Title: Pilot Study to Evaluate Combined Vbeam® Pulsed Dye Laser Treatment and RHOFADE™ (oxymetazoline hydrochloride) Topical Cream for Erythematotelangiectatic Rosacea

Protocol Number: DHF24671

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Study Type: Prospective, two-arm randomized, baseline-controlled, pilot study

Study Device: VBeam® Prima Pulsed Dye Laser System

Study Drug: RHOFADE™ (oxymetazoline hydrochloride)

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ABBREVIATIONS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ANOVA	analysis of variance
CFR	code of federal regulations
cm	centimeter
DCD	Candela's dynamic cooling device
FDA	food and drug administration
GCP	good clinical practice
HIV	human immunodeficiency virus
ICH	international conference on harmonization
IRB	independent review board
J	Joule
mJ	milliJoule
mm	millimeter
SAE	serious adverse event
SOP	standard operating procedure
Tx	Treatment
NSR	Non-Significant Risk
PIH	post-inflammatory hyperpigmentation

STUDY SYNOPSIS

Table 1 - Study synopsis

Proprietary Name	Candela *Vbeam*® Prima Pulsed Dye Laser System Allergen RHOFADE™ (Oxymetazoline Hydrochloride) Cream
Intended use	Vbeam – treatment of benign cutaneous vascular lesions, such as facial and leg telangiectasia and rosacea. RHOFADE™ (oxymetazoline hydrochloride) cream, 1% is indicated for the topical treatment of persistent facial erythema associated with rosacea in adults.
Design	Prospective, two-arm randomized, baseline-controlled, pilot study.
Study population	Up to 60 healthy male or female adult volunteers seeking facial treatment for erythematotelangiectatic rosacea, 18 to 75 years of age.
Study duration	The expected total duration of this study is up to 1 year.
Sites and Investigators	Two investigational sites.
Study Design:	Subjects in this study will be randomized to one of two treatment arms: Arm 1: subjects will receive three (3) monthly Vbeam PDL facial treatments at 4-week (± 1 week) intervals. Subjects will apply RHOFADE topical cream once daily for 4 weeks, with a 2-day wash-out period, prior to the 1st Vbeam PDL treatment. Subjects in Arm 1 will continue with daily use of RHOFADE topical cream during the study, according to the study protocol, with a 3-day wash-out period prior to each PDL treatment. Subjects in Arm 1 will apply RHOFADE topical cream in-office immediately following each Vbeam PDL treatment. Arm 2: subjects will apply RHOFADE topical cream once daily for the duration of the 6-month study. Subjects will not receive laser therapy. At the 1-week post first PDL treatment follow-up visit (1wk Post Tx.1 FU), subjects will be assessed for immediate treatment response and duration of treatment response. Both arms will be evaluated at each study visit (1, 2, 3 and 6 months post baseline visit). The 6-month follow-up is at (2 months following the third PDL treatment for Arm 1 and after 6 months of continuous drug therapy for Arm 2. Methodology described in the protocol to evaluate efficacy and safety of treatments will be carried out at each visit at the clinic.

Primary Objective	Evaluate the efficacy of combined Vbeam PDL and topical RHOFADE cream (Arm 1) for improvement in erythematotelangiectatic rosacea at the 6-month follow-up compared to baseline and compared to RHOFADE treatment alone at the 6-month follow-up (Arm 2).
Secondary Objectives	• Evaluate the efficacy of combined Vbeam PDL and topical RHOFADE cream (Arm 1) for improvement in erythematotelangiectatic rosacea at each treatment visit (pre-treatments 2 and 3) compared to baseline. • Evaluate the efficacy of combined Vbeam PDL and topical RHOFADE cream (Arm 1) for improvement in erythematotelangiectatic rosacea compared to RHOFADE treatment only (Arm 2) at each study visit (pre-treatments 2 and 3 and 6-month follow-up for Arm 1 and at the 2-, 3-, and 6-month follow-up visits for Arm 2). • Both arms: Evaluate improvement in vessel size at each study visit (1, 2, 3 and 6 months post baseline visit). • Both arms: Evaluate subject satisfaction at each study visit (1, 2, 3 and 6 months post baseline visit). • Both arms: Evaluate overall improvement (investigator and subject) at each study visit (1, 2, 3 and 6 months post baseline visit).
Efficacy Endpoints	• Clinician erythema assessment (CEA) – *Appendix II.* • Subject self-assessment (SSA) 5-point scale – *Appendix II.* • Investigator and subject assessment, using a Global Aesthetic Improvement (GAI) 5-point scale – *Appendix IV, Table 4.* • Investigator assessment of Improvement in vessel size – *Appendix IV, Table 5*. • Subject satisfaction 5-point scale – *Appendix IV, Table 6.*
Safety Endpoints	Evaluate the safety of the treatment (Arms 1 and 2): • Arm 1: Immediate treatment response – *Appendix IV, Table 3.* • Both Arms: Number, severity and type of any adverse event recorded throughout course of the study. • Arm 1: Discomfort level following PDL treatment – *Appendix III.*

BACKGROUND

Rosacea is a common chronic skin condition categorized into 4 subgroups based on clinical manifestations: erythematotelangiectatic, papulopustular, phymatous, and ocular [1]. Although the clinical features may

vary with rosacea, the most common primary feature of all subtypes is transient or persistent facial erythema [2,3]. Erythematotelangiectatic rosacea is primarily characterized by flushing and persistent central facial erythema [4].

Early diagnosis and treatment based on subtype are recommended to halt progression of symptom severity [5]. Flushing is better prevented rather than treated, by avoiding specific triggers, decreasing transepidermal water loss by moisturizers, and blocking ultraviolet light [5]. Nonselective β-blockers and α2-adrenergic agonists decrease erythema and flushing [5], while pulsed dye laser [5, 6] and intense pulsed light are used for telangiectasias [5]. Pulsed dye laser also addresses the diffuse erythema and enlarged pores characteristic of rosacea [6].

Oxymetazoline hydrochloride 1% cream (RHOFADE™) is a newly FDA-approved topical medication for adult rosacea patients. A primarily alpha-1a agonist, oxymetazoline hydrochloride (HCl) is thought to diminish erythema through vasoconstriction [7]. RHOFADE was evaluated for the treatment of persistent erythema associated with rosacea in two identical, randomized, double-blind, vehicle-controlled, parallel-group clinical trials [8]. A total of 489 subjects with persistent facial erythema associated with rosacea were treated with RHOFADE once daily for 4 weeks. An additional 440 subjects with persistent facial erythema associated with rosacea were also treated with RHOFADE once daily for up to one year in a long-term (open-label) clinical trial [8]. Disease severity was graded by the clinician using a 5-point clinician erythema assessment (CEA) scale [4] and by the subject on a similar 5-point subject self-assessment (SSA) scale, on which subjects scored either “moderate” or “severe” on both scales. Composite success, defined as the proportion of subjects achieving at least a 2-grade improvement on both CEA and SSA, was 15% in Trial 1 and 12% in Trial 2 on Day 29 of treatment [8].

Nonpurpuragenic pulsed dye laser (PDL) and intense pulsed light treatment have resulted in significant reduction in cutaneous erythema, telangiectasia and patient-reported associated symptoms of erythematotelangiectatic rosacea [9]. The PDL is an ideal energy-based device to treat the cutaneous vasculature of rosacea, since the 595nm wavelength is strongly taken up by the hemoglobin in blood vessels [6, 10]. With Vbeam 595nm PDL, ultra-long pulse durations reduce purpura while treating the telangiectasias associated with rosacea, which is more comfortable for patients [5, 6].

The cutaneous manifestations of rosacea significantly impact patients’ well-being, social and emotional health [5], and alternatives to further improve management and treatment of this condition are necessitated.

The objective of this pilot study is to evaluate the efficacy of Rhofade topical drug therapy combined with Vbeam PDL treatment. The study hypothesis is that a synergistic approach to treatment may improve the treatment course by a mechanism of action in which oxymetazoline acts as a vasoconstrictor, slowing down vascular flow and allowing for occlusion with PDL to close off the vessels quicker.

Study Device

The Candela Family of Pulsed Dye Laser Systems, including the 595nm pulsed dye laser wavelength, are FDA-cleared systems (K051359; K050673). The Vbeam 595nm PDL is indicated for treatment of benign cutaneous vascular lesions, benign epidermal pigmented lesions and periorbital wrinkles. The Vbeam is also indicated for treatment of inflammatory acne vulgaris.

The FDA-cleared Vbeam system includes spot sizes of 3, 5, 7, 10, 12 mm and 3x10 (elliptical). The study device is a modified version of the FDA-cleared system that includes an additional 15-mm spot size. The Vbeam and modified Vbeam are non-significant risk (NSR) devices. The modified Vbeam system provides epidermal cooling by either cryogen spray (Dynamic Cooling Device), as with the FDA-cleared system, or contact with a cooled window (termed contact-cooling). The modified Vbeam system (Vbeam Prima) recently received FDA clearance (K180593) on June 5, 2018.

Study Drug

RHOFADE™ is an alpha$_{1A}$ adrenoceptor agonist indicated for the topical treatment of persistent facial erythema associated with rosacea in adults [8].

There are no contraindications associated with topical use of RHOFADE for the topical treatment of persistent facial erythema associated with rosacea in adults.

There are warnings and precautions associated with use of the 1% topical cream, as indicated in the FDA-cleared package insert. These include the following:

- Alpha-adrenergic agonists as a class may impact blood pressure.
- Use with caution in patients with cerebral or coronary insufficiency, Raynaud's phenomenon, thromboangiitis obliterans, scleroderma, or Sjögren's syndrome.
- Advise patients to seek immediate medical care if signs and symptoms of acute narrow-angle glaucoma develop.

The most common adverse reactions (incidence > 1%) are application site dermatitis, worsening inflammatory lesions of rosacea, application site pruritus, application site erythema, and application site pain. In clinical trials, adverse reactions occurred in 1% - 2% of subjects treated with RHOFADE through 4 weeks of treatment. In the long-term (open-label) clinical trial, the rates of adverse reactions over a one-year treatment period were as follows: worsening inflammatory lesions of rosacea (3%), application site dermatitis (3%), application site pruritus (2%), application site pain (2%), and application site erythema (2%). Subjects with persistent erythema along with inflammatory lesions were allowed to use additional therapy for the inflammatory lesions of rosacea [8].

STUDY DESIGN

This is a prospective, two-arm randomized, baseline-controlled, pilot study to evaluate the efficacy of combined Vbeam PDL and topical RHOFADE cream for improvement in erythematotelangiectatic rosacea.

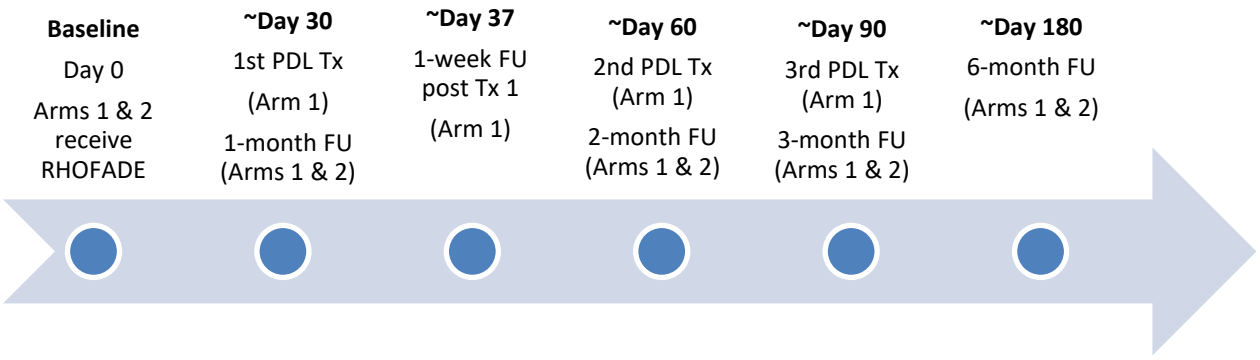
Up to 60 healthy male or female subjects will be enrolled at two investigational sites. All subjects will undergo an assessment of their general health. Following enrollment, subjects will be randomized to a study arm. Subjects in Arm 1 will receive RHOFADE topical cream at the screening visit and will be instructed to apply it daily for 4 weeks prior to the first PDL facial treatment. Arm 1 subjects will receive three (3) monthly PDL facial treatments at 4-week intervals. Subjects will apply RHOFADE topical cream once daily during the 6-month study, according to the study protocol, with a 3-day wash-out period prior to each PDL treatment. Immediately following the PDL treatment, subjects in Arm 1 will apply RHOFADE topical cream in-office. If subjects find it irritating to the skin to apply RHOFADE immediately after PDL treatment, then they may apply it within 24 hours of subsequent treatments.

Arm 2 subjects will receive RHOFADE topical cream at the screening visit and will be instructed to apply it daily for 6 months of continuous use until the 6-month post-baseline follow-up visit. . Subjects in Arm 2 will not receive laser therapy.

A one-week post first PDL treatment safety follow-up visit will be conducted (1wk FU post Tx.1) for Arm 1 subjects. In addition, efficacy and safety evaluations will be performed at each study visit (1, 2, 3 and 6 months post-baseline visit), as shown in Figure 1 below..

Erythema severity will be assessed at baseline and at each study visit. Improvement in erythema severity will be assessed at each post baseline visit. Additionally, investigator and subject questionnaires will be completed. Photography will be performed at each study visit under visible light conditions of the front full face, right and left 45-degree profile and right and left 90-degree profile. VISIA photography may also be performed for spectrometry measurements (optional). Safety assessments will be conducted at each study visit.

Study Flowchart



Primary Efficacy Objective:

To evaluate the efficacy of combined Vbeam Prima PDL treatment and topical RHOFADE cream for improvement in erythematotelangiectatic rosacea, at the 6-month follow-up compared to baseline and compared to Arm 2 at the 6-month follow-up (RHOFADE drug therapy only).

Secondary Efficacy Objectives:

- Evaluate the efficacy of combined PDL and topical RHOFADE cream (Arm 1) for improvement in erythematotelangiectatic rosacea at each treatment visit (pre-treatments 2 and 3) compared to baseline.
- Evaluate the efficacy of combined PDL and topical RHOFADE cream (Arm 1) for improvement in erythematotelangiectatic rosacea compared to topical RHOFADE cream only (Arm 2) at each study visit (pre-treatments 2 and 3 and 6-month follow-up for Arm 1 and at the 2-, 3-, and 6-month follow-up visits for Arm 2).
- Evaluate subject satisfaction at each study visit (1, 2, 3 and 6 months post-baseline).
- Evaluate overall improvement (investigator and subject) at each study visit (1, 2, 3 and 6 months post-baseline).
- Evaluate improvement in vessel size (investigator) at each study visit (1, 2, 3 and 6 months post baseline visit).

Safety Objectives:

- Evaluate the safety of combined PDL treatment and topical RHOFADE cream (Arm 1) during the study.
- Evaluate comfort level associated with PDL treatment (Arm 1).

Comfort assessment will be performed independently by the subject using a numerical scale response (NSR) scale 0=No pain to 10=Worst possible pain (*Appendix III*). Subjects will be asked to fill out a questionnaire after each PDL treatment (Tx.1 – Tx.3).

Primary Efficacy Endpoint:

- Clinician erythema assessment (CEA): 5-point scale (0=Clear to 4=Severe) at 6-month follow-up compared to baseline.
- Subject self-assessment (SSA) 5-point scale similar to CEA at 6-month follow-up compared to baseline.

Secondary Efficacy Endpoints:

- Investigator and subject assessment of overall changes in skin condition (skin texture, vessel size, flushing), using a Global Aesthetic Improvement (GAI) 5-point scale (0=Excellent improvement to 4=No difference) – *Appendix IV, Table 4.*
- Investigator assessment of improvement in vessel size – *Appendix IV, Table 5*.
- Subject satisfaction 5-point scale (0=Very satisfied to 4=Very dissatisfied) – *Appendix IV, Table 6.*

Safety Endpoints:

- The number, severity and type of any adverse event recorded throughout the study and post-treatment (discomfort (pain), immediate and delayed response).
- Occurrence of expected post-treatment immediate response following each treatment based on a predefined scale (*Appendix IV, Table 3).*
- Discomfort (pain) level using a 10-point visual analog scale will also be recorded after each PDL treatment, using a Numerical Scale Response (NSR) – *Appendix III.*

Study Duration

The duration of the entire study from first subject enrollment to last subject completing the 6-month follow-up, is expected to be approximately 1 year.

Subject Population

Up to 60 healthy male and female adults (greater than 18 years of age), who meet the inclusion and exclusion criteria.

Subjects enrolled in the study can discontinue their participation at any time, for any reason, without prejudice or reduction in the quality of their medical care. In addition, the investigator or the sponsor can terminate a subject's participation in this study to protect the subject's health or if the subject is not compliant with the study protocol and schedule. Subjects may be replaced if withdrawn or lost from the study.

All subjects enrolled into this study must meet the following criteria:

Inclusion Criteria:

1. Subject is a healthy male or female of 18 to 75 years of age.
2. Subject has erythematotelangiectatic rosacea with clinician erythema assessment (CEA) and subject self-assessment (SSA) of "moderate" or "severe" (Grade 3 or 4).
3. Fitzpatrick Skin Type I – VI.
4. Subject must be able to read, understand and sign the Informed Consent Form.
5. Subject must be willing and able to adhere to the treatment and follow-up schedule and post-treatment care instructions.
6. Subject must be willing to have limited sun exposure for the duration of the study, including the follow-up period up to 6 months post-baseline.
7. Subject is willing to have photographs taken of the treated area that will be used, de-identified, in evaluations and may be used, de-identified, in presentations and/or publications.
8. For female candidates – subject must be post-menopausal, or surgically sterilized, or using a medically acceptable form of birth control during the entire course of the study.

Exclusion Criteria:

1. Subject is pregnant or planning to become pregnant during the study duration.
2. Subject has an active electrical implant anywhere in the body, such as a pacemaker or an internal defibrillator.
3. Subject has an implant in the treated area (such as metal plates or screws) or an injected chemical substance.
4. Subject has a known collagen (connective tissue) disorder, vascular disease, scleroderma or other autoimmune disease (i.e. rheumatoid arthritis, lupus).
5. Subject has a history of diseases stimulated by heat or sun exposure, such as recurrent Herpes Simplex in the treated area, unless treatment is conducted following a prophylactic regimen.
6. Subject has a history of immunosuppression/immune deficiency disorders (including HIV infection or AIDS) or currently using immunosuppressive medications.
7. Having or undergoing any form of treatment for active cancer or having a history of skin cancer or any other cancer in the areas to be treated, including presence of malignant or pre-malignant pigmented lesions.
8. Subject is suffering from significant concurrent illness, such as such as cardiac disorders, diabetes (type I or II), or pertinent neurological disorders.
9. Subject has an infection or is suffering from current or has a history of significant skin conditions in the treated area or inflammatory skin conditions, including, but not limited to: photodermatoses, active acne, excessive skin dryness, psoriasis, eczema, rash, open wounds, varicella scars, open lacerations or abrasions and active cold sores or herpes sores prior to treatment (duration of resolution as per the Investigator's discretion) or during the treatment course.

10. Having a known anticoagulative or thromboembolic condition or taking anticoagulation medications one week prior to and during the treatment course (to allow inclusion, temporary cessation of use might be requested as per the subject's physician discretion).
11. Use of non-steroidal anti-inflammatory drugs (NSAIDS, e.g., ibuprofen-containing agents) one week before and after each treatment session.
12. Subject has a history of pigmentary disorders, particularly tendency for hyper- or hypo-pigmentation.
13. Subject has a history of keloid scarring or of abnormal wound healing.
14. Subject has a known photosensitivity to the device's laser wavelengths, history of ingesting medications known to induce photosensitivity, or history of seizure disorders due to light.
15. Subject has undergone any surgical, light-based therapy or RF procedures in the treatment area within 3 months of treatment or during the study.
16. Having undergone any other surgery in the treated area within 3 months of treatment (or more if skin has not healed completely) or during the study.
17. Subject has a tattoo or permanent make-up in the treated area.
18. Subject has systemically used retinoids or antioxidants within 1 month of treatment or during the study.
19. Excessively tanned in areas to be treated or unable/unlikely to refrain from tanning during the study.
20. Participation in a study of another device or drug within three months prior to enrollment or during the study.
21. As per the Investigator's discretion, any physical or mental condition which might make it unsafe for the subject to participate in this study.

Study Procedures

The following table provides a summary of the required study visits and the procedures and assessments performed at each visit.

Table 2: Study Schematics

Visit	Screening /Baseline	Tx 1* / 1-month FU	1-week (± 2 days) Safety Evaluation	Tx 2 - 3 / 2 & 3-Month FU Visits (4± 1 week)	6-Month (± 2 weeks) FU
Informed Consent	X				
Medical History	X				
Inclusion/ Exclusion Criteria	X				
Subject # Assignment	X				
Randomization to Study Arm	X				
Pregnancy Urine test	X				
Vbeam PDL test spots, (optional) – Arm 1	X	X		X	
Change to Medical History		X	X	X	X
Photographs, prior to any treatments		X	X	X	X
VISIA photographs, prior to any treatments (optional)		X	X	X	X
Clinician erythema assessment (CEA), prior to any treatments	X	X		X	X
Subject self-assessment (SSA), prior to any treatments	X	X		X	X
Vbeam PDL Treatment – Arm 1		X		X	
Tx Pain Assessment – Arm 1		X		X	
Immediate Treatment Response – Arm 1		X		X	

Visit	Screening /Baseline	Tx 1*/ 1-month FU	1-week (± 2 days) Safety Evaluation	Tx 2 - 3 / 2 & 3-Month FU Visits (4± 1 week)	6-Month (± 2 weeks) FU
Photographs, 10 mins post any treatment (optional) – Arm 1		X		X	
Global Aesthetic Improvement (GAI)		X		X	X
Vessel size assessment		X		X	X
Subject Satisfaction Questionnaire		X		X	X
Adverse Events and Serious Adverse Events	X	X	X	X	X
End of participation (Termination)					X

*For Arm 1, the 1st PDL treatment will be scheduled at approximately 4 weeks following the screening visit.

Screening Procedures

- A brief relevant medical history will be obtained to address inclusion/exclusion criteria for the study.
- Clinician erythema assessment (CEA) and subject self-assessment (SSA) will be obtained to address inclusion criteria for the study. Subjects with “moderate” or “severe” (Grade 3 or 4) are eligible for study participation (*Appendix II*).
- Pregnancy will be assessed for female subjects based on their last menstrual period, ability to become pregnant (surgical sterilization, birth control), and whether they have plans to become pregnant during the 6-month study period.
- The subject will undergo a standard skin exam to determine if they meet the study criteria.
- If the subject meets the criteria for the study, he or she will discuss with the study staff the study procedures, risks, benefits, and commitments associated with enrollment into the study. The staff will then review the consent form in detail with the subject, after which the subject will be given ample time to review the form. The subject will sign a consent form after the subject fully understands the possible risks/benefits of the study and wants to participate in study. The person conducting the session and the investigator will subsequently sign the consent form.
- Once the consent form is signed, the subject will be assigned the next consecutive subject number and will be randomized to a treatment arm.
- Women capable of childbearing will undergo a urine pregnancy test.

- Skin type will be recorded using the Fitzpatrick Scale.
- Test spots may be performed (optional) for subjects in Arm 1 to determine the subject's response to selected treatment parameters. Test spot locations will be selected by the investigator.
- Subjects in Arms 1 & 2 will be provided with RHOFADE topical cream and instructed to apply once daily, according to the drug insert instructions: apply a pea-sized amount once daily in a thin layer to cover the entire face (forehead, nose, each cheek, and chin) avoiding the eyes and lips.
- The RHOFADE topical cream will be applied daily for 4 weeks prior to the first PDL facial treatment.
- Subjects must discontinue topical use for a 3-day washout period prior to each PDL treatment.

Pre-Treatment PDL Care

In order to minimize pain during laser irradiation, subjects will be offered to use topical anesthetic cream (EMLA), which will be applied to the skin surface 30-60 minutes prior to laser irradiation.

PDL Treatment Procedure

- Treatments will be performed every 4 (±1) weeks. Subjects in Arm 1 must discontinue topical use for a 3-day washout period prior to each PDL treatment.
- Laser treatment procedures will conform to all laser safety instructions and should be conducted per the procedure described.
- The investigator, all personnel in the treatment room and the subject will wear protective eyewear, appropriately rated for the device wavelength(s) being operated.
- Based on the subject's response to the test spot evaluation (optional) or experience from treatment of prior subjects in this study or in practice, the investigator will select the parameters used for treatment, based on the threshold for nonpurpuragenic settings.
- Parameters include choice of: the 12 mm or 15 mm spot size, the laser fluence, the duration of the laser pulse exposures and the cooling procedure. The investigator will treat the face with the parameters chosen and will document the parameters.
- The treatment area will be photographed before each treatment and at each post-treatment follow-up visit. Optional photography can include photos at 10 minutes (approximately) after each treatment.
- All subjects will be treated as follows:
  - The 12 mm or 15 mm spot size will be used.
  - Treatment pulses will be delivered at the threshold for nonpurpuragenic settings.
- Subjects will be instructed to report any discomfort and/or comments during and post treatment. Discomfort will be rated on a scale from 0 = no pain to 10 = worst imaginable pain using the NRS scale (*Appendix III*).
- Immediate clinical response post-treatment will be recorded for: purpura, edema, erythema, and blistering, based on a predefined scale (*Appendix IV, Table 3*).
- Post-treatment photographs (optional) may be taken, approximately 10 mins post treatment, to document post treatment effects such as the collapse of blood vessels, or to document post treatment purpura, erythema, etc.

- Subjects will be instructed on post-treatment care, including the use of sunscreen.
- Subjects in Arm 1 will apply RHOFADE topical cream immediately (in-office) following the PDL treatment. If subjects find it irritating to the skin to apply Rhofade immediately after PDL treatment, then they may apply it within 24 hours of subsequent treatments.

1-Week Post-Treatment 1 Safety Evaluation:

Subjects in Arm 1 will be scheduled for a 1-week (±2 days) safety evaluation following the first PDL treatment. The following procedures will be conducted during this visit:

- A brief relevant medical history review for any changes from baseline.
- Skin evaluation of treatment area.
- Photographs of treatment area.
- Adverse event reporting.

Follow-up Study Visits:

The following procedures will be conducted during the 1-, 2-, 3- and 6-month study visits for subjects in both Arms 1 & 2:

- A brief relevant medical history review for any changes from baseline.
- Skin evaluation of treatment area.
- Photography will be performed according to the same procedure used at the baseline visit.
- VISIA photography (optional) may be performed according to the same procedure used at the baseline visit.
- Clinician erythema assessment (CEA) and subject self-assessment (SSA) will be recorded prior to treatment (*Appendix II*).
- Assessment of improvement (pretreatment) will be recorded by the investigator and subject using the Global Aesthetic Improvement Scale (GAI) —*Appendix IV, Table 4*.
- Improvement in vessel size will be evaluated by investigator—*Appendix IV, Table 5*.
- Subject satisfaction will be reported —*Appendix IV, Table 6.*
- Treatment will be performed (Arm 1).
- Subjects will be instructed to report any discomfort and/or comments during and post treatment (Arm 1). Discomfort will be rated on a scale from 0 = no pain to 10 = worst imaginable pain using the NRS scale (*Appendix III*).
- Immediate clinical response post-treatment (Arm 1) will be recorded for: purpura, edema, erythema, and blistering, based on a predefined scale (*Appendix IV, Table 3*).
- Post-treatment photographs (approximately 10 minutes post treatment) may be taken to document post treatment effects (Arm 1) such as the collapse of blood vessels in the lesion, or to document post treatment purpura, erythema, etc. (optional).
- Subjects in Arm 1 will be instructed on post-treatment care.

- Subjects in Arm 1 will apply RHOFADE topical cream immediately (in-office) following the PDL treatment. If subjects find it irritating to the skin to apply Rhofade immediately after PDL treatment, then they may apply it within 24 hours of subsequent treatments.
- Adverse event reporting.

Study Termination Procedure

The study termination visit occurs in parallel with the last follow-up visit. The only additional procedure required for the termination evaluation is to complete the study termination case report form (CRF).

Photographs

Photographs will be taken at each study visit, before and approximately 10 minutes after (optional) each treatment for subjects in Arm 1, and at the 6-month follow-up (2 months following the final PDL treatment for subjects in Arm 1). Photography will be standardized for reproducibility of photos (*Appendix I*): i.e., same photographer for each subject's study visits, use of the same camera, background, position of camera with respect to the treated area, same lighting and exposure conditions. These photographs will be taken for documentation, as well as for the investigator and subject assessments.

Post-treatment Care

After treatment, no special care is usually necessary for the treatment site. Aquaphor (similar to Vaseline) may be supplied to the subject to be applied to any area that feels irritated. The subject will also be instructed to apply cool compresses if they have any areas of swelling after treatment and to wash the treated area with soap or a gentle cleanser as they normally would for the week following treatment. The subject will be able to continue with their preferred routine skin care, excluding any method of wrinkle removal, the day after treatment. Sunscreen should be worn.

Data Recording

All data will be recorded in source documents and transcribed onto Case Report Forms (CRFs). Site will be monitored by Syneron staff or designees to assure adherence to the clinical trial requirements, subject safety, protocol procedures, and for data accuracy. The Case Report Forms and images will be reviewed and retrieved during the monitoring visit. All source documentation will remain in the subject's files at the site.

Protocol Revisions and/or Deviations

With the exception of emergency situations, no changes or deviations in the conduct of this protocol will be permitted without the prior approval of the sponsor.

The IRB/IEC that granted original approval for the study must be notified of all changes in the protocol and will approve any change or deviation that may increase risk to the subject, and/or that may adversely affect the rights of the subject or validity of the investigation.

In the event of an emergency, the Investigator will institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the sponsor and the IRB/IEC.

ADVERSE EVENTS (AE)

An adverse event (AE) is any adverse change in health or side effect that occurs in a study participant during their participation in the study.

Anticipated Adverse Effects

Anticipated adverse effects of laser-based treatments include: hyperpigmentation, blistering, crusting, bruising, scabbing, scarring, hypopigmentation, infection, and pinpoint bleeding. While unlikely, some adverse events may be permanent.

An adverse event (AE) is any undesired clinical occurrence in a study subject as indicated by signs, symptoms, illnesses, events that develop or worsen in severity in association with the study when deemed by the Investigator to be related to use of the device or study procedures. The Investigator will document all adverse signs and symptoms regardless of severity or frequency that are either volunteered by subjects or observed during the course of the study that are related to the device. The Investigator will also record adverse experiences of subjects resulting from concurrent illnesses, reactions to concurrent medications, or progression of disease states that the Investigator deems related to the device. Included in the description will be the nature of the sign or symptom, the date of onset, whether the event was serious, the severity, the relationship to study procedures or investigational device, the action taken, the date of resolution, and the outcome. The Principal Investigator will then determine the relationship of the adverse device effect to the investigational device.

Unanticipated Adverse Device Effects

For device studies, part 21 CFR 812.3(s) uses the term unanticipated adverse device effect which is defined 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.

<u>An unanticipated adverse effect will be graded as follows</u>:

Mild: Sign or symptom, usually transient, non-life-threatening requiring no special treatment and generally not interfering with usual activities.

Moderate: Sign or symptom, non-life-threatening which may be ameliorated by simple therapeutic measures and may interfere with usual activity.

Major: Sign or symptom that is intense or debilitating but non-life-threatening and that interferes with usual activities. Recovery is usually aided by therapeutic measures and the discontinuation of the study device may be required.

Severe: Any untoward medical occurrence that at any time results in death or life-threatening illness, resulting in persistent or significant disability/incapacity.

The relationship of the adverse effect to the study is defined as follows:

Probable: An adverse event has a strong temporal relationship to study device, and another etiology is unlikely or significantly less likely.

Possible: An adverse event has a strong temporal relationship to the study device, and an alternative etiology is equally or less likely compared to the potential relationship to study device.

Probably not: An adverse event has little or no temporal relationship to the study device and/or a more likely alternative etiology exists.

Not related: An adverse event has no temporal relationship to study device or has a much more likely alternative etiology.

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

The Investigator must report all unanticipated adverse device effects that are serious in nature to the clinical study monitor immediately or within twenty-four hours by telephone (see below). If such an unanticipated adverse device effect is reported after normal working hours, the Investigator will leave a voice message at the monitor's telephone number with accompanying report of the unanticipated adverse device effect faxed or sent to the fax number/e-mail address below:

Sharon Timberlake, Global VP of Clinical and Regulatory Affairs

Telephone Number (mobile): +1 (617) 957-1434

Email: sharont@syneron-candela.com

A written report prepared by the Principal Investigator must follow within five working days to both the IRB and to Candela and should include a full description of the event and sequence.

MEASURES TAKEN TO PROTECT THE RIGHTS AND WELFARE OF SUBJECTS

Research records will be available to study personnel, and the Institutional Review Board, where applicable. Research records may be used for purposes of medical education, after removal of patient names or other identifying information. Subjects will be required to provide permission for the

photographs taken of the treatment area during the study to be made available to the investigator and the sponsor for research and marketing purposes, after removal of identifying information. These photographs may be used for lectures, presentations or publications.

RISK/BENEFIT ANALYSIS

Risks

The use of the device used in this clinical study has been determined to present a non-significant risk in accordance with 21 CFR 812.3 for the intended use in this study.

Potential benefits to participating individuals

Subjects may benefit by achieving visual improvement of their erythematotelangiectatic rosacea as a result of treatment in this study. Not all subjects may have complete clearance of their erythematotelangiectatic rosacea.

DATA ANALYSIS

Copies of Case Report Forms and photographs will be collected by the sponsor during the monitoring visit when appropriate and will be used for analysis of efficacy and safety.

Efficacy

The efficacy of combined Vbeam Prima PDL and topical RHOFADE cream for improvement in erythematotelangiectatic rosacea compared to baseline will be assessed by clinician erythema assessment, subject self-assessment, and Investigator and subject assessment, using a Global Aesthetic Improvement 5-point scale and subject satisfaction 5-point scale.

Safety

Safety of treatments will be evaluated throughout this study. Each treatment area will be evaluated for severity of purpura, edema, erythema, hyperpigmentation, hypopigmentation, blistering and scarring. All clinical response and complications observed either immediately following each treatment or at follow-up visits will be noted on the data forms. These data will be descriptively tabulated by treatment area.

Pain scores will also be assessed for safety.

Interim and Final Data Analysis

Interim analysis can be performed at any time and used to terminate the study should it seem necessary to do so.

ETHICS AND GOOD CLINICAL PRACTICE

This study will be carried out in compliance with the following:

- Syneron Candela Standard Operating Procedures.
- Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo, 1975, Venice 1983, Hong Kong 1989, Seoul 2008 and Brazil 2013).
- US Code of Federal Regulations (Title 21CFR including parts 50, 56 and 812 governing informed consent and IRB regulations)
- International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP), 1996.

QUALITY ASSURANCE AND STUDY MONITORING

Study Monitoring/Auditing/Inspection

The Study Monitor will be responsible for monitoring the study sites to review the data being collected. The sponsor shall implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) to ensure that the trial is being conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements. Visits will be made prior to the initiation of the study, at scheduled intervals throughout the study, and at termination of the study.

Once enrollment and treatments have begun, monitoring visits will take place more frequently pending enrollment and study activities.

The sponsor and site will maintain regular phone and e-mail correspondence throughout the study to confirm compliance of study procedures.

The investigator/institution agrees to allow the monitor and other authorized personnel direct access to source data/documents for trial related monitoring, the clinical supplies storage/dispensing area and to provide all documents in the Investigator Regulatory Binder for review, and to assist site auditors in their activities if requested. Requests by the United States Food and Drug Administration (FDA) or regulatory agencies of other countries to inspect the study site may be made after adequate notification. The investigator may be required to assist the regulatory inspectors in their duties, if requested.

ADMINISTRATIVE PROCEDURES

Control & Disposition of the Study Device

The study device will be used according to the instructions of the Sponsor.

Informed Consent

The Study Personnel will obtain written Informed Consent prior to the subject's participation in any study procedures. The Study Personnel will inform the subjects about the experimental procedure to be utilized and assure the subjects that their decision regarding participation in the study will have no bearing on the quality of medical care received, and that their decision whether to participate in the study is strictly voluntary.

During the initial interview, subjects will be assured that they are free to change their mind and that their decision to participate in (or withdraw later from) the study will have no effect on their standard medical care.

Monitoring Plan

At least 3 monitoring visits are projected over the course of the study. The frequency of those visits will depend upon enrollment, study activities and the study visit schedule. The first visit is scheduled at the initiation of the study prior to the first subject treatment in the study. The second visit is scheduled after enrollment and treatment has been initiated and a third visit will be for a close-out visit for the study. Further interim visits may be conducted as needed to assure compliance to the study protocol and regulatory requirements. The number and frequency of monitoring visits may also be increased per the sponsor decision to collect data and images post treatment.

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APPENDIX I – Photography Guidelines

At each time point (before the treatments and at the follow-up visits), photographs of the treated facial areas should be taken in a standardized manner.

- Photographs should be taken in a private room or area of the clinic under controlled conditions, including the distance from the camera to the subject, height of the camera, background, camera positioning, subject's positioning and lighting in order to achieve high quality before & after sets.
- For consistency purposes, the same person should ideally take all study photographs, especially per subject.
- Subject's hair should be pulled by from the face with a hairband or shower cap.
- The digital files should follow a consistent standard naming scheme (including: date, subject study ID, subject initials, for example: 001TS_Tx.1_Mar 21 2015, etc.).

Specific photography details for facial area:

- Front face
- 90º right profile and left profile
- 45º right profile and left profile

APPENDIX II: Clinical Erythema Assessment Scale (NRS) *

❑ 0 = Clear	Clear skin with no signs of erythema
❑ 1 = Almost clear	Almost clear; slight redness
❑ 2 = Mild	Mild erythema; definite redness
❑ 3 = Moderate	Moderate erythema; marked redness
❑ 4 = Severe	Severe erythema; fiery redness

*Tan J, Liu H, Leyden JJ, Leoni MJ. Reliability of Clinician Erythema Assessment grading scale. J Am Acad Dermatol. 2014 Oct;71(4):760-3.

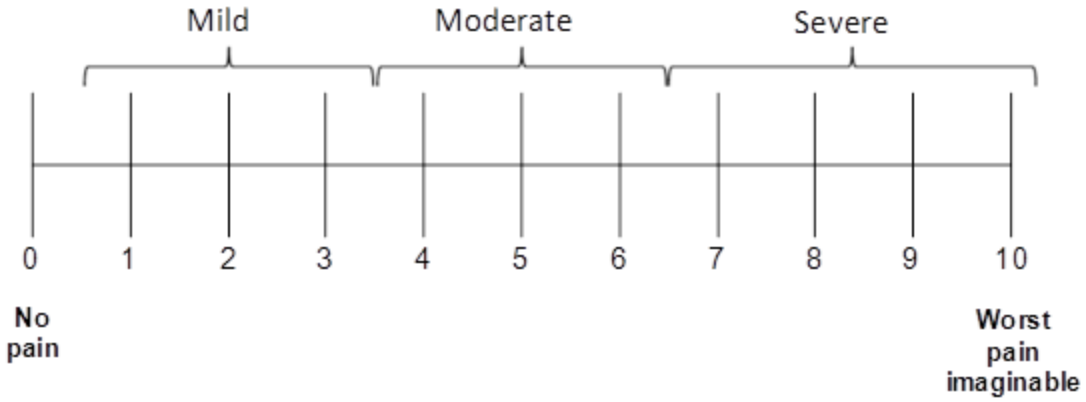
Subject Self-Assessment Scale (SSA)**

❑ 0 = Clear of unwanted redness
❑ 1 = Nearly clear of unwanted redness
❑ 2 = Somewhat more redness than I prefer
❑ 3 = More redness than I prefer
❑ 4 = Completely unacceptable redness

** DuBois J, Dover JS, Jones TM, et al. Phase 2 Randomized, Dose-Ranging Study of Oxymetazoline Cream for Treatment of Persistent Facial Erythema Associated With Rosacea. J Drugs Dermatol. 2018 Mar 1;17(3):308-316.

APPENDIX III: Numerical Response Scale for Rating Pain (NRS)

Please define how much pain you felt during the treatment by choosing a number from 0 to 10, with 0 being no pain and 10 - the worst pain imaginable.



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Appendix IV – Assessment scales

Table 3 – Post-treatment Side Effect Severity Scale

(0) Absent / None	❑
(1) Mild	❑
(2) Moderate	❑
(3) Severe	❑

Table 4 – Global Aesthetic Improvement (GAI) Scale

(0) Excellent improvement	❑
(1) Good improvement	❑
(2) Moderate improvement	❑
(3) Slight improvement	❑
(4) No change	❑

Table 5 – Improvement in Vessel Size

(0) 76–100% improvement (excellent)	❑
(1) 51–75% improvement (marked)	❑
(2) 26–50% improvement (moderate)	❑
(3) 1–25% improvement (mild)	❑
(4) No response	❑

Table 6 – Satisfaction Scale

(0) Very Satisfied	❑
(1) Satisfied	❑
(2) No Opinion	❑
(3) Dissatisfied	❑
(4) Very Dissatisfied	❑