

Clinical Trial Protocol

Clinical evaluation of Venus Versa SR Applicator using intense pulsed light on skin texture, for improving the appearance of Striae Distensae

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Study Synopsis

Study Title	Clinical evaluation of Venus Versa SR Applicator using intense pulsed light on skin texture, for improving the appearance of Striae Distensae	
Protocol No.	CS0315	
Device Name	Venus Versa IPL device	
Study design	Multi-center, Prospective, Open Label with Before-After Study Design. Each subject will receive 5 full treatments at 2 week intervals. Follow ups will take place 1 and 3 months after the last treatment.	
Projected Study period	Initiation Date: February 2015	Completion Date: February 2016
Study population	Up to 60 healthy subjects at 20 sites (up to 3 subjects at each site), age 24-65 year old with Striae Distensae that wishes to improve their skin appearance.	
Investigational treatment	The procedure will include an intense pulse light treatment.	
Study Duration	Each subject will participate in the study for up to 5.5 months (consultation to final follow up). Total study duration is estimated to be 8 months from enrollment of the first subject to the termination visit of the last subject.	
Main Inclusion Criteria:	<ul style="list-style-type: none"> • Health Female/Male, age 24-65 with Fitzpatrick skin phototype I-V. • Striae Distensae on abdomen or thighs of subjects who are able to comprehend and sign informed consent form. Subject who can commit to all treatments and follow up. 	
Main Exclusion Criteria:	<ul style="list-style-type: none"> • Any surgical procedure in the treatment area within the last six months or before complete healing. • Previous resurfacing treatments on the same area at least six months prior to this evaluation. • Active infections 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. • Deep suntan, recent suntan, sunburn or artificially tanned skin. • Current skin cancer. • History of skin cancer or pre-cancerous lesions at the treatment areas. • Subjects on any medication that would affect the characteristics of the skin (medical or hormonal), such as "accutane", within past 6 months or photosensitizing medications. • Pregnancy / breast feeding. 	

	<ul style="list-style-type: none"> • Tattoo or permanent makeup at the treatment area.
Objectives	<p>Primary objectives</p> <ul style="list-style-type: none"> • To evaluate the safety of Striae Distensae treatment using the Versa SR580 nm Applicator. • To evaluate the efficacy of Striae Distensae treatment using the Versa SR580 nm Applicator. <p>Secondary objectives</p> <ul style="list-style-type: none"> • To evaluate subject's assessment of comfort associated with treatments. • To evaluate subject's satisfaction with Striae Distensae treatments and assessment of improvement.
Hypothesis	<p>The study will confirm that the Versa SR580 nm applicator is safe for Striae Distensae, and will result in Striae Distensae improvement for patients with Fitzpatrick Skin Type I-V. Improvement will be defined as achieving improvement of at least 1 point on the Global Aesthetic Improvement Scale (GAIS) at 3 months.</p>
Criteria for Evaluation	<p>Efficacy</p> <p>Primary endpoint:</p> <ul style="list-style-type: none"> • Striae Distensae improvement by at least 1 point on the Global Aesthetic Improvement scale (GAIS) (see Table 3) from photographs 3 months following the last treatment - FU2, as compared to baseline based on before/after photos, as determined by 3 blinded reviewers (Dermatologists and/or plastic surgeons). <p>Secondary endpoints: Investigator Evaluation, Comfort & Satisfaction</p> <ul style="list-style-type: none"> • Striae Distensae improvement by at least 1 point on the Global Aesthetic Improvement scale (GAIS) (see Table 3) from photographs 1 & 3 months following the last treatment – FU1&FU2, as compared to baseline based on before/after photos, as determined by the investigator. • Subject assessment of pain and discomfort associated with treatments using a Pain Visual Analogue Scale (VAS), where 0 is "no pain" and 10 is "intolerable pain". • Subject's satisfaction with treatment outcome based on a 5-point Likert scale. <p>Safety</p> <ul style="list-style-type: none"> • 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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1 INTRODUCTION

1.1 Background

Striae Distensae

Research regarding the histology of mature Striae Distensae reveals thin and retracted collagen and elastin fibers resulting in a lack of supporting material and an atrophied epidermis. The three maturation stages of Striae Distensae include the acute stage (Striae rubrae) characterized by raised, erythematous Striae, the sub-acute stage characterized by purpuric Striae, and the chronic stage (Striae albae), characterized by white or hypo-pigmented, atrophic Striae. Striae Distensae occur equally among races, however, they are more prevalent in women. Striae may result from a number of causes, including, but not limited to, rapid changes in weight, adolescent growth spurts, corticosteroid use or Cushing Syndrome, and generally appear on the abdomen, buttocks, thighs, knees, calves or lumbosacral areas. In addition, approximately 90% of all pregnant women develop stretch marks either on their breasts and/or abdomen by the third trimester. Currently, there is no medical cure for Striae Distensae. Over the years, different treatment modalities were tested for their efficacy and safety in all skin types. Studies using topical tretinoin resulted in some improvements, but efficacy was limited to only early, active Striae (1, 2). A combined treatment using sand abrasion and 15% trichloroacetic acid has demonstrated efficacy in the treatment of all types of Striae; however, there is a learning curve for physicians using this open wound technique and a positive outcome is dependent upon the patient's strict adherence to post-wound care instructions. Additional drawbacks include the significant downtime, up to a week for large areas, and the increased risk of post-inflammatory hyper-pigmentation (PIH) for patients with darker skin types, e.g., skin types V and VI (3). Treatments with either UVB light therapy or XeCL 308 nm excimer laser yielded only transient results with study authors recommending that subjects receive additional treatments every one to four months to maintain benefits (4). Clinical studies examining the use of intense-pulsed light for Striae showed promising results (5, 6, 7).

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 eliminating unwanted hair, benign vascular/pigmented lesions and unwanted leg veins, as well as for performing various skin treatments (scars/striae, etc.). This light energy heats the deeper structures of the skin and has also been shown to promote new collagen formation (8,9).

1.2 Rationale for the Study

The SR580 applicator is intended to improve skin appearance treatment by enhancement of collagen synthesis as the result of the non ablative photothermolysis. This trial is intended to evaluate the effect of IPL treatment on the Striae Distensae.

The study hypothesis is that the SR580 applicator will improve the appearance of Striae Distensae by at least 1 point on the Global Aesthetic Improvement Scale (GAIS) (see Table 3) at 3 months follow-up compared to baseline in at least 50% of the study population.

2 The Investigational Device

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 applicator uses 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 (from user manual)

In this study, the IPL applicator SR580 will be evaluated for the treatment of Striae Distensae, depending on the patient's skin type.

2.1.1 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.

2.1.2 SR580 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 at a spectrum of 580-950nm. The IPL applicator also includes a sapphire cooled light guide of 10x30mm. The system controls the pulse shape and fluence.



Figure 2: Venus Versa aesthetic treatment system SR580 applicator (from user manual)

3 Study Design

This is a multi-site, prospective, open labeled clinical trial with before-after study design. This study is designed to evaluate the safety and efficacy of a series of treatments using the Venus Versa SR IPL applicator. See Figure 3 for an illustration of the study design and Table 1 for a summary of the study procedures.

This study will include up to 8 visits at the clinic: initial screening/consultation, 5 treatments (Tx) visits in 2 week intervals, and 2 follow-up (FU) visits at 1 and 3 months after the last treatment visit.

Up to 60 healthy subjects (5 at each site) age 24-65 with Striae Distensae that wish to improve their skin appearance will be enrolled by the investigator. 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 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 but will be included in the safety analysis. 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 recorded, analyzed and reported to local IRB or ethical committees. The first treatment visit will be scheduled 2 to 7 days after the screening.

The duration of the treatment session will be approximately 60 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 FU1 & FU2. The level of the subject's discomfort will be documented at the end of each treatment session. Subject satisfaction will be evaluated before TX3, TX5, FU1 & FU2. Evaluation by 3 blinded reviewers will be conducted based on before/after pictures of the baseline/3 months follow up using GAIS.

3.1 Primary effectiveness endpoint

- Improvement in treated area appearance at 3 months after the last treatment as determined by 3 blinded reviewers.

Success criterion

The treatment will be considered successful if the appearance of Striae Distensae improves by at least 1 point on the Global Aesthetic Improvement Scale (GAIS) (see Table 3) scale at 3 months follow-up compared to baseline in at least 50% of the study population.

3.2 Secondary effectiveness endpoints

- Improvement in treated area appearance at 1 and 3 months after the last treatment as determined by investigator compared to baseline using the GAIS.
- Subject assessment of pain and discomfort associated with treatments using Pain 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.

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 5.5 months from enrollment to termination (see Figure 3).

Study duration for entire study sample: Estimated to be 8 months from enrollment of first subject to the termination of the last (total number of subjects up to 60). This is based on estimate of 0.5 months for recruitment + 5.5 months subject participation + 2 months collecting data.

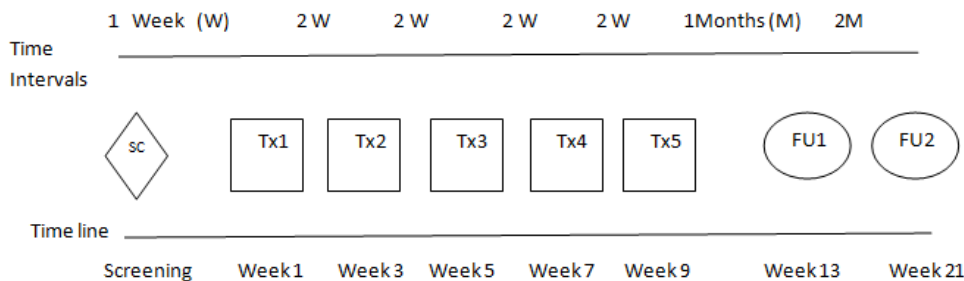


Figure 3: Study Design

3.5 Schedule of Times and Events

The following tables provide 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 - CS0315

Tx=Treatment; FU=Follow Up

Visit#	Visit #1	Visit #2	Visit #3	Visit #4	Visit #5	Visit #6	Visit #7	Visit #8
Study Activities	Screening & Test spot	Tx1	Tx2	Tx3	Tx4	Tx5	FU1	FU2
Timing (see Figure 3)		2-7 days post given ICF	2 weeks ± 5 days post 1 st TX	4 weeks ± 5 days post 1 st TX	6 weeks ± 5 days post 1 st TX	8 weeks ± 5 days post 1 st TX	1 month + 7 days after last Tx	3 months ± 7 days after last Tx
Informed Consent	X							
Eligibility assessment Demographic information Medical history & examination	X X X							
Test spots	X							
Photographs	X					X	X	X
Treatment		X	X	X	X	X		
Immediate/short term response		X	X	X	X	X		
Subjects discomfort assessment		X	X	X	X	X		
Subject satisfaction survey Appendix 2				X		X	X	X
Investigator evaluation using GAIS							X	X
Blinded reviewer evaluation using GAIS								X
Subject questionnaire								X
Adverse events recording	X	X	X	X	X	X	X	X
Study termination								X

3.6 Concurrent Control

There is no concurrent control in this study. Each patient’s efficacy results will be compared to baseline.

3.7 Blinding

Objective assessment of clinical improvement by GAIS will be achieved by sending before/after pictures (baseline/3months after last treatment) to 3 blinded reviewers at the end of the study.

4 Study Population and Subject Selection

4.1 Source and Sample Size

Up to 60 healthy subjects at 20 sites (up to 3 at each site) with skin phototype I-V shall be recruited by the investigator from within the investigator's subject population. Subjects shall have visible Striae Distensae at the designated treatment area. See Section 7.2 for sample size justification.

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, 24-65 years of age with Fitzpatrick-Goldman skin type I-V;
3. Having body areas with visible Striae Distensae to be treated (abdomen/thighs);
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.

4.2.2 Exclusion Criteria

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

1. Fitzpatrick-Goldman skin type VI;
2. Pregnant, intending to become pregnant during the course of study, less than 3 months postpartum or less than 6 weeks after completion of breastfeeding;
3. Heavy smoker (>1 pack of cigarettes a day);
4. Unable or unlikely to refrain from tanning, including the use of tanning booths, during the course of the study;
5. Use of photosensitive medication for which light exposure is contraindicated;
6. Use of oral isotretinoin (Accutane®) within 3 months of initial treatment or during the course of the study.
Note: skin must regain its normal degree of moisture prior to treatment;
7. Any dermal/epidermal damage or disorder, mainly vascular or textural lesions, in treated area;
8. Prior treatment, such as chemical peel (especially phenol-based) or dermabrasion, in treated area within 3 months of initial treatment or during the course of the study;
9. Prior skin laser/light or another device treatment in treated area within 6 months of initial treatment or during the course of the study;

10. Prior use of collagen, fat injections or other methods of skin augmentation (enhancement with injected or implanted material) in treated area within 12 months of initial treatment or during the course of the study. Treatment may not be performed at all over permanent dermal implants;
11. Prior use of Botox in treatment area within 6 months;
12. Prior ablative resurfacing procedure or face lift in treated area with laser or other devices within 12 months of initial treatment or during the course of the study;
13. Any other surgery in treated area within 9 months of initial treatment or during the course of the study.
14. Participation in a study of another investigational device or drug involving the same anatomical site within 3 months prior to enrollment or during this evaluation, or if not involving the same anatomical site, as per the Investigator's discretion;
15. History of keloid or any other type of hypertrophic scar formation or poor wound healing in a previously injured skin area;
16. Showing symptoms of hormonal disorders, as per the Investigator's discretion (such as Melasma, Chloasma);
17. Concurrent inflammatory skin conditions, open laceration or abrasion of any sort on area to be treated during the course of treatment;
18. Active Herpes Simplex at the time of treatment or having experienced more than three episodes of Herpes Simplex eruption within a year of study enrollment;
19. Multiple dysplastic nevi in area to be treated;
20. Having a bleeding disorder or taking anticoagulation medications, including heavy use of aspirin, in a manner which does not allow for a minimum 10 day washout period prior to treatment (as per the subject's physician discretion);
21. History of immunosuppression/immune deficiency disorders (including HIV infection or AIDS) or use of immunosuppressive medications;
22. Having any form of active cancer at the time of enrollment and during the course of the study or history of skin cancer;
23. Pigmented lesion in the treated area that appears cancerous or is not deemed suitable for photo therapy, as determined by a dermatologist;
24. Significant concurrent illness, such as uncontrolled diabetes, i.e., any disease state that in the opinion of the Investigator would interfere with the anesthesia, treatment, or healing process;
25. Active infections in the treated area.
26. Active cold sores, open lacerations or abrasions in the treatment area.
27. Deep suntan, recent suntan, sunburn or artificially tanned skin.
28. Tattoo or permanent makeup at the treatment area.
29. Mentally incompetent, prisoner or evidence of active substance or alcohol abuse;
30. Any condition which, in the Investigator's opinion, would make it unsafe (for the subject or for the study personnel) to treat the subject as part of this research study;

31. For subjects undergoing test spots: considerable undesired response consisting of skin hypopigmentation (long term whitening), a scar or pre-scar formation, or any response deemed by the Investigator as grounds for exclusion.

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 (abdomen or thighs) to ensure that it meets the study criteria.
- 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.
- 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.
- 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.
- Subjects will be given ample time to review the consent form and have the option to obtain legal advice prior to signing.
- The subject will be given verbal explanation of the procedure and study using common language and terms.
- Subjects will be encouraged to ask questions concerning the study and procedure

5.1.2 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. 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

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 and up to 48 hours (a longer waiting period should be established for darker skin types IV-V since the response may be less prominent). Therefore, the first treatment will be conducted 2 to 7 days following the test spot. It is important not to start treatment prior to full evaluation of the reaction to the test spot and having optimal parameters identified.

5.1.4 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 should be scheduled within 2 to 7 days after enrollment.

5.2 Treatment visits

Each subject will be enrolled and scheduled for 5 treatments at 2 week intervals and return for follow-up visits at one month FU1 (\pm seven days) and 3 months FU2 (\pm seven days after the last treatment) for evaluation of the treated areas. The duration of the entire treatment visit is approximately 60 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*

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 in the treatment area must be cleansed 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: 001TS_Tx1_abdomen.

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

- The treatment areas are divided into 2 treatment areas: abdomen or thighs. Each Subject will be allocated to one of them. Each site will recruit at least one subject for each of the treatment areas.
- 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/cm²): 5-20; Filters: 580 (refer to UM- table of presets).

Table 2: Treatment Parameters

Applicator	Fitzpatrick Skin Type	Energy Output (J/cm²)	Pulse Duration (ms)	Frequency (Hz)
SR580	I – II	14-20	10-20	Up to 3
	III	10-16	10-20	Up to 3
	IV	6-14	15-20	Up to 3
	V	5-10	15-20	Up to 3
	VI			

5.2.2.2 **Treatment procedure (also see user manual):**

- During each treatment session the subject will be treated with the Venus Versa system using the IPL applicator SR580. Treatment will take up to 50 minutes, therefore the entire treatment will be completed within 60 minutes.
- **IPL**
 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 IPL gel.
 4. On treatment screen set the energy level to 5-20 J/cm² and use SR580 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 1/3 of the previously treated skin.
 7. A single pass over the area is completed
 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 IPL gel and dry thoroughly.

5.2.3 Post-treatment Instructions

5.2.3.1 **Subject discomfort evaluation**

- The assessment of pain based on the subject’s report will be documented immediately after each treatment. The scale is detailed in Section 6.4.

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

- Skin immediate response (erythema, edema, etc.) will be evaluated immediately following treatment. See Section 6.3.2 for a detailed list of possible skin responses.
- 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®. 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 and should resume daily use of sunscreen (no less than 30 SPF), or as specified by the Investigator.

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 *GAI scale*

3 blinded reviewers will be required to evaluate the Striae Distensae using the GAIS (see Table 3) based on before/after photos of baseline/3 months FU.

5.3.3 Subject satisfaction

Subject will be asked to rate his/her satisfaction level (see Table 4).

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 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.

5.4 Termination visit

The termination visit occurs in parallel with the last follow-up visit (FU2).

5.4.1 Subject personal experience

Subjects will complete a personal experience questionnaire.

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 3 months after the last treatment as determined by 3 blinded reviewers.

The secondary endpoints include: subject satisfaction, & discomfort of the procedure.

6.1 Efficacy

6.1.1 GAI improvement scale:

In the first step Three (3) blinded reviewers will receive 2 photographs for each client (follow-up 2 visit 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 blinded reviewers will grade the improvement by comparing the before and after photographs.

Table 3: Global Aesthetic Improvement (GAI) scale

Investigator Global Aesthetic Improvement (GAI) Scale		
Score	Improvement	
(3)	Very Much Improved	Optimal cosmetic result in this subject.
(2)	Much Improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject.
(1)	Improved	Obvious improvement in appearance from the initial condition.
(0)	No Change	The appearance is essentially the same as baseline.
(-1)	Worse	The appearance is worse than the original condition
(-2)	Much Worse	Marked worsening in appearance from the initial condition.
(-3)	Very Much Worse	Obvious worsening in appearance from the initial condition.

6.2 Subject satisfaction

The subject's overall satisfaction, as well as satisfaction with treatment outcome, will be recorded on each visit beginning at treatment visit 2. The assessment will be based on a 5-point Likert scale detailed in Table 4, where 0 represents dissatisfied and 4 represents very satisfied.

Table 4: Subject satisfaction assessment scale

Subject satisfaction assessment scale (5-point Likert scale)	
Score	
(4)	Very Satisfied
(3)	Satisfied
(2)	Having no opinion
(1)	Unsatisfied
(0)	Very Unsatisfied

6.3 Safety

6.3.1 Immediate/short term response

Immediate response (erythema, edema, purpura, etc.) of the skin will be assessed within 20-30 minutes post treatment by a 5 level scale: (0) None / (1) Minimal / (2) Mild / (3) Moderate / (4) Severe.

Short-term response (dryness, sloughing/flaking etc.) of the skin are anticipated to appear several days after the treatment and disappear several days later. These responses are not considered as adverse events. 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. The skin reaction will be evaluated on-site and include the following clinical outcomes:

- Infection
- Presence of prolonged erythema
- Presence of prolonged edema
- Burn / Blistering

- Hyperpigmentation
- Hypopigmentation
- Contact dermatitis
- Pruritis/Scarring
- Herpes simplex virus outbreak
- Other

All adverse events will be categorized with respect to severity and device-relatedness.

Reports of adverse event by subjects and investigator will be documented in the designated section in the CRF of the specific visit in which the event was observed, as well as in the separate Adverse Events form.

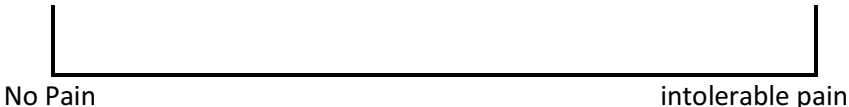
6.4 Subject Discomfort Evaluation

Subject assessment of discomfort from the procedure will be evaluated using a Pain Visual Analogue Scale (VAS), where 0 is "no pain" and 10 is "intolerable pain".

Immediately after treatment the subject will be asked to rate treatment related pain. The subject will be presented a VAS (below) with words along a horizontal line and asked to make a mark along the scale to rate 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 4: Pain VAS for Tolerability assessment

Please make a mark on the line below to indicate how much discomfort or pain you experienced when you were administered the treatment:



The figure shows a horizontal line representing a pain scale. At the left end of the line, there is a vertical tick mark with the text "No Pain" below it. At the right end of the line, there is another vertical tick mark with the text "intolerable pain" below it. The line itself is empty, intended for a subject to make a mark indicating their level of discomfort.

7 Study Analysis Plan

7.1 Study Hypothesis

The study hypothesis is that the treatment using SR applicator will improve the appearance of Striae Distensae by at least 1 on the Global Aesthetic Improvement Scale (GAIS) (see Table 3) at 3 months follow-up in at least 50% of the study population based on before-after photos.

7.2 Sample Size Justification

Based on previous experience with the IPL devices as indicated in the literature, low subject variance and high safety level of the tested element, the proposed study sample of 51 subjects will be sufficient to evaluate the safety and the efficacy of the treatment using the SR applicator and to obtain qualitative assessments of comfort levels experienced during treatments. A total of 60 patients are required to ensure sufficient subjects for statistical evaluation in case of dropouts.

7.3 Study Analysis

- Various evaluations will be done at baseline, prior to treatments, and following treatments. Additional follow-up evaluations will be performed one month and three months, after the final treatment.
- Subject demographics, baseline assessments, treatment parameters, treatment evaluations and follow-up assessments will be summarized and descriptive analysis will be performed.
- All statistical tests will be two-sided because potentially the treatment procedure may worsen the skin outcome. The level of statistical significance for effectiveness analyses is 5% 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 post treatment sessions. Descriptive statistics and correlations between variables will be performed.
- Adverse events reported will be listed, documenting course, outcome, severity, and possible relationship to the treatment.

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 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:

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:

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.

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 6 month follow-up period the Investigator will continue following the subject until the PIH is resolved or up to 6 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 +972-54-5341203.

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 Striae Distensae.

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

1. 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. Study documents will only be accessible to those who are approved as Principal Investigator and Sub-investigators. The subject's name will only appear on the ICF. The subject will be identified on all other documents and pictures by initials and study subject number.

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
- Signed Clinical Evaluation Agreement
- Curriculum vitae of the Principal Investigator
- Signed Financial Disclosure Statement for each investigator
- 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

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. The device to be used in this study belongs to the clinic and is used regularly for a variety of dermatological procedures. 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 2 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

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11 Abbreviations and Terms

AE	Adverse Event
CRF	Case Report Form
EC	Ethical Committee
GAIS	Global Aesthetic Improvement Scale
IRB	Institutional Review Board
SAE	Serious Adverse Event
VAS	Visual Analogue Scale
SR	Skin Rejuvenation

Appendix I
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 21 CFR Part 812 and all other applicable FDA regulations, the Medical Device Directive, 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

Appendix II

Subject Survey - using subject satisfaction assessment scale

Mark ONE of the boxes below to indicate today's follow up visit:

- 4 weeks post first treatment
- 8 weeks post first treatment
- 4 weeks post final treatment
- 12 weeks post final treatment

For each statement below, check ONE box that best describes your assessment of your treatment results.

1. Since the beginning of my treatment, when I look on my striae (stretch marks) size I'm

- Very Satisfied
- Satisfied
- Having no opinion
- Unsatisfied
- Very Unsatisfied

2. Since the beginning of my treatment, when I look on my striae (stretch marks) texture I'm

- Very Satisfied
- Satisfied
- Having no opinion
- Unsatisfied
- Very Unsatisfied

3. Since the beginning of my treatment, when I look on my striae (stretch marks) color I'm:

- Very Satisfied
- Satisfied
- Having no opinion
- Unsatisfied
- Very Unsatisfied

4. Overall, when I think about the treatment results I feel I am:

- Very Satisfied
- Satisfied
- Having No Opinion
- Unsatisfied
- Very Unsatisfied