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Clinical Trial Protocol

Clinical Evaluation of Venus Versa Diamondpolar Applicator Treatment Followed by AC Dual Applicator Treatment Using Two Intense Pulsed Light Wavelength Bands for Facial Acne Vulgaris

Sponsor: Venus Concept
Version Date: April 4, 2017
Amendment 2
Protocol number CS2715

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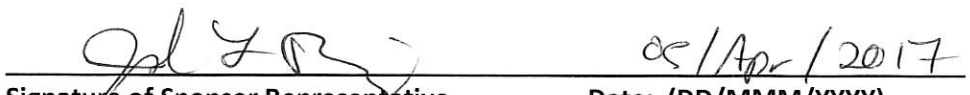

Signature of Sponsor Representative **Date: (DD/MMM/YYYY)**

STATEMENT OF CONFIDENTIALITY

The information contained herein is Confidential Information that remains the sole and exclusive property of Sponsor and is expressly subject to the terms and conditions of the Clinical Trial Research Agreement signed by both the Investigator and Venus Concept Ltd.,
Toronto, Canada.

Study Synopsis

Study Title	Clinical Evaluation of Venus Versa Diamondpolar Applicator Treatment Followed by AC Dual Applicator Treatment Using 2 Intense Pulsed Light Wavelength Bands for Facial Acne Vulgaris	
Protocol No.	CS2715	
Device Name	Venus Versa device	
Study design	Multi-center, prospective, open label with before-after study design. Each subject will receive 4 full treatments at 1 week intervals. Follow up will take place 6 weeks after the last treatment.	
Projected Study period	Initiation Date: **September 2016**	Completion Date**: December 2017**
Study population	Up to 50 healthy subjects, age 18 to 55 years with Acne Vulgaris who wish to improve their skin appearance will be enrolled in order for 20 subjects to complete with the adjusted (amendment 2) treatment parameters.	
Investigational treatment	The procedure will include an $(MP)^2$ (Multi Polar RF & Magnetic Pulse) treatment followed by intense pulse light treatment or intense pulse light treatment alone.	
Study Duration	Each subject will participate in the study for up to 11 weeks (consultation to final follow up). Total study duration is estimated to be 16 months from enrollment of the first subject to the termination visit of the last subject.	
Main Inclusion Criteria:	• Healthy Female/Male, age 18 to 55 years with all Fitzpatrick skin phototype. • Having mild to moderate acne vulgaris (as defined by the Acne Global Severity Scale) and have at least 10 inflammatory and 15 non-inflammatory lesions, but no nodulo-cystic lesions. • Subject who can commit to all treatments and follow up.	
Main Exclusion Criteria:	• Superficial metal or other implants in the treatment area. • Current or history of cancer, or current condition of any type of cancer, or pre-malignant moles. • Pregnancy and nursing. • Patients with cystic acne, acne conglobata, acne fulminans, or secondary acne (chloracne, drug-induced acne, etc) • Diseases which may be stimulated by light at the wavelengths used, such as history of Systemic Lupus Erythematosus, Porphyria, and Epilepsy. • Patients with history of diseases stimulated by heat, such as recurrent Herpes Simplex in the treatment area, may be treated only following a prophylactic regimen. • Poorly controlled endocrine disorders, such as Diabetes or Polycystic Ovary Syndrome. • Any active condition in the treatment area, such as sores, Psoriasis, eczema, and rash. • Tattoos, scars or piercings in the treated area. • History of skin disorders, keloids, abnormal wound healing, as well as very dry and fragile skin.	

	• Use of medications, herbs, food supplements, and vitamins known to induce photosensitivity to light exposure at the wavelengths used, such as Isotretinoin (Accutane) within the last six months, tetracyclines, or St. John's Wort within the last two weeks. • Any surgical procedure in the treatment area within the last three months or before complete healing. • Treating over tattoo or permanent makeup. • Excessively tanned skin from sun, tanning beds or tanning creams within the last two weeks. • As per the practitioner's discretion, refrain from treating any condition which might make it unsafe for the patient. • Exposure to investigational product within 3 months (or designated half-life) prior to enrollment. • Prior drugs, interventions, skin laser/light or another device for Acne treatment within 3 months of initial treatment or during the course of the study.
Objectives	**Primary objectives** • To evaluate the **efficacy** of facial acne vulgaris treatment using the Venus Versa (MP)^2 Diamondpolar applicator in combination with the Venus Versa AC dual applicator using two Intense Pulsed Light Wavelength Bands • To evaluate the **efficacy** of facial acne vulgaris treatment of the Venus Versa AC dual applicator using two Intense Pulsed Light Wavelength Bands. **Secondary objectives** • To evaluate subject's assessment of **improvement** & **satisfaction**. • To evaluate subject's assessment of **comfort** with the treatments. • To compare the efficacy of the combination treatment and IPL treatment alone.
Hypothesis	Both the combination treatment and the IPL treatment will result in Acne Vulgaris improvement. Improvement will be defined as achieving improvement of at least 2 points on the 5-point Global Acne Assessment Score (GASS) at FU (6 weeks following the last treatment) as compared to baseline.
Criteria for Evaluation	**Efficacy** **Primary endpoint:** • Acne Vulgaris improvement by at least 2 points on the Global Acne Assessment Score (GASS) from photographs 6 weeks following the last treatment - FU, as compared to baseline, based on before/after photos, as determined by up to 3 independent reviewers (dermatologists and/or plastic surgeons). **Secondary endpoints: Subject Evaluation, Comfort & Satisfaction** • Reduction of inflammatory lesions and non-inflammatory lesions as determined by investigator based on lesion count. • Improvement in subject satisfaction assessment scale with treatment outcome based on a 5-point Likert scale. • Improvement in subject self-assessment of Acne Vulgaris according to the Global Aesthetic Improvement Scale (GAIS) from photographs 6 weeks following the last

	treatment - FU, as compared to baseline, based on before/after photos. • Subject assessment of pain and discomfort associated with treatments using a 100 mm Visual Analogue Scale (VAS), where 0 is "no pain" and 10 is "intolerable pain". • Subject improvement assessment of "quality of life" using an acne related Quality of Life (QOL) questionnaire. **Safety** • Evaluate the safety of the treatment by recording the number and type of any adverse event recorded throughout the study. Adverse events will be reported and categorized based on severity and device-relatedness.

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INTRODUCTION

1.1 Background

Acne Vulgaris

Acne is a disease that affects almost 100% of the population, from ages 8 to 80. The symptoms range from rare, mild disease to severe, disfiguring disease, resulting in scarring. The more severe the disease, the higher the incidence of depression, even to the extent of suicidal thoughts. The clinical presentation ranges from comedonal disease (whiteheads and blackheads or "little bumps"), to red papules and large cysts ("big bumps"). Scarring is associated with cysts and "big bumps," as well as scratching, picking, or popping of lesions. The scarring can be extremely disfiguring. Adolescents with acne suffer greatly from their disease, affecting their social and academic growth. The cause is essentially unknown.

Most authorities agree that there is a genetic blueprint for the duration and severity of acne, which varies greatly from patient to patient. There is no ethnic predilection, but males are generally more severely affected since testosterone is an aggravating factor. The transition into puberty causes an increase in the size of sebaceous (oil) glands, as well as increased oil secretion. These changes, as well as a change in the keratinization of the hair follicle, cause occlusion, which results in comedone (whitehead and blackhead) formation. This occlusion allows the proliferation of Propionibacterium Acnes bacteria. This bacteria is felt to be the cause of larger acne lesions due to the immune system response to the bacteria, inflammatory enzymes produced by the bacteria, or both. Some feel the depth of the occlusion in the hair follicle determines the size of the resultant acne lesion, with a deeper occlusion resulting in a larger lesion. External factors vary from patient to patient. Stress is a universal aggravating factor. With the exception of dairy products in women, dietary triggers are more individual than universal (otherwise there would be no acne as no one would eat the offending trigger). Cosmetics generally do not play a role; however, thick theatrical make-up, as well as general cosmetics while sweating can aggravate the disease. Hair spray, hair oil, and mousse can aggravate the condition as can hats, sweat bands, and long hair (bangs as well as shoulder length). Some feel acne improves in the summer, either due to lack of stress or increased sun exposure[1].

In acne, blue light acts on chemicals called porphyrins[2]. It is known that P. acnes produce porphyrins during their normal life cycle, as part of their normal metabolism process. P. acne is capable of producing high amounts of endogenic porphyrins in the absence of any trigger molecules[3].

Intense Pulsed Light (IPL)

Intense Pulsed Light (IPL) technology uses light pulses delivered by a flashlamp with high peak power and short pulses. The light is directed by a reflector and then transmitted through various filters that cut off the lower wavelength range of the emitted light; therefore, only those wavelengths longer than that of the filters are transmitted. Applying the physical principle of selective photothermolysis, IPL is used for performing various skin treatments (acne vulgaris, scars, striae, etc.) as well as for eliminating unwanted hair, benign vascular/pigmented lesions and unwanted leg veins[4, 5].

Photo-biological Principles in Acne Treatment

A molecule that is absorbed in the skin is named a chromophore. Each and every photo-biological process starts in absorption of light energy by a selected chromophore. Every chromophore has a specific absorption spectrum of its own. After absorption, the chromophore is transformed from its stable state to the excited state. This unstable condition induces chemical reaction and a photoproduct. The biochemical changes cause reaction of the skin. In humans, the skin contains chromophores that are photo-dynamically active and photo-instable substances. The Gram-positive microaerophilic skin bacterium Propionibacterium acnes is implicated in the pathophysiology of acne vulgaris. As part of its normal metabolism process, P. acnes produce porphyrins, mainly protoporphyrin and coproporphyrin-photosensitizers. Photosensitizers are molecules that have the trait of absorbing light energy and using this energy to carry out chemical reactions in cells and the body tissues. Each photosensitizer has its proper wavelength of absorption, usually several, and a wavelength of emission. Excitation of the porphyrins by absorption of light causes the formation of singlet O2 and reactive radicals. Porphyrins are a ubiquitous class of naturally occurring compounds containing the porphin structure of four pyrrole rings connected by methane bridges in a cyclic configuration, to which a variety of side chains are attached, usually metalled, for example, with iron to form heme. In porphyrin-visible absorption spectra, the highly conjugated aromatic macrocycle shows intense absorption in the neighborhood of 400 nm; the highest peak of light absorption (and sensitizer activation) is called the ‘‘Soret Band’’. It is usually located in the blue and ultraviolet range. Because the highest peak of absorption of porphyrin is at blue light (415 nm), some light source systems use this spectrum for the treatment of acne. Visible spectra of porphyrins also show several weaker absorptions (Q Bands) at longer wavelengths (450 to 700 nm). The efficacy of P. acnes photo-inactivation is determined by the rate of production of excited porphyrins molecules. In order to achieve maximum process efficacy, the controlled parameters in this complex photobiological process - concentration of photons, temperature and the wavelength of photons - can be technologically optimized. Most of the existing laser/light-based devices, however, are limited by one of the previously mentioned parameters, which may alter P. acnes photo-inactivation efficiency[6].

Radio-Frequency (RF)

The RF energy is high frequency alternating electrical current that passes into the dermis and hypodermal tissues without disruption of the epidermal-dermal barrier. The high frequency oscillating electrical current results in collisions between charged molecules and ions and the micromolecular mechanical energy from these collisions is transformed into heat[7,8,9]. This biological RF heat occurs irrespective of chromophore or skin type and is not dependent upon selective photothermolysis.

Radio-Frequency (RF) biological Principles in Acne Treatment

The RF heat has different biological and hence, clinical effects, depending upon the tissue targeted. In the dermis, where the primary cellular element is the fibroblast and the extracellular matrix (ECM) is comprised of collagen, elastin and ground substances, the RF mediated thermal stimulation of the ECM results in an immediate and temporary **shrinkage of the collagen** triple helix[7,8,9]. Further, the RF thermal stimulation results in a micro-inflammatory stimulation of the fibroblast which in response produces new collagen (**neocollagenesis**) and new elastin (**neoelastogenesis**), and ground substances[8,9]. **This modality is said to also target the sebaceous gland, an important part in the pathogenesis of acne, by causing shrinkage and decreasing sebum output**[10]. Studies have shown that pore size is associated with high sebum output level

(seborrhea), aging, sex, genetic predisposition, chronic ultraviolet light exposure, and vitamin A deficiency. Previous studies have indicated that enlarged pores are attributable to skin aging caused by changes in the dermal matrix. In skin aging, photo-aging, one of the most important extrinsic factors, changes dermal thickness and disorientates the dermal matrix, including collagen and elastin, by upregulating the matrix metalloproteinases. It has been suggested that large pore size is more significantly associated with increased sebum output level than with sex or age. Excessive sebum excretion has been also accepted as one of the most important etiological factors in acne vulgaris and patients with acne tend to have enlarged facial pores[11]. Lee et al. demonstrated a positive therapeutic effect of FRM (Fractional Radiofrequency Microneedle) on inflammatory acne vulgaris and related scars after two sessions. The authors suggested that FRM might have a thermal inhibitory effect on sebaceous gland, but objective data regarding sebum excretion were lacking[10].

1.2 Rationale for the Study

The AC DUAL Intense Pulsed Light (IPL) applicator is indicated for the treatment of Acne Vulgaris. It uses a blue light (415 nm) to target the porphyrins produced by the P. Acne bacteria and destroy the bacteria, and also uses a red light (630 nm) to help reduce inflammation, inhibit sebum production and improve healing. This study is intended to evaluate the effect of IPL treatment on Acne Vulgaris.

The study hypothesis is that the use of the AC DUAL applicator combined with the Diamondpolar applicator will improve the appearance of Acne Vulgaris by at least 2 points on the Global Acne Assessment Score (GAAS) at 6 weeks follow-up compared to baseline in the study population and in addition, as a secondary success criteria, reduction of 25-50% of inflammatory lesions and non-inflammatory lesions. The combination treatment will also be compared to IPL treatment alone as a secondary endpoint.

2 The Investigational Device

The Venus Versa system is a multi-application device consist of a console and 10 detachable handpieces, or applicators. The Versa Console supports 3 types of energies: 1) IPL; 2) RF; 3) Magnetic Pulse $(MP)^2$. The detachable handpieces are operating via either IPL, fractional RF or a combination of RF with Magnetic Pulse $(MP)^2$.

IPL Based applicators: HR650, HR690, SR515, SR580, HR650XL, HR690XL, AC DUAL.

Fractional RF Based applicator: Viva.

RF and Magnetic Pulse $(MP)^2$ Based applicators: Diamondpolar, Octipolar.

The IPL applicators 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 applicator uses optical filters to optimize the energy delivered to the body, and match the spectrum of light delivered to the intended clinical application.

2.1 Venus Versa module

The Venus Versa system is designed to deliver optical energy to the skin via various applicators connected to the console. Each applicator delivers different wavelengths of the same Intense Pulsed Light source. The device provides individual adjustment of light fluency and pulse duration as appropriate for each patient. The applicator has integrated skin cooling to enhance safety and comfort of the treatment.

The Venus Versa system consists of a low voltage power supply (LVPS) unit, a capacitor charger, capacitors bank, switching module, water cooling system, controller and user interface, including a touch-screen LCD display.

2.2 AC DUAL applicator

The applicator is connected to the console via cables. It comprises an IPL source, a filter (designed to filter light in the optimal bands of the spectrum for specific treatments) and a cooled light-guide (sapphire) that contacts the patient's skin.

The IPL applicator operates a blue light (415 nm) and also red light (630 nm) simultaneously. The IPL applicator also includes a sapphire cooled light guide of 10x30mm. The system controls the pulse shape and fluence.

2.3 $(MP)^2$ Diamondpolar applicator

The Diamondpolar applicator of the Venus Versa system, has 4 electrodes. Each electrode and its surrounding coil simultaneously emit RF and Pulsed Magnetic Field. The RF current is produced between any two electrodes in the array by rapidly alternating RF current between the different electrodes; the device raises the temperature of the treatment area homogenously, without the RF focal “hot spots” seen with other RF devices.

3 Study Design

This is a prospective, open label clinical trial before-after study design. This study is designed to evaluate the safety and efficacy of the Venus Versa Diamondpolar applicator followed by AC DUAL applicator and the AC DUAL applicator alone in treating mild to moderate acne vulgaris.

This study will include up to 6 visits at the clinic: initial screening/consultation, 4 treatments (Tx) visits at 1 week intervals, and 1 follow-up (FU) visit at 6 weeks after the last treatment visit.

Up to 50 healthy subjects, age 18 to 55 years of age with mild to moderate acne vulgaris, defined as at least 10 inflammatory and 15 non-inflammatory lesions, with no odulocystic lesions will be enrolled. Subjects must meet the eligibility criteria detailed in the protocol and sign the informed consent form prior to any study

procedure. At the first treatment visit, the investigator will collect demographic and medical information and perform 3 test spots to evaluate skin sensitivity and choose appropriate presets. Subjects with skin type IV-V will be monitored 48-96 hours after the test spot for their skin reaction. Subjects that demonstrate excessive skin reaction to the test spot will be withdrawn from the study and will not be included in the study efficacy population or in the safety analysis since study treatment has not occurred. Should a subject (or the subject's legally authorized representative) decide to voluntarily withdraw, all efforts will be made to collect and report the final visit observations, and the reasons for withdrawal, as thoroughly and timely as possible. Withdrawals will be documented in the CRF and reported to local institutional review board (IRB) or ethical committees as required. The first treatment visit may occur on the same day as the screening visit but can be scheduled up to 30 days after the screening.

The duration of the treatment session will be approximately 40 minutes depending on the treated area size. Expected immediate response includes temporary mild to moderate erythema and/or edema. Skin safety assessments will be conducted by the investigator after each treatment session and at follow-up visits. Photography will be conducted at baseline, the beginning of last visit and at FU. The level of the subject's discomfort will be documented at the end of each treatment session. Subject satisfaction will be evaluated at FU. Evaluation by up to 3 independent reviewers will be based on before/after pictures of the baseline, before the last treatment and at the 6 week follow up visit using GAAS.

3.1 Primary effectiveness endpoint

- Improvement in treated area appearance at 6 weeks after the last treatment as determined by a independent review.

Success criterion

The treatment will be considered successful if the appearance of Acne Vulgaris improves by at least 2 points on the 5-point Global Acne Assessment Score (GAAS) at 6 weeks follow-up compared to baseline in the study population. This will be determined by calculating the mean difference GAAS–(μ_d) between the GAAS at 6 weeks follow-up and the baseline scores in the study population. This improvement will also be further tested by two-sided Wilcox on Signed-Ranks Test for Matched Pairs to establish that at 95% confidence level (α = 0.05) there is a statistical significant evidence that mean difference scores obtained $(\mu_d)_{is}$ not equal to zero.

3.2 Secondary effectiveness endpoints

- Reduction of inflammatory lesions and non- inflammatory lesions**.**
- Subject Improvement assessment in treated area appearance at 6 weeks after the last treatment compared to baseline using the Global Aesthetic Improvement Scale (GAIS).
- Subject assessment of pain and discomfort associated with treatments using a 100 mm Visual Analogue Scale (VAS), were 0 is "no pain" and 10 is "intolerable pain".
- Subject's satisfaction with treatment outcome based on a 5-point Likert scale.
- Subject improvement assessment of "quality of life" using QOL Questionnaire**.**
- Comparison of the two treatments for the primary and secondary endpoints.

3.3 Safety

- Safety will be evaluated based on the number and type of any adverse event recorded throughout the study. Adverse events will be reported and categorized based on severity and device-relatedness. In addition, immediate response following treatment associated with various settings (e.g., erythema, edema, purpura, etc.), although expected results of treatment that are not considered adverse events, will be collected and reported for purposes of completeness. Information will also be captured on the intensity of response and the time required for resolution.

3.4 Study duration:

Duration of subject's participation: Up to 11 weeks from enrollment to termination (see Figure 1).
Study duration for entire study sample: Estimated to be 16 months from enrollment of first subject to the termination of the last. This is based on estimate of 8 months for recruitment + 2 months subject participation + 1 months collecting data.

Figure 1: Subject Participation

Time Intervals		1 week	1 week	1 week	1 week	6 weeks
	Enrollment	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Follow-up
Timeline	Screening	Week 1	Week 2	Week 3	Week 4	Week 10

3.5 Schedule of Times and Events

The following table provides a summary of the required study visits and the procedures and assessments to be performed at each visit. Details of the procedures and assessments will be described subsequently in the protocol.

Table 1: Study Procedures - CS2715
Tx=Treatment; FU=Follow Up

Visit#	Visit #1	Visit #2	Visit #3	Visit #4	Visit #5	Visit #6
Study Activities	Screening & Test spot	Tx1	Tx2	Tx3	Tx4	FU
Timing (see Figure 1)		0-7 days post given ICF	1 week ± 5 days post 1st TX	2 weeks ± 5 days post 1st TX	3 weeks ± 5 days post 1st TX	6 weeks ± 7 days after last Tx
Informed Consent	X					
Eligibility assessment Demographic information Medical/surgical history Physical examination	X X X X					
Urine pregnancy test	X					X
Test spots	X					
Photographs		X			X	X
Lesion Count (FACE)	X	X	X	X	X	X
Treatment		X	X	X	X	
Immediate/short term response		X	X	X	X	
Subjects discomfort assessment (VAS)		X	X	X	X	
Subject improvement evaluation using GAIS						X
Subject satisfaction assessment scale (5-point Likert scale)						X
Subject improvement assessment of "quality of life" using QOL Questionnaire	X		X	X	X	X
Independent reviewer improvement evaluation using GAAS						X
Adverse events		X	X	X	X	X
Concomitant medications		X	X	X	X	X

3.6 Concurrent Control

For the primary endpoints, there is no concurrent control in this study. Each patient's efficacy results will be compared to baseline. A comparison between treatment will be performed as a secondary endpoint.

3.7 Blinding

Objective assessment of clinical improvement by GAAS will be achieved by sending before/after pictures (baseline/prior to last treatment/6 weeks after last treatment) to up to 3 independent reviewers at the end of the study. The reviewers will not know which are the before and which are the after pictures.

4 Study Population and Subject Selection

4.1 Source and Sample Size

Up to 50 subjects with all skin phototypes shall be recruited by the investigator from within the investigator's subject population. Subjects shall have mild to moderate acne vulgaris with at least 10 inflammatory and 15 non-inflammatory lesions, but no nodulocystic lesions.

4.2 Eligibility

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

4.2.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be entered into the study:

1. Able to read, understand and provide written Informed Consent;
2. Healthy adult, male or female, 18-55 years of age with Fitzpatrick-Goldman skin type I-VI.
3. Having mild to moderate acne vulgaris with at least 10 inflammatory and 15 non-inflammatory lesions, but no nodulocystic lesions.
4. Able and willing to comply with the treatment/follow-up schedule and requirements;
5. Women of child-bearing age are required to be using a reliable method of birth control (such as an intrauterine device, birth control pills, condom with spermicidal, Nuvaring, partner with vasectomy or abstinence) at least 3 months prior to enrollment and throughout the course of the study.
6. Negative urine pregnancy test.
7. Able to tolerate the treatment as determined by a test application.
8. Willing to avoid direct sunlight and willing to use topical sunscreen for the duration of the study

4.2.2 Exclusion Criteria

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

1. Superficial metal or other implants in the treatment area.
2. Current or history of cancer, or current condition of any type of cancer, or pre-malignant moles.
3. Pregnancy and/or nursing.

4. Diseases which may be stimulated by light at the wavelengths used, such as history of Systemic Lupus Erythematosus, Porphyria, and Epilepsy.
5. Patients with history of diseases stimulated by heat, such as recurrent Herpes Simplex in the treatment area.
6. Poorly controlled endocrine disorders, such as Diabetes or Polycystic Ovary Syndrome.
7. Any active condition in the treatment area, such as sores, Psoriasis, eczema, and rash.
8. History of skin disorders, keloids, abnormal wound healing, as well as very dry and fragile skin.
9. Use of medications, herbs, food supplements, and vitamins known to induce photosensitivity to light exposure at the wavelengths used, such as Isotretinoin (Accutane) within the last six months, tetracyclines, or St. John's Wort within the last two weeks.
10. Any surgical procedure in the treatment area within the last three months or before complete healing.
11. Excessively tanned skin from sun, tanning beds or tanning creams within the last two weeks.
12. As per the practitioner's discretion, refrain from treating any condition which might make it unsafe for the patient.
13. Tattoos, permanent makeup, scars or piercings in the treated area.
14. Exposure to investigational product within 3 months (or designated half-life) prior to enrollment.
15. Interventions, skin laser/light or another device for Acne treatment within the past 6 months.
16. Acne treatment with oral or topical medications within the last four weeks or their use during the course of the study.

4.3 Subject Withdrawal and Replacement

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's 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 (phone calls with three left messages on confidential voicemail if applicable) 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 a subject is followed for the remainder of the study even if subject is unable or unwilling to comply with the protocol.

5 Study Procedures

5.1 Screening Visit

5.1.1 Subject Enrollment

- 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 (facial acne vulgaris) to ensure that it meets the study criteria.
- If the subject has met the preliminary study criteria, an informed consent will be obtained from the subject, clearly indicating his/her understanding of the requirements and risks involved with study participation and other applicable treatment options.
- During the first visit, the investigator will ask women of child-bearing age for the date of their last period. If applicable, the investigator shall inquire about the form of contraceptive they use to confirm they meet the inclusion criteria. A urine pregnancy test will be performed.
- Male subjects should be informed that treatment in hair-bearing areas may result in some damage to the follicles and subsequent loss of hair, and as a consequence, hair growing zones should not be treated if a reduction of hair growth or ingrown hair is not desired.
- The investigator will perform an acne lesion count.
- Subjects will be asked to directly complete the CRF Acne Related Quality of Life Questionnaire worksheet which will be considered to be a source document.

5.1.2 Subject Identification

At enrollment, each subject will receive a unique identifying number that will be composed of the site number and a consecutive number with 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. Photographs will be stored on a secure computer that is password protected and they will be labeled and numbered by date with the patient ID only.

5.1.3 Test Spots

In order to assess tolerability prior to enrollment into the study, up to 3 test spots (behind the ear or on the shoulder) will be performed on the hinterland to observe the skin response (Are there are any side effects?) and 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. 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 output

setting 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 and up to 48 hours for skin types I-III and 48-96 hours for skin types IV-VI. The first treatment may be conducted on the same day as screening or up to 30 days after screening, depending on the response. It is important not to start treatment prior to full evaluation of the reaction to the test spot and having optimal parameters identified.

Scheduling treatment visits

Subjects recruited to the study that did not experience significant pain or skin sensitivity in response to the test spots can receive treatments. First treatment visit be conducted on the same day as screening or up to 30 days after screening.

5.2 Treatment visits

Each subject will be enrolled, randomly assigned to AC DUAL treatment (IPL alone) or Diamondpolar treatment (RF + PEMF) followed by AC Dual treatment (IPL) and scheduled for 4 treatments at 1 week intervals (± 5 days) and return for follow-up visit at 6 weeks after the last treatment (± 7 days) for evaluation of the treated areas. The duration of the entire treatment visit is approximately 40 minutes. During each visit various tasks will be performed.

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

5.2.1 Pre-Treatment Procedures

5.2.1.1 *Subject Skin care and medication*

- Subjects will be asked to refrain from using skin products or medications containing ingredients listed in the exclusion criteria, and may have to undergo washout periods for any such substances or medications prior to receiving treatment as part of this study. The Investigator should review the subject's skin care regimen and suggest appropriate alternatives for the course of the study, as needed.
- Subjects will be required to avoid sun exposure including use of tanning booths, tanning spray or cream during the course of the laser 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.

5.2.1.2 *Photography*

Standardized Photography

All subjects will be asked to remove all jewelry and piercings and wash the area to be photographed with provided cleanser to remove all makeup and skincare products. Subject will then wait 10 minutes for any washing related erythema to subside prior to initiation of photography session. All stray hairs will then be pulled away from the face using a black or white headband and subjects' collars will be masked by covering the neck and shoulders with a black photography drape. If seated photos, the stool height will be adjusted to ensure the subject's head, neck and spine are aligned and the subject is sitting up straight. Subject will then be positioned so they are centered in the frame using chin and forehead rests as applicable for seated

three-point photo capture and if standing, feet are aligned with standardized photo foot marking on the floor standing straight with back flat against the draped back drop (blue, green or white) wall. All photography is to take place within the same room with standardized lighting, no natural light, for the duration of the study.

Standardized photographs will be taken at 0°, 45° and 315° angles using the Visia® CR system (Canfield Imaging Systems, Fairfield). For each angle, a set of four different photographs will be taken including non-polarized, cross-polarized and parallel-polarized white light as well as UV light images. Photos will also be obtained using a mounted DSLR camera to obtain three photos (frontal 90°, right 45° and left 45°). These photographs will be used as an assessment tool for looking at disease state (independent evaluation). They may also be used for publication and/or presentation of the study findings and generalized characterization of the disease state. Moreover, they may use the photographs for marketing or other commercial purposes.

The photos should be taken in a private room or area. The investigative site will ensure that digital photography equipment with standardized illumination and background is available for use during this study. Digital photos will be stored on dedicated media. A copy of all study photographs will be transferred to Venus Concept at the end the study or as part of interim analysis. Only the subject code will appear on the records being transferred to the sponsor to ensure anonymity of the subjects.

- Study visits that include photography: All treatment and follow-up visits.
- Standard conditions: The photos should be taken in standardized conditions, including distance, angle, background, and illumination in order to achieve high-quality before & after sets. Do not use direct illumination.
- Preparing the subject: The skin of the treatment area must be cleansed and free from makeup prior to photography.
- Subject posture: The subject will 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.
- Photography angles: global frontal photo.
- Order of photos: the first photograph in each session should be of an identification card that will include subject code and visit details.
- File names: The digital files should follow a consistent standard naming scheme, for example: 01-001TS_Tx1_face.

5.2.1.3 ***Preparing the subject for the skin response post-treatment***

- The investigator will perform an acne lesion count prior to each treatment.
- Investigators should explain the following to the subjects: Post-treatment erythema, edema and some discomfort of the treated areas are possible and expected in some cases. In addition, some purpura

may be experienced in the treated areas which are expected to resolve within several days. Any symptoms that are not resolved within several days should be reported to the clinic.

5.2.2 Treatment

Table 2: Treatment Parameters as per Fitzpatrick Skin Type

Applicator	Fitzpatrick Skin Type	Energy Output (J/cm2)	Pulse Duration (ms)	Frequency (Hz)	Cooling
AC DUAL	I – II	8-14	10-15	Up to 2	100
	III	7-12	15	Up to 2	100
	IV	6-11	20	Up to 2	100
	V	5-6	20	Up to 2	100
	VI	5-6	20	Up to 2	100

- Determine why the patient is seeking treatment and what the expectations are.
- Inform the patient about the treatment protocol, typical treatment results and possible adverse effects and discomfort.
- Instruct the patient about the safety issues.
- Advise the patient to avoid skin irritation or intentional skin tanning. Sun-screen is advisable when outdoors during daylight hours.
- The patient should discontinue any irritant topical agents for 2-3 days prior to treatment.
- Remove any lotion, make-up, perfume, powder or bath/shower oil present on the patient's skin in the area to be treated. Wipe the treatment area with a non-alcoholic preparation.
- Avoid treating over hair. Shave any hair in the treated area prior to treatment.
- Make sure that all jewelry and/or metal items (including any belly rings) are removed from the treated area, to ensure treatment safety.
- Before each treatment clean the entire applicator surface with a medical disinfectant. Wipe the applicator tip with alcohol. Let the tip dry completely before pulsing. Cleaning of the applicator should always be done while system is set to Standby state or turned off.
- Appropriate eye protection and all other IPL safety means will be provided and enforced for all the subjects and personnel in the treatment room during the use of the device per the User Manual and local regulations.
- Subjects will be positioned during treatment in a manner that will enable the best access for treatment.
- The treatment parameters specific to the subject will be documented in the Case Report Form at every treatment visit.

5.2.2.1 *Treatment parameters guidelines*

- IPL: Energy range (J/cm^2): 8-16; Filters: 415 and 630 (refer to User Manual (UM)- table of pre-sets).

- RF: $(MP)^2$ energy percentage approximately up to 50% and skin temperature not higher than 40^oC

5.2.2.2 ***Treatment procedure (also see User Manual):***

During each treatment session, the subjects assigned to combination treatment will be treated with the Venus Versa system using the Diamondpolar applicator for 10-15 minutes treatment followed by 10 minutes treatment using the IPL AC DUAL applicator. Subjects assigned to IPL treatment alone will only be treated with the IPL AC DUAL applicator. Treatment will take up to 20-25 minutes, therefore the entire treatment will be completed within 40 minutes.

- **RF/PEMF (only for subjects assigned to combination treatment)**
  1. Prior to the treatment, glycerin in gel formulation should be applied thoroughly to the treatment area.
  2. In the initial treatment it is important to adjust the treatment required energy level to best suit the patient's tolerance to the treatment. Tolerance will increase as the patient becomes more familiar with the treatments.
  3. The aim of the procedure is to heat the surface of the skin on the treatment area and raise the temperature up to 40°C and maintain it for the remaining time of the treatment. The treatment should be monitored with an external infrared (IR) thermometer.
  4. During the procedure, the applicator's electrodes are gently pressed against the patient's skin, making sure that all electrodes are in contact with the skin as much as possible.
  5. The applicator strokes should be long and continuous, and performed in form of "8" figures, circles, ellipses or waves. The applicator must always be in motion, while in contact with the skin surface.
  6. If the measured skin surface temperature (as measured by the IR thermometer) is less than 40^oC, treatment is not optimal and the desired results will not be accomplished. The achieved skin temperature depends on the applicator movement speed and energy level. The lower the energy, the slower the movement should be and vice-versa.
  7. In the event that the patient experiences discomfort or pain during the treatment, either decrease the energy percentage, or apply more glycerin in gel, or perform wider and quicker movements, or stop the treatment.
- **IPL (for all subjects)**
  1. Before each treatment clean the entire applicator surface with a medical disinfectant. Cleaning of the applicator should always be done while system is set to Standby state or turned off.
  2. Fit the subject with appropriate protective eyewear.
  3. Apply a thin layer of ultrasound gel.
  4. On treatment screen set the energy level to 5-14 J/cm^2 and use AC DUAL applicator. Adjust treatment settings in case strong or persistent immediate responses (longer than 5 minutes) are observed.
  5. Place the applicator in close contact, perpendicular to the skin with no pressure applied. Pressing the applicator will fire the IPL pulse.
  6. Administer pulses throughout the treated area to ensure full coverage of the treated area with applicator overlap approximately 10% of the previously treated skin.
  7. A second pass of pulses may be administered to isolated areas of active acne with applicator overlap approximately 10% of the previously treated skin.
  8. During whole treatment duration, subject reaction must be monitored and if the subjects report an intolerable level of pain, treatment shall be ceased immediately.

9. Remove the remnants of the ultrasound gel and dry treated area thoroughly.

5.2.3 Post-treatment Instructions

5.2.3.1 ***Subject discomfort evaluation***

The subject will record their assessment of pain on a 100 mm VAS CRF page immediately after each treatment which will be considered to be a source document.

Subjects will be asked to directly complete the CRF Acne Related Quality of Life Questionnaire worksheet which will be considered to be a source document after Tx 2, Tx 4 and Tx 4.

5.2.3.2 ***Skin safety – immediate response after procedure***

- Local (dermal) tolerability examination (only on the face) will be performed immediately following treatment at the time-points given in the Study Visit Table and will include assessments of pain during treatment, hemorrhage, burn, erythema, edema or other reactions. All tolerability assessments must be completed by the same person throughout the study whenever possible. Local tolerability on the face will be rated as none, mild, moderate, or severe.
- Cold air or cold, wet but not frozen gauze pads may be placed on the treated area for post treatment cooling.
- Shortly after treatment, a topical emollient should be applied over the areas, without dressings of any sort.
- Subjects should remain in the research setting at least 30 minutes after treatment in order to ensure their well-being.

5.2.3.3 ***Home instructions***

- 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. Aloe Vera gel, Biafin cream, or any other anti-burn cream may be applied as well. Threolone ointment or its equivalents may be applied if any damage occurred to the skin or as a preventative measure. It is important to avoid mechanical damage to the treated area and it should not be rubbed, scratched or picked.
- If necessary, over-the-counter analgesics may be taken for pain management. It should be noted, however, that subjects should be instructed to use only acetaminophen-based ones, such as Extra Strength Tylenol®. Non-steroidal anti-inflammatory drugs (NSAIDS), such as Advil®, may affect microvasculature and hence may make the post-treatment erythema disappear artificially, thus hindering our ability to follow its natural resolution, which is part of the study's objectives.
- Subjects should avoid unprotected exposure to sunlight for the duration of the study and should use of sunscreen (no less than 30 SPF), or as specified by the Investigator. Subjects will be provided sunscreen for the duration of the study. It is recommended that subjects be provided with Neutrogena Clear Face Liquid Lotion Sunscreen Broad Spectrum sunscreen or an equivalent sunscreen that does not cause breakouts on acne-prone skin.

5.3 Follow-up visits

The procedures required at the follow-up visits are the following:

5.3.1 Photography: see section 5.2.1.2

5.3.2 Improvement assessments

5.3.2.1 GAAS and Lesion Count

Up to three independent reviewers will be required to evaluate the Acne Vulgaris grading using the GAAS based on before/after photos of baseline/6 weeks following the last Tx and to perform lesion count. The independent evaluators will not know which the baseline are and which the FU photos are.

The principal investigator or an appropriately trained designee will perform a lesion count at all visits.

5.3.3 Subject satisfaction

Subject will be asked to rate his/her:

- Improvement/satisfaction assessment using the Global Aesthetic Improvement Scale (GAIS)
- Overall satisfaction assessment with treatment outcome using a 5-point Likert scale
- Quality of life using the Acne Related QOL questionnaire

The subject will record their assessments directly on the CRF worksheet which will be considered to be a source document.

5.3.4 Subject compensation

Subjects will not pay for any office visits, examinations and procedures as part of this clinical study. Subjects may receive a stipend in order to cover transportation and related costs incurred as a result of their participation in the study according to each site's standard procedures and ethics 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.

5.4 Termination visit

The termination visit occurs in parallel with the last follow-up visit (FU).

Unscheduled visits may take place, as a precaution, in case a subject experiences an AE and needs to have an additional visit, per the investigator decision. For women of child-bearing potential, a urine pregnancy test will be performed at the termination visit.

5.4.1 Subject personal experience

Subjects will assess the treatment improvement using the GAIS (Global Aesthetic Improvement Scale).

5.4.2 Study termination CRF:

The termination CRF should be completed with the PI signature.

6 Endpoint Evaluations

The primary efficacy endpoint will be improvement in treated area appearance at 6 weeks after the last treatment as determined by a independent review using the GAAS.

The secondary endpoints include: subject satisfaction & subjects' assessment of improvement as well as subjects' assessment of discomfort with the procedure, subject's "Quality of Life", lesion count, and efficacy comparison of combination treatment and IPL treatment alone.

6.1 Efficacy

6.1.1 Global Acne Assessment Score:

In the first step, independent reviewers will receive 2 photographs for each client (visits 5 and 6 and an archival photograph taken at baseline) and they will need to determine which photograph represents "before" picture and which represents the "after" picture. Once this step is completed, in the next step the independent reviewers will grade the improvement by comparing the before and after photographs according to the GAAS.

6.1.2 Lesion Count (Face):

Lesion counts including inflammatory lesions and non-inflammatory lesions will be performed at visits. The lesion counts will be performed on the entire face, including the nose, and will be evaluated by the investigator or an appropriately trained designee. Facial inflammatory lesions (pustules, papules, and nodular lesions) and non-inflammatory lesions (open and closed comedones) will be counted and recorded separately.

The following lesion types will be evaluated:

- Inflammatory lesions
  - Papule – a small, red, solid elevation less than 1.0 cm in diameter
  - Pustule – a small, circumscribed elevation of the skin that contains yellow-white exudate
  - Nodule/cyst – a circumscribed, elevated, solid lesion generally more than 1.0 cm in diameter with palpable depth

- Non-inflammatory lesions
  - Open comedone – a pigmented dilated pilosebaceous orifice (blackhead)
  - Closed comedone – a tiny white papule (whitehead)

6.2 Subject self-assessment

The subject's overall satisfaction with treatment outcome, will be recorded at visit 6. The self-assessment will be based on a 5-point Likert scale (Subject Satisfaction Assessment Scale). Subjects will also rate their improvement using the Global Aesthetic Improvement Scale (GAIS) and their quality of life using the Acne-Related Quality of Life Questionnaire.

6.3 Safety

6.3.1 Immediate/short term response

Immediate response (pain during treatment, hemorrhage, burn, erythema, edema, etc.) of the skin will be assessed by the principal investigator or qualified designate within 30 minutes post treatment by a 4 level scale: (0) None / (1) Mild / (2) Moderate / (3) Severe.

Short-term response (dryness, sloughing/flaking etc.) of the skin may develop following each treatment which is expected to resolve within several days. These responses are not considered as adverse events since they are expected outcomes related to the treatment. However, if the principal investigator determines that the severity or duration of the short-term response is abnormal, then it will be documented as an adverse event. Again, for purposes of completeness, this information will be documented in the relevant CRF of the next visit.

6.3.2 Adverse events

Adverse events will be assessed throughout the duration of the study. All adverse events will be categorized with respect to severity and device-relatedness.

The following skin reactions are an expected outcome related to treatment:

- Dryness
- Sloughing/flaking of skin
- Infection
- Presence of prolonged erythema
- Presence of prolonged edema
- Burn / Blistering
- Hyperpigmentation
- Hypopigmentation
- Contact dermatitis
- Pruritus/Scarring
- Herpes simplex virus outbreak

Reports of all adverse events by subjects and investigator will be documented in the source documents and will be recorded in the Adverse Events form.

6.4 Subject Discomfort Evaluation

Subject assessment of discomfort and pain from the procedure will be evaluated using a 100 mm Visual Analogue Scale (VAS), were 0 mm is "no pain" and 100 mm is "intolerable pain".

Immediately after treatment the subject will be asked to rate treatment related pain. The subject will be presented the CRF page with the VAS (below) with words along a horizontal line and asked to make a mark along the 100 mm scale, representing their pain from no pain to intolerable pain (must stop the treatment). A

number will be derived by the research staff by measuring up to the point the subject has indicated versus the entire line.

Figure 2: Visual Analogue Scale (VAS)

No pain Pain as bad as it can be

The CRF page with the VAS will be considered to be a source document.

7 Study Analysis Plan

7.1 Statistical and Analytical Plans

This is the basis for the Statistical Analysis Plan for this study. This plan may be revised during the study to accommodate amendment to this Protocol and to make changes in relation to unexpected issues in study execution and data that affect planned analyses. Revisions to this protocol will be based on independent review of the study data and a final plan will be issued prior to data lock.

7.2 Study Hypothesis

The study hypothesis is that the treatment using Diamondpolar applicator followed by AC DUAL applicator and the AC DUAL applicator will improve the appearance of Acne Vulgaris by at least 2 points on the Global Acne Assessment Score (GAAS), at 6 weeks follow-up compare to baseline in the study population.

7.3 Sample Size Justification

This pilot study will enroll up to 50 patients in order to evaluate the safety and the efficacy of the treatment of acne using the Diamondpolar applicator followed by AC DUAL applicator and the AC DUAL applicator alone.

7.4 Study Analysis

- All subjects will be evaluated for efficacy and safety data at baseline, during treatments and at 6-week post treatment visit.
- The analysis set will be as complete as possible and as close as possible to ensure it complies with the intent-to-treat principle for all enrolled subjects
- Subject demographics, baseline assessments, treatment parameters, treatment evaluations, follow-up assessments and reported adverse events will be summarized and analyzed using the following statistical tools:
    - All summary tables for quantitative parameters will display mean, standard deviation, median and applicable descriptive statistics. Correlations between variables will also be performed where applicable.
    - All summary tables for qualitative parameters will show counts, percentages and orders.
    - Number of missing data will be displayed on all tables where applicable.
    - Inter-rater reliability test will be performed to assess agreement between reviewers.
    - All statistical tests will be two-sided. The level of statistical significance for effectiveness analyses is 5% ($\alpha = 0.05$) for all tests of differences. Paired t-test and/or Wilcoxon Signed-

Ranks Test for Matched Pairs will be used to compare the evaluations at the baseline and post treatment sessions.

- For all primary and secondary end-point data generated in this study, applicable data analysis tools listed above will be used to determine if the study meets its efficacy and safety criteria.

8 Adverse Events

8.1 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 subject, whether it is considered to be device related or not. If an adverse event occurs, the first concern will be the safety and welfare of the subject. Appropriate medical intervention will be made.

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

Each AE should be assessed according to the following criteria:

8.1.1 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.

8.1.2 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 the effect of the device.

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

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

Related: The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.

Not Related: There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

8.1.3 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.

8.1.4 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.

8.1.5 Anticipated Outcome Related Adverse Events

Anticipated adverse events in this study may include: Irritation, blistering, temporary skin color changes, burns, excessive edema or erythema (excessive consider as edema or erythema that do not resolve within 2-3 days), infection, PIH (post inflammatory hyperpigmentation) and scarring. If any antibiotic ointment will be required during the study it will be provided by the study doctor at no cost.

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 during the course of the 3 month follow-up period the Investigator will continue following the subject until the PIH is resolved or up to 3 months following the last treatment, whichever comes first.

8.1.6 Unanticipated Adverse Device Effects

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

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

Investigator will leave a voice message with an accompanying report of the AE. If the unanticipated AE, in the opinion of Venus Concept or the Investigator, is likely to affect the safety of the subjects or the conduct of the study, the IRB/ Helsinki/ other ethic committee will be notified of the effect within 10 working days after Venus Concept first receives notice of it.

8.1.7 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.

8.2 Reporting

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

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

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

8.2.2 Device Malfunctions

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

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

8.3 Risk/ Benefit Analysis

8.3.1 Risks

The potential risks for adverse effects of the treatment procedure include but are not limited to blistering, burns, excessive edema or erythema, infection, PIH and scarring, as detailed above in the Anticipated Adverse Events section.

8.3.2 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 participant. Potential benefits may include improvement of Acne Vulgaris.

9 Administrative Procedures

9.1 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.

9.2 Ethic committee Approval

This clinical study will be conducted according to all applicable regulations under 21 CFR Part 812 and all other applicable FDA regulations, 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.

9.3 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 documents 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.

9.4 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
- Curriculum vitae of the Principal Investigator
- Signed Financial Disclosure Statement for each investigator
- Written approval from the Ethical Committee of both the protocol and informed consent form

9.5 Device Use/Accountability

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

9.6 Training Requirements

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

9.7 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 subject, inclusion of new categories of subjects, etc.) must be approved by the local IRB or other relevant ethic committee prior to implementation.

9.8 Data Retention/Archiving Data

The Investigator must keep the following documents in a secure place for at least 5 years after the last clearance of a marketing application or at least 2 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.

9.9 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.

9.10 Termination of Study

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

Per protocol, termination of the study can occur upon achievement of total required enrollment, performance of all study related procedures (treatment and follow-up visits) and completion of Termination CRF form.

9.11 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's designee and the IRB or other relevant ethics committee a report of any serious adverse device effect, whether anticipated or unanticipated, that occurs during the study as soon as possible, but in no event later than 10 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 ethics 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 5 working days.
- Report to the IRB or other relevant ethics committee and Venus Concept, within 5 working days, the use of the study device without signed informed consent from the subject.
- Report adverse events in accordance with 21 CFR 812.
- Submit regular progress reports to the approval committee and Venus Concept or Venus Concept' designee, as requested by the investigators or IRB or other relevant ethics committee.
- Submitting a final report on the study to the IRB or other relevant ethics committee and Venus Concept or Venus Concept's designee within 3 months after termination or completion of the study.

10 References

1. "Acne Therapy. Experience with Palomar LuxV™ Intense Pulsed Light Therapy". Robert S. Berger. http://www.cosmediclinic.com/pdf/therapy-acne-treatment.pdf.
2. "Eradication of Propionibacterium acnes by its endogenic porphyrins after illumination with high intensity blue light. Ashkenazi, H., Malik, Z., Harth, Y. and Nitzan, Y. FEMS Immunol Med Microbiol 2003. 35: 17-24.
3. "Acne PhotoClearing (APC™) Using a Novel, High-Intensity, Enhanced, Narrow-Band, Blue Light Source". Shalita. A.R., Harth. Y., & Elman. M. Clinical Application Notes, Volume 9 No.1, 2001 1-4.
4. Goldman MP, Weiss RA, Weiss MA. Intense pulsed light as a nonablative approach to photoaging. Dermatologic surgery: official publication for American Society for Dermatologic Surgery [et al]. 2005;31:1179-87.
5. Weiss RA, Weiss MA, Beasley KL. Rejuvenation of photoaged skin: 5 years results with intense pulsed light of the face, neck, and chest. Dermatologic surgery: official publication for American Society for Dermatologic Surgery [et al]. 2002;28:1115-9.
6. "Light therapy in the treatment of acne vulgaris". Elman. M., & Lebzelter J. Dermatol Surg. 2004 Feb;30 (2 Pt 1):139-46.
7. Alster, TS, Lupton JR. Nonablative cutaneous remodeling using radiofrequency devices. Clin Dermatol 2007;25:487-91.
8. Zelickson BD, Kist D, Bernstein E, et al. Histological and ultrastructural evaluation of the effects of a radiofrequency based non-ablative dermal remodeling device: a pilot study. Arch Dermatol. 2004;140:204-9.
9. Hantash BM, Ubeid AA, Chang H, et al. Bipolar fractional radiofrequency treatment induces neoelastogenesis and neocollagenesis. Lasers Surg Med. 2009;41:1-9.
10. Yu JN, Huang P. Use of a TriPollar radio-frequency device for the treatment of acne vulgaris. J Cosmet Laser Ther. 2011 Apr;13(2):50-3. doi: 10.3109/14764172.2011.564626.
11. Cho SI, Chung BY, Choi MG, et al. Evaluation of the clinical efficacy of fractional radiofrequency microneedle treatment in acne scars and large facial pores. *Dermatol Surg*. 2012;38(7 Pt 1):1017–1024.

11 Abbreviations and Terms

AE	Adverse Event
CRF	Case Report Form
EC	Ethical Committee
GASS	Global Acne Severity Scale
GAIS	Global Aesthetic Improvement Scale
IRB	Institutional Review Board
SAE	Serious Adverse Event
UM	User Manual
VAS	Visual Analogue Scale

Appendix I
Clinical Trial Acknowledgement – Statement of Compliance

Clinical Evaluation of Venus Versa Diamondpolar Applicator Treatment Followed by AC Dual Applicator Treatment Using Two Intense Pulsed Light Wavelength Bands for Facial Acne Vulgaris Protocol CS2715

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

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.

Investigator's Signature	Date
Name	
Clinic	
Street Address	
City, State & Zip Code	
Country	
Phone #	
Fax #	
E-mail Address	