CLINICAL EVALUATION OF HAIR REMOVAL AND PERMANENT HAIR REDUCTION

FOR SKIN TYPES V-VI USING INTENSE PULSED LIGHT

Clinical Study Protocol

CLINICAL INVESTIGATION PLAN (CIP)

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Protocol # CS0115

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Study Synopsis

Study Title	Clinical evaluation of hair removal and permanent hair reduction for skin type V-VI using Intense pulse light.	
Protocol No:	CS0115	
Device Name:	Versa IPL device	
Design	Multi-center, blinded, baseline-controlled, prospective study	
Projected Study period	Initiation Date: **January 2015**	Completion Date: **March 2016**
Objectives	**Primary objectives** • To evaluate the safety of hair removal using the Versa HR 690 nm applicator. • To verify the efficacy of hair removal and permanent hair reduction using the Versa HR 690 nm applicator. **Secondary objectives** • To evaluate subject's assessment of comfort associated with treatments. • To evaluate subject's satisfaction with hair removal treatments and assessment of improvement.	
Hypothesis	The study will confirm that the Versa HR 690 nm applicator is safe for removal of unwanted hair, and will result in hair removal and permanent hair count reduction for patients with Fitzpatrick Skin Type V-VI.	
Study population	20 sites and One hundred and twenty (120) subjects, Fitzpatrick Skin Type V-VI. Up to 12 evaluable subjects will be enrolled per site.	
Main Inclusion Criteria	• Healthy adults, females or males older than 21 years of age with skin type V-VI; hair color Black or dark brown; having a suitable treatment area for hair removal. Two small anatomical areas (right and left axillae and double sided bikini line) or; • One double sided large area (right and left thighs)or; • One large area (whole back / abdomen) Other areas not defined above, as face, are not allowed to be treated.	
Main Skin Related Exclusion Criteria	• Active infections in the treatment area. • Dysplastic nevi in the treatment area. • Tattoos in the treatment area. • Significant concurrent skin conditions or any inflammatory skin conditions in the treatment area. • Active cold sores, open lacerations or abrasions in the treatment area. • Chronic or cutaneous viral, fungal, or bacterial diseases. • Deep suntan, recent suntan, sunburn or artificially tanned skin. • Current skin cancer. • History of skin cancer or pre-cancerous lesions at the treatment areas.	

Investigational Treatment and Study Duration	Each subject will receive six treatments at four to six weeks intervals and return for follow-up visits at one (±seven days), three (±seven days) and six (±seven days) months after the last treatment for evaluation of the treated areas.
Criteria for Evaluation	**Primary endpoints** • Hair count reduction from photographs 3 months following the last treatment - FU2, as compared to baseline (hair removal) • Hair count reduction from photographs 6 months following the last treatment - FU3, as compared to baseline (permanent hair reduction) **Secondary endpoints** • Hair count reduction from photographs 1 month following the last Treatment - FU1 • Subject's assessment of comfort associated with treatments using a VAS scale, following each of the 6 treatments. • Subject's satisfaction with hair removal treatments and assessment of improvement using a five point scale, at visit 3, 6, 7, 8 & 9. • Immediate response following each treatment, defined as type and intensity of response and the time it takes for it to subside. Should be removed any adverse events associated with various setting used during the treatment and follow-up period.

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1 Introduction

1.1 Background

The use of intense pulsed light (IPL) for hair removal dates back well over 20 years. The first IPL dedicated solely for hair removal was appropriately researched and the findings published on its safety and efficacy following a single treatment, as well as long-term safety and efficacy with one- and two-year results[1–3]. These studies proved that an IPL is a legitimate and useful light source for effective hair removal. Clinical results of the IPL for hair removal on darker skin types were also published, showing that with appropriate cut-off filters, the IPL can be used successfully in all skin types. Other investigators verified this results[4–6]. The effect of IPL is based on well-known principles of selective photothermolysis, developed both theoretically and practically during the last two decades. One of the most common applications that demonstrate the principle of photothermolysis is IPL based hair removal. In hair removal, an optical energy source focuses on the chromophore melanin, which is mainly found in the hair shaft, with a small amount present in the upper third of the follicular epithelium. Melanin is considered the primary chromophore for all hair removal IPL based treatments. The IPL source can cause localized damage by selectively heating dark target matter, melanin, in the area that causes hair growth, the follicle, while only minimally heating the rest of the skin.

1. Gold MH, Bell MW, Foster TD, Street S. Long-term epilation using the EpiLight broad band, intense pulsed light hair removal system. Dermatol Surg. 1997:23(10):909–913.
2. Gold MH, Bell MW, Foster TD, Street S. One-year follow-up using an intense pulsed light source for long-term hair removal. J Cutan Laser Ther. 1999:1(3):167–171.
3. Gold MH, Bell MW, Foster TD, Street ST. Long-term hair removal utilizing the intense pulsed light source—two year follow-up. Int J Cosm Surg Aesthet Derm. 2002;4(1):15–18.
4.Weiss RA, Weiss MA, Marwaha S, Harrington AC. Hair removal with a non-coherent filtered flashlamp intense pulsed light source. Lasers Surg Med. 1999:24(2):128–132.
5. Troilus A, Troilus C. Hair removal with a second generation broad spectrum intense pulsed light source-a long term follow-up. J Cutan Laser Ther. 1999:173–178.
6. Sadick NS, Shea CR, Burchette JL, Prieto VG. High intensity flash lamp photo epilation. Arch Dermatol. 1999:135(6):668–676.

1.2 Rationale for Evaluation

IPL technology works on the principle of selective absorption of energy by components of the hair follicle. The target chromophore is melanin in the hair bulb and outer root sheath zones of the hair follicle, while the competing chromophores are any other melanin-containing components of the skin and other light-absorbing components such as haemoglobin in blood vessels. Therefore, patients with darker skin types present a greater treatment challenge; the goal for these patients is to deliver the highest fluence to the hair follicles without causing injury to the epidermis. Many factors influence the efficacy of treatment such as spot size, divergence/convergence of the beam and wavelength that determines the depth of penetration, pulse duration, fluence and the adjacent cooling system[7].

This clinical protocol is using a Versa IPL device with hair removal 690 nm wavelength applicator. The assumption is that the device physical characteristics of wave length, pulse duration and the rectangular type pulse together with an advanced cooling system will enable safe and effective hair removal and permanent hair reduction in subjects with dark skin type.

7. Liew SH (2002) Laser hair removal: guidelines for management. Am J Clin Dermatol 3:107–115

The objective of this clinical study is to evaluate the safety of hair removal and to verify the hair removal and permanent hair reduction for skin type V-VI using the Versa 690 nm applicator, as assessed by hair counts.

The use of the Versa 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 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 approved by the Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

2 Study Design

This is a Multi-center, blinded, baseline-controlled, prospective study. One hundred and twenty (120) subjects that meet the inclusion criteria will be enrolled from the site's pool of patients, up to 12 subjects per site. Subjects should be of Fitzpatrick Skin Type V-VI, and have a suitable treatment area for hair removal.
Subjects will receive six treatments with the study device, at four to six week intervals upon re-growth of hair, followed by three and six month follow-up visits after the last treatment.

3 Study Objectives

3.1 Primary Objectives

- To evaluate the safety of hair removal using the Versa HR690 nm applicator.
- To verify hair removal and permanent hair reduction using the Versa HR 690 nm applicator, assessed by hair counts.

3.2 Secondary Objectives

- To evaluate subject's assessment of comfort associated with treatments.
- To evaluate subject's satisfaction with hair removal treatments and assessment of improvement.

4 Outcome Measures

4.1 Primary Effectiveness Endpoints

- Hair count reduction, as calculated from photographs and defined as (count-baseline)/baseline*100; 3 months following the last treatment FU2 (hair removal).

- Hair count reduction, as calculated from photographs and defined as (count-baseline)/baseline*100; 6 months following the last treatment FU 3 (permanent hair reduction).

4.2 Secondary Endpoints

- Hair count reduction, as calculated from photographs and defined as (count-baseline)/baseline*100; 1 months following the last treatment FU1 (hair removal).
- Subject's assessment of comfort associated with treatments using a VAS scale.
- Subject's satisfaction with hair removal treatments and assessment of improvement using a five point scale.

4.3 Safety Endpoint

- Immediate response following treatment, defined as intensity of response and the time it takes for it to subside.
- Any adverse events associated with various setting used during the treatment and follow-up period.

5 Patient Population

5.1 Source and Sample Size

Subjects shall be recruited by the investigator from within the investigator's patient population. Subjects shall be with skin types V-VI and have visible hair at the designated treatment area.

Each site participating in this study will enroll up to 12 subjects according to the inclusion/exclusion criteria. Each subject (120 subjects) included for treatment will receive six treatments at four to six week intervals upon re-growth of hair and return for follow-up visits at one month FU1 (±seven days) , three FU2 (±seven days) and six FU3 (±seven days) months after the last treatment for evaluation of the treated areas. Enrolled subjects that did not complete the full course of the study will be replaced.

5.2 Eligibility

Each subject will be evaluated by the Investigator to assess his/ her suitability for entry into this study according to the following criteria:

5.2.1 Inclusion Criteria

<u>Subjects must meet all of the following inclusion criteria to be entered into the study:</u>

1. Able to read, understand and provide written Informed Consent;
2. Subject has black or dark brown terminal hairs in the areas to be treated.
3. Terminal hair density requirement of greater than 15 hairs within the hair count site (3x3 cm area) as determined by manual hair count performed by the study investigator.
4. Healthy adult, male or female, 21 years of age or older with skin type V-VI;
5. Having a suitable treatment area for hair removal;
6. Able and willing to comply with the treatment/follow-up schedule and requirements;
7. 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 at least three months prior to enrollment and throughout the course of the study.

5.2.2 Exclusion Criteria

Any of the following will exclude the subject from the study:

1. Subject has light ,gray terminal or fine hairs in all/some parts of the treated area;
2. Pregnant, expectation of pregnancy, postpartum or nursing (<6 months);
3. Hormonal disorders that may affect hair growth;
4. Immunosuppressive diseases, including AIDS and HIV infection, or use of immunosuppressive medications;
5. Livedo reticularis;
6. Uncontrolled systemic diseases such as diabetes;
7. Active infections in the treated area;
8. Dysplastic nevi;
9. Significant concurrent skin conditions or any inflammatory skin conditions;
10. Active cold sores, open lacerations or abrasions;
11. Chronic or cutaneous viral, fungal, or bacterial diseases;
12. Current cancer;
13. History of skin cancer or pre-cancerous lesions at the treatment areas;
14. Use of Accutane™ (Isotretinoin) within the past six month;
15. Keloid or Hypertrophic scar formation in the treatment area;
16. Tattoos in the treatment area;
17. Bleeding coagulopathies or use of anticoagulants;
18. Auto-immune disorders;
19. Erythema abigne, when identified treatments should be discontinued;
20. Photosensitivity disorder that can be exacerbated by laser or intense light;
21. Herpes simplex in the treatment area;
22. Use of medications, herbal supplements, perfumes or cosmetics that may affect sensitivity to light;
23. Poor wound healing;
24. Sunburns;
25. 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;
26. Prior skin treatment with laser or other devices on the same treated areas within the last six months prior to study enrollment or during the course of the study.

6 Materials

6.1 Device Description

The Venus Versa system is a multi-application device intended to be used in aesthetic and cosmetic procedures.

The Venus Versa system consists of a console and 4 detachable applicators that deliver optical energy in the form of Intense Pulsed Light to the patient skin. The intense pulsed light lamp delivers non-coherent light distributed over a range of wavelengths from 500 nm to 1200 nm. Different filters are embedded in the different applicators so that each applicator can deliver the desired spectrum according to the indications to be treated.

The energy delivered to the patient's skin is used to treat various conditions via the mechanism of Selective Photothermolysis. The selective absorption of different wavelengths by the skin and its components (e.g. blood vessels, hair follicles, etc.) lead to localized heating and thermal lysis of the anatomic target. The different applicators use optical filters to optimize the energy delivered to the body, and match the spectrum of light delivered to the intended clinical application.

Figure 1: Venus Versa aesthetic treatment system and HR 690 applicator

The applicator that will be used for this study (HR 690) has a wavelength of 690 nm and has a spot size (treatment area) of 30 mm by 10 mm. The clinician is able to control the settings of IPL from the user interface (LCD GUI) display on the main console.

IPL settings: The available settings for this applicator are:

- Wave Length 690 nm.
- Spot size 30mmX10mm.
- Pulse duration of 20 – 50 ms.
- Fluence/Energy density of 5-20 J/cm^2.
- Pulse repetition rate of up to 3 Hz.

6.2 Measurement Equipment

6.2.1 Standard High Resolution Digital Camera

The investigative site will ensure the digital photography equipment is available for use during this study. Venus Concept will supply photo storage media for use with the digital camera during the study which must be returned to Venus Concept upon conclusion of the study. Digital photographs will be provided by the site to Venus Concept on compact flash cards, CD-ROMS, or similar media.

Photographs of the treated areas will be taken at various visits as detailed in the schedule of events chart.

Level of improvement and satisfaction

Subject's Improvement and Satisfaction with treatment will be recorded by a 5-point Scale: 1=None; 2=Slight; 3=Moderate; 4=Good; 5=Very Good.

Table 1– Clinical Evaluation Tools and appendix I.
For consistency purposes, all images throughout the study must be taken, using the same camera and lighting settings, preferably by the same photographer, the photography should be taken from the same angle.
Subject anonymity will also be assured for the images by deleting any ID detail. Only the code for the Case Number in the study will appear on the records being transferred to the sponsor.

6.2.2 Labels for hair count

Customized hair count sticker templates will be supplied by the sponsor. Templates consist of a rectangular frame sticker with a rectangular window sized 3*3 cm. The sticker template will be placed directly on the skin and the hairs in this window will be counted at specific visits during the study as detailed in section 7.2.1.1. For identification, the subject's ID, treatment area and visit date shall be filled out on the designated area upon the template frame. These photographs will be evaluated and counted by 2 blinded reviewers.

7 Study Procedures

7.1 Study duration and timelines

Each subject will be enrolled and scheduled for six treatments at approximately four to six week intervals upon re-growth of hair and return for follow-up visits at one month FU1 (±seven days) three month FU2 (±seven days) and six month FU3 (±seven days) after the last treatment for evaluation of the treated areas. During each visit various tasks will be performed as detailed in the study flow chart.
Level of improvement and satisfaction
Subject's Improvement and Satisfaction with treatment will be recorded by a 5-point Scale: 1=None; 2=Slight; 3=Moderate; 4=Good; 5=Very Good.

Table 1– Clinical Evaluation Tools.

Each subject will therefore participate in the study for a period of at least 11 months. The study is anticipated to be completed within twelve months.

7.2 Evaluation Assessments

Various assessments will be performed throughout this clinical study. The hair count that is done on the photographs of the treated area will be performed by 2 blinded evaluators.

7.2.1.1 Post Treatment Responses

Immediate and short term responses (erythema, edema, purpura, etc.) will be assessed for severity immediately and up to 30 min post treatment, by a 5 level scale: 1=none; 2=trace; 3=moderate; 4=marked; 5=severe.

7.2.1.2 Hair reduction assessment

Hair counts will be accomplished by analysis of photographs. The original image of the photographs will be saved and archived in its original form by the site and a copy will be sent to the sponsor. The image will be enlarged to a uniform size to facilitate counting and the file shall be saved (locked) into a PDF format.

At baseline, immediately before treatment 3 and 6, 1M FU1, 3M FU2 and 6M FU3, a copy of the image shall be printed. Each image will be reviewed by the investigator or his/her designees. Additional copies of baseline, 1M FU1, 3M FU2 and 6M FU3 will be sent to two other reviewers who are blinded to the treatments. The reviewer will mark each hair identified with a red pen, and each of these marks will be tallied to obtain hair count. For a detailed hair count explanation please refer to section 7.4.2.2.

7.2.2 Subject Subjective Assessments

7.2.2.1 Level of comfort

Treatment associated level of comfort experienced by the subjects will be measured on a 10cm Visual Analogue Scale (VAS) were 0 cm is ‘no pain’ and 10 cm is ‘intolerable pain’. The subjects will be given a VAS and be asked to mark their perception of pain immediately following each treatment.

7.2.2.2 Level of improvement and satisfaction

Subject’s Improvement and Satisfaction with treatment will be recorded by a 5-point Scale: 1=None; 2=Slight; 3=Moderate; 4=Good; 5=Very Good.

Table 1– Clinical Evaluation Tools

Claim/task	When to conduct?	Tool
Photography	Baseline, immediately before treatments 3, 6, 1M±7D FU1, 3M±7D FU2 and 6M±7D FU 3	Standardized digital photographs
Hair count by single study personnel	Baseline, immediately before treatments 3, 6, 1M±7D FU1, 3M±7D FU2 and 6M ±7D FU3	Standardized digital photographs
Hair count by blinded reviewers	Baseline, 1M ±7D FU1, 3M ±7D FU2 and 6M ±7D FU3	Standardized digital photographs
Immediate and short term response	Immediately following treatments 1-6	Examination of skin in the treated area based on 5 level scale
Subjects comfort assessment	Immediately following treatments 1-6	VAS
Subjects improvement/ satisfaction assessment	Treatments 3, 6, 1M ±7D FU1, 3M ±7D FU2 and 6M ±7D FU3.	5 point scale
Safety	Throughout study	Examination of skin in the treated area, interview subjects

7.3 Screening Procedures

7.3.1 Subject Enrollment

If the subject has met the preliminary study criteria the study doctor, and/or his 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 designee, will screen the subject for eligibility to participate in the clinical study using the Inclusion, Exclusion criteria. During screening the study doctor will review the subject's medical history, and examine the subject's targeted area to ensure that it meets the study criteria. The subject will complete screening and the treatment will be scheduled. Treatment may be performed on the day the subject was enrolled or no later than one week following enrollment and screening.

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.

7.3.2 Subject Identification

At enrollment each subject will receive a unique identifying number that will be composed of a consecutive number and his/her initials. This unique identifier will be used throughout the entire study and will be entered in the subject's CRF for each treatment and photographs.

7.4 Pre-Treatment Procedures

7.4.1 Subject Skin care and medication

- Subjects will be instructed to avoid sun exposure for at least four weeks before treatment and to use broad spectrum sunscreen of no less than 30 SPF on a daily basis, replenishing it as often as needed throughout the course of the study. In addition Tanning is to be strictly avoided.
- Subjects should not pluck, tweeze, wax, use depilatory creams, electrolysis, hair bleaching agents, hair growth inhibitors (such as Vaniqa®) or any treatment with a laser or other devices in the study treatment throughout the course of this study and follow-up examinations.
- Immediately before treatment, the area will be shaved to the skin surface using foam or gel to minimize skin irritation.

7.4.2 Photography and hair count

7.4.2.1 Photography

Photographs are mandatory for this research; they may also be used by the Sponsor (Venus Concept Ltd.) for future educational and marketing purposes.
Photographs will be taken prior to treatment and throughout the study according to specified time points detailed in Table 1, utilizing standard scientific equipment.

The photos should be taken in a private room or area of the clinic under controlled conditions, including the distance, angle, background and lighting in order to achieve high-quality before & after sets. Do not use direct illumination. The subject should be placed in the same position each time. As each photograph is taken, it should be viewed to ensure that it is in focus and is similar to its baseline counterpart in all technical aspects, including lighting, distance and angle.

For consistency purposes, the same person should ideally take all study photographs, especially per subject. The digital files should follow a consistent standard naming scheme, for example: 001TM_Tx1_right axillae.

In each photography session the order of photos should be as follows:

1. First photo is of the whole treatment area including a small sticker with the subject initials and date.
2. A close up photo graph including the hair count sticker template as detailed in the section below.

Effort will be made to ensure subject privacy when taking photographs of the groin/ bikini area. Black uniform undergarment should be used when photographing the treatment area.

7.4.2.2 Hair count

The customized hair count sticker templates detailed in section will be supplied by the sponsor. Templates consist of a rectangular frame sticker with a one square inch rectangular window (25.4mm x 25.4mm). The sticker template will be placed directly on the skin and the hairs in this window will be counted at specific visits during the study as detailed in section 7.2.1.1. For identification, the subject's ID, treatment area and visit date shall be filled out on the designated area upon the template frame.

The following procedure is intended to ensure that the template is placed in the same position during subsequent visits:

7.4.2.2.1 Baseline visit (prior to the 1st treatment):

1. The appropriate treatment area will be decided.
2. The hair in the area to be treated will be scissor trimmed to 2 mm to facilitate hair counts for photography.
3. The template will be completed with the subject ID, treatment area and date.
4. The template will be placed directly on the skin, in the area to be treated.
5. A clear transparency sheet will be placed over the treatment area, over the template.
6. The transparency sheet will be marked with a permanent marker to indicate anatomical landmarks and the sticker template location.
7. A general photograph of the sticker template, overlaid with the transparency sheet will be taken, as well as a close-up picture.
8. The transparency sheet will be removed and an additional close-up picture of the sticker template will be taken for the baseline hair count.

7.4.2.2.2 "Hair count" treatment visits [3, 6, 1M±7D FU1, 3M±7D FU2 and 6M±7D FU 3]:

1. The hair in the area to be treated will be scissor trimmed to 2 mm to facilitate hair counts from photography.
2. The template will be completed with the subject ID, treatment area and date.
3. The sticker template will be placed on the area to be treated using anatomical landmarks and the baseline picture to properly position the transparency sheet prepared in the baseline visit.
4. A close-up photograph of the sticker template will be taken.
5. The sticker will then be removed, the area shaved to the skin surface and treatment performed.

7.4.3 Test spots

Up to 3 test spots will be performed in the selected treatment area to determine the optimal parameters / setting combinations prior to the first treatment and later on in the treatment scheme if any alternations in treatment parameters are needed. It is important to consider all possible treatment parameters (fluence, pulse duration, # of pulses, etc.). It is always recommended to start with a low energy level and observe the skin's reaction before gradually increasing the energy. The Investigator will start the test spot at a low fluence and adjust it upwards based upon the skin response and the subject's feedback. Subjects may feel slight warmth of the skin, or minimal discomfort during treatment, but should not experience significant pain.

Assessment of the test spot will be performed following at least 2 hours. It is important not to start treatment prior to full evaluation of the reaction to the test spot and optimal parameters identified.

Table 2 - Guidelines Test Spot Treatment Parameters

Skin Type	Fluence Set point (J/cm^2)	Pulse Time (ms)	# of Pulses	Notes for next set of Test Spots
V	5-10J/cm^2	35-50 ms	1	If No AE/Pain/clinical endpoint: increase fluence, decrease pulse duration. If AE/Pain does occur: decrease fluence; or increase pulse duration.
VI	5- 10 J/cm^2	35-50 ms	1	If No AE/Pain/clinical endpoint: increase fluence; and/or # of pulses. If AE/Pain does occur: decrease # of pulses; and/or fluence.

7.5 Treatment

The treatment areas are divided into 3 groups. Each Subjects will be allocated to one of the following groups::

- Two small anatomical areas (right and left axillae and double sided bikini line) or;
- One double sided large area (right and left thighs) or;
- One large area (whole back / abdomen)

Other areas not defined above, as face, are not allowed to be treated.

Each site will recruit four subjects for each one of the three treatment groups (as specified above or in this section)

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 treated anatomical site. The positioning of subjects during treatment will be contingent on the location of the treated anatomical site.
Before starting treatment apply a layer of conductive gel to the treatment area.
After applying the conductive gel, locate the applicator in close contact, perpendicular to the skin with no pressure applied. Pressing the applicator will fire the IPL pulse. In order to ensure full coverage of the treatment area applicator placement should overlap approximately 1/3 of the previously treated skin.
During whole treatment duration, the safety of the subject and study personnel must be secured via the use of adequate safety eye protection.
During whole treatment duration, subject reaction must be monitored and if the subjects report an intolerable level of pain, treatment shall be ceased immediately. The treatment session will last until the required treated area is covered.

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

7.6 Post-treatment Instructions

7.6.1 Post treatment

The assessment of pain based on the subject's report will be documented immediately after each treatment test spot in the anatomical area treated. The Investigator should also examine and record the skin immediate response following treatment.

Cold packs may be placed on the treated area for post-treatment cooling. 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. They may also experience some purpura in the treated areas which would be expected to resolve within several days.

Subjects will have to be instructed not to tweeze, pluck, wax, use depilatory creams, or any other hair removal methods in the treated areas throughout the evaluation. Seven days prior to each treatment and follow-up visits subjects shall not shave the treatment areas in order to obtain accurate hair counts.

7.7 Follow-up regimen

Follow-up visits will occur for all subjects one month FU1 (±seven days) three FU2 (±seven days) and six FU3 (±seven days) months after the last treatment as detailed in table 1 and Appendix I.

8 Study Analysis Plan

8.1 Study Hypothesis

The study will confirm that the Versa HR 690 nm applicator is safe for removal of unwanted hair, and will result in hair removal and permanent hair count reduction for patients with Fitzpatrick Skin Type V-VI.

8.2 Sample Size Justification

The proposed study sample of 120 subjects will be sufficient to evaluate the safety and the efficacy of the treatment using the HR applicator in 5 distinguished anatomical areas and to obtain qualitative assessments of comfort levels experienced during treatments. Based on previous experience with other IPL hair removal systems, low subject variance of the tested element, the proposed study sample of 40 subjects per each anatomical area (total of 120) will be sufficient to evaluate the safety and the efficacy of the treatment and to obtain qualitative assessments of comfort levels experienced during treatments.

8.3 Study Analysis

The objective of this clinical study is to evaluate the safety of hair removal and to verify hair removal and permanent hair reduction using the Versa HR 690 nm applicator assessed by hair counts. For this purpose an average of hair count of 2 blinded reviewers will be done at baseline, following treatments, and at follow up visits. In case of a big discrepancy between 2 blinded reviewers, the hair count will be redone by a third blinded evaluator.

An intermediate safety report will be produced based on analysis of data collected post treatment number one of all the enrolled subjects. A Hair Removal report will be produced based on analysis of data collected at the three-month follow-up visit and a Permanent Hair Reduction report based on the analysis of data collected at the six-month follow-up visit will be the final report. The interim reports will not affect the continuation of the study. The study will regardless of the interim report results, be finalized according to this protocol.

The study reports will provide information for use in research & development, and future planned study.
All statistical tests will be two-sided. The level of statistical significance for effectiveness analyses is five percent for all tests of differences. Paired t-test and/or Wilcoxon signed rank test will be used to compare the evaluations at the baseline and follow up sessions. Descriptive statistics and correlations between variables will be performed.

Safety: Adverse events reported will be listed, documenting course, outcome, severity, and possible relationship to the treatment.

9 Adverse Events

9.1 Adverse Events Definitions

In this study, an Adverse Event (AE) is any undesirable clinical occurrence (sign, symptom, illness, or other medical event), that appears or worsens during the clinical study, or requires medical treatment or intervention to a subjects, whether it is considered to be device related or not. If adverse event occur, the first concern will be the safety and welfare of the patient. Appropriate medical intervention will be made.
Any AE or complication reported by the patient or observed by the physician that occur during or after treatment with the device will be recorded in the medical record or source document and on the Case Report Form. The investigator will determine if the AEs are device related or procedure related. This assessment shall include the onset date, resolution date, severity, seriousness, frequency, treatment and outcome.
Each AE should be assessed according to the following criteria:

9.1.1 Severity

Each AE should be assessed for its severity, or the intensity of an event experienced by the subject.
Mild: Awareness of a sign or symptom that does not interfere with the subject's activity or is transient resolved without treatment and has no sequelae.
Moderate: May interfere with the subject's usual activity and require additional intervention and/or treatment, and may have additional sequelae.
Severe: Significant discomfort to the subject and/or interferes with the subject's activity. Additional intervention and or treatment are necessary. Additional sequelae occur. Severe is used to describe the intensity of an event experienced by the subject.

9.1.2 Relationship of AE to the Device

Each AE should be assessed for its relationship to the device or procedure as identified as follows:
Device: This category should be restricted to adverse events directly attributable to Venus Concept

Procedure: A procedure is any activity that supports the usage of the device
Use the following categories for assigning the certainty of the relatedness:
Definitely Related: An AE is definitely related if it is obvious, certain or there is little doubt regarding the relationship.
Possibly Related: An AE is possibly related if it is capable of being related but relatively unlikely.
Not Related: An AE is not related if it is determined that there is no plausible association.
Unknown: Use this term if there is insufficient information to determine if the AE is related to the device or procedure.

9.1.3 Serious Adverse Events

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;

9.1.4 Pre-existing Conditions

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

9.1.5 Diagnosis of Adverse Event

There should be an attempt to report a “diagnosis” rather than the individual signs, symptoms and abnormal laboratory values associated with the diagnosis. However, a diagnosis should be reported only if, in the Investigator’s judgment, it is relatively certain (i.e., definite or possible). Otherwise individual signs, symptoms and abnormal laboratory values should be reported as the adverse events.

9.1.6 Anticipated Outcome Related Adverse Events

Anticipated adverse events in this study may include: blistering, burns, excessive edema or erythema (excessive considered as edema or erythema that do not resolved within 2-3 days), infection, PIH and scarring.

Any anticipated AE that occurs at any time during or after the use of the study device must be reported by the Investigator to Venus Concept. If the anticipated AE, in the opinion of Venus Concept or the Investigator, is likely to affect the safety of the subjects or the conduct of the study, the IRB/ Helsinki/ other ethic committee will be notified of the effect within 10 working days after Venus Concept first receives notice of it. In this study if an adverse event of PIH occurs the Investigator will continue following the subject until the PIH is resolved or up to 6 months following the last visit, whichever comes first.

9.1.7 Unanticipated Adverse Device Effects

An unanticipated adverse device effect as defined by the Federal Regulations [21 CFR 812.3(s)] is "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects." From a practical perspective, an unanticipated adverse device effect means a serious adverse event that is not listed in the device labeling, or the frequency or severity is greater than reported in the device labeling.

In the event of a serious (or unanticipated) adverse event, the Investigator will immediately notify the Venus Concept monitor by telephone. If such an adverse event is being reported after normal working hours, the Investigator will leave a voice message with accompanying report of the AE.

9.2 Reporting

9.2.1 Adverse Events (AE) and Severe Adverse Events (SAE) Reporting

All serious AE, whether or not deemed expected or device-related, must be reported to the clinical monitor immediately or within 24 hours by telephone (see below). A written report must follow within five working days and is to include a full description of the event and sequence. If the Venus Concept monitor cannot be reached, the site personnel will directly contact the Regulatory manager of Venus Concept @ 972-54-5341203.

In addition to reporting adverse events within the context of this clinical study, 21 CFR Part 803 Medical Device reporting requirements and any applicable local device reporting requirements will be followed.

9.2.2 Device Malfunctions/Medical Device Reporting

Each device failure/adverse event will be assessed for possible reporting as a Medical Device Report (MDR), and a determination will be made in accordance with the Sponsor's standard operating procedure. MDRs will be reported in accordance with 21 CFR 803.

9.3 Risk/ Benefit Analysis

9.3.1 Risks

Eye injuries are possible to the operator, but should be entirely preventable by proper use of dedicated eye shields, which will be worn by staff/ subjects in the presence of laser irradiation.

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 PIH, as detailed above in the Anticipated Adverse Events section. In the case of an infection evolving in the treated area the subject will be provided antibiotics for the treatment of the infection at no cost.

9.3.2 Anticipated Benefits

If the subject agrees to participate in this study, he/she will be contributing to the understanding of the device's impact and the biological processes that are occurring in the different skin layers. This understanding may lead to optimization of the treatment of these devices. There is no direct benefit to the participating subjects.

10 Administrative Procedures

10.1 Investigator Selection

The investigator must be of good standing as an investigator and knowledgeable in relevant areas of clinical research to ensure adherence to the requirements of the protocol, including the protection of human subjects. Other site personnel must have appropriate research experience and infrastructure to ensure adherence to the protocol and enrollment of sufficient numbers of evaluable subjects. The curriculum vitae (CV) of the Investigator will be maintained in the Sponsor files as documentation of previous medical training, and federal databases will be searched to ensure that the investigator is in good standing with the FDA or as applicable. The Principal Investigator will sign the signature page of this protocol, agreeing to comply with all applicable government regulations and the requirements of this study.

10.2 Ethic committee Approval

This clinical study will be conducted according to all applicable regulations under 21CFR, the Medical Device Directive and in accordance with the ICH Good Clinical Practice and local laws and regulations relevant to the use of medical devices.

An Ethical Committee (EC or IRB) will approve the clinical study protocol prior to study initiation. Approval will be indicated in writing with reference to the final protocol number and date.

Details regarding the EC/IRB's constitution including the names of its members, their qualifications and what function they perform on the board (e.g., chairman, specialist, lay-member) will be made available to enable Venus Concept and the Investigator to conform to regulations governing research on experimental devices.

10.3 Informed Consent

Prior to the procedure, the Investigator must explain to each subject nature of the study, its purpose, expected duration, and the benefits and risks of study participation. After this explanation and before entering the study, the subject must voluntarily sign and date the approved Informed Consent form.

10.4 Subject Withdrawal/Dropouts

The subjects will be advised in the written Informed Consent form that they have the right to withdraw from the study at any time without prejudice, and may be withdrawn at the Investigator's/Venus Concept' discretion at any time. 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.

The following are possible reasons for subject dropout/withdrawal:

- Adverse event that would prevent subject compliance with the protocol;
- Subject withdrawal of consent;
- Subject lost to follow-up (e.g., subject cannot be located or contacted and does not return for follow-up visits);
- Subject death;
- Investigator/Venus Concept requested subject to be withdrawn.

However, every effort should be made to see that subject is followed for the remainder of the study even if subject is unable or unwilling to comply with the protocol.

10.5 Case Report Forms/Data Collection

The Investigator is responsible for completely and accurately recording study data in the appropriate sections of the CRFs provided by Venus Concept. The CRFs must be signed by the Investigator or by his/her authorized person as designated in the Signature Authorization Log.

Data recorded on the CRF and photographs will serve as a source document for the study data.

The monitor will ensure the quality of data recording at each investigational site by comparison to supporting source documents during periodic site visits. Adherence to proper recording of information as well as assuring that corrections are being made will also be addressed during these periodic visits.

10.6 Required Documentation

Prior to starting the clinical study, the following documents must be submitted or returned to Venus Concept by the Investigator:

- Signed Clinical Trial Acknowledgement for the protocol
- Signed Clinical Evaluation Agreement
- Curriculum Vitae of the investigator
- Signed Financial Disclosure Statement
- IRB or other ethic committee Assurance of Compliance form or equivalent
- Written approval from the Ethical Committee of both the protocol and informed consent form

10.7 Subject's Financial Compensation

Subjects will not pay for any office visits, examinations and procedures as part of this clinical study.

Subjects may receive a stipend for participation in the study according to each site's standard procedures and IRB approval. Any such stipend will be detailed in the Informed Consent Form and Clinical Trial Agreement. Any subject stipend will be given after the last follow-up visit or after the subject's last visit as part of the study, whichever comes sooner.

10.8 Device Use/Accountability

The evaluation site personnel will maintain records of the model and serial number of the devices (if appropriate) used for treatment during the conduct of the study. The devices along with the associated delivery applicators and accessories are to be maintained by the research sponsor with reasonable care being taken by the Investigators and facility to prevent damage to, or unauthorized use of, the equipment. The equipment will be returned to the sponsor at the end of the study.

10.9 Training Requirements

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

10.10 Modification of Protocol

The protocol may be amended with the agreement of the sponsor and upon notification of and approval by the IRB or other relevant ethic committee.

Investigators should review the contents of this protocol. Subsequent alterations should only be made in written conjunction with the sponsor.

Medically significant amendments to the protocol (e.g., changes that increase the risk or the inconveniences for the patient, inclusion of new categories of patients, etc.) must be approved by the local IRB prior to implementation.

10.11 Data Retention/Archiving Data

The Investigator must keep the following documents in a secure place for at least two years after the last clearance of a marketing application or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product.

A signed copy of the final protocol and amendments.

Copies of the subjects' evaluation forms, data clarification forms and any associated subject-related raw data or where applicable, authorized copies of raw data.

Clinical photographs stored on CD-ROM or similar electronic media.

The subjects' signed Informed Consent forms.

10.12 Site Monitoring

The study monitors are designated as agents of Venus Concept and are assigned to oversee the conduct and progress of the study and to be the principal communication link between Venus Concept and investigator. The study monitors will be involved in monitoring of sites and records, to ensure continued compliance with the protocol and adequacy of the investigator and the facility to carry out the study.

The study will be monitored by representatives of Venus Concept Medical, Ltd. by telephone, in writing and during on-site visits. At a minimum, site visits will be scheduled prior to the initiation of the study, on the occasion of the initial use of investigational devices, and at the end of the study. The purpose of site visits will be to ensure compliance with the investigational plan, to ensure appropriate use of investigational devices, and to inspect and retrieve study data.

10.13 Termination of Study

Venus Concept reserves the right to discontinue the study at any time for administrative or other reasons. Written notice of study termination will be submitted to the investigator in advance of such termination. Termination of a

specific site can occur because of (but is not limited to) inadequate data collection, low subject enrollment rate, achievement of the total enrollment, or non-compliance with the protocol or other clinical research requirements

10.14 Reporting Requirements

The investigator must promptly report to Venus Concept any withdrawal of IRB or other relevant ethic committee approval at the site. Additional reporting requirements include:

Notify Venus Concept' designee and to the IRB or other relevant ethic committee a report of any severe adverse device effect, whether anticipated or unanticipated, that occurs during the study as soon as possible, but in no event later than ten working days after the investigator first learns of the effect. This report is to include a description of the effect, subsequent treatments, clinical outcomes, and outcome diagnoses. If the site personnel are not sure whether an event meets these criteria they should call the clinical monitor.

Notify Venus Concept or Venus Concept's designee and the IRB or other relevant ethic committee immediately (within 24 hours) if an emergency situation arises in which the subsequent treatment, in the best interests of the subject, requires a deviation from the protocol. This should be followed with written confirmation that describes the emergency action and outcomes, to Venus Concept and the IRB or other relevant ethic committee within five working days.

Report to the IRB or other relevant ethic committee and Venus Concept, within five working days, the use of the study device without signed informed consent from the subject.

Report adverse events in accordance with 21 CFR 803.

Submit regular progress reports to the IRB and Venus Concept or Venus Concept' designee, as requested by the investigators or IRB or other relevant ethic committee.

Submitting a final report on the study to the IRB and Venus Concept or Venus Concept's designee within three months after termination or completion of the study.

10.15 Confidentiality

The study records will be available for inspection by the FDA, the monitor/auditor, IRB and other regulatory agencies. Study-related records will be kept confidential, and to the extent permitted by applicable laws and/or regulations will not be made publicly available. In the case of the study results being published, the subjects' identities will remain confidential.

10.16 Posting of research study on web

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. Law.

11 Abbreviations and Terms

AE	Adverse Event
SAE	Serious Adverse Event
EC	Ethical Committee
IRB	Institutional Review Board
CRF	Case Report Form
VAS	Visual Analogue Scale

12 Appendices

Appendix I

Study Flow Chart

Study Activities	Visit #0*	Visit #1***	Visit #2	Visit #3	Visit #4	Visit #5	Visit #6	Visit #7$	Visit #8$	Visit #9$$
	Pre-Tx	Tx #1 Up to 7 days after Visit 0	Tx #2 4-6 WKS POST Tx1	Tx #3 4-6 WKS POST Tx2	Tx #4 4-6 WKS POST Tx3	Tx#5 -6 WKS POST Tx4	Tx #6 4-6 WKS POST Tx5	FU #1 1M±7 D FU	FU #2 3M±7 D FU	FU #3 6M±7 D FU
Qualify for study: Informed Consent, Eligibility assessment, Demographic information, Medical history & treatment related medical examination	X									
Test spots**		X Pre-Tx								
Photographs	X			X Pre-Tx			X Pre-Tx	X	X	X
Treatment		X	X	X	X	X	X			
Immediate and short term response		X	X	X	X	X	X			
Hair Count by study personnel	X			X			X	X	X	X
Hair Count by blinded evaluators (to be conducted post study)	X							X	X	X
Subject's comfort assessment		X	X	X	X	X	X			
Subject's improvement/satisfaction				X			X	X	X	X
Adverse events recording		X	X	X	X	X	X	X	X	X
Study termination										X

* Visit #0 includes various screening activities and explanations to the candidate regarding the evaluation; should the subject sign the Informed Consent Form, complete the test spot procedure and undergo treatment during Visit #0, it will effectively become merged with Visit #1.

** Test spots should be performed prior to Tx #1 and with any treatment parameter alternation later on in treatment regime.

*** An Intermediate Safety report will be performed following Tx #1.

$ A Hair Removal report will be performed following FU #1 and FU #2 of 1M ±7D; 3M ±7D.

$$ A Permanent Hair Reduction report will be performed following FU #3 of 6M±7D.

Appendix II
Clinical Trial Acknowledgement

I have read and understand the foregoing protocol, and agree to conduct the clinical trial as outlined herein and in accordance with 21CFR and Good Clinical Practices (ICH-E6) as well as with local and universal regulations pertaining to clinical trials.

Investigator's Signature

Date

Name

Clinic

Street Address

City, State & Zip Code

Country

Phone #

Fax #

E-mail Address