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoint #1: The FWES is based on an ordinal scale (from 1-9) and will be measured as a single endpoint.

Secondary endpoint #2: The GAIS is a 7-point (-3 to 3) ordinal scale and will be a repeated measure.

Secondary endpoint #3: The subject satisfaction score is a 5-point Likert scale and will be a repeated measure.

10.4.4 SAFETY ANALYSES

There are no formal safety endpoints in this study, however all AEs and relevant information related to the incidents (start date, stop date, severity, relationship, outcome, and duration) will be recorded and reported. Adverse events leading to premature discontinuation from the study and serious treatment emergent AEs will be presented in a table.

10.4.5 ADHERENCE AND RETENTION ANALYSES

Not applicable.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics including age, Fitzpatrick skin type, and initial Cutometer® readings will be reported using descriptive statistics.

10.4.7 PLANNED INTERIM ANALYSES

10.4.7.1 SAFETY REVIEW

Not applicable.

10.4.7.2 EFFICACY REVIEW

Not applicable.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

For all endpoints, additional sub-group analysis may be performed based on age group and Fitzpatrick skin type.

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

Not applicable

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

Individual participant data will be listed by time point.

10.4.11 EXPLORATORY ANALYSES

Not applicable.

10.5 SAMPLE SIZE

The PI has used G*Power 3.10.10 software[4] to generate *a priori* minimal sample size calculations for the primary study endpoint: changes in *gross elasticity* (GE) repeated measure face measurement in a sample of consented eligible women at three time points: a) prior to RF/PEMF, b) at time of RF/PEMF completion, and c) three months after treatment completion.

These calculations indicate that a minimal sample size of approximately **45** patients would easily afford at least a 0.804784 1 minus β level of statistical power to detect statistically significant RF/PEMF sample subgroup measurement differences observing a coefficient Alpha of 0.05 two-tailed level of significance. This sample size is based on both a conservative 0.3 (i.e., *Medium*) Effect Size for RF/PEMF treatment and pre-post procedure Cutometer® face gross elasticity measurement differences reported in Krueger, et. al (2011).[5]

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 two-digit subject code in numerical sequence. (Example: 10-05 corresponds to site #10, subject #5.)

Due to the nature of the treatment, it is not possible to blind subjects.

Photographic imaging provided to the raters will not contain any participant identifying information or dates. The physician raters will be blinded to which stage of treatment (if any) completed by the subject in the photograph.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Not applicable.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

There are no instances in which the blind will need to be broken for the physician raters.

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 ICH E6, ISO 14155:2011 and regulatory and institutional requirements for the protection of confidentiality of participants.

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, 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. For this protocol, responses to subject questionnaires and scales will be collected on two-part no carbon required (NCR) paper CRF pages. One copy will be collected by the sponsor with the remaining copy left at the investigation site.

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.

Source documents for this study will include:

- Digital photographs - will be kept in a password-protected file on the secure server at the investigation site. Only the PI and SI will have access to the digital files. Participants will sign a photograph waiver at the beginning of the study which will describe in detail how these photos may be used, such as web-based marketing purposes or academic publications.

- CRFs - will be in paper format. There will be one CRF for each participant in the study, which will be kept in a locked drawer at the investigation site. At the completion of the study, the CRFs will be scanned to pdf format and stored in a password-protected file on the secure server at the investigation site. After the paper forms are scanned and digitized, they will be shredded and properly disposed as sensitive medical records.

- Recorded data from Cutometer® - all data is electronically recorded and saved in a software program on the PI's password-protected desktop computer at the investigation site.

- Subject questionnaires - will be in paper format, then scanned to pdf format and stored in a password-protected file on the secure server at the investigation site. After the paper forms are scanned and digitized, they will be shredded and properly disposed as sensitive medical records.

- Rater data collection sheets - will be in paper format, then scanned to pdf format and stored in a password-protected file on the secure server at the investigation site. After the paper forms are scanned and digitized, they will be shredded and properly disposed as sensitive medical records.

12 QUALITY ASSURANCE AND QUALITY CONTROL

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.

Following written SOPs, the 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 Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6, ISO 14155:2011, the Declaration of Helsinki, Council for International Organizations of Medical Science (CIOMS), International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), or another country's ethical policy statement, whichever provides the most protection to human subjects.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the 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 IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made 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 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56), another country's ethical policy statement and/or ICH GCP. Prior to the beginning of a trial, the investigator should have the 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 study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

The following consent materials are submitted with this protocol:

- Consent to participate in study
- Photograph consent

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 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, and potential risks of the study and of 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. This confidentiality is extended to cover testing of biological samples and genetic tests 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 IRB or company supplying study device 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 local IRB and regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the statistician coordinating center. 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 the clinical site and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Art of Facial Surgery.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

Storage: Access to data and photographs will be limited using password protection. Data will be stored using codes assigned by the investigators. Data will be kept in password- protected computers. Only investigators will have access to the photographs and data.

13.5 FUTURE USE OF STORED SPECIMENS

Data collected for this study will be analyzed and stored at the Art of Facial Surgery. After the study is completed, the de-identified, archived data will be stored at this site.

When the study is completed, access to study data will be provided only through written consent by the PI or SI through the Art of Facial Surgery.

Patient photographs will be stored on the password protected server at the investigation site, and will only be used as expressly permitted on the Photograph Consent. Steps will be taken to ensure anonymity of the subject in the photograph.

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 PI. 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 paper 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 electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data from paper CRFs will be collected by the study sponsor and will be entered into a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly onto paper CRFs from the source documents.

14.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 5 years which is the projected time life of the device. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor. 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 noncompliance with the clinical trial protocol, GCP, or MOP requirements. 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 ICH E6:

- 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.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the PI. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the Monitoring Plan.

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, including pharmacokinetic measures 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. For interventional clinical trials, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDA Administration Amendments Act mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials:

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;

- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post market surveillance studies.

At the end of the study, the PI will make results of the research available to the research community and public at large.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The Study Team will govern the conduct of the study. The Study Team will be composed of the PI, SI and representatives of the sponsor, Venus Concept. The Study Team will meet in person at least annually.

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the medical 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 study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

17 LITERATURE REFERENCES

1. Ryu, HS, Joo, YH, et al. Influence of age and regional differences on skin elasticity as measured by the Cutometer. Skin Research and Technology 2008; 14: 354–358

2. Kreuger, N, Levy, H, Sadick, N. Safety and Efficacy of a New Device Combining Radiofrequency and Low-Frequency Pulsed Electromagnetic Fields for the Treatment of Facial Rhytides. Jour Drugs in Derm. Vol 11 Issue 11 Nov 2012

3. Hardin J, Hilbe J. Generalized Estimating Equations. 2003. London: Chapman and Hall/CRC.

4. Faul F, Erdfelder E, Buchner A Lang AG. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behav Res Methods. 2009, 41(4): 1149-1160.

5. Kreuger, N, Luebberding, S, et al. Age-related changes in skin mechanical properties: a quantitative evaluation of 120 female subjects. Skin Research and Technology 2011; 17:141-148

APPENDIX

Version	Date	Significant Revisions