CLINICAL EVALUATION OF THE TOLERABILITY OF USING A POST TREATMENT TOPICAL ADJUVANT COMBINATION FOLLOWING FRACTIONAL RADIOFREQUENCY ABLATION USING THE VENUS Viva™

Protocol Number CS0116

October 18, 2016 Version 5.0

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19/Oct/2016

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CONTENTS

APPENDICES

1. SCHEDULE OF EVENTS

Visit:	***Screening & Test Spot***	***Tx 1[1]***	***Tx 2***	***FU1***
Day:	***0***	***7***	***21***	***24***
Inclusion/ Exclusion	+			
Informed Consent Form	+			
Demographics, Medical / Medication History, Skin type	+			
Fitzpatrick Wrinkle and Elastosis Scale evaluation	+			+
Test spot	+			
Treatment		+	+	
Subject discomfort assessment (VAS)		+	+	
Subject Self-Report Adverse Event Questionnaire		+[2]	+[3]	+
Subject Tolerability Scale (5-point Likert scale)		+[2]	+[3]	+
Investigator improvement evaluation using GAIS				+
Adverse Events / Concomitant Medications		+	+	+

[1]The baseline visit and 1st treatment visit may be scheduled on the same day.

[2] Telephone call to subject 24 hrs and 72 hrs post first treatment; Subject Tolerability Scale 0; Subject Home Tolerability Scale 24hrs and 72hrs post treatment

[3] Telephone call to subject 24 hrs post second treatment; Subject Tolerability Scale 0; Subject Home Tolerability Scale 24hrs post treatment

2. PROTOCOL SYNOPSIS

Study design	Randomized, open-label, multi-centre study to evaluate the tolerability of the application of a combination of a serum containing human bone marrow stem cell derived growth factor and cytokines (SCR Complex™) and a botanical lipid based occlusive (Bio Cel™) following facial fractional RF treatments using the Venus Viva™ SR system. Each subject will receive 2 treatments separated by a 3-week interval. Subjects will complete a VAS and Tolerability Scale immediately following each treatment. Telephone follow-up calls by the site will ask the subject to respond to the Self-Report Adverse Event Questionnaire 24 and 72 hours after the first treatment and 24 hours after the second treatment. Subjects will complete a Home Tolerability Scale 24 and 72 hours after the first treatment and 24 hours after the second treatment. Subjects will return for the final FU visit and be asked to respond to the Self-Report Adverse Event Questionnaire and complete the Home Tolerability Scale for 72 hours. The investigator will also evaluate the subject's improvement using the GAIS at this visit.
Study center / country	2 Study Centres; USA
Study duration	1) For each subject, study duration will be approximately 30 days, including study follow-up. 2) Anticipated start date: July 2016; Anticipated stop date: September 2016.
Investigational product	**Venus Viva**™ SR system is intended for dermatological procedures requiring ablation and resurfacing of the skin. **SCR Complex™** contains human growth factors and cytokines derived through laboratory culture of human bone marrow mesenchymal stem cells. It is indicated for use immediately following and for the first few days of the acute healing phase after treatment with the Venus Viva™ device. **Bio Cel™** is a botanical lipid-based gel occlusive. It is indicated for use as an occlusive barrier following ablative and semi-ablative skin treatments, regardless of modality.
Planned number of participants	A total of up to 100 evaluable male or female subjects (Fitzpatrick Skin types I – VI) will be enrolled. Subjects will present with acne scars, general skin texture irregularities and/or rhytides.
Study objectives	Clinical evaluation of the tolerability of using a post-treatment topical adjuvant combination immediately following RF fractional ablation using the Venus Viva™ SR system.
Key Inclusion Criteria	• Male or non-pregnant, non-nursing female at least 21 years of age and less than 75 years of age. • Undergoing a dermatological procedure requiring ablation and resurfacing of the facial skin utilizing the Venus Viva™ SR system.
Key Exclusion Criteria	• Superficial metal or other implants in the treatment area. • Tattoos, permanent makeup, scars or piercings in the treatment area. • Any active condition in the treatment area, such as sores, psoriasis, eczema and rash.

	• Any surgical procedure in the treatment area within the last three months or before complete healing.
Primary endpoint	The primary end point will be the tolerability of the application of the stem cell recovery complex (SCR Complex™) and a botanical lipid based occlusive (Bio Cel™) as compared with standard of care immediately following fractional RF treatments.
Secondary endpoints	The secondary outcomes will be the subject's degree of discomfort and/or pain as measured by the visual analogue scale (VAS), the incidence of spontaneous adverse events (AEs) and the investigator's assessment of improvement using the Fitzpatrick Wrinkle and Elastosis Scale scores before and after treatment as well as the Global Aesthetic Improvement Scale (GAIS) for each subject.
Statistical Methodology	All subjects who received any amount of treatment will be included in the report. The primary outcome measure is the subject's overall tolerability of the adjuvant combination treatment as compared to the standard of care post fractional RF treatment. The self-assessment will be based on a 5-point Likert scale - Subject Tolerability Scale (Appendix A). Summary statistics will be generated for subject tolerability immediately after treatment, 24 hours and 72 hours following treatment as per the terms: Very tolerable, tolerable, having no opinion, intolerable and very intolerable. Summary statistics will also be generated to present the degree of discomfort and/or pain following the procedure, all treatment emergent adverse events (TEAs) and the GAIS scores for the treatment group and standard of care group.

3. INTRODUCTION

Radiofrequency (RF) devices are safe and effective. The RF energy is delivered to the skin in a chromophore non-specific manner, heating the underlying dermal tissue at different levels. This heat results in a wide range of mechanisms from stimulation to ablation. The RF Scan delivers RF energy in a non-homogenous fractional form, selectively heating the dermis while protecting the overlying epidermis. The array of multi-electrode pins delivers bipolar RF energy to dry, non-moisturized skin. The procedure is carried out while leaving areas that have been exposed to slight impact, in-between the targeted areas, which help to maintain the integrity of the treated skin and serve as a reservoir of cells that accelerate and promote the healing process.

SCR Complex™: The cells of our bodies communicate with one another using a complex bio-molecular language. Growth factors and cytokines are the "words" that control embryogenesis, growth, immunologic defenses, and tissue healing. Of the more than 200 types of cells in the body, bone marrow mesenchymal stem cells are the ones that act as commander-in-chief of healing in all tissues, including skin. These cells are mobile, migrating from the bone marrow into the blood stream where they gain access to all parts of the body. When they encounter injury, they serve as smart local "drugstores", secreting pro-healing anti-inflammatory bio-signals. The number of these cells plummets with age, accounting in large measure for the less robust healing of later decades. Topical application of growth factors and cytokines obtained through laboratory culture of bone marrow stem cells is thoughtto improve the appearance of the signs of aging skin.

Because aging skin is injured skin, some benefit has been seen with the topical application of bone marrow stem cells bio-signal products in anti-aging formulations. Improvement has also been seen when used with dermal needling, and with fractional CO2 laser resurfacing in which "downtime" has been reduced by up to 40%.

Bio Cel™: Ablative and semi-ablative skin treatments result in increased trans-dermal water loss and potential for environment contamination. Occlusive dressings are typically used as part of post-procedure treatment of treated skin. Bio Cel™ occlusive gel is based on botanical lipids instead of petroleum, and has been used with benefit for over two years following laser resurfacing treatments. A boron-based molecule (hydrogen orthoborate) adds analgesic, anti-inflammatory, and bacteriostatic benefit. Tocopherol acetate (vitamin E) helps reduce erythema, edema, and acts as an antioxidant against free radical damage. Recombinant TGB-beta 3 provides anti-inflammatory benefit.

4. PURPOSE

The purpose of the study is to compare the tolerability of the application of a combination of a serum containing human bone marrow stem cell derived growth factor and cytokines (SCR COMPLEX™) and a botanical lipid-based occlusive (Bio Cel™) immediately following fractional RF treatment using the Venus Viva™ versus standard of care.

5. STUDY DESIGN

This is a randomized, open-label, multi-centre study to evaluate the tolerability of the application of a combination of a serum containing human bone marrow stem cell derived growth factor and cytokines (SCR Complex™) and a botanical lipid based occlusive (Bio Cel™) following facial fractional RF

treatments using the Venus Viva™ SR system.

Subjects will be asked to attend up to four visits to the clinic: Screening/consultation, 2 treatment visits - 3 weeks apart and 1 follow-up (FU) visit 3 days after the last treatment. Subjects will also receive a telephone call to evaluate response at 24 hours after each treatment as well as 72 hours after the first treatment. The first treatment visit may occur on the same day as the screening visit. RF treatments will be conducted as detailed in the Venus Viva™ User Manual. For each subject, study duration will be approximately 30 days, including study follow-up. It is anticipated that the study will start July 2016 with an anticipated stop date of September 2016. Changing of these dates will not require a protocol amendment.

Up to 100 healthy subjects from 2 centres who meet the inclusion and exclusion criteria will be enrolled and randomized to the study. The trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements. The Sponsor, Venus Concept, will maintain oversight and management of the study.

6. PRIMARY ENDPOINT

The primary outcome measure will be the tolerability of the application of the stem cell recovery complex (SCR Complex™) and a botanical lipid based occlusive (Bio Cel™) as compared with standard of care following fractional RF treatments.

7. SECONDARY ENDPOINTS

The secondary outcomes will be the subject's degree of discomfort and/or pain as measured by the visual analogue scale (VAS), the incidence of spontaneous adverse events (AEs) and the investigator's assessment of improvement using the Fitzpatrick Wrinkle and Elastosis Scale scores beforeand after treatment as well as Global Aesthetic Improvement Scale (GAIS) for each subject.

8. RANDOMIZATION

Subjects will be randomized to receive either standard of care (SOC) treatment (no topical therapy for 24 hours post fractional RF treatment) or a topical adjuvant combination treatment utilizing SCR Complex™ and Bio Cel™. The order of treatment will be assigned to subjects through subject number. All subjects will resume skin care as per VenusSkin protocol 24 hours post fractional RF treatments.

9. SUBEJCT SELECTION AND WITHDRAWAL

Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Male or non-pregnant, non-nursing female at least 21 years of age and less than 75 years of age.
2. Undergoing a dermatological procedure requiring ablation and resurfacing of the facial skin utilizing the Venus Viva™ SR system.

3. Women of child-bearing age are required to be using a reliable method of birth control prior to enrollment and throughout their participation in the study.
4. Able to tolerate the treatment as determined by a test spot application(s).
5. Mentally and physically competent to sign an informed consent document indicating that they understand the purpose and procedures required for the study and are willing to participate.
6. Able and willing to comply with the treatment/follow-up schedule

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Superficial metal or other implants in the treatment area.
2. Tattoos, permanent makeup, scars or piercings in the treatment area.
3. Current or past history of significant systemic illness.
4. Any active condition in the treatment area, such as sores, psoriasis, eczema and rash.
5. Subjects with a pacemaker or planned cardioversion in the future.
6. Receiving therapies or medication that may interfere with the study treatment.
7. Any surgical procedure in the treatment area within the last three months or before complete healing.
8. Currently receiving or received within 6 months before the planned start of treatment, an investigational drug / experimental medical device.
9. Any physical or mental condition, as per the investigator's discretion, which may make it unsafe for the subject to participate in this study.

Subject Withdrawal Criteria:

A subject has the right to withdraw from the study at any time, for any reason, without prejudice to her future medical care by the physician or the institution. Should a subject (or the subject's legally authorized representative) decide to withdraw, all efforts will be made to collect and report the final visit observations as thoroughly and timely as possible. Permission to contact subjects for the purpose of determining their status even after participation in the study is complete will not require additional ethics approval.

Subjects may be removed from the study if any one or more of the following events occur:

- Refusal of the subject to continue treatment and/or observations
- Decision by the Investigator that termination is in the subject's best medical interest
- Device failure
- Subject is lost to follow-up
- Other ethical or clinical considerations

Subjects will be recruited through chart review from the investigator sites, referrals or any type of media advertising. All screened subjects will be recorded on a screening log. Any information given to subjects and any advertisements intended for use for this study must be approved by the site's ethics board prior to use.

10. DEVICE and INVESTIGATIONAL PRODUCTS

10.1 Venus Viva™ System

The Venus Viva™ system is a fractional RF system that is intended for dermatological procedures requiring ablation and resurfacing of the skin. The Venus Viva™ device is a non-significant risk device. Consistent with 21 CFR 812.66, the device does NOT meet the criteria for significant risk device:

- It is not an implant and does not present a potentially serious risk.
- The device does not support or sustain human life, or present a potential for serious risk.
- The device is not used for a substantial importance in: diagnosing, curing, mitigating, or treating disease, or preventing impairment of health. The investigational device could not cause significant harm to any of the subjects.

The device could not cause any of the following potential harmful situations.

- Life threatening
- Permanent damage to body function
- Permanent damage to body structure
- Necessitate medical or surgical intervention
- Preclude permanent impairment of a body function
- Preclude permanent damage to body structure

The device does not appear on the FDA significant risk device list.

Maintenance

The part of the system that touches the subject's body (applied PINS) is disinfected prior to each treatment using a brush and disinfectant provided by Venus Concept®. The applicator is allowed to dry off completely between each use.

10.2 Topical Study Treatments

SCR Complex™ contains human growth factors and cytokines derived through laboratory culture of human bone marrow mesenchymal stem cells. Science recognizes these cells as "commander in chief" of healing in all tissues. These are migratory cells that "patrol" all tissues via the blood stream. In culture they produce patterns of growth factors and cytokines that are pro-healing and anti-inflammatory. Their numbers plummet with age so that by age 50 only 4% of the relative number at birth remains. Additional recombinant technology derived growth factors help promote fetus-like, non-fibrotic, anti-inflammatory healing.

Topical application of these bio-signals in conjunction with fractional laser resurfacing and dermal needling has resulted in enhanced healing and aesthetic improvements when combined with dermal needling.

Bio Cel™ is a botanical lipid-based gel occlusive that provides effective reduction in trans-dermal water loss and environmental contamination following ablative and semi-ablative procedures. Other

ingredients include a patented lipid soluble form of boric acid (provides bacteriostatic, anti-inflammatory and analgesic properties), tocopheryl acetate, and TGF-beta 3, a powerful anti-inflammatory growth factor.

Packaging

Topical study treatments (**SCR Complex** and **Bio Cel Occlusive)** will be provided to the study sites as commercially available product labeled for use in clinical trials only. In accordance with laws and regulations, the label will include the trade name, name and address of the manufacturer, quantity of contents, batch code and all other essential information.

Receipt, Storage, and Destruction

Topical study treatments will be shipped to the site from a central facility.

At the site, the topical study treatments will be stored at room temperature.

At the completion of the study, the topical study treatments will be destroyed as per the site's normal standard of practice for topical treatments.

11 STUDY PROCEDURES

Section 1, Schedule of Events, summaries the type and frequency of each study procedure to be performed in this study.

11.1 Screening Visit

The following procedures will be performed at the screening visit:

- Written informed consent
- Assign unique identifying number
- Inclusion/exclusion criteria
- Demographics
- Physical examination
- Medical history
- Concomitant medications
- Skin type (Fitzpatrick Scale)
- Wrinkle evaluation (Fitzpatrick Wrinkle and Elastosis Scale)
- Test spot

Test Spot

In order to assess tolerability to treatment, up to three test spots will be performed on the area adjacent to the ear on the side of the neck close to the back (so as it is not visible). Test spots should be based on skin type and desired outcome as per the chart below. The test spots will be used to determine the optimal parameters / setting combinations prior to the first treatment and later, the second treatment.

- Following the test spot, wait to ensure that the chosen parameters indeed lead to the appropriate immediate response.

- If slight erythema and edema and no adverse events occurred, treatment should be continued using the same setting or increase by not higher than ~10% parameters for each session.
- If no results are observed, the treatment parameters should be increased.
- If the patient has experienced adverse events along with improvement, the treatment parameters should be decreased.
- Fine-tuning of the parameters can be done before proceeding to treat the entire sub-area with the chosen parameters. Modification of parameters per treated area within a treatment session should only be carried out if required due to safety concerns.

Assessment of the test spot will be performed following at least 2 hours and up to 48 hours depending on skin type. As such, the first treatment may be conducted on the same day as screening. It is important to not start treatment prior to full evaluation of the reaction to the test spot and having optimal parameters identified.

Table 1 - Test spot and treatment parameter chart

Starting parameters			
Skin Type	Mild	Moderate	Intense
I-II	220v / 30ms	250v / 15ms	280v / 15ms
III-IV	220v / 15ms	240v / 15ms	240v / 30ms
V-VI	220v/ 10ms	230v / 5ms	240v / 5ms

Test Spots Mild			
Skin Type	Mild spot 1	Mild spot 2	Mild spot 3
I-II	220v / 5ms	220v / 15ms	220v / 30ms
III-IV	220v / 5ms	220v / 10ms	220v / 15ms
V-VI	220v/ 5ms	220v / 8ms	220v / 10ms

Test Spots Moderate			
Skin Type	Moderate spot 1	Moderate spot 2	Moderate spot 3
I-II	250v / 5ms	250v / 10ms	250v / 15ms
III-IV	240v / 5ms	240v / 10ms	240v / 15ms
V-VI	225v / 5ms	225v / 10ms	230v / 5ms

Test Spots Intense			
Skin Type	Intense spot 1	Intense spot 2	Intense spot 3
I-II	270v / 5ms	280v / 5ms	280v / 15ms
III-IV	240v / 5ms	240v / 15ms	240v / 30ms
V-VI	230v / 5ms	235v / 5ms	240v / 5ms

It is recommended to perform three test spots on the area adjacent to the ear on the side of the neck close to the back (so it is not visible). Test sports should be based on skin type and desired outcome as per the chart above. A test spot should be performed at the energy settings recommended in the chart above.
It is recommended that each subsequent treatment you increase the total % of energy no higher than 10% for each session.

11.2 Treatment Visits

Subjects that did not experience significant pain or skin sensitivity in response to the test spots can receive treatments. Each subject will be enrolled and scheduled for two treatments, three weeks apart and return for a follow-up visit three days after the second treatment for evaluation of the treatment area.

The following procedures and assessments are required at the treatment visits:

Pre-treatment

- Confirm continued eligibility regarding inclusion/exclusion criteria
- Review any changes in medication, health status or AE from last visit
- Assessment of adverse events including a photograph of the affected treatment area if an adverse event occurred
- Assessment of concomitant medications
- Assign randomized treatment (after 1st treatment visit only)
- Apply a topical anesthetic preparation over the treatment areas, if required. (If used, record in the CRF.)

Treatment

No lotion, gel or coupling medium is to be used in this treatment. The distal part of the applicator should be clean and dry before fitting it with a new 160 pins tip. The skin in the treated area should also be cleaned well (for removal of any lotions, make-up residues, topical anesthetic cream, etc.) and patted dry. Hairs that exist in the areas should be shaved off.

- Treatment should be performed while the subject is lying down comfortably; the operator should have easy access to the subject's treatment area.
- Areas of dental crowns, caps, braces, or other metal dental implants may be more sensitive to treatment and the clinician may use dental rolls, gauze or a tongue depressor to isolate the area and make the treatment more comfortable (if the face is treated).
- Treatment of subjects in hair-bearing areas may result in some damage to the follicles and subsequent loss of hair. Avoid the beard area (if face is treated) and other hair growing zones if the patient doesn't wish to have reduction of the hair growth. This treatment may also result in in-grown hairs.
- The applicator should be held perpendicular to and in close contact with the skin.
- Pressing the trigger will release the RF energy to the skin, creating a stamped imprint in a shape and intensity depending on energies.

- The immediate responses, indicative of the desired effect, are erythema and edema in the immediate area of the stamp and possibly also around it. The edema usually appears 1-2 minutes post-treatment 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, so the edema will indicate a more significant effect in these subjects.
- Treatment consists of a single pass over the designated area.
- Unless otherwise instructed, the energy parameters can be modified between the treatment visits, as per the Investigator's discretion.
- It is recommended that throughout the study, that one staff member administer the treatments and another staff member perform the evaluations of the treatment area.

Post Fractional RF Treatment

- Subject Discomfort Assessment recorded on a 100mm visual analogue scale (VAS) immediately post treatment.
- Subject Tolerability Scale immediately post treatment.
- Subjects will receive either the adjuvant combination treatment (SCR Complex™ followed by Bio Cel™ occlusive gel applied to the treatment area) or SOC (no topical applications to treatment for 24 hours post fractional RF treatment).
- Subjects will be asked to complete the Subject Home Tolerability Scale at 24 hours and 72 hours post-treatment
- Subjects will be provided with the Subject Home Instruction Sheet (Appendix B).
- A follow-up telephone call will be made to the subject 24 and 72 hours after the first treatment and 24 hours after the second treatment. Study staff will ask the subject to report on the treatment using the Self-Report Adverse Event Questionnaire (Appendix C) and remind the subject to complete and return to the clinic with their completed Subject Home Tolerability Scale at each visit.

11.3 Follow-up/Termination Visit

Subjects will be scheduled for a follow-up/termination visit 72 hours after the second treatment. The following procedures will be performed:

- The subject will be asked to report on the comfort(s)/discomfort(s) associated with the second treatment as per the Self-Report Adverse Event Questionnaire.
- Wrinkle evaluation (Fitzpatrick Wrinkle and Elastosis Scale)
- Global Aesthetic Improvement (GAI) Scale (Appendix D) as evaluated by the investigator.
- Subject Tolerability Scale 72 hours post second treatment
- Assessment of concomitant medications

The subject's participation in the study is now complete. In case of early termination, the date and reason for early termination will be recorded in the CRF. Subjects will also be asked to return to the clinic to complete follow-up/termination visit procedures.

12. SAFETY ASSESSMENT

Adverse Events Definitions

In this study, an Adverse Event (AE) is any undesirable clinical occurrence (sign, symptom, illness, or other medical event), that appears or worsens during the clinical study, or requires medical treatment or intervention to a subject, whether it is considered to be device related or not. If an adverse event occurs, the first concern will be the safety and welfare of the subject. Appropriate medical intervention will be made.

Any AE or complication reported by the subject or observed by the physician that occurs during or after treatment with the device will be recorded in the subject's medical record or source document and on the Adverse Event Case Report Form. The investigator will determine if the AEs are device related or procedure related. This assessment shall include the onset date, resolution date, severity, seriousness, frequency, treatment and outcome.

Each AE should be assessed according to the following criteria:

Severity
Each AE should be assessed for its severity, or the intensity of an event experienced by the subject.

Mild: Awareness of a sign or symptom that does not interfere with the subject's activity or is transient resolved without treatment and has no sequelae.

Moderate: May interfere with the subject's usual activity and require additional intervention and/or treatment, and may have additional sequelae.

Severe: Significant discomfort to the subject and/or interferes with the subject's activity. Additional intervention and or treatment are necessary. Additional sequelae occur. Severe is used to describe the intensity of an event experienced by the subject.

Adverse Device Effect (ADE)
Each AE should be assessed for its relationship to the device or procedure as identified as follows:

Device: This category should be restricted to adverse events directly attributable to the effect of the device.

Procedure: A procedure is any activity that supports the usage of the device.

Use the following categories for assigning the certainty of the relatedness:

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.

Pre-existing Conditions
A pre-existing condition should not be reported as an adverse event unless there has been a substantial increase in severity or frequency of problems, which has not been attributed to natural history.

Diagnosis of Adverse Event
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 the adverse events.

Anticipated Outcome Related Adverse Events
Anticipated adverse events in this study may include: temporary minor skin irritation, redness or swelling which may last from a few minutes to a few hours, minor swelling in the treated area for up to a week or slight heat discomfort during treatment. Very rarely, there may be possible bruising, burns, hyperpigmentation (skin turns darker) or hypopigmentation (skin turns lighter).

Any anticipated AE that occurs at any time during or after the use of the study device must be reported by the Investigator to Venus Concept. If the anticipated AE, in the opinion of Venus Concept or the Investigator, is likely to affect the safety of the subjects or the conduct of the study, the Research Ethics Board (REB)/Institutional Research Board (IRB) will be notified of the event within 10 working days after Venus Concept first receives notice of it.

Unanticipated Adverse Device Effects (UADE)
An unanticipated adverse device effect as defined by the Federal Regulations [21 CFR 812.3(s)] as "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." From a practical perspective, an unanticipated adverse device effect means a serious adverse event that is not listed in the device labeling, or the frequency or severity is greater than reported in the device labeling.

In the event of a serious (or unanticipated) adverse event, the Investigator will immediately notify the Venus Concept monitor by telephone. If such an adverse event is being reported after normal working hours, the Investigator will leave a voice message with an accompanying report of the AE. If the unanticipated AE, in the opinion of Venus Concept or the Investigator, is likely to affect the safety of the subjects or the conduct of the study, the IRB/ Helsinki/ other ethic committee will be notified of the effect within 10 working days after Venus Concept first receives notice of it.

Serious Adverse Event (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 event that:

- Results in, or contributes to a death;
- Is immediately life-threatening (injury or illness);
- Results in hospitalization, or prolongs an existing hospitalization;
- Results in permanent impairment of body structure or function, or in persistent or significant disability/incapacity;
- Results in an injury that requires medical intervention to prevent permanent impairment of body structure or function;
- Is a device malfunction or deterioration in the characteristics and/or performance of the device that results in death or serious deterioration in health;
- Is a device malfunction or deterioration in the characteristics and/or performance of the device that, if it were to occur again, could result in death or serious deterioration in health;
- Results in a congenital anomaly or birth defect;
- Is any medically significant injury, event or experience that requires medical/surgical intervention to prevent one of the outcomes listed above;
- Results in end-organ toxicity, including hematological, renal, cardiovascular, hepatic, gastrointestinal, and central nervous system events.

Reporting

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

All serious AEs, whether or not deemed expected or device-related, must be reported to the clinical monitor immediately or within 24 hours by telephone (see below). A written report must follow within five (5) working days and is to include a full description of the event and sequence. If the Venus Concept monitor cannot be reached, the site personnel will directly contact Joseph Reiz, Director of Clinical Research at 888-907-0115 or designate.

In addition to reporting adverse events within the context of this clinical study, any applicable local device reporting requirements will be followed.

Device Malfunctions

All investigational device malfunctions will be documented on the CRF and reported in the clinical results. Devices that malfunction during the procedure will be returned to the sponsor for analysis.

Device Malfunction: A device malfunction means the device did not meet its performance specifications, including specifications in the labeling, or otherwise perform as intended.

13. CLINICAL MONITORING

Pre study visit

- Assess the site's infrastructure (staff and facility) for the capability to conduct the study.
- Evaluate Investigator and staff's Experience, Qualifications and Capabilities-signed and dated CV.

Study Initiation visit

Orients the investigator's staff involved in the study on:

- The study protocol;
- Case report form (CRF);
- HIPAA, GCP and other regulatory requirements;
- Informed Consent Form and process;
- AE, SAE, Safety reporting;
- Subject information - subject's identification log, subject screening log, subject enrollment log, subject study visit log;

Study monitoring;

- Investigator's study files;
- Report of AE back from the Sponsor to the site;
- Expectations from the site regarding data collection and timelines.

Regular Monitoring visits

- Check on the progress of the study;
- Protocol and GCP compliance;
- Informed Consent Form and process;
- CRF completion, correction, source data verification
- AE, SAE, Safety reporting;
- Investigational product;
- Investigator's study files. Detailed monitoring schedule to be provided at study initiation

Final Study visit Close out monitoring visit

- Ensure Investigator understands the on-going responsibilities
- Record archival practices for source documents & CRF's after completion of the study -up to 15 years;
- Follow-up of on-going adverse events - up to 30 days after completion of the study;
- Notify the sponsor in the event of Health Authority inspection.

14. STATISTICAL CONSIDERATIONS

Statistical Design

This study is a randomized, open-label, multi-centre study.

Sample Size

Enrollment will continue until up to 100 evaluable subjects have been recruited to the study. Any subject removed from the study in accordance with the provisions of this protocol will be replaced by other subject.

Statistical Methods

All subjects who received any amount of treatment will be included in the report. The primary outcome measure is the subject's overall tolerability of the adjuvant combination treatment as compared to the standard of care post fractional RF treatment. The self-assessment will be based on a 5-point Likert scale - Subject Tolerability Scale (Appendix A). Summary statistics will be generated for subject tolerability immediately after treatment, 24 hours and 72 hours following

treatment as per the terms: Very tolerable, tolerable, having no opinion, intolerable and very intolerable.

The secondary outcomes measures are the subject's degree of discomfort and/or pain as measured by the visual analogue scale (VAS), the incidence of spontaneous adverse events (AEs) and the investigator's assessment of improvement using the Fitzpatrick Wrinkle and Elastosis Scale scores before and after treatment as well as Global Aesthetic Improvement Scale (GAIS) for each subject. VAS scores from the treated group will be compared with the VAS scores of the standard of care group. The investigator's assessment of improvement using the Fitzpatrick Wrinkle and Elastosis Scale from the treatment group will be compared with that of the standard of care group. The GAIS scores for both groups will also be compared.

Summary statistics will also be generated for all treatment emergent adverse events (TEAs). The following types will be reported:

- Overall TEAEs
- Severe TEAEs
- TEAEs related to treatment
- Serious Adverse Events (SAEs)
- SAEs related to treatment
- TEAEs leading to treatment discontinuation

15. DATA HANDLING and RECORD KEEPING

Confidentiality

This clinical study is confidential and should not be discussed with individuals outside the study. Additionally, the information in this document and in the study may contain secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by federal or state law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the study that have a need to know, but all such persons must be instructed not to further disseminate this information to others. The data may be used now and in the future for presentation or publication at the investigator and/or sponsor's discretion or for submission to governmental regulatory agencies. All reports and communications relating to subjects in the study will identify each subject only by the subject's initials and by the subject's study number.

Source Documents

Source documents are the initial documents whereon subject data are recorded. This includes, but is not limited to, original subject files, hospital records, and original recordings/tracings from automated instruments (e.g., ECG, Blood tests, etc.), X-ray films, and laboratory notes. The information contained within the source documents is used to complete the CRF worksheets.

All information captured on the CRF worksheets should be accurately supported by the source documents unless specifically approved by Venus Concept® and written so in a certification document

filed in the site and study folders. (e.g., Subject questionnaires will be cleared to be included as part of the CRF worksheets and considered as source documents).

Study Records/Source Document Inspection
The investigator will allow representatives of Venus Concept®, its monitoring team, the Health Authority or other governmental regulatory agencies to audit all study records, worksheets, and corresponding portions of the subject's office and/or hospital medical records at regular intervals throughout the study. These inspections are conducted to verify adherence to the protocol, integrity of the data being captured on the worksheets and compliance with applicable regulations. Venus Concept® agrees that subjects' medical records will be maintained in a confidential manner. Study reports will not identify subjects by name.

Any additional information relevant to the study should be included in the subject's source documents. In particular, any deviations from the study protocol or procedures should be recorded in the source documents.

For example, if study required procedures or visits are not completed or are completed outside the time frame specified in the protocol, the reasons for the departure should be explained in the source documents. The investigator must maintain all study documentation at least 2 years after the last approval of marketing application in and until there are no pending or contemplated marketing application or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements (in Israel for 15 years) or by an agreement with the sponsor. The sponsor should inform the investigator in writing when the trial-related records are no longer needed.

Data Collection Method
Data from the subject's permanent medical records (see source documentation section) will be recorded on worksheets supplied by the investigator and approved by the sponsor. These worksheets (comprising the CRF's) will be used to transmit the information collected in the performance of this study to the clinical database either manually or by site data entry (a third party vendor may be used for this). CRF's should be filled no longer than 2 weeks after each visit. All worksheets must be typewritten or filled out in black ink, accurately and promptly following each examination or procedure. No questions will be left blank. Corrections will be made only by lining out (single line) incorrect data and writing in the revisions. All corrections must be initialed and dated by the individual performing/recording the correction. If the reason for the change is not obvious, an explanation for the change will be recorded. Blacking out or using correction fluid or an eraser will not be used to eliminate data. The investigator must review the worksheets for completeness and accuracy and must sign/date the forms where indicated. Signature stamps or substitutes are not acceptable. The investigator will retain originals of all source documents, subject consent forms, and study data as a permanent record. Each set of original worksheets should be reviewed for accuracy and completion (signatures, dates, adverse events, serious adverse events, protocol departures) and maintained in the investigator's study files.

16. QUALITY ASSURANCE AND QUALITY CONTROL

Monitors
Each study will be monitored by a representative of Venus Concept® at regular intervals throughout the course of the study according to a pre-defined monitoring plan. On site monitoring of the investigator's facilities aids in ensuring compliance with the protocol. Any deficiency noted during the monitoring visits will be discussed with the investigator and the corrective actions to be taken agreed upon. Should the sponsor determine, at any time during the study that the investigator is not in regulatory/protocol compliance, measures necessary to establish compliance will be implemented. If compliance cannot be maintained, the sponsor will suspend or terminate the study.

Device Use/Accountability
The evaluation site personnel will maintain records of the model and serial number of the devices (if appropriate) used for each treatment during the conduct of the study. If the clinic does not own the device to be used in this study, then it will be provided by Venus Concept for the duration of the study. The device and any additional equipment dedicated to the clinical study that was provided by the Sponsor will be returned to the Sponsor at the end of the study.

Training Requirements
Both the Investigator and the Sponsor, prior to any independent use of the device, will agree upon the Investigators' training requirements. Prior to the study, the Sponsor will ensure that each investigator has received in depth training on the use of the device.

17. ETHICAL AND REGULATORY CONSIDERATIONS

Ethical Conduct of the Study
The investigator is responsible for ensuring that this study is conducted according to the protocol, current International Conference on Harmonization (ICH) guidelines on good clinical practice (GCP), the latest revision of the 'Declaration of Helsinki', all applicable Federal and local government regulations.

An ethical committee will approve the clinical study protocol and related documents prior to site study initiation. Approval will be indicated in writing with reference to the final protocol number and date.

Details regarding the ethic committee constitution, including the names of its members, their qualification and what function they perform on the board, will be made available to enable Venus Concept® and the investigator to comply with internationally accepted guidelines governing good clinical research practices. A statement that the ethics committee is organized and operates according to GCP and the applicable laws and regulations must also be available.

This study will be conducted in compliance with the protocol after approved by Venus Concept® and site investigators. No deviation from the protocol will be implemented without the prior review and approval of Venus Concept® except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to Venus Concept® as soon as possible.

Sponsor's Obligations
A Sponsor must assume the following responsibilities and must keep the required records. The Sponsor must:

- Provide the Investigator with the necessary information - Protocol and Device User's Manual or Instructions for Use.
- Inform the Investigator of all new information that may affect his/her decision of whether to continue their participation in the study.
- Provide the supplies (Venus Viva™) for the investigation.
- Ensure the investigator is of good standing and knowledgeable in relevant areas of clinical research, including the protection of human subjects.
- Ensure that other site personnel have appropriate research experience and infrastructure to ensure adherence to the protocol and enrollment of sufficient evaluable subjects.
- Maintain the following records:
  1. A signed protocol and CRF
  2. All correspondence that relate to the clinical trial
  3. Signed Investigator Agreement
  4. Signed curriculum vitae (CV) and current medical license for all investigators and sub-investigators.
  5. Records of device shipment and disposal (shipping receipts, material destruction records, etc.)
  6. Other records as required by the Health Authority

Investigator's Obligations
Upon signing the protocol, the Investigator agrees to assume the following responsibilities;

- To keep the required records for a period of fifteen years following completion of the study
- To file the required reports in a timely manner:
- Conduct the Investigation in compliance with the protocol.
- Changes to the protocol may only be made after approval by the Sponsor, or when necessary to protect the safety, rights or welfare of a subject.
- Personally conduct or supervise the investigation.
- Read and understand the information in the Protocol and Investigator Brochure.
- Be aware of the potential risks and side effects of implanting the Venus Viva™ treatment.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations.
- Inform all subjects that the device is being used for investigational purposes and ensure that the requirements related to obtaining the informed consent are met.
- Dispose of remaining supplies as directed by the Sponsor.
- Maintain the following records (for a period of 15 years following completion of the study):
  1. Signed copy of the protocol.
  2. Signed consent forms
  3. All correspondence as relates to the clinical trial
  4. Case Report Forms
- File the following reports:
  1. Severe adverse device related effects must be reported to the sponsor by phone within 24 hours. A written report must follow within five working days.

2. Unanticipated adverse device related effects must be reported to the sponsor as soon as possible, within 10 working days.
3. Deviations, which were made from the protocol for emergency use, must be reported to the sponsor as soon as possible, but no later than five working days after its occurrence.

Informed Consent Procedure

- In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements, and should adhere to GCP and HIPAA.
- Prior to the beginning of the trial, the investigator should have the Ethics Committee written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.
- The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the Ethics Committee's approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.
- Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.
- The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information given approval/favorable opinion by the Ethic Committee.
- Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.
- Prior to a subject's participation in the trial, the written Informed Consent Form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who is authorized to conducted the informed consent discussion.
- Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written Informed Consent Form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.
- Subject or the subject's legally acceptable representative must provide informed consent and sign and date with his hand writing an Informed Consent Form (ICF) prior to any study related procedures being performed. The person reviewing the ICF with the subject must also sign and date the ICF. Each of the signers must sign and date in the presence of the other signer. If subject or the subject's legally acceptable representative is unable to comprehend and sign the Consent Form, subject must not be enrolled in the study.

18. STUDY COMPLETION

The PI will complete and report the study in satisfactory compliance with the protocol. It is agreed that, for any reasonable cause, either the PI or the sponsor, Venus Concept®, may terminate this study, provided a written notice is submitted at a reasonable time in advance of intended termination. If the study is terminated for safety reasons, the investigator will be notified immediately by telephone, followed by written instructions for study termination notification.

19. INVESTIGATOR AGREEMENT FOR PROTOCOL

I have read the foregoing protocol

"CLINICAL EVALUATION OF THE SAFETY OF USING A POST TREATMENT TOPICAL ADJUVANT COMBINATION FOLLOWING RF FRACTIONAL ABLATION USING THE VENUS Viva™"

and agree to:

Conduct the study as outlined herein;

Maintain the confidentiality of all information received or developed in connection with this protocol and
Conduct this study in accordance with GCP Standards and any other applicable local/state laws and regulations;

Comply with the signed investigators agreement.

Name: (Please print)._____

Telephone:_____

Signature: _____

APPENDIX A

SUBJECT HOME TOLERABILITY SCALE- PROTOCOL CS0116

RETURN COMPLETED FORM AT NEXT CLINIC VISIT

Please circle the Score that best describes your tolerability of the study procedure.

Date: _____

Subject Tolerability Scale – *24hrs* after Treatment	
Score	
(4)	Very Tolerable
(3)	Tolerable
(2)	Having no opinion
(1)	Intolerable
(0)	Very Intolerable

Please circle the Score that best describes your tolerability of the study procedure.

Date: _____

Subject Tolerability Scale – *3 days* after Treatment	
Score	
(4)	Very Tolerable
(3)	Tolerable
(2)	Having no opinion
(1)	Intolerable
(0)	Very Intolerable

_____ Subject Initials

_____ DD-MMM-YYYY

APPENDIX B

Subject Home Instruction Sheet

Clinical Evaluation of the Tolerability of Using a Post Treatment Topical Adjuvant Combination Following Fractional Radiofrequency Ablation Using the Venus Viva™- Protocol CS0116

- Tiny scabs about the size of a small pinprick will usually form 24-72 hours post-treatment. The scabs should not be scratched and should be allowed to shed off naturally, usually 1-2 days after their formation. In case of discomfort, cool/cold compress (but not ice packs) may be applied.
- On the day after the treatment, activities where potential damage due to overheating, direct rubbing or other contact may occur (e.g., Jacuzzi, kickboxing, massage) should be avoided.
- No moisturizer or other topicals should be applied after the treatment. Make-up may be applied only 24 hours after each treatment, unless an adverse event occurs in the area.
- You may use regular soaps, but not scrub soaps or exfoliants to clean the treatment area.
- Tanning of any sort is not allowed of the treated areas. Use a high factor sunscreen with SPF of at least 30 and to protect the treated area from direct sunlight for the entire period of the study.
- A follow-up telephone call will be made to you 24 and 72 hours after the first treatment and 24 hours after the second treatment to see how you are doing and to remind you to complete and return the Subject Tolerability Scale at your next visit.

Site contact information.

APPENDIX C

Self-Report Adverse Event Questionnaire

Date:	___ / _____ / _____ Patient Code: ____/_____/_____ DD MMM YYYY Site # Pt. Initials Pt. #
Have there been any changes in your health since your last visit? Yes / No If Yes, please describe the event in detail:	
Have there been any changes in your treatment area since your last visit? Yes / No If Yes, please describe the event in detail:	
Have there been any changes in your medications? Yes / No If Yes, please specify:	
Remind subject to complete the Subject Home Tolerability Scale. Yes / No	

Evaluator Name / Signature

DD-MMM-YYYY

APPENDIX D

Global Aesthetic Improvement (GAI) Scale		
Score		
(3)	Very Much Improved	Optimal cosmetic result.
(2)	Much Improved	Marked improvement in appearance from the initial condition, but not completely optimal.
(1)	Improved	Obvious improvement in appearance from the initial condition.
(0)	No Change	Appearance is essentially the same as baseline.
(-1)	Worse	Appearance is worse than the original condition
(-2)	Much Worse	Marked worsening in appearance from the initial condition.
(-3)	Very Much Worse	Obvious worsening in appearance from the initial condition.