THE SAFETY AND EFFICACY OF BROADBAND LIGHT TREATMENT FOR REFRACTORY DRY EYE DISEASE

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THE SAFETY AND EFFICACY OF BROADBAND LIGHT (BBL) TREATMENT
FOR REFRACTORY DRY EYE DISEASE (DED)

1. BACKGROUND

1.1. BROADBAND LIGHT TREATMENT

Broadband light (BBL) is a comprehensive phototherapy system that incorporates dual flashlamp technology, interchangeable filters, snap on adapters, and a precise thermoelectric cooling system for treatment that is safe, effective, with a high ease of use. BBL treatment uses intense pulses of non-coherent light over an approximate 400 – 1400 nanometers (nm) wavelength range. Dual Xenon flash lamps produce high output bursts of broad spectrum light. Various cutoff filters are available to filter out specific frequencies and narrow the spectrum of light to target specific chromophores in the skin. Adjustable cooling is also provided to protect the skin surface in contact with the device.

Broadband light (BBL) treatment has been widely used in dermatologic applications for improvement in rosacea and acne. To address rosacea, BBL can be filtered to deliver wavelengths of light that are absorbed by hemoglobin to result in damage to the vessels that are responsible for the visible flushing seen in rosacea. Controlled injury to the blood vessels may initiate the body's natural response to breakdown and remove the damages vessels. As an acne treatment, a BBL filter can be selected to target the bacteria *Propionibacterium acnes* which causes acne. *Propionibacterium acnes* absorbs the light energy, resulting in the selective destruction of bacteria.

The well characterized effects of BBL treatment to improve rosacea and acne will be applied to the symptoms of DED. Chronic inflammation of the eyelids and conjunctiva is proposed to be one of the major causes of DED. BBL treatment can alleviate inflammation by removing the bacteria from the eyelids and eyelashes. BBL can also diminish telangiectasias, which are correlated with DED. Removal of telangiectasias and excess blood vessels around the eye can decrease the cytokines and inflammatory mediators in the eye region.

2. STUDY RATIONALE

2.1. RESEARCH HYPOTHESIS

Broadband light (BBL) treatment is safe and provides improvement in the symptoms of refractory dry eye disease (DED).

2.2. RATIONALE

With an estimated prevalence of 7-33%, DED is a frequently encountered ocular morbidity, resulting in a $3.8 billion economic burden on the USA healthcare system. The meibomian glands, located in the upper and lower eye lids, produce the tear film. Evaporative dry eye occurs from the disruption of the top layer of the tear film. Bacteria occurring on the eyelashes or within the meibomian glands can result in chronic irritation and inflammation, subsequently causing meibomian gland dysfunction (MGD).

Broadband Light (BBL) technology is FDA cleared for indications including rosacea and the improvement of cutaneous vascular lesions. BBL may alleviate DED symptoms by reducing inflammatory blood vessels and by improving meibomian gland function, thereby providing an effective DED treatment with a high safety profile.

3. CRITERIA FOR SUBJECT SELECTION

3.1. NUMBER OF SUBJECTS

In this prospective study to determine safety and efficacy, a minimum of twenty subjects will be treated to detect improvement after BBL treatment for DED.

3.2. STUDY POPULATION

Subjects that are aged eighteen years or older with refractory DED will be enrolled in the study. Refractory will be defined as having persistent dry eye signs and or symptoms after at least one prior DED treatment modality. Subjects of both genders will be included in study enrollment. Only English speaking subjects will be enrolled.

3.3. INCLUSION CRITERIA

A subject will be eligible for inclusion in the study if ALL of the following criteria apply:

- Aged eighteen or older
- Having Fitzpatrick Skin Type I-V
- Must be diagnosed with DED and meibomian gland dysfunction (MGD)
- Persistent dry eye signs and or symptoms after at least one prior DED treatment modality
- Must be willing and able to adhere to the study schedule and protocol requirements
- Signed the informed consent form prior to any study related procedure

3.4. EXCLUSION CRITERIA

The subject will not be eligible for inclusion in the study if ANY of the following criteria apply:

- Prior IPL treatment for DED within the past six months
- Prior Lipiflow treatment for DED within the past three months
- History of trauma-induced ocular surface disease (thermal burns, chemical burns)
- Subject is pregnant
- History of seizures
- Having significant unprotected sun exposure within the treatment area
- Use of Accutane within the last six months
- Use of doxycycline in the last 1 month
- Allergy to proparacaine or lidocaine
- Having active herpes simplex virus infection within the treatment area
- Laser eye surgery (LASIK) within the past twelve months
- History of abnormal response to sunlight
- Having an active medical condition that may affect normal healing
- Having active infections or compromised immune system
- History of basal cell carcinoma in the treatment area within the past twelve months
- History of keloid scar formation

3.5. VULNERABLE SUBJECTS

Vulnerable subjects will not be included in the study. Children, pregnant women, nursing home residents, and persons with limited autonomy or decisional incapacity are examples of vulnerable subjects that will not be included in the study.

4. STUDY DESIGN

This is a prospective, open-label trial to evaluate the safety and efficacy of BBL treatment for DED. A minimum of twenty subjects with DED and meibomian gland dysfunction (MGD) will be enrolled at one clinical site. The enrolled subjects will already be in need of medical treatment for refractory DED, where refractory is defined as having failed (persistent dry eye signs and or symptoms) after at least one prior DED treatment modality. All subjects will undergo a full ophthalmic exam, DED diagnostic testing, and BBL treatment procedure.

The Clinical Investigator and study staff will recruit subjects for study participation. The Clinical Investigator will screen subjects to determine enrollment eligibility. If the subject selection criteria are met, informed consent will be obtained, and each subject will be assigned a unique enrollment identification number and will be randomized by coin flip into protocol 1 or 2. They will immediately proceed to the run-in phase, where the subjects will undergo a full ophthalmic exam and DED diagnostic testing. Additionally, clinical photographs of the face, eyes, and meibomian glands will also be collected, and subjects will complete DED questionnaires (the Standardized Patient Evaluation of Eye Dryness (SPEED) questionnaire and Visual Analogue Scale (VAS)).

Two weeks following the screening visit, subjects will visit the clinical site on a once per month basis (or within a four day visit window) to initiate the treatment phase of the study. Subjects will undergo a full ophthalmic exam, DED diagnostic testing, collection of photographs, and complete self-reported questionnaires. Subjects will undergo the BBL treatment, which consists of topical anesthetic application, and subsequent BBL administration to the malar and periorbital region (Figure 1). The completion of three treatment passes defines the clinical endpoint of BBL treatment. The subjects will complete a series of three treatments at monthly intervals (with a 1 week visit window).

One month following the completion of the series of three BBL DED treatments, the subjects will return to the clinical site for the follow-up visit. All subjects will undergo a full ophthalmic exam, DED diagnostic testing, collection of photographs, and completion of self-reported questionnaires.

5. STUDY METHODS AND PROCEDURES

For all enrolled subjects, the study will be divided into three sections – (1) study screening, (2) treatment, and (3) follow-up periods:

5.1. SCREENING (TWO WEEKS)

Subject screening (study week minus two weeks) is designed to determine whether the subjects are eligible for study enrollment and to facilitate completion of the run-in period. The Clinical Investigator and study staff will recruit subjects by offering participation to existing patients at the evaluation site and by referrals. Eligible subjects are defined as those that meet all the Inclusion Criteria and meet none of the Exclusion Criteria. During subject screening and enrollment the following information will be collected:

- Evaluation of subject eligibility
- Fitzpatrick skin type
- A complete medical history
- A complete ophthalmic history
- Information on all concomitant medications

- Clinical photographs of face, eyes, and meibomian glands before treatment
- Persistent dry eye signs and or symptoms after at least one prior DED treatment modality
- Signed Informed Consent Form

At the discretion of the Clinical Investigator, subjects who fail screening may be re-screened once, at a later date once the subject has met the criteria. The Clinical Investigator or study staff will obtain the signed informed consent form before any study specific procedures are performed. Each subject will be assigned a unique screening number, which will correspond to his/her unique enrollment identification number.

Potential subjects will be given ample time to ask questions and get their questions answered in regards to their participation in the study. The questions will be answered in a manner that is understandable to the subject. Subjects will be told that whether or not they choose to participate in the study, it will not affect their relationship with their physician.

After eligibility is confirmed the subject will immediately proceed to the run-in phase. This phase will be completed to ensure complete collection of subject baseline values. Subjects will be instructed not to use any artificial tears for at least 2 hours before testing. They will also be instructed to continue any over-the-counter habitual artificial tears at the same frequency and will be instructed not to change any of their current therapy for their DED. All subjects will undergo a full ophthalmic exam and DED diagnostic testing, which will include clinical evaluations for Dry eye: All sites will perform osmolarity, and Inflammadry test strips for level of MMP-9, staining pattern on cornea (using oxford scale) with Fluorescein, Tear Break Up Time (TBUT), 5 minute Schirmer's testing with anesthesia. USC site will obtain swabs for evaluation of ocular surface microbiome, to be sent to a core facility.

Additionally, clinical photographs of the face, eyes, and meibomian glands will also be collected, and subjects will complete DED questionnaires (SPEED and VAS). All subjects will undergo BBL treatment for a series of 3 treatments after being randomized to treatment protocol 1 or 2 (protocol 1 includes 420nm and 560nm treatment settings, protocol 2 includes only 560nm treatment settings, see Table 2 below). To demonstrate effects of DED treatments, baseline values will later be compared to values following treatment.

5.2. BBL TREATMENT

The BBL system has FDA clearance for use in the treatment of benign pigmented lesions, cutaneous lesions, benign cutaneous vascular lesions, mild to moderate acne, and the temporary increase in local circulation. The treatments will consists of 3 such treatments, 3-5 weeks apart.

The BBL system is comprised of:

- Device console - The device console is connected to the footswitch, the cable arm for the treatment handpiece, and the user screen. The device console houses the light source and the power supply.
- Footswitch - The footswitch is connected to the device console. Footswitch depression by the clinician enables energy delivery.

- Cable arm - The cable connects the device console and the treatment handpiece. The cable provides free range of motion for the treatment handpiece.
- Handpiece - The handpiece is connected to the cable arm, and steers the pattern of energy onto the patient.
- User Screen - The user screen is connected to the console, and serves as an interface to allow the clinician to select different treatment parameters.

5.2.1. ANESTHETIC APPLICATION

For the skin of the malar region, topical anesthetic consisting of lidocaine cream is applied for 30 minutes prior to treatment.

The subject's head will be tilted back and the eyelid pulled away from the eye. A single drop of an ophthalmic solution USP, of 1% proparacaine hydrochloride will be administered into the eye as a local anesthetic. With a single drop, the onset of anesthesia begins within thirty seconds and persists for fifteen minutes or longer.

5.2.2. PREPARING THE SUBJECT FOR TREATMENT

Protective eye shields to safeguard against light exposures will be provided to the subjects and personnel in the treatment room will wear protective goggles. The patient eye shields will remain in place until after the completion of the treatment. For the subject, protective opaque metal eye shields will be placed on the surface of the eye, covering the entire cornea and fitting inside the palpebral fissure (eyelids) to protect from exposure to the BBL light.

To prepare the subject and the BBL device for treatment:

- Disinfect the treatment handpiece
- Cleanse treatment area skin with alcohol
- Confirm absence of recent sun exposure on the subject's skin
- Apply topical lidocaine cream to malar skin and eyelids
- Instill 1% Proparacaine into each eyePlace protective metal eye shields onto ocular surface
- Apply a thin layer of ultrasound gel over the entire treatment area (malar skin)
- Select proper treatment settings. The settings will vary by subject's Fitzpatrick Skin Type and randomization (refer to BBL safe start settings Table 1).
- Select the appropriate filter and insert into treatment handpiece
- Place the appropriate adapter over the sapphire crystal on the treatment handpiece

5.2.3. TEST SPOT

On a site located below the hairline near the tragus, a test spot will be performed to assess the clinical response of the epidermis. After delivery of one pulse, the ultrasound gel is removed and the test spot is assessed. Treatment settings (Table 1) are then adjusted as indicated by the epidermal response. If the reaction is too severe (intense erythema, purpura, immediate white skin), settings should be decreased in intensity by the following actions in the following order:

1. Decrease fluence by 1-5 J/cm^2
2. Increase pulse width by 5-10 msec
3. Decrease cooling temperature 5-10°C

5.2.4. TREATMENT AREA

The BBL treatment will be delivered on the malar and periorbital region of the face (see Table 2 and Figure 1 below).

The BBL treatment will be delivered following treatment parameters described in Table 2:

1. Using the 15 x 15 mm adapter, fire pulses across the malar treatment area (Figure 1).
2. Using the 3 or 7mm round adapter, fire pulses across both lower eyelids and upper eyelids, while shielding the eyelashes.
3. Protocol 1 includes two malar treatment passes at 420 and one lower eyelid pass at 420nm, followed by one malar treatment pass at 560nm and one upper and lower eyelid treatment pass at 560nm.
4. Protocol 2 includes two treatment passes at 560nm and one upper and two lower eyelid treatment passes at 560nm.

5.2.5. POST BBL TREATMENT OBSERVATIONS AND INSTRUCTIONS

- Erythema – Erythema may be apparent for several hours after treatment.
- Sunscreen – Sunscreen with at least SPF 30 is recommended on the facial treatment locations for at least two weeks following each BBL treatment.

5.3. FOLLOW UP VISIT AFTER COMPLETION OF TREATMENT SERIES (FOUR WEEKS POST TREATMENT)

Four weeks following the final BBL treatment, the subjects will return to the clinical site for the follow up visit. The subject will undergo a full ophthalmic exam and the same DED diagnostic measurements and tests that were done at baseline. Photographs of the subject's face, eyes, and meibomian glands will also be collected. Subject questionnaires will be completed.

6. RISK AND BENEFIT ASSESSMENT

There are both risks and benefits associated with enrollment and treatment in the clinical study.

6.1. POTENTIAL RISKS OF TOPICAL ANESTHETIC USE ON EYE

There are both risks and complications associated with the application of anesthetics.

- Irritation – Temporary burning, stinging, or redness of the eye.
- Permanent corneal opacification and vision loss – under rare conditions of prolonged use.

6.2. POTENTIAL RISKS OF BROADBAND LIGHT TREATMENT

There are both risks and complications associated with the application of light treatments.

- Pain – This is a common adverse reaction and can be minimized by the use of anesthetic.
- Swelling – May occur around the eyes and bridge of the nose immediately after treatment.
- Purpura – May occur from having the pulse width too short and/or fluence too high during treatment, or from the concomitant use of anticoagulant medications.
- Pigmentary changes – Hyperpigmentation or hypopigmentation may occur in the treatment area.
- Urticaria – In some subjects, a histamine or hive reaction may occur in the treatment area.
- Scarring – In rare occurrence following any intense pulsed light (IPL) treatment.

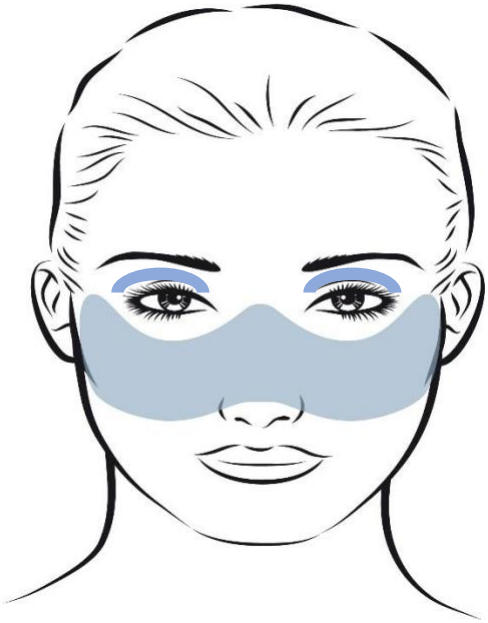
- Lack of permanent results – Treatment may not completely improve or prevent future eye or skin symptoms. Additional medical procedures may still be necessary to further improved DED.
- Hair loss/eyelash thinning— Repeated treatment to hair follicles may result in reduction of hairs/eyelashes; care is taken during the procedure to block exposure to eyelash follicles.
- Intraocular damage and inflammation may occur if treating without proper eye shielding

6.3. POTENTIAL BENEFITS

The benefits of study enrollment and treatment are related to the objectives and endpoints of the study. The study aims to provide a safe and efficacious treatment to reduce or alleviate the signs and symptoms of DED.

7. TABLES AND FIGURES

7.1. FIGURE 1. SCHEMATIC OF BBL TREATMENT REGION



7.2. TABLE 1. BBL SAFE START TREATMENT SETTINGS

SKIN TYPE	BBL FILTER	FLUENCE (J/cm^2)	PULSE WIDTH (ms)	TEMPERATURE (°C)
I-II	420nm	7	200	20
III-IV	420nm	6	200	20
V	420nm	5	200	20
I-II	560nm	15	20	20
III-IV	560nm	13	20	20
V	560nm	11	20	20

1.1. TABLE 2. BBL TREATMENT PROTOCOL

Table 2a. Protocol 1: 420nm and 560nm filter

PASS	FILTER (nm)	FINESSE ADAPTER	ANATOMICAL REGION
1	420	15x15mm square	temple to temple
2	420	15x15mm square	temple to temple
3	420	3mm round	lower lid
4	560	15x15mm square	temple to temple
5	560	3mm round	Upper and lower lid

Table 2b. Protocol 2: 560nm filter only

PASS	FILTER (nm)	FINESSE ADAPTER	ANATOMICAL REGION
1	560	15x15mm square	temple to temple
2	560	15x15mm square	temple to temple
3	560	3mm round	lower lid
4	560	3mm round	Upper and lower lid