Official Title: Intense Pulsed Light Study for Dry Eye Disease

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A. Study Hypothesis and Objectives

Dry eye disease (DED) is defined as a "multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface[1]." This condition may also compromise surgical outcomes and patient satisfaction following cataract, refractive surgery[2], and corneal transplants[3]. DED can also impact everyday tasks such as reading, using a computer, driving, and watching television which can be up to three times more difficult[4]. Worker productivity is potentially adversely affected by DED and scales with disease severity[5]. In addition, depression is more prevalent in DED patients[6], further evidence of the disease's debilitating effects. Current treatments options are limited and a recent study found 75% of DED patients report inadequate relief despite treatment. There is a critical barrier to provide efficacious treatment modalities to improve quality of life and to improve ocular surface health affected by DED.

A new treatment called Intense Pulsed Light (IPL) shows promise to reduce signs and symptoms in preliminary studies. IPL is a broad spectrum, non-coherent light treatment applied to the face and lower lids followed immediately by meibomian gland expression. Unfortunately, rigorous peer-reviewed studies on IPL are largely missing. Additional controlled, clinical studies are critical to better understand the potential of IPL to minimize objective measures of DED and improve patient quality of life.

i. Study Aim

The aim of this project is to rigorously evaluate the efficacy of IPL and to determine whether quality of life improvements can result from its implementation. Our hypothesis is that IPL can provide reduction and potential elimination of symptoms for patients with the evaporative form of DED by improving the meibomian gland expression quality and quantity resulting in a more stable, intact tear layer. We believe that the IPL treatment will deliver these results above and beyond meibomian gland expression alone.

ii. Research Goals

a. Substantiate the efficacy of IPL treatment for DED. Our study will collect objective measures of DED disease at baseline and after each of four IPL treatments. Our study design is a prospective, randomized, single masked trial. This evidence will assist practitioners, patients, and third parties to understand the value of this procedure and who will most likely benefit.

b. Determine the potential improvement in quality of life measures with IPL. DED has a substantial negative impact on quality of life. We will measure patient symptoms before and after each IPL treatment to assess the change in subjective quality of life measures using two validated questionnaires.

c. Demonstrate that IPL treatment improves DED above and beyond meibomian gland expression alone. There is limited evidence to support if the efficacy of IPL treatment is merely from IPL or the meibomian gland expression alone. Our proposed study is intended to clarify whether adding IPL before meibomian gland expression improves the outcomes. To our knowledge, no previous studies have addressed this question.

B. Background Information

Dry eye symptoms are common complaints in an estimated 25% of all eye doctors visits[7]. In the US population over 50 years of age, there are approximately 1.68 million men and 3.23 million women with diagnosed DED[8, 9]. The U.S. healthcare cost attributed to DED is approximately $3.84 billion[5]. The symptoms of this disease can range from a mild annoyance to extremely debilitating. Common symptoms include burning, stinging, tearing, blurred vision, foreign body sensation, contact lens intolerance, redness, chronic pain, and photophobia. Current treatments include topical tear supplements, environmental modifications to minimize tear evaporation, punctal occlusive treatments, ocular surface barriers, lid treatments, and immunomodulatory agents. Despite these various treatments, inadequate relief is common and there is a critical barrier to provide efficacious treatment modalities to improve quality of life and to improve ocular surface health affected by DED. We propose to test the hypothesis that IPL therapy will provide relief of evaporative DED symptoms by improving meibomian gland expression.

IPL uses a xenon lamp that delivers pulsed, broad spectrum, non-coherent light with wavelengths from 500-1200nm. During this selective photothermolysis, the light is absorbed by chromophores in the skin, melanin, and hemoglobin and converted to heat[10].

IPL was first FDA approved in 1995 for dermatology[11] and is commonly used for treatment of facial rosacea, acne, and hair, wrinkle and lesion removal. IPL for dry eye and ocular rosacea is currently off- label but is in the process of approval and is already approved for use in Europe and Australia.

The exact mechanism for the impact of IPL on dry eye is not completely understood. The theories include: ablation of superficial blood vessels which may deliver inflammatory mediators to the glands, connective tissue remodeling, reduction in eyelid bacterial and parasitic growth, such as demodex, and liquefication of the meibomian gland secretions[12].

i. Preliminary Data

We have previously performed IPL at our center on a total of 22 patients (age range 37-90, 18 females/4 males). Prior to treatment, the mean baseline total Ocular Surface Disease Index (OSDI) score was 23.79 and improved to 12.4 after three treatments (Figure 1). The baseline mean TBUT (tear break-up time) was 1.05 seconds and improved to 5 seconds after three treatments (Figure 2). Both subjective and objective measures suggest a positive impact on DED with IPL treatment.

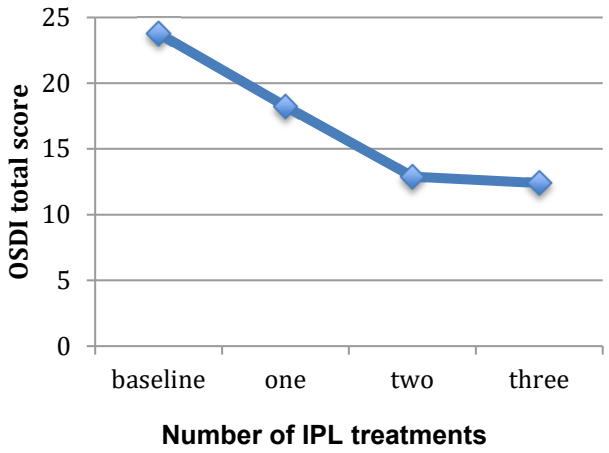

Figure 1: Mean OSDI total score

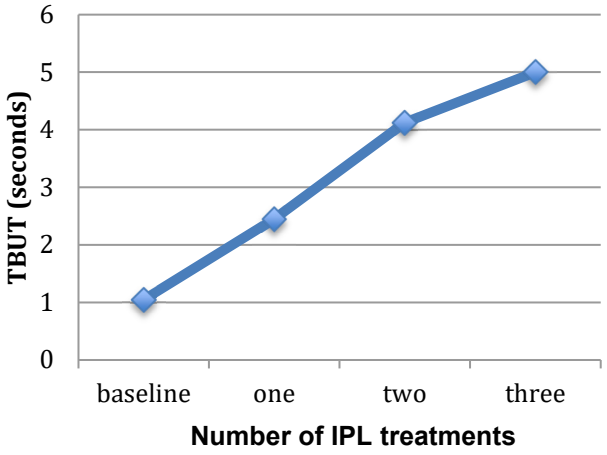

Figure 2: Mean TBUT during IPL

ii. Safety Data

In our preliminary treatments, no severe adverse events occurred. One patient noted a small blister on the cheek that resolved after one day and they continued with future treatments. Toyos[13]

noted of 91 subjects in a retrospective study, 14% had an adverse event that was most often mild, transient periorbital swelling and no serious events occurred. This treatment appears to be safe.

C. Study Design

There are two classifications of DED: aqueous deficient and evaporative[1]. There is some overlap, but the vast majority of dry eye is evaporative. Meibomian gland dysfunction (MGD) is the most common cause of evaporative dry eye. Intense Pulsed Light (DermaMed Solutions, Lenni, PA; Lumenis Ltd., Yokneam, Israel) will be applied to the lower eyelids and face with the intent to improve MGD. We will test our hypothesis and complete our goals by conducting an intervention to one eye and the fellow eye will serve as a control to compare the effects of IPL in patients who have evaporative DED due to MGD.

The study is a prospective, randomized, controlled, single masked trial. The randomization is based on IPL treatment to one eye and sham treatment to the fellow eye. The randomization will occur via a random number generator. The masking is based upon the cornea specialist's examination. The primary outcome measures include tear break up time (TBUT) and the Ocular Surface Disease Index (OSDI) symptom survey. Exploratory outcome measures will include the National Eye Institute Visual Function Questionnaire (NEI-VFQ), changes in MGD quantitated by lid margin photography and meibography before and after IPL, and other standard dry eye clinical evaluation tools.

All enrolled participants will be assigned a number, and the link between the number and participant will be secured. All data collection will comply with HIPPA guidelines. Data collection will include: clinical exam data, eyelid and facial photography, and meibography which will be de-identified.

i. Participant Eligibility Criteria

a. Inclusion Criteria

1. Willing and able to provide informed consent;
2. 18 years of age or older;
3. Diagnosed with evaporative dry eye disease with symptoms for 6 months or more;
4. Able and willing to comply with follow-up visits, phone calls and IPL treatments;
5. Agree to using an effective method of birth control during the course of the study;
6. Agree to continue current dry eye treatments during the course of the study;
7. Fitzpatrick skin scale[14] of 1 (very fair) to 4 (olive) as determined by an investigator.

b. Exclusion Criteria

1. Darker skinned individuals defined by the Fitzpatrick scale 5 and 6 as determined by an investigator;
2. Neurotrophic keratitis;
3. Ectropion, trauma, or any other lid abnormalities;
4. Previous diagnosis of Stevens Johnson syndrome or graft versus host disease;
5. Ocular burn, active ocular infection, or active ocular inflammation;
6. Currently pregnant or trying to become pregnant in the next 5 months;
7. Systemic conditions or currently taking medications which makes light therapy contraindicated (the use of doxycycline is allowed);
8. Tattoos in the treatment area;
9. Patients who have had IPL, Lipiflow or Meibothermoflo within the past six months;
10. Contact lens wear more than one time/week or history of refractive surgery;
11. Glaucoma drop use
12. Ophthalmic steroid use within the past 30 days;
13. Punctal plugs if instilled within 30 days of the start of the study;

14. Obvious asymmetry between the two eyes deemed significant by the investigators (such as punctal plugs or cautery in only one eye, etc);
15. History of a trabeculectomy or tube surgery;
16. Uncontrolled ocular or systemic disease;
17. Ocular or eyelid surgery within the last 6 months;
18. Any condition which leads the investigator to believe that the patient cannot comply with the study requirements and/or the patient may be placed at risk with participation.

ii. Study Procedures

Potential participants will provide written informed consent prior to any baseline testing (visit 1). All participants will be asked to complete 5 in-clinic study visits and 2 telephone calls over the course of approximately 7 months. Women of child bearing potential will be asked to provide a urine sample for a pregnancy test at the baseline visit. The investigator may ask for an additional pregnancy test at subsequent visits if they deem necessary.

The patients will be evaluated at baseline (visit 1) and return once a month for a total of 5 months (visits 2, 3, 4 and 5). They will be asked to complete study testing and will be evaluated by a masked corneal specialist at each visit. The phenotypic characterization for dry eye will include the following tests for both eyes: tear break-up time (TBUT) in triplicate using a timer, lissamine green staining of conjunctiva (grading 1-4, noted temporally and nasally), corneal staining with fluorescein (grading 1-4, breaking the cornea into 4 sections), meibomian gland health with the Meibomian Gland Evaluator (TearScience, Morrisville, NC), tear osmolarity, and 5-minute Shirmers under anesthetic using a timer. All patients will also undergo standardized slit lamp eyelid margin photography that includes upper and lower lids, have facial photography and meibography of the lids. Other testing that will be completed at certain time points include pinholed ETDRS visual acuity testing and the measurement of intraocular pressure. We will also obtain information about the participant's medical history (review of systems), and current ocular and systemic medications.

All participants will take the Ocular Surface Disease Index (OSDI)[15] and 25-item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ)[16]. Both questionnaires will be administered at each visit. These surveys do not allow for separating the response between each eye.

The participants will also be contacted over the phone by a member of the study team approximately 1 week and 7 months after their baseline visit.

iii. Study Design

Once the patient has signed informed consent, completed the baseline testing, and is determined to be eligible by an investigator, they will have one eye randomized to receive the IPL treatment and the fellow eye will receive a sham treatment.

a. Intervention with IPL

IPulse Quadra Q4 and Lumenis M22 devices will be provided by the cornea clinic at Kellogg Eye Center.

Prior to treatment, eye shields will be placed over both eyes of the participant. On the side that was randomly selected to receive the IPL treatment, ultrasound gel will be applied around the eye, lower eyelid, cheek, side of nose and temple. The PI will then administer approximately 15 light spots in areas where the ultrasound gel was applied.

All IPL treatments will be performed by the same investigator, the PI, who will not be masked. Each subject's eyes will be randomized with one eye/side of the face receiving IPL treatment (Figure 3), and the fellow eye serving as a control. At the first IPL treatment, the energy level (range of 8-18 joules) will be individually determined based the patient's skin Fitzpatrick scale phototype. The IPL instrument, Quadra Q4®, includes four pulse levels (1-4) each with six sublevels (A-F). The pulse intensity is inversely related to the skin phototype scale, and as noted in subject inclusion and exclusion criteria above, we will only treat patients who are phototype 1 through 4. The sublevel D is used for the initial treatment unless the patient cannot tolerate it and then a lower sublevel will be used. Future treatments sublevels will be increased gradually unless the examiner determines this is unsafe for the patient.

The Lumenis M22 IPL device requires the user to input fluence (joules/cm2) level prior to treatment. The below graph shows the fluence levels of the Dermamed Quadra Q4® that coorelate to the fluence levels of the Lumenis M22.

		Fitzpatrick Skin type		
	1	**2**	**3**	**4**
A	10J/cm2	9J/cm2	8J/cm2	8J/cm2
B	11J/cm2	10J/cm2	9J/cm2	8.5J/cm2
C	12J/cm2	11J/cm2	9.5J/cm2	9J/cm2
D	13J/cm2	12J/cm2	10J/cm2	9.5J/cm2
E	14J/cm2	13J/cm2	10.5J/cm2	10J/cm2
F	15J/cm2	14J/cm2	11J/cm2	10.5J/cm2

Figure 3. IPL treatment. After placing eye shields, an ultrasound gel is applied. Treatments spots are done around the eye, lower eyelid, cheek, side of nose and temple.

b. Sham Treatment

With the eye shields still in place, the fellow eye will be treated with approximately 15 spots of pressure around the eye, lower eyelid, cheek, side of nose and temple with the IPL device. No light energy will be applied. The PI will only place the device on the participant and press to mimic actual IPL treatment. Ultrasound gel will be applied to these areas prior to the sham treatment to prevent unmasking of the participant.

c. Post-Treatment

After the IPL and sham treatments have been completed, the eye shields will be removed, and the face cleaned. The upper and lower lids of both eyes will be expressed with a meibomian gland expressor while being positioned at the slit lamp.

After treatment, as recommended by the manufacturer, each subject will be asked to use ketorolac twice a day for three days and to wear SPF 30 sunscreen for one week. During the course of the treatment period, any adverse events will be noted per the adverse reporting guidelines outlined in section D.

d. 1 Week Safety Follow Up Phone Call (+/- 2 days)

Approximately one week after the participants have completed the baseline visit and received the IPL and sham treatments, a member of the study team will contact the participants to answer any questions and to document any adverse events.

e. Follow Up Visits (+/- 10 days)

Participants will return to the clinic for 4 additional visits after the baseline visit (visit 1).

At visits 2, 3, and 4, participants will be evaluated by a corneal specialist who is masked to the IPL treatment randomization, complete the testing outlined in the schedule of events (appendix A), and receive IPL and sham treatments accordingly. Participants will receive a total of 4 IPL and sham treatments throughout the duration of the study.

Participants will be asked to return to the clinic approximately 16.5 weeks after their baseline visit to complete visit 5. They will complete the testing outlined in the schedule of events but will not receive IPL or sham treatments.

f. 7 Month Follow Up Phone Call (+/- 5 days)

After the participant's final visit (visit 5) a member of the study team will contact the participant approximately 7 months after their baseline visit. Participants will be asked to complete the OSDI and NEI-VFQ questionnaires over the phone. After completion of the questionnaires, the study team member will inform the participant of which eye received the IPL treatment and which eye received the sham treatment. Also during this call, the participants will be offered to complete an optional visit. At this optional visit they will be asked to complete the testing outlined in the schedule of events and will be offered IPL treatment on both eyes free of charge. Patient's that do not wish to come in for the optional visit and IPL treatments, end their participation after completing the questionnaires, if they did not choose to end it sooner.

D. Reporting Procedures

i. Adverse Events

a. Adverse events (AEs) and complications determined by the investigator to be "possibly", "probably" or "definitely" related to the IPL treatment or study procedures will be recorded and reported to the IRB according to their reporting guidelines.

b. Any AE that is determined by the investigator to meet the definition of an unanticipated problem involving risks to subjects or others will be reported within 7 days to the IRB if is determined to be a serious problem. If the unanticipated problem is determined to be non-serious, it will be reported to the IRB within 14 days.

ii. Serious Adverse Events

a. Any AE which meets the FDA definition of serious and determined by the investigator to be "possibly", "probably" or "definitely" related to the IPL treatment or study procedures will be recorded and reported to the IRB within 7 days.

iii. Other Reportable Occurrences

a. All protocol deviations will be reported to the IRB at the continuing renewal.

b. Any privacy violation or breach of confidentiality will be reported to the IRB within 7 days and within 24 hours to the UMHS Privacy Office.

iv. Unmasking

a. Unmasking of the participant will occur after completion of the ODSDI and NEI-VFQ questionnaires during the 7 month follow up call.

b. Unmasking may occur at any time point throughout the trial if it is determined by an investigator to be in the best interest of the participant.

E. Statistical Methods

i. Sample Size and Power

The primary study outcome (pre to post change in TBUT within the treated eye and also the untreated, control eye) dictated the use of a paired statistical approach to sample size estimation. Based on our preliminary data, other published dry eye studies[17], and recent meeting abstract (ASCRS 2014; Gupta PK et al.) the expected, clinically relevant pre to post TBUT increase of 3 seconds with a standard deviation of 4.5 seconds was used. Type I and II error estimates used were standard for a non-pivotal study, 0.05 & 0.20. The estimated the sample size needed detect this difference in TBUT is 27 subjects. We will recruit 30 subjects allowing for an anticipated 10% drop-out rate.

All three study goals have a paired design wherein the first two goals contrast pre- to post-treatment measures in the treated eye, and the 3rd compares the treated eye to the control eye. The primary analysis for each objective will apply the paired, Student's t-test to contrast the continuous outcome variables for efficacy assessment (TBUT, Shirmer's test, corneal staining) in the treated eye (Goal 1) and the patient's quality of life (Goal 2), and the treated vs. control eye measures (Goal 3) from pre-treatment to post-4th treatment times. If the parametric assumptions of this test are not met, the non-parametric equivalent test, the Wilcoxon signed rank test, will be applied. In all cases, the null hypothesis to be tested is one of no change from pre- to post treatment, with a Type I error probability of 0.05 for the primary outcome assessment. The pattern of change over the 4 treatment visits in these continuous variables will be assessed using mixed, linear regression. SAS version 9.4 statistical software (SAS Institute, Cary, NC) will be used.

F. Summary and Long-Term Plan

Dry eye disease is a prevalent ocular condition with inadequate treatments available for proper relief. IPL has the potential to help those with evaporative dry eye due to meibomian gland dysfunction. This is a new treatment that needs to be studied with more rigor to understand the magnitude of the benefit for the relief of symptoms and reduced clinical signs. This study will provide answers to these questions in a prospective, masked design with the hope of providing an improved quality of life to those with DED.

We plan to use the anticipated results from this pilot study to apply for funding for a larger, prospective study on a specific population at high risk for severe DED, those with graft versus host disease. These patients often have extreme dry eye due to damage to the lacrimal and meibomian glands. Kellogg Eye Center has a large volume of these patients from the University of Michigan Cancer Center. Often the current dry eye treatments are not sufficient to effectively treat their DED. There are currently no studies on the efficacy of IPL on this population. This project would require additional funding through another grant. With addition funding, we also

hope to purchase a meibographer to image the entire meibomian glands in the tarsal plate to detect atrophic glands which are unlikely to respond to treatment.

G. References:

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Appendix A: Schedule of Events

Procedure	Baseline (Visit 1)	1 week phone call (+/- 2 days)	Visit 2, 4.5 weeks (+/- 10 days)	Visit 3, 8.5 weeks (+/- 10 days)	Visit 4, 12.5 weeks (+/- 10 days)	Visit 5, 16.5 weeks (+/- 10 days)	7 month phone call (+/- 5 days)	Optional Visit (e)
Informed Consent (a)	X							
Pregnancy Test (a)	X							
Review of Systems (a)	X		X	X	X	X		
Ocular and Systemic Medications (a)	X		X	X	X	X		
Adverse Event Assessment (a)		X	X	X	X	X		
Pinholed ETDRS Visual Acuity (a)	X		X	X	X	X		X(f)
OSDI Questionnaire (a)	X		X	X	X	X	X	
NEI-VFQ Questionnaire (a)	X		X	X	X	X	X	
Tear Osmolarity (a)	X					X		
Eyelid Photography at Slit Lamp (a)	X					X		
Facial Photography (a)	X					X		
Meibography (a,c)	X					X		
TBUT (b)	X		X	X	X	X		X
Fluorescein Staining (b)	X		X	X	X	X		X
Lissamine Green Staining (b)	X		X	X	X	X		
Meibomian Gland Evaluation (b)	X		X	X	X	X		

Schirmers Test (c)	**X**		**X**	**X**	**X**	**X**		
Intraocular Pressure Measurement (c)	**X**		**X**	**X**	**X**	**X**		
Randomization (c)	**X**							
Unmasking (d)							**X**	
IPL and Sham Treatment (c)	**X**		**X**	**X**	**X**			**X** (IPL to both eyes)
Expression of Upper and Lower Lids (c)	**X**		**X**	**X**	**X**			**X**
Begin ketorolac Instillation (twice a day for three days) (c)	**X**		**X**	**X**	**X**			**X**

** All tests are completed on both eyes except that IPL treatment is performed on one eye and the sham treatment is performed on the other.

** Fluorescein staining, lissamine green staining and Meibomian gland evaluation are to be completed right eye and then left eye.

a- Indicates that it is to be completed by study coordinator/technician (excludes the optional visit).
b- Indicates that it is to be completed by a masked corneal specialist (excludes the optional visit).
c- Indicates that it is to be completed by the unmasked PI.
d- Unmasking of the participant will occur after completion of the ODSDI and NEI-VFQ questionnaires.
Unmasking may occur at any time point throughout the trial if it is determined by an investigator to be in the best interest of the participant.
e- Can be completed entirely by Unmasked PI
f- ETDRS visual acuity testing may be substituted for standard Snellen visual acuity at optional visit