Clinical Evaluation of the Safety and Efficacy of a 1060 nm Diode Laser for Non-invasive Fat Reduction of the Abdomen

Protocol Identifying Number: CS1317

Funded by: Venus Concept Ltd.

Version Number: v 1.0

19 September 2018

NCT03756350

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Paul Cardarelli 24/09/18

Signature of Sponsor Representative **Date: (DD/MM/YYYY**

Table of Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CFR	Code of Federal Regulations
CRF	Case Report Form
CW	Continuous Wave
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GUI	Graphical User Interface
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
IRB	Institutional Review Board
ISO 14155:2011	International Organization for Standardization Good Clinical Practices for Clinical
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SLIQ	Simple Lifestyle Indicator Questionnaire
US	Ultrasound
UP	Unanticipated Problem

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.

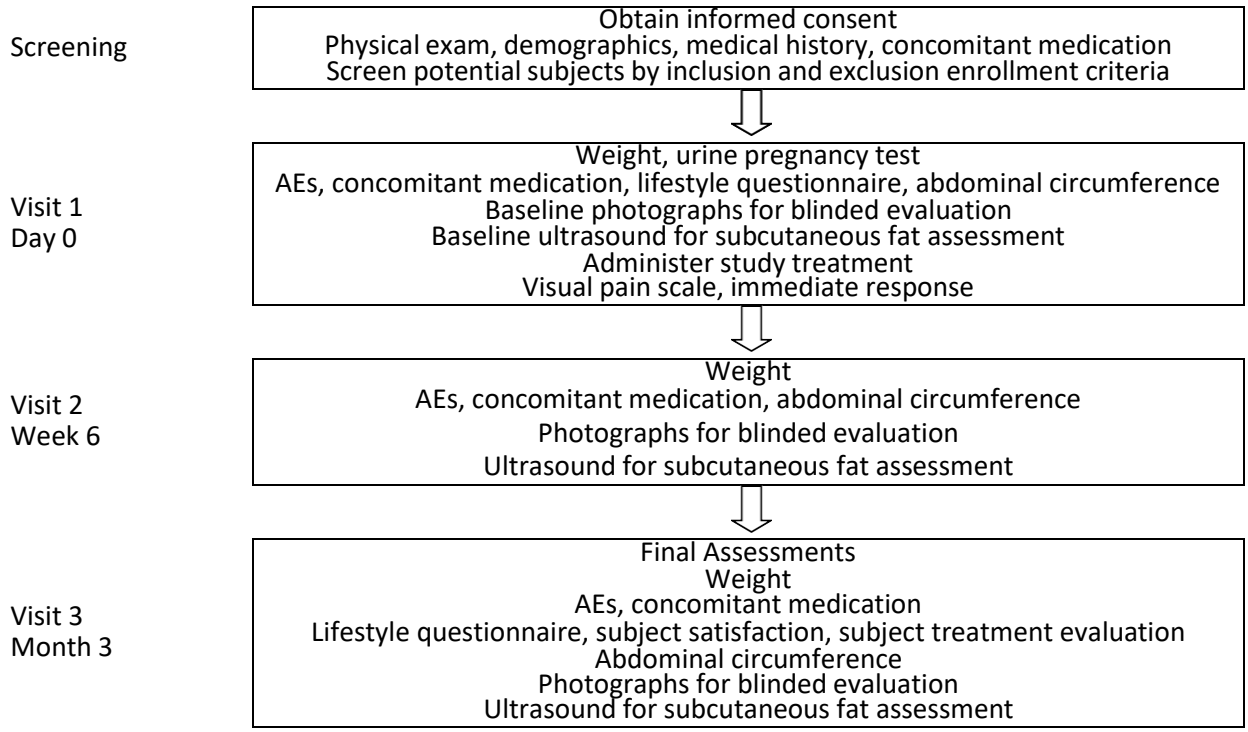
Principal Investigator: _____
Print/Type Name

Signed:_____Signature Date: _____

PROTOCOL SUMMARY

TITLE	Clinical Evaluation of the Safety and Efficacy of a 1060nm Diode Laser for Non-Invasive Fat Reduction of the Abdomen
SUMMARY	Open-label, baseline-controlled, evaluator-blind multi-center study evaluating a 1060 nm diode laser for non-invasive fat reduction of the abdomen. The study will enroll up to 50 subjects requesting non-invasive lipolysis of the abdomen. Each subject will receive a single study treatment. Subjects will be followed at six weeks and twelve weeks post-treatment. Twelve week outcomes will be compared to baseline.
OBJECTIVE	The objective of this clinical study is to assess the safety and efficacy of using a 1060 nm diode laser for non-invasive fat reduction of the abdomen.
ENDPOINT	Primary endpoints • Photographic evaluation by independent, blinded reviewers with correct identification of pre-treatment baseline images when compared to post-treatment images taken at twelve weeks Secondary endpoints • To determine the change in thickness of the adipose layer as measured by ultrasound (US) at twelve weeks post-treatment as compared to baseline • To determine the change in abdominal circumference at twelve weeks post-treatment as compared to baseline • To assess subject satisfaction with treatment at twelve weeks using the 5-Point Likert Subject Satisfaction Scale Safety • Subject's assessment of discomfort and pain post-treatment as measured by the Wong-Baker Faces Pain rating scale • Subjects experiencing a treatment-related adverse event (AE)
POPULATION	The study will enroll up to 50 male and female subjects, 18 to 60 years of age who are seeking fat reduction of the abdomen.
PHASE	Pre-Market
NUMBER OF SITES	Up to 5 sites
DESCRIPTION OF DEVICE	The investigational device (Venus Bliss™) is a non-invasive medical aesthetic device designed for body contouring. The device is comprised of a console, four 1060 nm diode laser applicators (60 mm x 60 mm). A belt is included to allow the operator to secure the laser applicators on the lipolysis treatment area, allowing hands free operation.
STUDY DURATION	Twelve months
PARTICIPANT DURATION	Three months

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

There are multiple, non-invasive fat reduction procedures currently available for non-surgical body-contouring. Technologies include cryolipolysis, radiofrequency, high frequency focused ultrasound, and photobiomodulation. All modalities deliver some form of energy that creates changes in the adipocytes. Studies show that these therapies are safe and effective.

Many non-invasive laser technologies have been studied with the efficacy of laser therapy purported to be related to the wavelength and the energy delivered. Initial lasers studied include the neodymium-doped yttrium aluminum garnet (Nd:YAG) laser delivering 1064nm and 1320nm wavelengths. Diode lasers were introduced delivering energy at 980nm, 924nm, 975nm and 920nm wavelengths. The quest for the most effective laser diode wavelength for lipolysis with the least adverse effect continues, most recently with the 1060nm wavelength.

The 1060nm laser diode leads to the injury of the adipocytes through direct heating of the tissue. The energy delivered 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 with results at 6 weeks but optimally at 12 weeks. The 1060nm wavelength has a particular affinity for adipocytes with low absorption within the dermis. In addition, melanin is minimally targeted so the device can be used in all skin types. (Schilling L et al)

This study will investigate whether a single treatment with a 1060nm laser delivered by the Venus Bliss™ investigational device is safe and efficacious for the reduction of abdominal fat. In addition, the study will investigate whether the effects of this single treatment are maintained at six months post-therapy.

2.2 RATIONALE

The use of 1060nm laser diode technology has been shown in clinical studies to be safe and effective for lipolysis. The objective of this clinical study is to evaluate the safety and efficacy of the use of the Venus Bliss™ investigational medical device for non-invasive fat reduction of the abdomen.

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

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

Furthermore, the use of the non-invasive 1060nm laser diode technology for lipolysis has been reported without incidents or significant complications by Bass LS et al, 2018; Decorato, JW et al, 2017 and Katz B et al, 2018.

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

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Expected adverse events of the laser treatment procedure include transient tenderness, erythema, edema, and/or induration in the treated area lasting from one to three weeks after the treatment. In addition, other adverse events may include and include localized firmness, ecchymosis, skin burn, hyperpigmentation, hypopigmentation, blister and changes in skin laxity. Rarely, skin contour irregularities, dimpling, asymmetry (uneven appearance due to uneven anatomy or uneven treatment of the area), necrosis (tissue death), hardness and nodules occur. Protective laser eyewear will be worn by the subject and operator providing the procedure.

The device has a contact tissue cooling system in place during the procedure to minimize thermal discomfort and prevent damage to the treatment area. Expected adverse events related to the contact cooling include tingling, itching, decreased sensation, numbness, erythema and tenderness.

The boundaries of the treatment area will be marked with a semi-permanent tattoo ink using a microblade. The ink markings should dissipate within one year. Microblade marking may be associated with tenderness.

There are minimal risks associated with the use of ultrasound. The use of the ultrasound may cause redness of the skin. Skin rashes rarely occur with the use of ultrasound gel.

Risks will be mitigated by conducting this protocol with an investigator experienced in the therapeutic area of the clinical investigation. The investigator will be trained by the sponsor on the use of the device. The device design incorporates safety mechanisms which minimize risks. Patients will also be rigorously screened prior to their enrollment and 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 safety and efficacy of the use of this investigational device for abdominal fat reduction. 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 objective of this clinical study is to assess the safety and efficacy of using a 1060 nm diode laser for non-invasive fat reduction of the abdomen.

Primary objectives

- To determine proportion of independent, blinded reviewers who correctly identify pre-treatment baseline images and images taken at twelve weeks post-treatment

Secondary objectives

- To determine the change in thickness of the adipose layer as measured by ultrasound at twelve weeks post-treatment as compared to baseline
- To determine the change in abdominal circumference at twelve weeks post-treatment as compared to baseline
- To assess subject satisfaction with treatment at twelve weeks using the 5-Point Likert Subject Satisfaction Scale

Safety

- Subject's assessment of discomfort and pain post-treatment as measured by the Wong-Baker Faces Pain rating scale.
- 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, baseline-controlled, evaluator-blind multi-center study evaluating one treatment with a 1060 nm diode laser for non-invasive fat reduction of the abdomen.

4.2.1 PRIMARY ENDPOINTS

- Photographic evaluation by independent, blinded reviewers with correct identification of pre-treatment baseline images when compared to post-treatment images taken at twelve weeks

4.2.2 SECONDARY ENDPOINTS

- To determine the change in thickness of the adipose layer as measured by ultrasound at twelve weeks post-treatment as compared to baseline
- To determine the change in abdominal circumference at twelve weeks post-treatment as compared to baseline
- To assess subject satisfaction with treatment at twelve weeks using the 5-Point Likert Subject Satisfaction Scale

Safety Endpoints:

- Report subject's assessment of discomfort and pain as measured by the Wong-Baker Faces Pain rating scale.
- Report subjects experiencing a treatment-related adverse event (AE).

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

1. Able to read, understand and voluntarily provide written informed consent .
2. Healthy male or female, ≥ 18 years of age seeking treatment for unwanted fat in the abdomen.
3. BMI score is less than 30.
4. Agree to not making any major changes in their diet or lifestyle during the course of the study.
5. Able and willing to comply with the treatment/follow-up schedule and requirements.
6. Women of child-bearing age are required to be using a reliable method of birth control at least 3 months prior to study enrollment and for the duration of the study, and have a negative Urine Pregnancy test at baseline.

5.2 PARTICIPANT EXCLUSION CRITERIA

1. Pregnant in the last 3 months, intending to become pregnant, postpartum or nursing in the last 6 months.
2. Any previous liposuction/lipo-sculpture or any type of surgical procedure in the treatment area in the past 12 months.
3. History of immunosuppression/immune deficiency disorders (including AIDS and HIV infection) or use of immunosuppressive medications, 6 months prior to and during the course of the study.
4. History of hyperlipidemia, diabetes mellitus, hepatitis, blood coagulopathy or excessive bleeding.
5. Use of antiplatelet medications (81 mg acetylsalicylic acid daily permitted), anticoagulants, thrombolytics or anti-inflammatory medications within 2 weeks of treatment.
6. Having a history of skin cancer or any other cancer in the areas to be treated, including presence of malignant or pre-malignant pigmented lesions.
7. Having a permanent implant in the treatment area such as metal plates or an injected chemical substance such as silicone or parenteral gold therapy (gold sodium thiomalate).
8. Use of medications, herbs, food supplements, and vitamins known to induce photosensitivity to light exposure at the wavelength used or history of photosensitivity disorder.
9. Suffering from significant skin conditions in the treatment area or inflammatory skin conditions including but not limited to open lacerations, abrasions, herpes sores, cold sores, active infections.
10. Tattoos in the treatment area.
11. Poor skin quality (severe laxity).
12. Abdominal wall, muscular abnormality or hernia on physical examination.
13. Unstable weight within the last 6 months (± 3% weight change in the prior six months).
14. Use of retinoids such as oral isotretinoin (Accutane™) within the past six months or during course of the study.
15. Participation in another clinical study involving the same anatomical areas within the last 6 months.
16. History of keloid or hypertrophic scar formation or poor wound healing in the treatment area.
17. As per the investigator's discretion, any physical or mental condition which may make it unsafe for the subject to participate.

18. Unable or unlikely to refrain from sun exposure, artificial tanning, including the use of tanning booths, prior to (six weeks) and during the course of the evaluation.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Up to 50 subjects will be enrolled at up to 5 sites. It is anticipated that it will take up to twelve months to complete the study. Subjects requesting non-invasive lipolysis of the abdomen will be recruited primarily from the investigator's clinic. Any advertising campaigns and materials will be reviewed and approved by an institutional review board (IRB) before implementation. Due to the duration of the study, 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 CRF form should be completed. On the withdrawal 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.

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 conduct a final visit and 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

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

A principal investigator (PI), 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 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 protocol 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 and the like as the case may be are addressed and satisfy the sponsor, IRB and/or regulatory authorities.

6 STUDY DEVICE

6.1 STUDY DEVICE AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

The Venus Bliss™ 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 devices and the study.

6.1.2 DEVICE SPECIFIC CONSIDERATIONS

The Venus BLISS™ investigational device is a 1060nm diode laser system intended for non-invasive lipolysis of the abdomen in individuals with a Body Mass Index (BMI) of less than 30. The device consists of a console, four laser applicators and a belt that secures the laser applicators in place securely to the subject's selected treatment area. Each applicator includes contact tissue cooling and has an active area of 60mm x 60mm.

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

- Optical power up to 1.4 W/cm2 at 1060nm

Treatment time is 25 minutes.

6.2 STUDY DEVICE ACCOUNTABILITY PROCEDURES

The device and applicators will be shipped to the site by the sponsor. Traceability shall be achieved during and after the clinical investigation by assignment of serial numbers to device and applicators and accounting for the device and applicators returned to the sponsor by each site.

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

Physical examination (as per site's standard of care)
Assessment of eligibility
Urine pregnancy test for women of child bearing potential (visit 1 only)
Treatment area marking
Abdominal circumference measurements
Photographs (visit 1, visit 2 and visit 3)
Ultrasound subcutaneous fat (visit 1, visit 2 and visit3)
Administration of a questionnaires/scales for patient-reported outcomes (visit 1 and visit 3 only)
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. 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. 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) and for each treatment.

During screening visit, the study investigator, and/or his/her designee, will assess 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 treatment areas to ensure they meet the study criteria.

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.

The investigator will ask women of child-bearing potential for the date of their last period. The investigator shall inquire about the form of contraceptive they use to confirm they meet the inclusion criteria.

The subject will complete screening and the treatment will be scheduled. Treatment may be performed on the day the subject was enrolled if the results of the urine pregnancy test are available (and negative) and the subject has avoided sun exposure of the target treatment area for at least six weeks.

7.3.2 ENROLLMENT/BASELINE

Enrollment/Baseline/Treatment Visit (Visit 1 – Day 0)

Pre-Treatment

The investigator will confirm that the subject continues to meet the inclusion and none of the exclusion criteria. Adverse events, weight and any changes to concomitant medications will be recorded. The subject will complete the modified Simple Lifestyle Indicator Questionnaire (SLIQ).

The location and size of the treatment area will be left to the principal investigator's judgement based on his/her assessment of individual subject requirements for treatment. The defined abdominal treatment area will be marked with a semi-permanent pigment using a treatment template as per the sponsor's instructions. Photographs of the marked treatment area followed by ultrasound measurements of the marked treatment area will be made as per the instructions supplied by the sponsor. Measurement of the abdominal circumference will be made with the sponsor supplied tape measure using the marked boundaries as a guide for replication.

Treatment

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

Based on the mild nature of treatment, anesthesia is not required. The treatment procedure should include positioning of the patient in a manner that enables access to the target treatment anatomical site.

The belt will be positioned on the subject as per the marked treatment template. Laser applicators will be secured in place by the belt with the areas treated for up to 25 minutes. The laser energy will be delivered to the area while cooling is administered to the skin surface to increase subject comfort. Treatment will continue until the total treatment area has been treated. The subject will receive one treatment session only.

The assessment of discomfort/pain during the treatment procedure will be assessed using the Wong-Baker Faces Pain rating scale with treatment parameters adjusted according to patient's comfort level.

Post Treatment

Assessment

The investigator will examine the treated areas and report 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.

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

The normal response to this treatment is transient tenderness, edema and/or induration in the treated area which should resolve within one to two weeks. If any other side effects occur or persist for longer than expected, they must be recorded in the adverse event (AE) section of the case report form (CRF).

For post-treatment cooling and/or discomfort, cold packs can be applied to treatment area if needed with acetaminophen at recommended doses used to alleviate pain as needed.

During the day following treatment, care should be taken to prevent any mechanical or thermal damage to the treated sites: avoid hot baths, massage, contact sports, swimming, etc. The treated areas should be kept clean to avoid contamination or infection. The subject should be reminded to not make any major changes in their diet or lifestyle during the course of the study.

Subjects will be discharged from the clinic and will be scheduled to return for the six week assessment.

7.3.3 FOLLOW-UP 1

Visit 2, Week 6 (± 3 days)

Subjects will return to the clinic six weeks after the treatment. Adverse events, weight and any changes to concomitant medications will be recorded.

Measurement of the abdominal circumference will be made with the sponsor supplied tape measure using the marked boundaries as a guide for replication.

Photographs of the marked treatment area followed by ultrasound measurements of the marked treatment area will be made as per the instructions supplied by the sponsor.

Subjects will be discharged from the clinic and will be scheduled to return for the Twelve week (Final) assessment.

7.3.4 FINAL STUDY VISIT

Visit 3, Week 12 (± 7 days)

Subjects may return to the clinic twelve weeks after the treatment. Adverse events, weight and any changes to concomitant medications will be recorded.

Subjects will be asked to complete the lifestyle, 5-point Likert subject satisfaction and treatment evaluation questionnaires. Measurement of the abdominal circumference will be made with the sponsor supplied tape measure using the marked boundaries as a guide for replication.

Photographs of the marked treatment area followed by ultrasound measurements of the marked treatment area will be made as per the instructions supplied by the sponsor.

The End of Study form will be completed and subjects will be discharged from the clinic and terminated from the study.

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

7.3.5 EARLY TERMINATION VISIT

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

7.3.6 SCHEDULE OF EVENTS TABLE

Procedures	Screening (-6 weeks)	Enrollment/Treatment (Visit 1, Day 0)	Follow-up 1 Visit 2, Week 6 (±3 days)	Follow-up 2 (Visit 3, Week 12 (±7 days)
Informed consent	X			
Inclusion/exclusion criteria	X	X		
Demographics	X			
Medical history	X			
Physical exam	X			
Weight		X	X	X
Urine pregnancy test[a]	X			
Lifestyle Indicator Questionnaire		X		X
Abdominal circumference		X	X	X
Photographs		X	X	X
Ultrasound subcutaneous fat		X	X	X
Administer Treatment		X		
Discomfort/Pain Visual Pain Scale		X		
PI immediate response		X		
Blinded reviewers GAIS		X		X
Subject satisfaction questionnaire				X
Treatment evaluation questionnaire				
Concomitant medication	X	X	X	X
Adverse event evaluation		X	X	X

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, antiplatelet medications, thrombolytics, anti-inflammatory medicatons and anticoagulant medications is to be avoided. Herbal supplements, perfumes, cosmetics and/or medications that may affect sensitivity to light are prohibited. The use of Accutane™ (Isotretinoin) within the past six months is also strictly prohibited.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

None.

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

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

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

The event will be reported to the 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 visual pain scale and the principal investigator will examine the treated area and report immediate response.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

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

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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 of the treatment include transient tenderness, erythema, edema, and/or induration in the treated area lasting from one to three weeks after the treatment.

The device has a contact tissue cooling system in place during the procedure to minimize thermal discomfort and prevent damage to the treatment area. Expected adverse events related to the contact cooling include tingling, itching, decreased sensation, numbness, erythema and tenderness.

An AE or suspected adverse reaction is considered "unexpected" if it is not known to occur for the study treatment 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).

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 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 10 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 SAP will be completed and issued prior to database lock and unblinding 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: Statistical hypothesis will not be applied in the analysis of the study's primary endpoint

- Secondary Efficacy Endpoint(s):
  - Null Hypothesis *(H_o: $\mu_d = \mu_{post} - \mu_{baseline} = 0$)* – There is no change in thickness of the adipose layer as measured by ultrasound (US) at twelve weeks post-treatment as compared to baseline.

    Alternative Hypothesis *(H_a: $\mu_d = \mu_{post} - \mu_{baseline} \neq 0$)* – There is a change in thickness of the adipose layer as measured by ultrasound (US) at twelve weeks post-treatment as compared to baseline. The efficacy endpoint to treatment will be defined by reduction in abdominal fat determined by decrease in thickness of the adipose layer as measured by ultrasound (US) at twelve weeks post-treatment as compared to baseline.

  - Null Hypothesis *(H_o: $\mu_d = \mu_{post} - \mu_{baseline} = 0$)* – There is no change in abdominal circumference at twelve weeks post-treatment as compared to baseline.

    Alternative Hypothesis *(H_a: $\mu_d = \mu_{post} - \mu_{baseline} \neq 0$)* – There is a change in abdominal circumference at twelve weeks post-treatment as compared to baseline. The change will

be defined by reduction in abdominal circumference at twelve weeks post-treatment as compared to baseline.

- Null Hypothesis *(H_o: $\mu_d = \mu_{post} - \mu_{pre} = 0$)* – There is no satisfaction with the treatment at twelve weeks using the 5-Point Likert Subject Satisfaction Scale as assessed by the subjects.

  Alternative Hypothesis *(H_a: $\mu_d = \mu_{post} - \mu_{pre} \neq 0$)* – There is satisfaction with the treatment at twelve weeks using the 5-Point Likert Subject Satisfaction Scale as assessed by the subjects.

- Safety Endpoint: Statistical hypothesis will not be used in the analysis of the study's safety endpoint.

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 Venus Bliss™ treatment.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

This is an open-label, baseline-controlled, evaluator-blind multi-center study evaluating one treatment with a 1060 nm diode laser for non-invasive fat reduction of the abdomen.

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 photograph and measurement performed before the first treatment on Visit 1.

All statistical tests will be two-sided, where applicable. 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 at twelve weeks post-treatment as compared to baseline. 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.

In order to accommodate imbalances of some baseline of scores or measurements, covariate adjustment analysis may be performed in SAP to estimate adjusted treatment effects for the primary endpoint analysis.

The assumption for the statistical test is that variables are normally distributed within study group and the variation of scores or measurements at twelve weeks post-treatment as compared to baseline is not reliably different.

The safety analysis will be done by analyzing spontaneous reports of adverse events (AE), subjects' completed 10 cm discomfort/pain visual pain scale 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 ENDPOINTS

The following will be consider for the analysis primary endpoints:

The results of each Blinded Reviewer's evaluation of photographs taken at three and six moth compared to baseline will be analyzed and the results will be reported as a % of the correctly identified post treatment photographs chosen per Blinded Reviewer. An average of the % of the correctly identified post treatment photographs chosen by Blinded Reviewer will be calculated and used to determine

Bar, pie charts or graphs indicating percentages of the correctly identified post treatment photographs chosen by Blinded Reviewer may also be used to analyse efficacy.

The efficacy endpoint to treatment will be defined by an average of the 80% of the correctly identified post treatment photographs chosen by Blinded Reviewer This will be used to determine if the study meets the primary endpoint expectation.

The % of the correctly identified post treatment photographs chosen by Blinded Reviewer of all subjects who received at least one treatment of Venus Bliss™ and for whom at least one valid 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 ENDPOINTS

For the analysis of changes in change in thickness of the adipose layer, abdominal circumference and subjects' assessment of satisfaction with the treatment secondary endpoints the following analysis will be considered:

Summary tables of changes in thickness of the adipose layer measured by ultrasound (US), abdominal circumference, and subjects' assessment of satisfaction at twelve weeks post-treatment as compared to baseline will be displayed as mean difference, standard deviation and standard error.

Bar charts, pie chart, graphs or any other descriptive statistical displays indicating scores, percentages and/or proportions of changes in thickness of the adipose layer measured by ultrasound (US), abdominal circumference, and subjects' assessment of satisfaction at twelve weeks post-treatment as compared to baseline will be used where applicable 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 of changes in thickness of the adipose layer measured by ultrasound (US), abdominal circumference, and subjects' assessment of satisfaction at twelve weeks post-treatment as compared to baseline. Analysis of Covariance (ANCOVA) may also be used where appropriate.

Change in thickness of the adipose layer measured by ultrasound (US), abdominal circumference, and subjects' assessment of satisfaction assessments at twelve weeks post-treatment as compared to baseline of all subjects who received at least one treatment of Venus Bliss™ 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.

10.4.5 SAFETY ANALYSIS

The safety analysis will be done by analyzing spontaneous reports of adverse events (AE), subjects' completed 10 cm discomfort/pain visual pain scale and a response questionnaire as well as analysis of 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.

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

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

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

A summary table of the 10 cm discomfort/pain visual pain scale scores post treatment will be displayed as mean difference, standard deviation and standard error. The 10 cm discomfort/pain visual pain scale is a 11-level (0 to 10) ordinal scale tool for assessing pain.

The overall percentage or proportion of subject that recorded marked or severe post treatment discomfort/pain visual pain scale scores may be calculated and compared to those with none, trace, low or moderate discomfort/pain using a bar or pie chart.

10.4.6 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.

10.4.7 BASELINE DESCRIPTIVE STATISTICS

Subjects baseline measurements and scores of all applicable endpoints will be compared using descriptive statistics such as mean score, standard deviation, standard error, range and graphical presentations.

10.4.8 PLANNED INTERIM ANALYSES

No interim analysis is planned.

10.4.8.1 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.

10.4.8.2 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.

10.4.9 ADDITIONAL SUB-GROUP ANALYSES

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

10.4.10 MULTIPLE COMPARISON/ MULTIPLICITY

Not applicable.

10.4.11 TABULATION OF INDIVIDUAL RESPONSE DATA

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

10.4.12 EXPLORATORY ANALYSES

Not applicable.

10.5 SAMPLE SIZE

The change in thickness of the adipose layer as measured by ultrasound (US) at twelve weeks post-treatment as compared to baseline secondary endpoint outcome measures was used to calculate the study sample size.

Sample size calculation using secondary endpoint outcome measure;

- Null and alternate hypotheses:

  Null Hypothesis *(H_o: $\mu_d = \mu_{post} - \mu_{baseline} = 0$)* – There is no change in thickness of the adipose layer as measured by ultrasound (US) at twelve weeks post-treatment as compared to baseline.

  Alternative Hypothesis *(H_a: $\mu_d = \mu_{post} - \mu_{baseline} \neq 0$)* – There is a change in thickness of the adipose layer as measured by ultrasound (US) at twelve weeks post-treatment as compared to baseline. The efficacy endpoint to treatment will be defined by reduction in abdominal fat determined by decrease in thickness of the adipose layer as measured by ultrasound (US) at twelve weeks post-treatment as compared to baseline.
  Expected reduction in abdominal fat of 2.65 + 1.41 obtained from a similar study (,Bass LS et al) will be used to determine the sample size.
- In view of the nature of this study in regard to number of visits, we make provision for 10% 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, expected reduction in abdominal fat measured from baseline to 3 month post treatment visit under H_a	2.65
σ, Standard Deviation (obtained from a study)	1.41
$Z_{1-\alpha/2}$	1.96
$Z_{1-\beta, (for\ 80\%)}$	0.84
Estimated Sample Size	**40**
Estimated Sample Size of each equal group + 10% drop out	**44**

Conclusion: The estimated sample size for the study and the additional 10% provision for drop out **(44 subjects)** obtained from the secondary endpoint outcome measure calculation is required for this study. However, to ensure statistical significance, up to 50 subjects will be enrolled.

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. 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) and for each treatment. Subjects are not randomized; this is an open-label, baseline-controlled, evaluator-blind multi-center study.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

This is an open-label, baseline-controlled, evaluator-blind multi-center study; only the independent reviewers will be blinded.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Not applicable.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with 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 modified Simple Lifestyle Indicator Questionnaire, 5-point Likert Subject satisfaction Scale, treatment evaluation and visual pain scale data for this study will be collected on the CRF. The immediate response as assessed by the principal investigator will be collected on the CRF 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 Bliss™ investigational 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

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APPENDIX

Version	Date	Significant Revisions