Feasibility Study of a 950 nm Wavelength LED Device for Non-invasive Lipolysis of the Flanks

Protocol Identifying Number: CS0117

Principal Investigator: Dr. Neil Sadick

Funded by: Venus Concept

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Science
CRF	Case Report Form
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IRB	Investigational Review Board
ISO 14155:2011	International Organization for Standardization Good Clinical Practices for Clinical Investigations of Medical Devices
LED	Light emitting diode
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOC	System Organ Class
UP	Unanticipated Problem
VAS	Visual Analog Scale

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

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

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

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

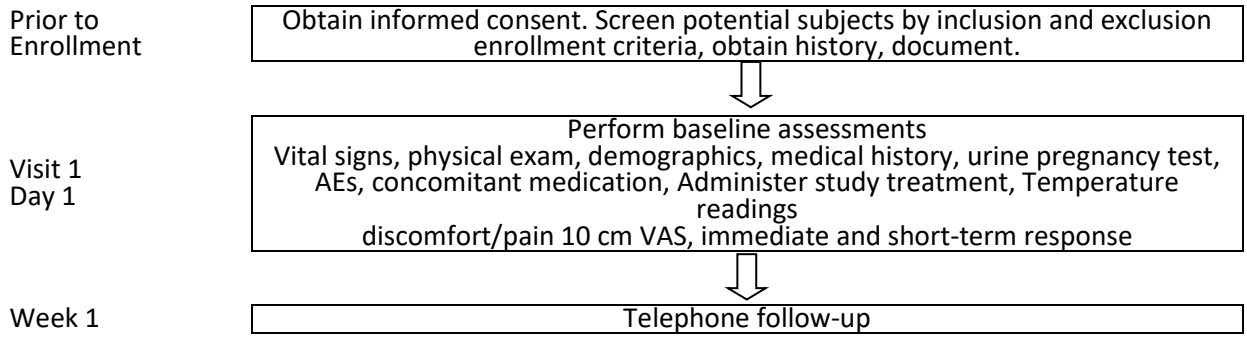
Principal Investigator: _____
Print/Type Name

Signed: _____ Signature Date: _____

PROTOCOL SUMMARY

TITLE	Feasibility Study of a 950 nm Wavelength LED Device for Non-invasive Lipolysis of the Flanks
SUMMARY	Open-label, feasibility study comparing the tissue temperature profile of a 950 nm LED device and a 1060 nm diode laser for non-invasive lipolysis of the flanks. The study will enroll up to 10 subjects requesting non-invasive lipolysis of the flanks. Each subjects will receive a single treatment with each device on opposite flanks. Tissue temperatures in the treated areas will be recorded and compared.
OBJECTIVES	The objective of this clinical study is to compare the tissue temperature profiles of the LED device and diode laser device and to compare safety in the treatment of lipolysis of the flanks.
ENDPOINT	Primary objective • Temperature profile comparison at various tissue depths. Safety • Subject's assessment of discomfort and pain as measured by a 10 cm visual analog scale (VAS). • Subjects experiencing a treatment-related adverse event (AE).
POPULATION	The study will enroll up to 10 male and female subjects, ≥ 18 years of age who are seeking non-invasive lipolysis of the flanks.
PHASE	Feasibility
NUMBER OF SITES	one
DESCRIPTION OF DEVICE	The investigational device uses LED technology. The 1060 nm diode laser has been approved by the FDA for non-invasive lipolysis of the flanks.
STUDY DURATION	Two months
PARTICIPANT DURATION	One day plus a telephone follow-up after one week

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Non-invasive body contouring is gaining popularity in the United States and the field is advancing at a fast pace with the vast majority of cases using non-invasive methods. Various technologies exist today including cryolipolysis, radiofrequency, ultrasound, injection lipolysis and laser. When advancing to a non-invasive approach to lipolysis, an external device is required. In 2015, the FDA approved a 1060 nm diode laser for fat reduction (Cynosure SculpSure). The laser leads to injury of the adipocytes through direct heating of the tissue. Energy creates movement within the molecules of the exposed tissue, which then generates heat. A controlled temperature of 42-47 °C must be maintained at the site of adipocytes. At this temperature, the cell membranes of the adipocytes lose their structural integrity leading to cell death. Upon cell injury and death, the body naturally eliminates the contents of the adipocytes. The laser targets unwanted adipocytes while leaving the overlying skin and adnexal structures unharmed. In addition, melanin is minimally targeted so the device can be used in all skin types.

2.2 RATIONALE

A new emerging technology in the area of aesthetic medicals device is LED (light-emitting diode) photo-modulation. It is currently being used to stimulate fibroblasts to produce collagen and to destroy bacteria on the skin. In this study, a 950 nm LED investigational device is being evaluated to determine if it is able to target adipocytes by maintaining a controlled temperature of 42-47 °C, similar to the reference device. In addition, the safety of the LED device will be compared to the reference device.

The use of this LED device has been determined to present non-significant risk for the intended use in this study, because the device is not:

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

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

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

The potential risks for adverse effects of the treatment procedure include but are not limited to blistering, burns, excessive edema or erythema, infection, scarring and post-inflammatory hyperpigmentation.

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 safety and efficacy of the device. This understanding may lead to optimization of the treatment with this device. In addition the subject may benefit from reduction in unwanted adipocytes.

3 OBJECTIVES AND PURPOSE

The study is being conducted to evaluate the feasibility and safety of a LED device for non-invasive treatment of the flanks.

Primary objectives

Tissue temperature profile of the LED device compared to the diode laser device.

Safety

Subject's assessment of discomfort and pain as measured by a 10 cm visual analog scale (VAS).

Subjects experiencing a treatment-related adverse event (AE).

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is an open-label, comparative, single-center study to evaluate the feasibility and safety of a LED device and a diode laser device for non-invasive lipolysis of the flanks.

4.2.1 PRIMARY ENDPOINTS

Tissue temperature profiles compared to the reference device.

4.2.2 SECONDARY ENDPOINTS

Safety objectives

Subject's assessment of discomfort and pain as measured by a 10 cm visual analog scale (VAS).

Subjects experiencing a treatment-related adverse event (AE).

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

1. Able to read, understand and provide written Informed Consent.
2. Healthy adult, male or female, ≥ 18 years of age or older with skin types 1-VI.
3. Having moderate excess bilateral fatty tissue of the flanks, suitable area for non-invasive lipolysis.
4. Able and willing to comply with the treatment/follow-up schedule and requirements.
5. Women of child-bearing potential (women who have not had a hysterectomy, bilateral oophorectomy or are not postmenopausal) are required to be using a reliable method of birth control for at least three months prior to enrolment and throughout the course of the study and have a negative urine pregnancy test at baseline.

5.2 PARTICIPANT EXCLUSION CRITERIA

1. Pregnant, expectation of pregnancy, postpartum or nursing (<6 months).
2. History of skin disease in the area to be treated over the last 6 months.
3. Previous surgical intervention to the treatment area.
4. History of skin cancer or pre-cancerous lesions at the treatment areas.
5. Having any electrical implant anywhere in the body, such as a pacemaker or an internal defibrillator.
6. History of immunosuppressive diseases, including AIDS and HIV infection, or use of immunosuppressive medications;
7. Uncontrolled systemic diseases such as diabetes.
8. Active infections in the treatment area.
9. History of dysplastic nevi.
10. Significant concurrent skin conditions or any inflammatory skin conditions.
11. Active herpes simplex infections (e.g. cold sores), open lacerations or abrasions in the treatment area.
12. Chronic or cutaneous viral, fungal, or bacterial diseases.
13. Use of Accutane™ (Isotretinoin) within the past six months.
14. Keloid or hypertrophic scar formation in the treatment area.
15. Tattoos in the treatment area.
16. History of auto-immune disorders.
17. Erythema abigne, when identified treatments should be discontinued.
18. History of photosensitivity disorder that can be exacerbated by laser or intense light.
19. Use of medications, herbal supplements, perfumes or cosmetics that may affect sensitivity to light.
20. History of poor wound healing in the treatment area.
21. Sunburns.
22. Unable or unlikely to refrain from artificial tanning, including the use of tanning booths, prior (at least a month) and during the course of the evaluation.
23. Prior skin treatment with laser or other devices on the same treatment area within the last six months prior to study enrollment or during the course of the study.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Up to 10 subjects will be enrolled at a single site. It is anticipated that it will take up to two months to complete the study. Subjects requesting non-invasive lipolysis of the flanks will be recruited primarily from the principal investigator's clinic. Any advertising campaigns and materials will be reviewed and approved by an institutional review board (IRB) before implementation. Due to the short duration of the study (single treatment), subject retention will not be an issue.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

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

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

An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the 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 efficacy study endpoints. Every effort will be made to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs), and unanticipated problems (UPs).

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

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

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

- Determination of unexpected, significant, or unacceptable risk to participants

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

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

6 STUDY DEVICE

6.1 STUDY DEVICE(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

The investigational device will be shipped to the investigative site directly from the sponsor. Training on the use of the device will be provided by the sponsor. The investigative site will not perform any treatments until all regulatory and IRB approvals are in place and the site has received training for both the device and the study.

6.1.2 DEVICE SPECIFIC CONSIDERATIONS

The Venus LED device is intended to be used in aesthetic and cosmetic procedures. The device consists of a console and an applicator belt that delivers the treatment LED to the patient's skin.

The clinician is able to control the settings from the user interface (LCD GUI) display on the main console. The available settings for this applicator is:

- Power density up to 1.4 W/cm2

The duration of exposure and frequency of exposure to the LED will be one 24 minute session.

6.2 STUDY DEVICE ACCOUNTABILITY PROCEDURES

The device will be shipped to the site by the sponsor. The device will be labeled as an investigational device and will require protocol and device training from the sponsor.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

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

Demographics
Medical / surgical history (obtained by interview or from medical records)
Assessment of eligibility

Vital signs [including height (visit 1 only), weight, temperature, respiratory rate, heart rate and blood pressure] assessed at every study visit
Administration of questionnaires and scales for patient-reported outcomes
Temperature measurements
Adverse event recording
Concomitant medications

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

For women of child-bearing potential, urine pregnancy test to be performed according to local site standards within 24 hours of study intervention and results must be available prior to administration of the treatment.

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, clearly indicating his/her understanding of the requirements and possible risks involved with study participation and other applicable treatment options.

During the first visit, the study investigator, and/or his/her designee, will screen the subject for eligibility to participate in the clinical study using the inclusion/exclusion criteria. A urine sample for the pregnancy test will be obtained for female subjects of child-bearing potential. During screening, the study doctor will review the subject's medical/surgical history, and examine the target treatments areas to ensure they meet the study criteria. The subject will complete screening and the treatment will be scheduled. Treatment may be performed on the same day the subject was enrolled if the result of the urine pregnancy test is available and negative.

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

Pre-Treatment

Subjects will be instructed to avoid sun exposure of the target treatment areas for at least six weeks before treatment and to use broad spectrum sunscreen of no less than 30 SPF daily, replenishing it as often as needed throughout the course of the study and for six weeks after the treatment. In addition, tanning is to be strictly avoided. Subjects should not receive any treatment with a laser or other devices in the study treatment area throughout the course of this study and follow-up examinations.

Protective eye goggles will be worn by both the patient and site staff performing the treatment for the duration of the treatment session.

7.3.2 ENROLLMENT/BASELINE

Enrollment/Baseline Visit (Visit 1 – Day 1)

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

Treatment

Based on the mild nature of treatment, anesthesia is not required. Treatment procedure should include positioning of the patient in a manner that enables access to the target treatment anatomical site. A water-based spray should be applied to the treatment area immediately prior to treatment.

Each subject will receive two consecutive treatments in the following order: the left flank of the abdomen will be treated with the diode laser device and the right flank of the abdomen will be treated with the LED device. The exact placement on the flank will be left to the principal investigator's judgement based on his assessment of individual subject requirements for treatment. Subejects will be treated on the same bilateral location with each device to ensure consistency of measurements. Both laser and LED applicators will be set to same output power level. Two levels will be used 41W (1.17W/cm^2) and 29W (0.83W/cm^2). The first level of 41W corresponds to initial heating for 4 minutes and the second level corresponds to duty cycle of 25 sec on and 10 sec off time. Total treatment time with each device will be 24 minutes (first 4 min at full power and next 16 min at duty cycle 25/10). Both device applicators have same output window dimensions and area 7x5 cm (35 cm^2). Both applicators are cooled by water chiller and therefore provided the same surface cooling temperature on skin.

Immediately (within 2 minutes) after treatment, 3 sterile thermocouple needles of different lengths (7-15 mm), will be inserted into the center of each applicator footprint. Temperature readings from each thermocouple needle will be recorded.

During treatment, subject reaction must be monitored and if the subjects verbally report an intolerable level of pain, treatment shall be ceased immediately.

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

Post Treatment

For post-treament cooling, cold packs can be applied to treatment sites with protective gauze barrier immediately following cessation of treatment for up to 10 minutes, repeating as needed with rest periods of 5 minutes between applications. On the night following treatment, subjects should generally avoid hot water, cleanse their skin gently with tepid water, and hydrate the skin with a suitable moisturizer.

Subjects should be aware that post treatment erythema, edema and some discomfort of the treated areas are possible and should not be a cause for concern. Subjects may use NSAIDs to treat their pain. They may also experience some purpura in the treated areas which would be expected to resolve within several days.

Assessment

The assessment of discomfort/pain based on the subject's report will be documented immediately (within 5 minutes) after treatment and before any subsequent treatment using the 10 cm VAS.

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

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

7.3.3 FINAL STUDY VISIT

Subjects will contacted by telephone within one week to determine if there are any ongoing adverse events. The termination form will be completed and subjects 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.

7.3.4 EARLY TERMINATION VISIT

Subjects who terminate the study early for whatever reason, will be asked to provide a reason for their early termination. Adverse events and the reason for early termination will be recorded.

7.3.5 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.

7.3.6 SCHEDULE OF EVENTS TABLE

Procedures	Screening	Enrollment Baseline Visit 1, Day 1	Follow up Contact ≤ 7 days
Informed consent	X		
Inclusion/exclusion criteria	X	X	
Demographics	X		
Medical history	X		
Physical exam	X		
Vital signs		X	
Urine pregnancy test[a]	X		
Administer Treatment		X	
Temperature measurements		X	
Subject Discomfort/Pain VAS		X	
PI immediate & short-term response		X	
Concomitant medication		X	X
Adverse event evaluation		X	X

Telephone contact			X
[a]For women of child-bearing potential			

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

N/A

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 and non-prescription medications.

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

The use of immunosuppressive medications, anticoagulants and medications, herbal supplements, perfumes or cosmetics that may affect sensitivity to light are prohibited. The use of Accutane™ (Isotretinoin) within the past six months is also prohibited.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Apply a water-based spray to the treatment area prior to treatment.

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

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

Immediate triage and treatment of the patient shall be determined by the treating physician and based upon severity and type of burn identified.

The event will be reported to the 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.

A copy of the patient chart and treatment parameters are to be forwarded to the study Director within 24 hours.

The study Director will be responsible for issuing a written report to the company and the IRB Chairman no later than 7 days from the incident.

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

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

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

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

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

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

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

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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

A serious AE is any event that:

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

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

This definition includes an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other

unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

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

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

8.2.3 EXPECTEDNESS

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

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

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

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

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

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

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

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

8.4.2 SERIOUS ADVERSE EVENT REPORTING

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

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Phone: 888-907-0115 ext. 563
Email: *jreiz@venusconcept.com*
Address: 255 Consumers Road, #110, Toronto, Ontario, Canada, M2J 1R4

A written report prepared by the Principal Investigator 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, the 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 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 and to the IRB 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 and the IRB within 10 business days.

8.5 STUDY HALTING RULES

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

8.6 SAFETY OVERSIGHT

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

9 CLINICAL MONITORING

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

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

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

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

10.2 ANALYSIS DATASETS

Temperature and safety analyses will be carried out on all subjects.

10.3 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

This is an open-label, comparative feasibility study of an investigational LED device and a diode laser device for non-invasive lipolysis of the flanks.

Mean temperature reading from each device and each thermocouple will be calculated and temperature differences will be determined.

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

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

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

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

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

10.4 SAMPLE SIZE

Since this is a feasibility study, no formal sample size calculation is required. The study will recruit up to 10 subjects.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, ISO 14155:2011, HIPAA and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the study sponsor and 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, 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 subject self-reported VAS data for this study will be collected on CRFs with 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 Velocity 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 ICH-GCP and 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 Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6, the Declaration of Helsinki, Council for International Organizations of Medical Science (CIOMS), ISO 14155:2011, International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), or another country's ethical policy statement, whichever provides the most protection to human subjects.

13.2 INSTITUTIONAL REVIEW BOARD

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

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Informed consent is required for all subjects in a study. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, or equivalent local regulatory regulations or guidelines and/or ICH GCP. Prior to the beginning of a trial, the investigator should have the IRB's written approval for the

protocol and the written informed consent forms(s) and any other written information to be provided to the participants. Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

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

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

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

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or 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, local IRB and any other regulations.

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 PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

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

Copies of the paper CRF will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the 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 recorded on the non-carbon 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 collected by the study sponsor and will be entered directly onto paper CRFs from the source documents.

14.2 STUDY RECORDS RETENTION

Study documents, including copies of the paper CRFs, signed informed consent forms, photographs, laboratory results, medical records, data clarification forms and regulatory documents, should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. 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 ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

The sponsor or designated principal investigator will register and report results of certain "applicable clinical trials":

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

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

Schilling L, Saedi N, Weiss R. 1060 nm Diode Hyperthermic Laser Lipolysis: The Latest in Non-Invasive Body Contouring. J Drugs Dermatol. 2017 Jan 1;16(1):48-52.

APPENDIX

Version	Date	Significant Revisions