Clinical Evaluation of the Safety and Efficacy of RF and PEMF for the Treatment of Soft Tissue Injury

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BPI-SF	Brief Pain Inventory (Short Form)
BP	Blood Perfusion
CRF	Case Report Form
EC	Ethics Committee
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HC	Health Canada
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISO 14155:2011	International Organization for Standardization Good Clinical Practices for Clinical Investigations of Medical Devices
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
PEMF	Pulsed ElectroMagnetic Fields
QC	Quality Control
RF	Radiofrequency
ROM	Range of Motion
SAE	Serious Adverse Event
SAP	Statistical and Analytical Plan
US	Ultrasound
VAS	Visual Analog Scale

STATEMENT OF COMPLIANCE

This clinical study will be conducted in compliance with the latest version of:

- Declaration of Helsinki (2013)
- ISO 14155:2011 (Clinical investigation of medical devices for human subjects - Good clinical practice)
- Medical Devices Directive 93/42/EEC, MEDDEV 2.7/3
- Therapeutic Products Directorate (TPD) Health Canada, Medical Devices Division
- United States 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)

and any of the applicable regional or national regulations pertaining to conduct of a clinical investigation of a medical device.

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

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

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

INVESTIGATOR SIGNATURE PAGE

Protocol #:	CS1217
Protocol Title:	Clinical Evaluation of the Safety and Efficacy of RF and PEMF for the Treatment of Soft Tissue Injury
Protocol Version:	2
Protocol Date:	15 October 2018

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

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

Institution:

_____

_____

Principal Investigator (Printed name)

_____ _____

Principal Investigator (Signature) Date

PROTOCOL SUMMARY

Title: Clinical Evaluation of the Safety and Efficacy of RF and PEMF for the Treatment of Soft Tissue Injury

Objectives: The objective of this evaluation is to determine the degree of pain, range of motion (ROM) and blood perfusion (BP) in subjects with soft tissue injuries who have undergone treatment with radiofrequency (RF) and pulsed electromagnetic fields (PEMF) as compared to subjects who have undergone treatment with ultrasound (US).

Endpoint

Primary endpoints

- Change in pain severity during daily activity at Visit 4 compared to Baseline as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.
- Change in pain interference during daily activity at Visit 4 compared to Baseline as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.
- Change in range of motion pre- and post-treatment at Visit 4 compared to Baseline as measured by Goniometer in the RF and PEMF arm as compared to the US arm.
- Changes in range of motion at Visit 7 compared to Baseline as measured by Goniometer in the RF and PEMF arm as compared to the US arm.
- Change in tissue blood perfusion (BP) pre- and post-treatment at Baseline, Visit 3 and Visit 6 as measured by perfusion imaging in the RF and PEMF arm as compared to the US arm.

Secondary endpoints

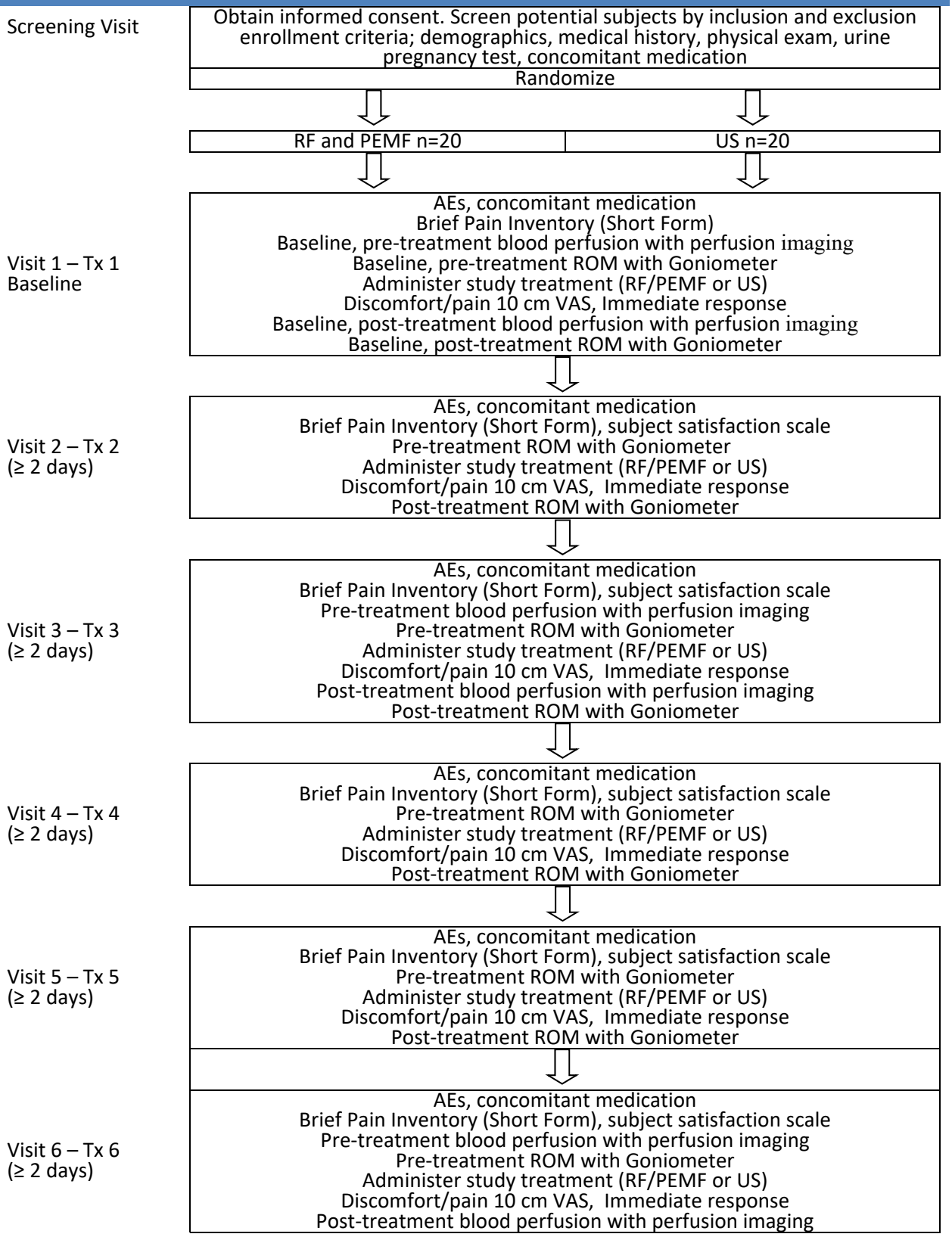
- Change in pain severity during daily activity at Visit 6 as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.
- Change in pain interference during daily activity at Visit 6 as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.
- Change in range of motion pre- and post-treatment at Visit 6 as measured by Goniometer in the RF and PEMF arm as compared to the US arm.
- Subjects' assessment of satisfaction with the treatment at Visit 4, Visit 6 and Visit 7 as measured with a 5-point Likert Satisfaction scale in the RF and PEMF arm as compared to the US arm.
- Change in tissue blood perfusion (BP) compared to Baseline at Visit 7 as measured by perfusion imaging in the RF and PEMF arm as compared to the US arm.

Safety

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

Population:	The evaluation will enroll up to 60 healthy male and female subjects, 18 - 75 years of age, who are seeking treatment for pain associated with soft tissue injuries.
Phase:	Pre-Marketing
Number of Sites enrolling participants:	Up to wo Sites
Description of Study Devices:	The Venus HEAL™ is an investigational device delivering multi-polar RF and PEMF energies. The device utilizes two applicators which are ergonomically designed to fit different treatment areas and are equipped with an integrated thermometer and automatic temperature control (ATC). The Dynatron Solaris® Series ultrasound device is a FDA and Health Canada cleared device delivering electrical stimulation, ultrasound and/or a combination electrical stimulation and ultrasound energies. The ultrasound energy is cleared for the relief of pain, muscle spasms and joint contractures. The device utlilizes an ultrasound transducer to administer treatment.
Study Duration:	Approximately 6 months
Participant Duration:	Twenty-one Days

SCHEMATIC OF STUDY DESIGN



	Post-treatment ROM with Goniometer
	⇩
Visit 7 1 week FU (+/- 2 days)	AEs, concomitant medication Brief Pain Inventory (Short Form), subject satisfaction scale Blood perfusion with perfusion imaging and Final ROM with Goniometer

1 KEY ROLES

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Incidence rate of soft tissue injuries is on a continuous rise. These injuries are caused by disruption of soft tissues including muscles, tendons, ligaments, nerves, fascia, fat, fibrous tissues, blood vessels and synovial membranes. These injuries result in acute pain, swelling, bleeding, bruising and loss of function (Sports Medicine Australia, ND). There is an increasing number of patients suffering from soft tissue injuries due to sports, life and work style and aging. Furthermore, with an increasing population of young adults participating in organized sports and physical activities, the incidence of soft tissue injuries is increasing (Kellett J, 1986). Soft tissue injuries can occur in different regions of body including limbs, neck, back or trunk (Hung K. *et. al*, 2018).

The process of soft tissue healing is slow. It may take up to 6 months to a year to heal depending upon the severity of injury. Tissue healing is spread over 3 phases:

- Acute inflammatory Phase: The phase starts right after the injury and lasts up to 72 hours depending upon the severity of injury and may be accompanied by bleeding and inflammation. The patient feels the most pain in this phase of the healing. (Kellett J, 1986).
- Repair Phase: The Repair phase last from 48 hours up to 6 weeks. During this phase, synthesis and deposition of collagen and vascular budding takes place at the site of injury. Collagen production continues for up to 6 weeks and macrophages are employed to remove clots, cellular debris and red blood cells from the site of the injury (Kellett J, 1986).
- Remodeling Phase: Remodelling phase may last from 3 weeks up to a year as collagen is remodelled to increase functional capabilities of ligament and tendon. Normal ligaments are different from the repaired ligaments in their collagen content. Normal ligaments are primarlily composed of collagen type I while repaired ligaments contain a significantly higher proportion of collagen III, which is different in the number of cross linkages between and within the collagen subunits (Kellett J, 1986).

Currently practiced soft tissue injury management methods include RICE (Rest, Ice, Compress by bandage and Elevate) and No HARM (Heat, Alcohol, Running and Massage) protocols. The RICE method relies on rest, icing the injury, compression by bandage to avoid swelling or further bleeding and elevating the injury above the heart to reduce swelling. The No HARM protocol complements the RICE protocol and demands no heat, alcohol, running or massage to avoid the excessive blood flow in the injured area. There is a range of other treatment modalities including thermal therapies, ultrasound,

Transcutaneous Electrical Nerve Stimulation (TENS), Low Level Laser therapy (LLLT), cryotherapy, Light Emitting Diodes (LEDs), Pulsed Electromagnetic fields (PEMF) , Radiofrequency (RF), shockwave, vacuum and mechanical therapy (massage, mechanical traction).

Ultrasound (US) is a commonly used treatment modality for the management of soft tissue injury. As a deep-heating agent that increases intramuscular tissue temperatures, US promotes healing and reduces muscle spasm, pain and chronic inflammation and increases blood flow and collagen extensibility within the tissue (Draper D et al., 1995, Gange K et al., 2017, Miller D et al., 2012). Thermal effects of ultrasound and the resulting reaction of tissue heating, directly increases tissue metabolism which increases blood flow improving scar tissue and fibrosis, and leads to greater range of motion and less pain (Baker R et al., 1991, Morishita K et al., 2014). Physiologic effects of ultrasound as measured by laser Doppler flowmetry show significant increases in cutaneous blood flow (Baker R et al., 1991, Noble J et al., 2007).

Venus HEAL™ combines multi-polar radiofrequency (RF) and pulsed electromagnetic fields (PEMF) technologies - $(MP)^2$ technology. Multi-polar RF and PEMF work synergistically. The device employes RF energy to achieve uniform heat distribution between 8 electrodes of the applicator for homogenous deep tissue heating and tissue regeneration and remodelling. RF stimulates fibroblast migration leading to increased collagen production and myogenic precursor cells (MPCs). Anabolic processes at the site of injury increase blood flow to promote healing. (Oliveira T, et al, 2017). Furthermore, the heat generated by RF leads to hydrogen bonds disruption in the collagen structure, leading to partial protein denaturation and stimulating collagen synthesis, which may positively influence the healing process in soft tissue injuries (Weiss, R.A, 2013). PEMF has been demonstrated to increase fibroblast derived collagen production through a non thermal mechanism of membrane stimulation and stimulation of fibroblast mediated angiogenesis which facilitates and enhances wound healing in tissues (Akira S et al., 2008, Murray JC, Ferndale RW, 1985 and Tepper OM et al., 2004).

The study will investigate whether the impact of PEMF and RF therapies is safe and efficacious for the treatment of pain associated with soft tissue injuries as compared to treatment with US, and to show the effects of PEMF and RF therapies on range of motion and blood flow associated with soft tissue injuries as compared to US therapy.

2.2 RATIONALE

The combination of multi-polar radiofrequency (RF) and pulsed electromagnetic fields (PEMF) technology has been shown in clinical studies to safely and efficiently alternate collagen structures. This may assist in the soft tissue injury healing process and give pain relief (Gold MH, 2015). The synergistic effect of RF and PEMF energies also stimulates angiogenesis providing the oxygen and nutrient requirements of healing tissue leading to a shorter rehabilitation period and pain reduction (Oliveira T, et al, 2017). Therapeutic ultrasound is one of the most widely used physical modalities in rehabilitation clinical practice. Physiological effects of thermal therapeutic ultrasound include increased tissue temperature, increased local blood flow, increased extensibility of tissue, increased range of motion and a reduction in viscosity of fluid elements in the tissue (Draper D, et al., 1995, Gange K et al., 2017, Miller D et al., 2012, Morishita K, et al., 2013, Speed, C, 2001, Wong R et al., 2007).

The objective of this evaluation is to determine the degree of pain, range of motion (ROM) and blood perfusion (BP) in subjects with soft tissue injuries who have undergone treatment with radiofrequency

(RF) and pulsed electromagnetic fields (PEMF) as compared to subjects who have undergone treatment with ultrasound (US).

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

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

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

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Expected adverse events of the RF/PEMF and ultrasound treatment procedures include but are not limited to mild discomfort, heat sensation during and following treatment and transient edema and erythema in the treated area for up to two hours following treatment.

The following events are also identified as low probability anticipated adverse events related to RF/PEMF: pain, tenderness, blistering, burns, excessive redness or swelling, infection, scarring, potential damage to hair follicles within treatment zones, hypopigmentation and hyperpigmentation.

Further information about risks associated with the use of the Venus HEAL™ device are reported in the device User Manual.

Residual risks will be mitigated as follows:

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

2.3.2 KNOWN POTENTIAL BENEFITS

If the subject agrees to participate in this study, he/she will be contributing to the understanding of the Venus HEAL™ device's impact and the biological processes that are occurring during soft tissue healing. This understanding may lead to optimization of the treatment with this device for this indication. In addition, the subject may benefit from improvement in the treated areas.

3 OBJECTIVES AND PURPOSE

The objective of this evaluation is to determine the degree of pain, range of motion (ROM) and blood perfusion (BP) in subjects with soft tissue injuries who have undergone treatment with radiofrequency (RF) and pulsed electromagnetic fields (PEMF) as compared to subjects who have undergone treatment with ultrasound (US).

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a randomized, controlled study of the safety and efficacy of a radiofrequency (RF) and pulsed electromagnetic fields (PEMF) device compared to ultrasound (US) for the treatment of pain associated with soft tissue injuries, and to show the comparative effects on blood perfusion (BP) and range of motion (ROM). Total expected duration of the clinical study is approximately 6 months (enrollment period of 4 months and a follow-up period of 3 weeks) while individual participation will take three weeks.

4.2.1 PRIMARY ENDPOINT

- Change in pain severity during daily activity at Visit 4 compared to Baseline as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.
- Change in pain interference during daily activity at Visit 4 compared to Baseline as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.
- Change in range of motion pre- and post-treatment at Visit 4 compared to Baseline as measured by Goniometer in the RF and PEMF arm as compared to the US arm.
- Changes in range of motion at Visit 7 compared to Baseline as measured by Goniometer in the RF and PEMF arm as compared to the US arm.
- Change in tissue blood perfusion pre- and post-treatment at Baseline, Visit 3 and Visit 6 as measured by perfusion imaging in the RF and PEMF arm as compared to the US arm.

4.2.2 SECONDARY ENDPOINTS

- Change in pain severity during daily activity at Visit 6 as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.
- Change in pain interference during daily activity at Visit 6 as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.
- Change in range of motion pre- and post-treatment at Visit 6 as measured by Goniometer in the RF and PEMF arm as compared to the US arm.
- Change in tissue blood perfusion (BP) compared to Baseline at Visit 7 as measured by perfusion imaging in the RF and PEMF arm as compared to the US arm.
- Subjects' assessment of satisfaction with the treatment at Visit 4, Visit 6 and Visit 7 as measured with a 5-point Likert Satisfaction scale in the active arm as compared to the sham arm.

Safety endpoints:

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

4.2.3 EXPLORATORY ENDPOINTS

None

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

1. Able to read, understand and provide written informed consent to receive treatment.
2. Healthy, adult male or female, 18 - 75 years of age.
3. Sustained recent (within 30 days), painful unilateral mild to moderate soft tissue injury.
4. Seeking treatment for pain associated with mild to moderate soft tissue injury.
5. BMI score is greater than 18.5 and less than 29.9.
6. Able and willing to comply with the treatment and follow-up schedule and requirements.

5.2 PARTICIPANT EXCLUSION CRITERIA

1. Pregnant, planning to become pregnant or nursing during the ocurse of the study.
2. Open wound or infection at site of soft tissue injury.
3. Evidence of severe injury, including fracture or nerve injury.
4. History of musculoskeletal disorders, including arthritis, tendonitis, bursitis, ankylosing spondylitis.
5. Moderate to severe ligament tear.
6. Having a known anti-coagulative or thromboembolic condition or taking anticoagulation medications one week prior to and during the treatment course (to allow inclusion, temporary cessation of anticoagulant use as per the subject's physician discretion is permitted).
7. History of immunosuppression/immune deficiency disorders (including HIV infection or AIDS) or currently using immunosuppressive medications.
8. Having an anesthetic or corticosteroid injection within 4 weeks of study enrollment.
9. Having any active electrical implant anywhere in the body, such as a pacemaker or an internal defibrillator.
10. Having a permanent implant in the treated areas, such as metal plates and screws or an injected chemical substance.
11. History of any form of cancer or pre-malignancy in the treatment area.
12. Severe concurrent conditions, such as cardiac disorders, uncontrolled hypertension, etc.
13. Patients with history of diseases stimulated by heat, such as recurrent herpes simplex in the treatment area.
14. History of epidermal or dermal disorders (particularly if involving collagen or microvascularity).
15. Poorly controlled endocrine disorders, such as diabetes.
16. Skin piercings in the treatment area.
17. Having a history of anxiety-depression syndromes.
18. Any condition which in the opinion of the investigator may jeopardize the patient’s safe participation.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Up to 40 healthy male and female subjects, 18-75 years of age who are seeking treatment for pain associated with soft tissue injuries will be enrolled. It is anticipated that it will take up to 6 months to

complete the study. Qualified sports medicine physicians will be the recruited to participate as investigators. Subjects will be recruited from the investigator's practice. Any advertising campaigns and materials will be reviewed and approved by an Ethics Committee or Institutional Review Board (EC or IRB) before implementation. Subjects will be contacted by the investigative site on a regular basis in order to enhance retention.

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 End of Study/Early Discontinuation case report form (CRF) should be completed. On the discontinuation page, the Investigator should record the date of the withdrawal and the reason for withdrawal.

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

The investigator may terminate participation in the study if:

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

5.4.2 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 performance study endpoints. Every effort will be made to conduct an exit visit (final study visit, see section 7.3.5) to withdrawn patients, and to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs) and device deficiencies.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

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

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

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

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

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

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

If suspension or premature termination occurs,

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

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

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

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

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

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

6 INVESTIGATIONAL DEVICE

6.1 INVESTIGATIONAL DEVICE AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

The Venus HEAL™ is an investigational device which will be provided by the sponsor to the site for this investigation. An activation code will be required to activate the device. This code will not be provided to the investigative site until all regulatory and EC or IRB approvals are in place and the site has received training for both the device and the study.

6.1.2 DEVICE SPECIFIC CONSIDERATIONS

- Device model - Venus HEAL™
- Device settings and programming – 30-80% as per treatment area selected and applicator selected
- Duration of exposure and frequency – 10-20 minutes depending on the treatment area selected

The Venus HEAL™ is a non-invasive medical device, which will be used in treating soft tissue injuries. The system consists of two applicators ergonomically designed to fit different soft tissue treatment areas and each is equipped with an integrated thermometer and automatic temperature control (ATC).

Further details about the Venus HEAL™ can be found in the device User Manual.

The comparative ultrasound device, one of the Dynatron Solaris® series (model numbers 709, 708, 706 and 705 or equivalent) will be used as the comparator. The series system consists of ultrasound transducers in various sizes which are able to deliver 1, 2 and 3 MHz frequencies dependent upon the size of the treatment area and the depth of treatment required. Further device details can be found in the User Manuals for each of the models.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

Accountability shall be achieved during and after the clinical investigation by assignment of serial numbers to device and applicators.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

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

Demographics
Medical /surgical history (obtained by interview and/or medical records)
Physical examination
Assessment of eligibility
Randomization to study treatment arm
Urine pregnancy test (visit 1 only)
Administration of questionnaires and scales for subject reported outcomes
Administration of testing modality to measure Cutaneous Blood Flow (Doppler Flowmetry)
Administration of testing modality to measure Range of Motion (Goniometer)
Assessment of treatment area after each treatment

Adverse event recording
Concomitant medications

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

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

7.2.2 OTHER ASSAYS OR PROCEDURES

None

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Screening Visit

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

Subjects 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 case report form (CRF).

During the first visit, the study investigator, and/or his/her designee, will screen the subject for eligibility to participate in the clinical study using the inclusion/exclusion criteria. A urine sample for the pregnancy test will be obtained for patients of child-bearing potential. During screening, the study doctor will review the subject's medical/surgical history, and examine the subject's targeted area to ensure that it meets the study criteria. Targeted treatment area will be located at the area of the soft tissue injury site as defined by the Investigator. The subject will complete screening and the treatment will be scheduled. Treatment may be performed on the day the subject was enrolled, Visit 1, Treatment 1, (if the result of the urine pregnancy test is available for female subjects of child bearing potential).

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

7.3.2 ENROLLMENT/BASELINE

Enrollment/Baseline Visit (Visit 1, Treatment 1)

Once a subject has been confirmed that they continue to meet the inclusion and none of the exclusion criteria, each subject will be randomized, in a 1:1 ratio, to receive either RF and PEMF treatment or US treatment according to a randomization code supplied by the sponsor.

Concomittant medications and adverse events will be recorded.

Pre-Treatment

Brief Pain Inventory (Short Form) (BPI-SF)

Prior to any study procedure, subjects will complete the Brief Pain Inventory (Short Form) (BPI-SF).

Pre-treatment ROM and BP measurements

Prior to either study treatment (RF/PEMF or US), subjects' blood perfusion measurements for the identified treatment area will be obtained with the use of the perfusion modality as measured by the Investigator and as instructed by the User Manual for the device. Subjects' range of motion will be measured by the Investigator in the identified treatment area using the Goniometer instrument.

Pre-Treatment – Venus HEAL™

Anesthesia of the treatment area is not required. Treatment procedure should include positioning of the patient in a manner that enables comfortable access to the treated anatomical site.

Before each treatment, the applicator surface should be clean and disinfected with a medical disinfectant. Remove any jewelry/metal items from the vicinity of the treatment area. Apply a thin layer of Glide™ (medical grade glycerin) to the treatment area.

Pre-Treatment – Dynatron Solaris® Series Ultrasound

Treatment procedure should include positioning of the patient in a manner that enables comfortable access to the treated anatomical site. Remove any jewelry/metal items from the vicinity of the treatment area. Apply ultrasound gel to the treatment area.

Treatment

RF and PEMF Treatment: On treatment screen, set the energy level 30-80% depending on the treatment area selected and the applicator chosen.

Place the applicator in contact with the skin, and start moving the applicator on the treatment area. After 1 minute, the temperature must be taken using the IR thermometer to confirm that the subject has reached 42-45 degrees centrigade in the treatment area (treatment target temperature). The automatic temperature control (ATC) will maintain the treatment target temperature. The treatment should be applied in a slow and steady pace covering the area in random movements but ensuring that the area is completely and uniformly covered.

If the patient feels discomfort or finds it too warm, reduce the percent of energy by 5-10% at a time (5% for the small applicator and 10% for the larger applicator). If the skin drops below treatment temperature, the applicator is being moved too fast or the power has been decreased too much. The percent of energy can be increased by 5-10% at a time (5% for the small applicator and 10% for

the larger applicator) at a time until the treatment area temperature returns to the treatment target temperature.

After the first treatment, the beginning and ending parameters (percent of energy) are recorded. These are now the base line parameters to be used for subsequent treatments with this patient. Once the patient's personal parameters are established, begin the next treatment at this energy setting and reduce the parameters to the last comfortable recorded energy used during the last treatment once the skin temperature has reached therapeutic levels and the patient states they are too warm. The area should be treated for 10-20 minutes depending on the treatment area size and the applicator used. Keep in mind that the treatment time does not include time to get to therapeutic which is between 1-5 minutes (typically 1-3).

During whole treatment duration, subject reaction must be monitored and if the subject reports an intolerable level of pain or temperature, treatment shall be ceased immediately.

Once the treatment is completed, remove the remnants of Glide™ using warm wet towels and dry the treatment area thoroughly.

US Treatment:

Ultrasound treatment provided over the affected treatment area will be applied as instructed in the appropriate User Manual and determined as per the investigator's standard of care for treating a soft injury tissue in the identified area.

After the first treatment, the treatment parameters (frequency and number of mintures treated) are recorded. These are now the base line parameters to be used for subsequent treatments with this patient.

Once the treatment is completed, remove the remnants of ultrasound gel using warm wet towels and dry the treatment area thoroughly.

Post-Treatment - Venus HEAL™ and Ultrasound

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

Subjects will complete the 10 cm discomfort/pain VAS immediately after treatment.

The normal response to these treatments is transient erythema and edema which may last from a few minutes to a few hours. If any other side effects occur, as indicated in the protocol, they must be recorded as adverse events.

Post-treatment ROM and BP measurements

Following either study treatment (PEMF/RF or US), subjects' blood perfusion measurements for the identified treatment area will be obtained with the use of the perfusion modality as measured by the Investigator and as instructed by the User Manual for the device. Subjects' range of motion will be measured by the Investigator in the identified treatment area using the Goniometer instrument.

Following the post-treatment ROM and BP measurements, subjects have completed their first clinic treatment and will be instructed to return for the next treatment.

7.3.3 FOLLOW-UP

Visit 2, Treatment 2 (≥ 2 days)

Adverse events, and any changes to concomitant medications will be recorded. Subjects will record their satisfaction with the treatment on the 5-point Likert satisfaction scale and complete a Brief Pain Inventory (Short Form) prior to any study treatment.

Prior to treatment, the range of motion measurement will be obtained as described in section 7.3.2.

Subjects will receive treatment as described in section 7.3.2. Following treatment, the investigator will examine the treated area and report immediate response. Subjects will complete the 10 cm discomfort/pain VAS immediately after treatment.

Following treatment, the range of motion measurement will be obtained as described in section 7.3.2.

Subjects will be instructed to return to clinic in two days (at least 48 hours) for the next treatment.

Visit 3, Treatment 3 (≥ 2 days)

Adverse events and any changes to concomitant medications will be recorded. Subjects will record their satisfaction with the treatment on the 5-point Likert satisfaction scale and complete a Brief Pain Inventory (Short Form) prior to any study treatment.

Prior to treatment, the blood perfusion and range of motion measurements will be obtained as described in section 7.3.2.

Subjects will receive treatment as described in section 7.3.2. Following treatment, the investigator will examine the treated area and report immediate response. Subjects will complete the 10 cm discomfort/pain VAS immediately after treatment.

Following treatment, the blood perfusion and range of motion measurements will be obtained as described in section 7.3.2.

Subjects will be instructed to return to clinic in two days (at least 48 hours) for the next treatment.

Visit 4, Treatment 4 (≥ 2 days)

Adverse events, and any changes to concomitant medications will be recorded. Subjects will record their satisfaction with the treatment on the 5-point Likert satisfaction scale and complete a Brief Pain Inventory (Short Form) prior to any study treatment.

Prior to treatment, range of motion measurements will be obtained as described in section 7.3.2.

Subjects will receive treatment as described in section 7.3.2. Following treatment, the investigator will examine the treated area and report immediate response. Subjects will complete the 10 cm discomfort/pain VAS immediately after treatment.

Following treatment, the range of motion measurements will be obtained as described in section 7.3.2.

Subjects will be instructed to return to clinic in two days (at least 48 hours) for the next treatment.

Visit 5, Treatment 5 (≥ 2 days)

Adverse events and any changes to concomitant medications will be recorded. Subjects will record their satisfaction with the treatment on the 5-point Likert satisfaction scale and complete a Brief Pain Inventory (Short Form) prior to any study treatment.

Prior to treatment, the range of motion measurement will be obtained as described in section 7.3.2.

Subjects will receive treatment as described in section 7.3.2. Following treatment, the investigator will examine the treated area and report immediate. Subjects will complete the 10 cm discomfort/pain VAS immediately after treatment.

Following treatment, the range of motion measurement will be obtained as described in section 7.3.2.

Subjects will be instructed to return to clinic in two days (at least 48 hours) for the next treatment.

Visit 6, Treatment 6 (≥ 2 days)

Adverse events and any changes to concomitant medications will be recorded. Subjects will record their satisfaction with the treatment on the 5-point Likert satisfaction scale and complete a Brief Pain Inventory (Short Form) prior to any study treatment.

Prior to treatment, the blood perfusion and range of motion measurements will be obtained as described in section 7.3.2.

Subjects will receive treatment as described in section 7.3.2. Following treatment, the investigator will examine the treated area and report immediate response. Subjects will complete the 10 cm discomfort/pain VAS immediately after treatment.

Following treatment, the blood perfusion and range of motion measurements will be obtained as described in section 7.3.2.

Subjects will be instructed to return to clinic in one week after their treatment for the final study visit.

7.3.4 FINAL STUDY VISIT

Visit 7, 1 week Follow-up Post-Treatment (± 2 days)

Adverse events and any changes to concomitant medications will be recorded. Subject will record their satisfaction with the treatment on the 5-point Likert satisfaction scale and complete a Brief Pain Inventory (Short Form) prior to any study treatment.

Final blood perfusion and range of motion measurements will be obtained as described in section 7.3.2.

Subjects will have completed all study treatments and visits, and will be 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 7). Adverse events and the reason for early termination will be recorded.

7.3.6 UNSCHEDULED VISIT

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

7.3.7 SCHEDULE OF EVENTS TABLE

Procedures	Screening	Baseline (Visit 1, Treatment 1)	Follow-up (Visit 2, Treatment 2) (≥ 2 days)	Follow-up (Visit 3 Treatment 3) (≥ 2 days)	Follow-up (Visit 4, Treatment 4) (≥ 2 days)	Follow-up (Visit 5, Treatment 5) (≥ 2 days)	Follow-up (Visit 6, Treatment 6) (≥ 2 days)	Final Follow-up/Study Visit (Visit 7, 1 week post final treatment) (±2 days)
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographics	X							
Medical history	X							
Physical exam	X							
Vital signs		X	X	X	X	X	X	X
Urine pregnancy test[a]	X							
Randomization		X						
Brief Pain Inventory (Short Form)		X	X	X	X	X	X	X
Blood Perfusion		X		X			X	X
Range of Motion		X	X	X	X	X	X	X
Administer Treatment		X	X	X	X	X	X	
Discomfort/Pain VAS		X	X	X	X	X	X	
PI immediate response		X	X	X	X	X	X	
Subject 5-Point Likert satisfaction scale			X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X
Adverse event evaluation		X	X	X	X	X	X	X

[a] For women of child-bearing potential.

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

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

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

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

Subjects are permitted to use simple analgesic or anti-inflammatory medications to manage pain associated with the soft tissue injury.

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

The use of anesthetic or corticosteroid injections of the treatment area during the study is prohibited. The use of anticoagulation medications, immunosuppressive medications or retinoid medications during the treatment period is prohibited.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

The external applicator should be cleaned and disinfected prior to each treatment as per instructions found in the appropriate User Manual.

Medicinal grade glycerin (Glide™, Venus Concept Ltd.) must be applied to the treatment area prior to each treatment with the Venus HEAL™.

Apply ultrasound gel to the treatment area prior to each treatment with the Dynatron Solaris Series.

At the end of the treatment session, the applicator should be thoroughly cleaned and as per instructions found in the appropriate User Manual.

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. In the unlikely event that 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 or other incident identified.
- The event will be reported to the sponsor study Director within 24 hours of occurrence. If the event meets the criteria of a SAE, then it must be reported on the SAE form.

- An anonymized copy of the patient chart and treatment parameters are to be forwarded to the sponsor study Director within 24 hours.

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

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

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

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

8 ASSESSMENTS OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

In addition to spontaneous reports of adverse events, subjects will complete a 10 cm discomfort/pain VAS and a Brief Pain Inventory (Short Form). 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, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or the comparator. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices (ISO 14155:2011).

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

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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

A serious AE is any adverse event that:

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

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

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

8.1.3 DEFINITION OF SERIOUS ADVERSE DEVICE EFFECT (SADE)

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

8.1.4 DEFINITION OF SERIOUS ADVERSE DEVICE EFFECT (SADE)

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

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

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

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

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

8.2.2 RELATIONSHIP TO STUDY AGENT

The clinician's assessment of an AE's relationship to the investigational device is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs

must have their relationship to investigational device assessed. In a clinical trial, the study product must always be suspect. To help assessment, the following guidelines are used.

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 (anticipated) adverse reactions are AEs that are common and known to occur for the study devices being investigated. Expected adverse events of the RF/PEMF and ultrasound treatment procedures include but are not limited to mild discomfort, heat sensation during and following treatment and transient edema and erythema in the treated area for up to two hours following treatment. These anticipated AEs do not need to be reported.

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 investigational device and study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

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

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

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

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

8.4.2 SERIOUS ADVERSE EVENT REPORTING

All serious AEs, 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: Andrea Biro, Clinical Research Manager
Phone: 888-907-0115 ext. 132
Email: *abiro@venusconcept.com*
Address: 255 Consumers Road, #110, Toronto, Ontario, Canada, M2J 1R4

A written report prepared by the Principal Investigator 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 a Serious Adverse Event / Serious 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 Health Canada (HC), the United States Food and Drug Administration (FDA) or local regulatory agency 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 Health Canada, the FDA or local regulatory agency requests.

8.4.3 UNANTICIPATED PROBLEM (UP) 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 Health Canada, the FDA or local regulatory agency 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 FDA (21 CFR 812.150(b)(1)) or local regulatory agency requests.

8.4.4 REPORTING OF PREGNANCY

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

8.5 STUDY HALTING RULES

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

8.6 SAFETY OVERSIGHT

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

8.7 TRAINING REQUIREMENTS

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

9 CLINICAL MONITORING

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

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

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

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

10.2 STATISTICAL HYPOTHESES

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

- Primary Efficacy Endpoints:
  - Null Hypothesis *(H_o: $\mu_d = \mu_{visit4} - \mu_{baseline} = 0$)* – There is no change in pain severity during daily activity at Visit 4 compared to Baseline as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.

    Alternative Hypothesis *(H_a: $\mu_d = \mu_{visit4} - \mu_{baseline} \neq 0$)* – There is a change in pain severity during daily activity at Visit 4 compared to Baseline as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.
    The efficacy endpoint to treatment will be defined by decrease in mean BPI-SF scores at Visit 4 compared to Baseline in the RF and PEMF arm as compared to the US arm. The decrease in BPI-SF mean difference score of 2, will be used to establish improvement in pain severity during daily activity at Visit 4.

  - Null Hypothesis *(H_o: $\mu_d = \mu_{visit4} - \mu_{baseline} = 0$)* – There is no change in pain interference during daily activity at Visit 4 compared to Baseline as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.

    Alternative Hypothesis *(H_a: $\mu_d = \mu_{visit4} - \mu_{baseline} \neq 0$)* – There is a change in pain interference during daily activity at Visit 4 compared to Baseline as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.
    The expected change will be defined by decrease in mean BPI-SF scores at Visit 4 compared to Baseline.

  - Null Hypothesis *(H_o: $\mu_d = \mu_{visit4} - \mu_{baseline} = 0$)* – There is no change in range of motion pre- and post-treatment at Visit 4 compared to Baseline as measured by Goniometer in the RF and PEMF arm as compared to the US arm.

Alternative Hypothesis *(H_a: $\mu_d = \mu_{visit4} - \mu_{baseline} \neq 0$)* – There is a change in range of motion pre- and post-treatment at Visit 4 compared to Baseline as measured by Goniometer in the RF and PEMF arm as compared to the US arm.
The expected change will be defined by improvement (increase) in subjects' Goniometric assessment of range of motions at Visit 4 compared to Baseline.

- Null Hypothesis *(H_o: $\mu_d = \mu_{visit4} - \mu_{baseline} = 0$)* – There is no change in range of motion pre- and post-treatment at Visit 4 compared to Baseline as measured by Goniometer in the RF and PEMF arm as compared to the US arm.

  Alternative Hypothesis *(H_a: $\mu_d = \mu_{visit4} - \mu_{baseline} \neq 0$)* – There is a change in range of motion pre- and post-treatment at Visit 4 compared to Baseline as measured by Goniometer in the RF and PEMF arm as compared to the US arm.
  The expected change will be defined by improvement (increase) in subjects' Goniometric assessment of range of motions at Visit 4 compared to Baseline.

- Null Hypothesis *(H_o: $\mu_d = \mu_{post} - \mu_{pre} = 0$)* – There is no change in tissue blood perfusion pre- and post-treatment at Baseline, Visit 3 and Visit 6 as measured by perfusion imaging in the RF and PEMF arm as compared to the US arm.

  Alternative Hypothesis *(H_a: $\mu_d = \mu_{post} - \mu_{pre} \neq 0$)* – There is a change in tissue blood perfusion pre- and post-treatment at Baseline, Visit 3 and Visit 6 as measured by perfusion imaging in the RF and PEMF arm as compared to the US arm.
  The expected change will be defined by improvement (increase) in subjects' pre- and post-treatment tissue blood perfusion at Baseline, Visit 3 and 6.

- Secondary Efficacy Endpoint(s):
  - Null Hypothesis *(H_o: $\mu_d = \mu_{post} - \mu_{pre} = 0$)* – There is no change in pain severity during daily activity at Visit 6 as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.

    Alternative Hypothesis *(H_a: $\mu_d = \mu_{post} - \mu_{pre} \neq 0$)* – There is a change in pain severity during daily activity at Visit 6 as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm. The expected change will be defined by decrease in mean BPI-SF scores.

  - Null Hypothesis *(H_o: $\mu_d = \mu_{post} - \mu_{pre} = 0$)* – There is no change in pain interference during daily activity at Visit 6 as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.

    Alternative Hypothesis *(H_a: $\mu_d = \mu_{post} - \mu_{pre} \neq 0$)* – There is a change in pain interference during daily activity at Visit 6 as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm. The expected change will be defined by decrease in mean BPI-SF scores.

- Null Hypothesis *(H_o: $\mu_d = \mu_{post} - \mu_{pre} = 0$)* – There is no change in range of motion pre- and post-treatment at Visit 6 as measured by Goniometer in the RF and PEMF arm as compared to the US arm.

  Alternative Hypothesis *(H_a: $\mu_d = \mu_{post} - \mu_{pre} \neq 0$)* – There is a Change in range of motion pre- and post-treatment at Visit 6 as measured by Goniometer in the RF and PEMF arm as compared to the US arm.

- Null Hypothesis *(H_o: $\mu_d = \mu_{post} - \mu_{pre} = 0$)* – There is no satisfaction with the treatment at Visit 4, Visit 6 and Visit 7 as measured with a 5-point Likert Satisfaction scale in the RF and PEMF arm as compared to the US arm.

  Alternative Hypothesis *(H_a: $\mu_d = \mu_{post} - \mu_{pre} \neq 0$)* – There is satisfaction with the treatment at Visit 4, Visit 6 and Visit 7 as measured with a 5-point Likert Satisfaction scale in the RF and PEMF arm as compared to the US arm. The satisfaction with treatment will be defined by 5-point Likert scale at Visit 4, Visit 6 and Visit 7 compared to baseline as assessed by the subjects.

- Null Hypothesis *(H_o: $\mu_d = \mu_{visit4} - \mu_{baseline} = 0$)* – There is no change in tissue blood perfusion at Visit 7 compared to Baseline as measured by perfusion imaging in the RF and PEMF arm as compared to the US arm.

  Alternative Hypothesis *(H_a: $\mu_d = \mu_{visit4} - \mu_{baseline} \neq 0$)* – There is a change in tissue blood perfusion at Visit 7 compared to Baseline as measured by perfusion imaging in the RF and PEMF arm as compared to the US arm.
  The expected change will be defined by improvement (increase) in subjects' perfusion modality assessment of tissue blood perfusion at Visit 7 compared to Baseline.

- Safety Endpoint:
  - Null Hypothesis *(H_o: $\mu_d = \mu_{post} - \mu_{pre} = 0$)* – There is no difference in subject's assessment of discomfort and pain with treatment as measured by a 10 cm visual analog scale (VAS) at baseline and Visit 4 in the RF and PEMF arm as compared to the US arm subjects.

  - Alternative Hypothesis *(H_a: $\mu_d = \mu_{post} - \mu_{pre} \neq 0$)* – There is a difference in subject's assessment of discomfort and pain with treatment as measured by a 10 cm visual analog scale (VAS) at baseline and Visit 4 in the RF and PEMF arm as compared to the US arm subjects.

    This will be assessed by mean difference in subjects' 10 cm discomfort/pain VAS score experienced after Visit 4 treatment and that of baseline treatment (Visit 1) for each group. Expected mean difference is maximum VAS score of 1.

10.3 ANALYSIS DATASETS

The Intention-to-Treat Analysis Dataset will be used; efficacy and safety analyses will be carried out on all subjects who underwent an attempted treatment of Venus HEAL™ system.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

This is a randomized, controlled study of the safety and efficacy of a radiofrequency (RF) and pulsed electromagnetic fields (PEMF) device in comparison to ultrasound (US) for the treatment of pain associated with soft tissue injuries, also showing the comparative effects on range of motion (ROM) and blood perfusion (BP).

All summary tables for quantitative parameters will display mean, standard deviation, median, range (minimum and maximum), percentages as well as number of missing data (if relevant). All summary tables for qualitative parameters will display counts, percentages and number of missing data if relevant. Baseline data are defined as the last measurement performed before the first treatment on Visit 1.

All statistical tests will be two-sided. The level of statistical significance for effectiveness analyses is 5% ($\alpha = 0.05$) for all tests of differences. Where appropriate, t-test and/or two-proportion z-test will be used to compare outcome measures at the baseline and after initial treatment sessions and between groups at respective visits (Visit 4, Visit 6 and Visit 7). This test will enable us to accept or reject the null hypotheses. Rejection of null hypotheses will establish that:

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

Upon rejection of null hypotheses, further statistical test tools such as Confidence Interval, and/or One-way ANOVA and/or descriptive statistical tools may be used to determine the performance of the treatment.

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

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The following will be consider for the analysis primary endpoints:

Summary table for differences of baseline and Visit 4 pain severity during daily activity as measured by Brief Pain Inventory (Short Form) (BPI-SF) scores in the RF and PEMF arm compared to the US arm will be displayed as mean difference, standard deviation and standard error. The BPI-SF is a self-administered questionnaire used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning.

Bar, pie charts or graphs indicating scores, percentages of subjects' pain severity BPI-SF scores may also be used to analyse efficacy.

All statistical tests will be two-sided. The level of statistical significance for effectiveness analyses is 5% ($\alpha = 0.05$) for all tests of differences. Where appropriate, t-test will be used to compare the primary endpoint outcome measured at baseline and Visit 4 in the RF and PEMF arm and the US arm. Analysis of Covariance

(ANCOVA) may also be used where appropriate. To accommodate imbalances of some baseline measures, covariate adjustment analysis may be performed in SAP to estimate adjusted treatment effects for the primary endpoints analysis.

The t-test will be used to compare outcome measures at the baseline and post treatment sessions and between groups. This test will enable us to accept or reject the null hypotheses. Rejection of null hypotheses will establish that:

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

Upon rejection of null hypotheses, futher statistical test tools such as Confidence Interval, and/or One-way ANOVA and/or descriptive statistical tools may be used to test expected primary endpoints; that is alternative hypothesis that there is a change in the measured pain severity. This will be used to determine if the study meets the primary endpoints expectations of 2 score decrease in BPI-SF score.

Brief Pain Inventory (Short Form) scores of all subjects who received at least one treatment of Venus HEAL™ system and for whom at least one valid post-baseline BPI-SF assessment were obtained will be analysed for the primary endpoint. Mutiple imputation method or modelling of available data may be used for missing data as appropriate.

The following analysis will be considered for the primary endpoint analysis of changes in subjects in the RF and PEMF arm as compared to changes in the US arm assessed to have improvement in pain interference during daily activity (measured by BPI-SF), range of motion (measured by Goniometer) and tissue blood perfusion (measured by perfusion imaging) observed at Visit 3, Visit 4, Visit 6 and Visit 7 (as applicable) compared to baseline:

Summary tables for differences between recorded baseline data and Visit 3, Visit 6 and 7 tissue blood perfusion data, Visit 4 pain interference during daily activity, Visit 7 range of motion will be displayed as mean difference, standard deviation and standard error. The point level for each of these ordinal scale assessment tools will be put into consideration where applicable.

Bar charts, pie chart, graphs or any other descriptive statistical displays indicating scores, percentages or measurement of subjects' improvement (differences) scores and measurements in the RF and PEMF arm and the US arm will be used to analyse efficacy.

All statistical tests that will be two-sided. The level of statistical significance for effectiveness analyses is 5% ($\alpha = 0.05$) for all tests of differences. Where appropriate, two-proportion z-test will be used to compare the differences between changes of subjects assessed to have improvement in the the RF and PEMF arm and US arm observed at applicable visits. Analysis of Covariance (ANCOVA) may also be used where appropriate.

The pain interference during daily activit BPI-SF scores, range of motion and tissue blood perfusion measurements of all subjects who received at least one treatment of Venus HEAL™ system and for whom at Visit 4 post-baseline assessment were obtained will be analysed for these primary endpoints. Mutiple imputation method or modelling of available data may be used for missing data as appropriate.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For the analysis of changes in pain severity during daily activity, pain interference during daily activity, range of motion, and subjects' assessment of satisfaction with the treatment secondary endpoints the following analysis will be considered:

Summary tables for changes and measurements of subjects assessed to have improvement in the RF and PEMF and US arms observed at respective treatment visits for the pain severity during daily activity, pain interference during daily activity, range of motion, and subjects' assessment of satisfaction assessments will be displayed as mean difference, standard deviation and standard error. The point level for each of these ordinal scale assessment tools will be put into consideration where applicable.

Bar charts, pie chart, graphs or any other descriptive statistical displays indicating scores, percentages and/or proportions of subjects' pain severity during daily activity, pain interference during daily activity, range of motion, and subjects' assessment of satisfaction improvement scores and measurements will be used to analyse efficacy.

All statistical tests that will be two-sided. The level of statistical significance for effectiveness analyses is 5% ($\alpha = 0.05$) for all tests of differences. Where appropriate, two-proportion z-test will be used to compare the differences between changes of subjects assessed to have improvement in the the RF and PEMF arm and US arm observed at applicable visits (Visit 4, Visit 6 and Visit 7). Analysis of Covariance (ANCOVA) may also be used where appropriate.

Pain severity during daily activity, pain interference during daily activity, range of motion, and subjects' assessment of satisfaction scores and measurements of all subjects who received at least one treatment of Venus HEAL™ system and for whom at least one valid post-baseline assessment were obtained will be analysed for these secondary endpoints. Mutiple imputation method or modelling of available data may be used for missing data as appropriate.

10.4.4 SAFETY ANALYSES

The safety analysis will be done by analyzing spontaneous reports of adverse events (AE) by physicians and subjects' completed 10 cm discomfort/pain VAS as well as analysis of immediate response reports by the principal investigator from his/her observation/examination of the treated area. These data from the RF/PEMF arm subjects will be compared to that of the US arm to determine safety of this device. Appropriate Medical Dictionary for Regulatory Activities (MedDRA) code will be used to describe all spontaneously reported or other study related adverse events.

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

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

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

- The overall frequency of subjects with each adverse event (pain during treatment, hemorrhage, burn, erythema, edema, purpura, other)
- Frequency of subjects with specific severity/intensity for each event using a 5 points scale: 1=none; 2=trace; 3=moderate; 4=marked; 5=severe

- The overall percentage or proportion of subject observed with marked or severe intensity of any event will be calculated and compared to those with none, trace or moderate severity/intensity with the aid of a bar or pie chart.

Comparative analysis of these data obtained from the RF/PEMF arm subjects and that of the US arm will be used in determining safety of this device for this treatment.

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

Summary table for differences of baseline and Visit 4 discomfort/pain VAS scores obtained in study's RF/PEMF and US arm subjects will be displayed as mean difference, standard deviation and standard error. The 10 cm discomfort/pain VAS is a 11-level (0 to 10) ordinal scale tool for assessing pain.

Bar, pie charts or graphs indicating scores, percentages or proportions of subjects' Visit 3 and baseline VAS scores difference that is < 1 cm and >1 cm will be used to analyze subjects' tolerability to this treatment.

Comparative analysis of these data obtained from the RF/PEMF arm subjects and that of the US arm will be used in determining safety of this device for this treatment.

All statistical tests will be two-sided. The level of statistical significance for effectiveness analyses is 5% ($\alpha = 0.05$) for all tests of differences. Where appropriate, t-test will be used to compare Visit 4 and baseline VAS scores differences obtained between the RF/PEMF and US arm subjects.

The t-test will enable us to accept or reject the null hypotheses. Rejection of null hypotheses will establish that:

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

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

10.4.5 ADHERENCE AND RETENTION ANALYSES

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

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Subjects baseline scores of all endpoints (BPI-SF, 5-Point Likert Satisfaction Scale, BP, ROM and VAS) will be compared using descriptive statistics such as mean score, standard deviation, standard error, range and graphical presentations.

10.4.7 PLANNED INTERIM ANALYSES

No interim analysis is planned.

10.4.7.1 SAFETY REVIEW

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

10.4.7.2 EFFICACY REVIEW

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

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

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

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

Not applicable.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

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

10.4.11 EXPLORATORY ANALYSES

Not applicable.

10.5 SAMPLE SIZE

The primary endpoint Brief Pain Inventory (Short Form) score outcome measures was used to calculate the study sample size.

Sample size calculation using primary endpoint outcome measure;

- Null and alternate hypotheses:

  Null Hypothesis *(H_o: $\mu_d = \mu_{visit4} - \mu_{baseline} = 0$)* – There is no change in pain severity during daily activity at Visit 4 compared to Baseline as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.

  Alternative Hypothesis *(H_a: $\mu_d = \mu_{visit4} - \mu_{baseline} \neq 0$)* – There is a change in pain severity during daily activity at Visit 4 compared to Baseline as measured by the Brief Pain Inventory (Short Form) in the RF and PEMF arm as compared to the US arm.
  The efficacy endpoint to treatment will be defined by decrease in mean BPI-SF scores at Visit 4 compared to Baseline in the RF and PEMF arm as compared to the US arm. The decrease in BPI-SF mean difference score of 2, will be used to establish improvement in pain severity during daily activity at Visit 4.

- In view of the nature of this study in regard to number of visits, we make provision for 20% study drop out, withdrawal or loss to follow-up.
- 2- Tailed Sample Size calculation formula for two Samples was used in the table below:

(1-β), Desired Power	0.8
α, Level of Significance	0.05
μ_d, change in BPI-SF mean score from baseline to Visit 4 under H_a	2
σ, Standard Deviation (obtainable BPI-SF score range i.e. 0 to 10 ÷ 4) = [(10-0)÷4])	2.5
$Z_{1-\alpha/2}$	1.96
$Z_{1-\beta, (\text{for } 80\%)}$	0.84
Sample Size of each equal group	**25**
Estimated Sample Size of each equal group + 20% drop out	**30**
Total Sample Size for both equal group (N)	**60**

Conclusion: The estimated sample size for each group and the additional 20% provision for drop out **(30 subjects)** obtained from the primary endpoint outcome measure calculation will be used subjects for this study.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

At screening, once a subject has signed the informed consent, and inclusion/exclusion criteria has been met, a subject number will be assigned. The subject number will consist of a two-digit code corresponding to the site and a three-digit subject code in numerical sequence. (Example: 10-005 corresponds to site #10, subject #5.)

Each subject will be randomized, in a 1:1 ratio, to receive either RF/PEMF or US treatment according to a randomization code supplied by the sponsor. The subject's study treatment will be the next treatment listed in sequence in the randomization log.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

This is not a blinded study, therefore not applicable.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Not applicable as not a blinded study and an interim analysis will not be conducted.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The site will maintain appropriate medical and research records for this trial, in compliance with ISO 14155:2011, and regulatory and institutional requirements for the protection of confidentiality of participants. The site will permit authorized representatives of the study sponsor, ethics committee and/or regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records

for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

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

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

- Subject self-reported VAS, 5-point Subject Satisfaction Scale, Brief Pain Inventory (Short Form)
- Investigator reported immediate (immediately post-treatment) safety response.

The remainder of the data collected from other sources.

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

12 QUALITY ASSURANCE AND QUALITY CONTROL

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

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

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

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

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

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

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

13.2 ETHIS COMMITTEE AND COMPETENT AUTHORITIES

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

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

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

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be EC or IRB approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, potential risks of the study and their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by

emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

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

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

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

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

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

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

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

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

Copies of the paper CRF will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the CRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official study record. Self-reported subject data and investigator CRF reported data recorded on the copy CRF page is permitted. The original form will be collected by the sponsor and the copy will remain at the site.

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

14.2 STUDY RECORDS RETENTION

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

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or GCP 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 ISO 14155:2011 and 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. 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.

14.4 PUBLICATION AND DATA SHARING POLICY

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be

registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. The Declaration of Helsinki current revision (2013) states that every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject (sec.35).

The sponsor or its designee will register the CS1217 study into a publicly accessible database. All data generated from this study are the property of Venus Concept Ltd and shall be held in strict confidence along with all information furnished by Venus Concept Ltd.

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

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

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The study will be administered by the sponsor.

16 CONFLICT OF INTEREST POLICY

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

17 LITERATURE REFERENCES

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APPENDIX

Version	Date	Significant Revisions
1.0	May 14, 2018	
2.0	October 15, 2018	• Substitution of the use of investigational Venus HEAL™ for the Venus Freeze Plus™ • Inclusion criteria revised to align with the broad definition of acute injury. • Change from blood 'flow' measurement to blood 'perfusion' measurement due to change in measurement device, measurement units and imaging criteria. • Added secondary endpoint of tissue blood perfusion (BP) compared to Baseline at Visit 7. • Minor administrative changes.