DRCR Retina Network

A Pilot Study Evaluating Photobiomodulation Therapy for Diabetic Macular Edema (Protocol AE)

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Sponsor: Jaeb Center for Health Research (JCHR)

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Signature Page

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31 March 2020

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
anti-VEGF	Anti-Vascular Endothelial Growth Factor
CI-DME	Central-Involved Diabetic Macular Edema
CRF	Case Report Form
CST	Central Subfield Thickness
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
DSMC	Data and Safety Monitoring Committee
E-ETDRS	Electronic-Early Treatment Diabetic Retinopathy Study
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IRB	Institutional Review Board
JCHR	Jaeb Center for Health Research
LED	Light Emitting Diode
OCT	Optical Coherence Tomography
PBM	Photobiomodulation
SAE	Serious Adverse Event
SD	Standard Deviation
UADE	Unanticipated Adverse Device Effect

PROTOCOL SUMMARY

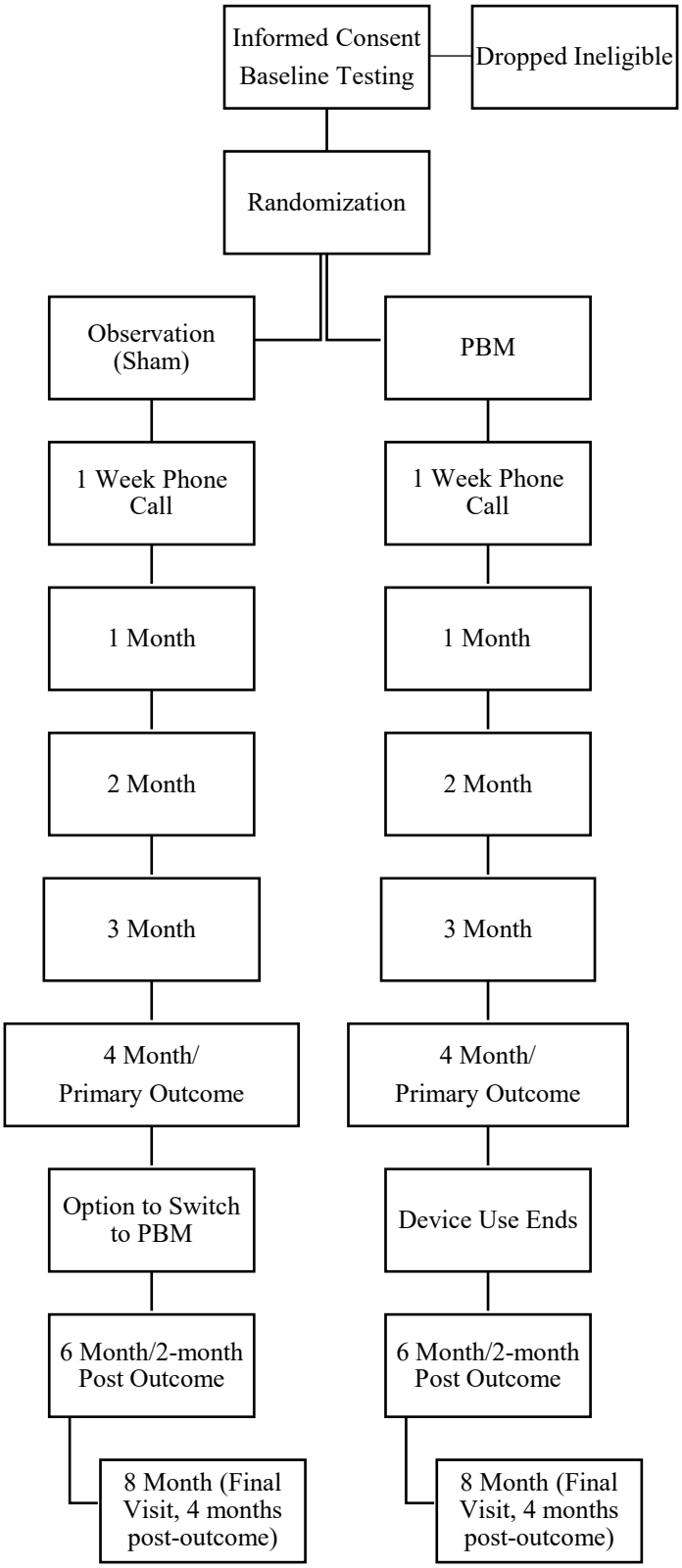
SUBJECT AREA	DESCRIPTION
Title	A Pilot Study Evaluating Photobiomodulation Therapy for Diabetic Macular Edema (DME)
Précis	Randomized clinical trial evaluating the effect of photobiomodulation compared with sham on central subfield thickness (CST) in eyes with central-involved DME and good vision.
Objectives	This study is being conducted to assess the effects of photobiomodulation on CST compared with sham in eyes with central-involved DME and good vision. Photobiomodulation is irradiation by light in the far-red (FR) to near-infrared (NIR) region of the spectrum (630-900 nm). Furthermore, this pilot study is being conducted to determine whether the conduct of a pivotal trial has merit based on an anatomic outcome and provide information on outcome measures needed to design a pivotal trial.
Study Design	Randomized, multi-center, sham-controlled clinical trial. There are two phases of the study; the primary outcome will be evaluated at the end of phase 1 (first 4 to 8 months). At the primary outcome visit, participants originally assigned to active will end device use and participants originally assigned to sham will switch to active. The switch serves two purposes: 1) to provide participants originally assigned to sham the opportunity to receive the active treatment and 2) to explore the post-outcome effects within treatment group. No statistical comparisons will be performed in Phase 2 to compare treatment groups. Note: This is not a crossover design.
Number of Sites	Approximately 40
Endpoint	**Primary Efficacy Outcome:** • Mean change in CST from baseline to primary outcome visit

SUBJECT AREA	DESCRIPTION
	Key Secondary Efficacy Outcomes: *Treatment Group Comparisons* • Mean change in retinal volume from baseline primary outcome visit • Percentage of eyes with CST below OCT machine- and gender-specific threshold for DME at primary outcome visit • Percentage of eyes receiving alternative treatment for DME by primary outcome visit • Percentage of eyes with a ≥5 letter loss in visual acuity • Patient compliance • Exploratory assessment of treatment effect after the device is stopped or started (see section 7.10 for more details)

Population	**Key Inclusion Criteria**
	• Age ≥18 years
	• Type 1 or type 2 diabetes
	• At least one eye with each of the following:
	  • Best corrected E-ETDRS visual acuity letter score ≥ 79 (i.e., 20/25 or better)
	  • Ophthalmoscopic evidence of central-involved DME in study eye confirmed by CST on spectral domain OCT:
	  ▪ Zeiss Cirrus: ≥290 µm in women, and ≥305 µm in men
	  ▪ Heidelberg Spectralis: ≥305µm in women, and ≥320 µm in men
	Key Exclusion Criteria
	• No history of prior laser, surgical, intravitreous, or peribulbar treatment for DME or DR in the study eye within the prior 12 months
	  ○ *If more than 12 months ago, no more than 4 prior intraocular injections*
	  ○ *Enrollment will be limited to a maximum of 15% of the planned sample size with any history of anti-VEGF treatment and a maximum of 15% with any history of PRP.*

SUBJECT AREA	DESCRIPTION
Sample Size	134
Treatment Groups	Random assignment (1:1) to photobiomodulation (PBM) or sham
Participant Duration	The trial will last up to 12 months for each participant (primary outcome at 4 to 8 months and final visit at 8 to 12 months)
Protocol Overview	1. Informed consent will be obtained. 2. Study eligibility will be assessed. 3. Prior to randomization, the participant's willingness to proceed into the randomized trial will be confirmed. 4. Eligible eyes (one per participant) will be randomly assigned to photobiomodulation or sham. If a participant has two eligible eyes, the eye with the greatest CST will be selected as the study eye and the non-study eye will be followed to evaluate any potential contralateral effect. 5. Training for at-home use will be performed with the randomized device on the day of randomization. 6. A follow-up phone call is performed at 1 week. 7. Participants will return for a follow-up visit every month for the first ~4 months and then every 2 months for 4 months after the primary outcome. The primary outcome assessment will be at ~4 months. 8. Following the primary outcome assessment, participants in the active group will end device use and participants in the sham group will be given the option to switch to the active treatment for the next 4 months. Participants in both groups who do not continue treatment will be given the option to end study participation after the primary outcome visit. A summary of treatment procedures is included below.

SCHEMATIC OF STUDY DESIGN



SCHEDULE OF STUDY VISITS AND PROCEDURES

	Baseline	1-week Phone Call	Interim Visits (1, 2, 3, 6M)	Primary Outcome and Final Visits	DME Tx Initiation Visit*
Device Training	X				
Randomization	X				
E-ETDRS Best Corrected Visual Acuity[†]	X		X	X	X[‡]
Spectral Domain OCT[§]	X		X	X	X
OCTA[ǀ]	X			X	
Eye Exam[¶]	X		If Needed	X	X
Blood Pressure	X				
HbA1c[**]	X				
Compliance Assessment		X	X	X	

Notes

Testing is only required for the study eye unless otherwise specified below.

*Alternative DME treatment (e.g. anti-VEGF) should not be performed unless protocol criteria are met. If alternative DME treatment is planned at an unscheduled visit, study testing must be completed prior to treatment.

[†]Visual acuity performed on both eyes at each visit, including protocol refraction on both eyes at baseline, 4-month, and final visit, and on the study eye only at all other protocol visits.

[‡]Usual care vision may be used if eye has already been dilated when treatment is planned.

[§]OCT in both eyes at all visits; OCT may be obtained with Zeiss Cirrus or Heidelberg Spectralis OCT machines only.

[ǀ]Baseline and 4-Month visit only at select sites with OCTA capabilities

[¶]Both eyes at baseline visit, study eye only at 4 month and 8-month visits. Ocular exam at interim visits is at investigator discretion. In general, an ocular exam should be completed if the OCT and/or visual acuity have worsened since baseline.

**Does not need to be repeated if HbA1c available from within the prior 3 months; if not available, can be performed within 3 weeks after randomization.

CHAPTER 1: INTRODUCTION

1.1 Introduction

1.1.1 Diabetic Macular Edema and Public Health Impact

In the United States, an estimated 30.2 million adults have diabetes mellitus (23 million diagnosed, 7.2 undiagnosed).[1] From 2005 to 2008 diabetes was reported to be the leading cause of new cases of blindness among adults in the United States.[2] Nearly 8 million people over the age of 40 in the United States are estimated to have diabetic retinopathy (DR).[3] Diabetic macular edema (DME), a consequence of retinopathy, is the most common among the conditions that contribute to vision loss in persons with diabetes; nearly half of all people with DR will develop DME.[4]

1.1.2 Current Treatment for DME

DME is a manifestation of diabetic retinopathy that produces loss of central vision. Although prior studies have clearly demonstrated that intravitreous anti-VEGF is the most effective monotherapy for central-involved DME (CI-DME) and decreased vision[10,10-13,11-13], anti-VEGF treatment does have disadvantages including the need for recurrent injections as often as once a month and a small risk of serious complications, such as endophthalmitis. Moreover, evidence indicates that DME is not satisfactorily resolved in all patients. Thus, there is an ongoing need to identify novel therapies that are both effective for DME treatment and that also avoid the potential adverse events or costs associated with current ocular interventions.

Furthermore, baseline cohort characteristics from the Early Treatment Diabetic Retinopathy Study (ETDRS) suggest that a substantial percentage of eyes with CI-DME may retain good vision. At baseline in the ETDRS, of all eyes in the focal laser and observation group, center involved macular edema on fundus photographs was present in approximately 42% of eyes. Of these eyes, 64% had baseline visual acuity ≥ 79 letters (approximately 20/25 or better). (Personal communication Adam R. Glassman) Several questions remain regarding treatment of the cohort of eyes with CI-DME and good visual acuity. In a review of early studies concerning the natural history of DME, Ferris and Patz found that 53% of 135 eyes with DME lost two or more lines of visual acuity over a two year period.[14] Furthermore, without intervention, 33% of 221 eyes included in the Early Treatment Diabetic Retinopathy Study (ETDRS) with central-involved DME experienced "moderate visual loss" (defined as a 15 or more letter score decrease in visual acuity) over a three year period.[15] Thus, there may be rationale for initiating treatment for CI-DME as soon as DME meets clinically significant criteria but before vision begins to decline.[16] The advent of OCT now allows us to determine the presence of and monitor changes in CI-DME with increased sensitivity over the fundus photographic grading method used in the ETDRS. Given the potentially large numbers of patients with CI-DME and good vision, and the current lack of guidance regarding best treatment practice for this group of eyes, evaluation of a low-risk, non-invasive treatment alternative to anti-VEGF in this cohort is warranted.

While focal photocoagulation (direct treatment to microaneurysms and grid treatment to diffuse edema) was shown in the ETDRS to reduce the risk of moderate visual loss from DME by approximately 50%,[17] this direct treatment with high-intensity light also causes retinal scarring and loss of photoreceptors.[18] More recent studies, however, have found that specific wavelengths of *low-intensity* light that are absorbed by cellular photoreceptor molecules result in activation of signaling pathways that cause biological changes on a cellular level without the destructive properties found in high-intensity lasers.

1.1.3 Photobiomodulation

Irradiation by light in the far-red (FR) to near-infrared (NIR) region of the spectrum (630-900 nm) collectively termed "photobiomodulation" (PBM) can restore the function of damaged mitochondria, upregulate the production of cytoprotective factors, decrease inflammation and prevent cell death. PBM has been applied clinically in the treatment of soft tissue injuries and acceleration of wound healing for more than 50 years. Recent studies have demonstrated that FR/NIR photons penetrate diseased tissues including the retina. The therapeutic effects of PBM have been hypothesized to result from intracellular signaling pathways triggered when FR/NIR photons are absorbed by cellular photo-acceptor molecules, such as mitochondrial cytochrome c oxidase, culminating in improved mitochondrial energy metabolism, decreased inflammation and cell survival. Investigations in animal models of retinal injury and retinal disease including diabetic retinopathy, age-related macular degeneration and retinitis pigmentosa have demonstrated the PBM attenuates cell death, protects retinal function and exerts anti-inflammatory actions. An increasing number of small clinical studies have documented therapeutic efficacy of PBM in AMD and diabetic retinopathy. In addition to wound healing, FR to NIR light (630-1000nm) has now been reported to be beneficial in a variety of conditions including recovery from ischemic injury to the heart,[19] treatment of gingival incisions,[20] peripheral nerve repair after trauma,[21, 22] and treatment of acute soft tissue injuries.[23] The FDA approved the use of low-light therapy for carpal tunnel syndrome in 2003.[24] Far-red light likewise has been found to inhibit production of the proinflammatory cytokines, IFN-γ and TNF-α, and to upregulate anti-inflammatory cytokines, IL-4 and IL-10 in experimental autoimmune encephalomyelitis.[25]

FR/NIR light (commonly 660-670 nm) has also has beneficial effects on the retina. Eells *et al.,*[26] reported the first direct link between the actions of far-red light on mitochondrial bioenergetics *in vitro* and retinoprotection *in vivo* using an established model of retinal mitochondrial toxicity, methanol intoxication. Accumulation of formic acid generated from methanol oxidation in the course of methanol poisoning produces toxic injury to the retina and optic nerve, resulting in blindness[14] An acute toxic exposure to methanol results in an increase in tissue formic acid concentrations, metabolic acidosis and visual toxicity within 72 hours of ingestion.[27] Formic acid is the mitotoxic metabolite in methanol intoxication. Formic acid inhibits cytochrome c oxidase by reversibly binding to the same site as cyanide and azide[14]. These studies demonstrated that three brief 670 nm LED treatments (160 sec at 25 mW/cm^2 producing a fluence 4 J/cm^2 at the surface of the eye) (Spectralife, Quantum Devices Inc., Barneveld WI) treatments delivered at 5, 25, and 50 h of methanol intoxication, attenuated the retinotoxic effects of methanol-derived formate. The authors documented a significant protection against formate-induced retinal dysfunction during the course of intoxication. 670 nm light also protected the retina from the histopathologic changes induced by methanol-derived formate. These findings provided the first link between the actions of FR light on mitochondrial oxidative metabolism *in vitro* and retinoprotection *in vivo*. Moreover, they were the first studies to suggest that FR PBM had therapeutic potential for the treatment of retinal injury and disease. Subsequent studies have documented retinoprotection in rodent models of high intensity light damage, retinitis pigmentosa, diabetic retinopathy and age-related macular degeneration.[28]

1.1.4 Relevent Prior Studies of PBM (670nm)

1.1.4.1 Animal Studies

Diabetes results in increases in oxidative stress in the retina, and increased expression of pro-inflammatory proteins. Oxidative stress and proinflammatory proteins in the retina are important

in diabetes, because previous studies have shown that vascular lesions of early diabetic retinopathy are significantly inhibited in animal models if oxidative stress and inflammatory changes are inhibited.[29, 30] Consistent with this, diabetic-like concentrations of glucose (20-30 mM) likewise result in increased superoxide production, inflammatory biomarker expression, and cell death in cultured retinal cells. PBM was able to inhibit these abnormalities in vitro.

Tang et al.[31] investigated the therapeutic efficacy of 670-nm PBM in albino rats (Lewis) which had been made diabetic with streptozotocin. With daily 4-minute PBM treatment (6 J/cm2) for 10 weeks from the onset of diabetes, there was significant inhibition in the diabetes-induced death (apoptosis) of retinal ganglion cells (Figure 1), as well as a 50% improvement of the ERG amplitude (photopic b wave responses) (Figure 2) (both $P < 0.01$), indicating both structural and functional benefit of PBM in diabetes.[31]

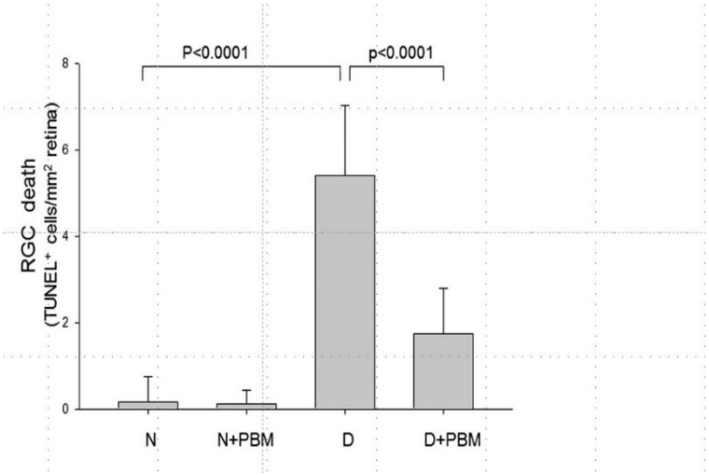


Fig 1.

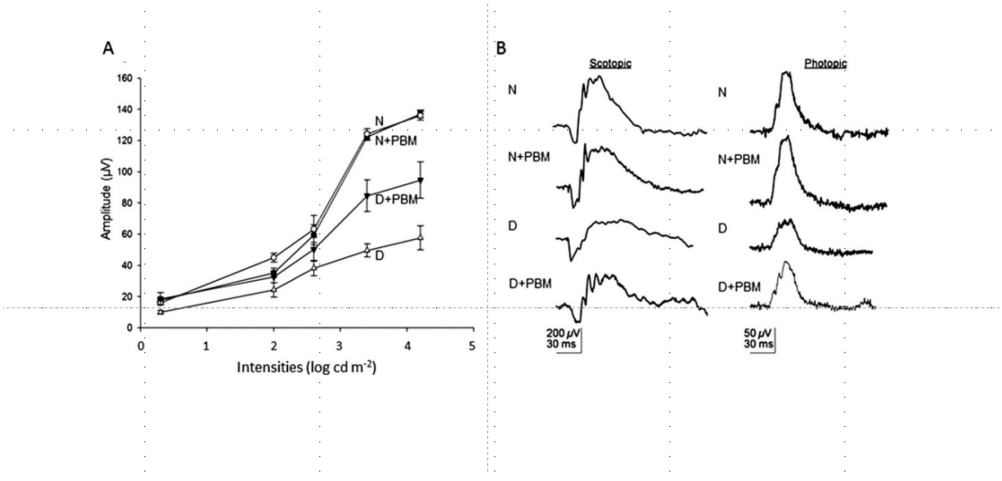


Fig 2.

PBM also inhibited the diabetes-induced generation of superoxide (Fig 3), induction of markers of inflammation (leukostasis, expression of the Inducible isoform of Nitric Oxide Synthase (iNOS) (Fig 4), and preserved MnSOD expression (an enzyme that helps protect against superoxide

damage; not shown) in vivo.[31] Daily application of the light therapy was more efficacious than every other day administration.

Fig 3. Diabetes (2 months) increased superoxide production by retina, and this increase was inhibited by 4 minutes per day PBM. Administration of PBM either daily or only three times per week both significantly inhibited the superoxide generation, but daily therapy was more effective.

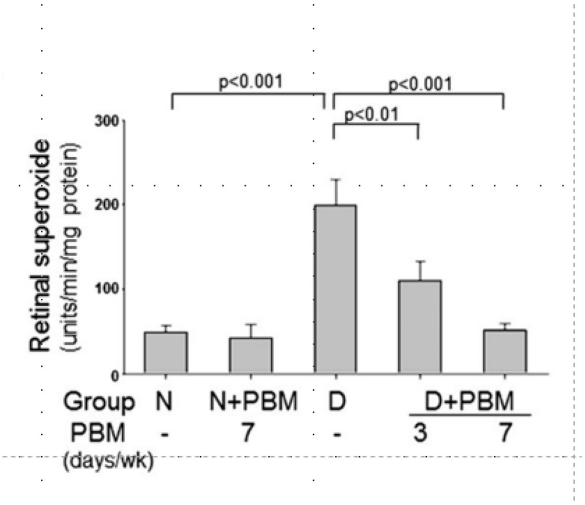


Fig 3.

While diabetes significantly increased both leukostasis and expression of ICAM-1, they showed that PBM essentially prevented both of these abnormalities (Fig 4A and 4B, respectively).[31] These data indicate that the PBM inhibited at least some key aspects of the diabetes-induced local oxidative stress and inflammation in the retina.

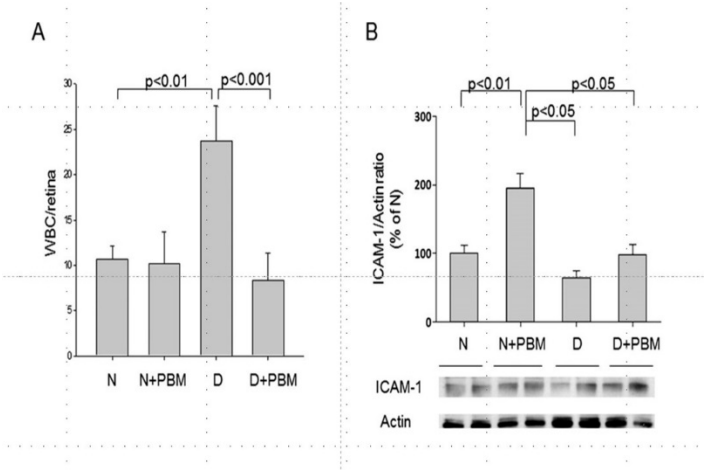


Fig 4.

More recently, Saliba, et al.[32] further tested whether the beneficial effects of PBM for retinal disease seen in the aforementioned studies would extend to (i) other species, (ii) in the presence of heavy pigmentation (C57Bl/6J mice), and (iii) as an intervention therapy after diabetes onset. PBM was applied to pigmented mice for 4 min/day for 10 weeks, starting 4 weeks after the induction of diabetes. The results indicated that PBM significantly reversed the diabetes-induced increase in retinal superoxide and leukostasis (Fig 5a and 5b, respectively), and significantly inhibited also the diabetes-induced increase in retinal ICAM-1 expression (not shown). The intervention with PBM also significantly inhibited the development of a diabetes-induced defect in visual function as measured by spatial frequency threshold ($p<0.0001$).

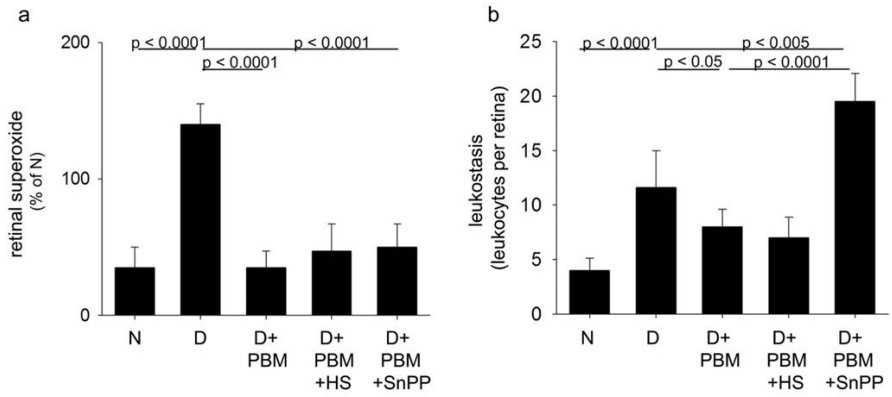


Fig 5.

Interestingly, at least some of the beneficial effects of PBM were demonstrated also in a second group of mice in which the PBM was unable to directly shine on the eyes, as a result of a lead shield covering the head during the PBM to prevent direct irradiation to the eye.

In an effort to determine which retinal cell-types the PBM was affecting, light-induced movement of ions into retinal cells was assessed in diabetic and nondiabetic mice using Manganese-enhanced MRI. Manganese is used as a surrogate of calcium for these studies, since manganese is known to be transported into cells via calcium channels, and unlike calcium, it can be detected by MRI. These studies demonstrated that diabetes reduced transport of manganese (and presumably calcium) into photoreceptor cells and essentially all other secondary neurons, and PBM treatment largely inhibited this except in the presumptive rod inner segment layer.

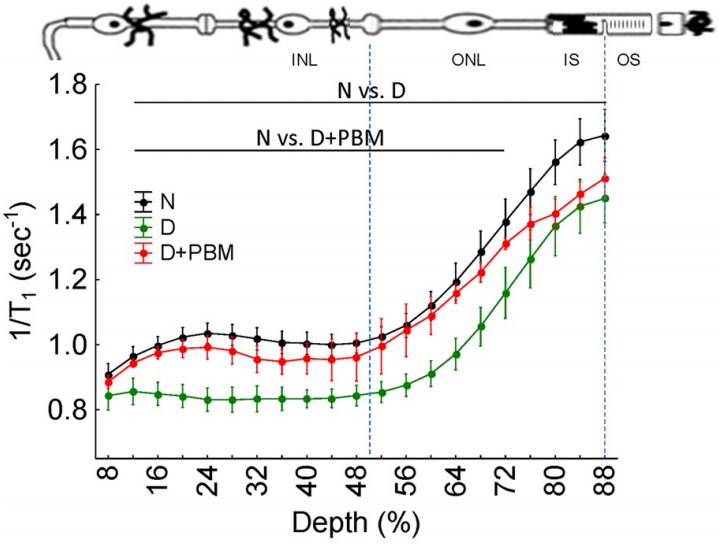


Fig 6.

Most importantly, long-term (8 months) daily application of PBM (670 nm, 4 min/day) recently has been shown to inhibit the development of clinically meaningful lesions of early DR in mice.[33] PBM was administered daily from the onset of diabetes, and the daily light therapy significantly inhibited the diabetes-induced leakage in each of the 3 layers of the retinal microvasculature (Fig 7) and degeneration of retinal capillaries (Fig 8), and also significantly inhibited the diabetes-induced reduction in visual function (visual acuity [spatial frequency threshold] and contrast sensitivity; not shown).

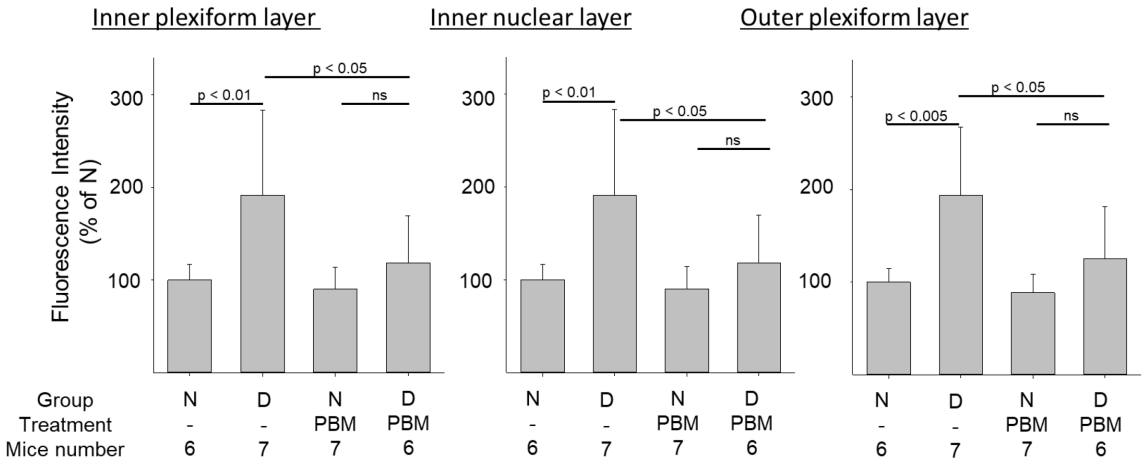


Fig 7.

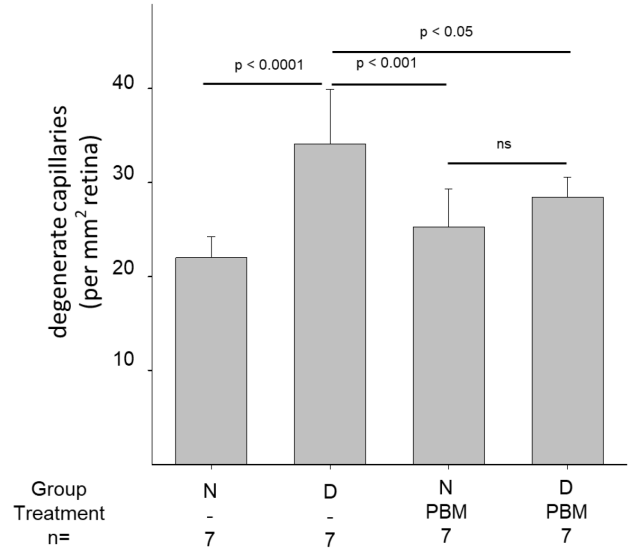


Fig 8.

These animal studies provide evidence of beneficial actions of PBM on numerous key early changes of diabetic retinopathy, and on clinically meaningful morphologic lesions of the retinopathy.

1.1.4.2 Clinical Studies in Diabetic Retinopathy

Following the promising results seen in the above-mentioned animal studies, PBM has now been evaluated in two small clinical studies of treatment for diabetic macular edema. Tang, et al. reported the results of a non-randomized, consecutive case series that evaluated PBM for non-center involving DME involving four patients with bilateral edema who were treated in one eye and the fellow eye served as the untreated control. After treatment for 160s per day (9 J/cm^2) for 2 to 9 months, thickened areas on spectral domain OCT were reduced by a mean of 20% (±11.7%) in the treated eyes and mean change in the untreated eyes was -3% (±8%).[34] Percent area of thickened retina across the macular region was determined manually on the Spectralis-generated color thickness map (Fig 9).

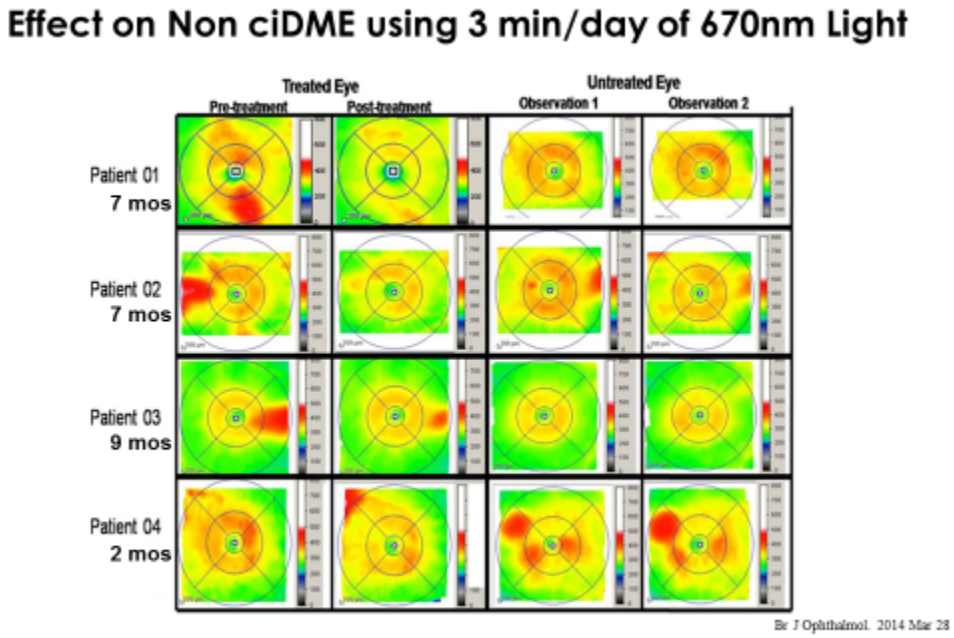


Fig 9.

Eells et al conducted a randomized prospective study in 10 patients with treatment resistant DME, randomized to either standard treatment with continued anti-VEGF alone or anti-VEGF plus PBM. Light treatment was administered at a dose of 4.5 J/cm^2 three consecutive days per week for 8 weeks using a 670 nm LED Array (WARP-10, Quantum Devices, Inc., Barneveld, WI) positioned 2.5 cm from the closed treatment eye. Functional and anatomic assessments were made at baseline, 8 weeks and 24 weeks. The authors reported a change from baseline at 24 weeks in central retinal thickness of -24±5 microns in the PBM group (N=6) and +120±97 microns in the standard treatment group (N=4). Visual acuity also improved by an average of 6±5 letters in the PBM group, compared with a 3±4 letter decrease in VA in the standard treated group. No adverse effects attributable to 670 nm PBM were noted by the patients or study investigators during the study period. Although the sample size is small, the findings show a reduction in DME and an improvement in VA following NIR-PBM. Results support the application of NIR-PBM for the treatment of DME in eyes refractory to anti-VEGF treatments. (ARVO 2017 presentation)

1.1.4.3 Clinical Studies in Dry Age-Related Macular Degeneration

A clinical study sponsored by the National Eye Institute was recently completed in Toronto under the direction of Dr. Robert Devenyi and Dr. Samuel Markowitz (LIGHTSIGHT I, Clinical Trials.gov # NCT02725762).[35] The LIGHTSITE I study enrolled 30 dry AMD subjects that were randomized (1:1) and received either 9 PBM or sham treatments with over 3-4 weeks with a second series 6 months from baseline (BL). Each treatment consisted of exposure to a combination of wavelengths of light (590 nm, 670 nm and 850 nm) administered by the LT-300 device. The total treatment regimen lasted 4 min minutes per treatment per eye. Dry AMD patients treated with PBM demonstrated both functional and anatomical improvements following PBM treatment. PBM- treated patients showed reductions in drusen volume and thickness demonstrating potential disease-modifying effects on key anatomical disease features. Improvements in Contrast Sensitivity and Visual Acuity were seen immediately after the 3 weeks of treatment and were maintained out to 3 to 6 months. PBM retreatment times of 6 months are suggested to maintain clinical outcome benefits. No device related adverse effects were seen in the study.

1.1.5 Other Blue-Green Light Modulation of Dark Adaptation

A recent Phase III clinical trial (CLEOPATRA) examined light-at-night delivered by sleep masks as a non-invasive intervention to prevent the progression of diabetic retinopathy and DME[39]. It is important to note key differences between the mechanism of action of retinal exposure to far-red (670 nm) light and retinal exposure to blue-green (505 nm) light used in the CLEOPATRA trial. Arden and colleagues showed that that blue-green (505nm) light may mitigate the complications of diabetic retinopathy by modulating the metabolic activity of the retina.[36, 37] Their studies are based on evidence that dark-adaptation exacerbates hypoxia in the diabetic retina, acting as a powerful stimulus for the overproduction of VEGF and other less well understood factors. Several small clinical trials have shown that the prevention of dark adaptation ameliorates clinical signs of diabetic retinopathy[37,38] The outcome of the CLEOPATRA trial was negative, showing that the 505nm light mask did not confer long term therapeutic benefit on non-center-involving diabetic macular edema.

A significant problem in the CLEOPATRA study was patient compliance. Although earlier studies showed short-term improvement in diabetic edema and diabetic retinopathy using 505 nm light masks, this study showed that compliance wearing the light masks during sleep is challenging and is therefore not a sustainable option. In contrast far-red light treatment is brief lasting only 90 seconds and should be less burdensome in terms of patient compliance.

1.1.6 Study Device

PBM Device

The advantages of LEDs are that they are compact, lightweight, and can be designed to produce many wavelengths and in an array of any shape. The Warp 10 device used in prior human studies is a portable handheld device that emits red colored light of 670nm at a dose of 4.5 J/cm^2 at 1 inch. The device to be used in this study has been designed by PhotoOptx, LLC (Solon, OH) specifically for trial use. It is worn as a single eye patch to maximize treatment effect. The active treatment version will emit light of 670nm at a dose of 4.5 J/cm^2 with an irradiance not greater than 50 mW/cm^2. The device includes a controller module to collect compliance data, which will be downloaded by site personnel at each visit. The device includes an auto shut off after the desired treatment time.

Sham Device

The sham device is identical, except that the light will be a blue-filtered white light at a low power. The sham device is not expected to have any anatomic effect since the energy of the light in the far red to near-infrared/far red spectrum delivered by this device will be minimal and far below the thresholds used in previous preclinical and clinical studies to generate cellular or anatomic responses in the retina.

1.2 Study Rationale

There is evidence from prior preclinical and clinical studies to suggest that PBM may have a beneficial effect on DME by inhibiting diabetes-induced oxidative stress and inflammation in the retina. PBM is a novel, non-invasive, potentially inexpensive treatment option with low treatment burden and no known side effects. This would be a major public health contribution if this non-invasive treatment is effective in treating DME and can be implemented into clinical care.

The proposed study will evaluate PBM compared with sham for eyes with CI-DME and good vision to determine whether there is a short-term effect on CST on OCT. If there is a short-term anatomic effect in these eyes, a larger study would be needed to definitively establish the safety and efficacy of this novel treatment for DME.

1.3 Study Objectives

This study is being conducted to assess the effects of PBM on CST compared with sham in eyes with central-involved DME and good vision.

Furthermore, this pilot study is being conducted to determine whether the conduct of a pivotal trial has merit based on an anatomic outcome and provide information on outcome measures needed to design a pivotal trial. This study is not designed to definitively establish the efficacy of PBM in the treatment of DME.

1.4 Potential Risks and Benefits of PBM Device

1.4.1 Known Potential Risks

PBM treatment using LEDs is simple, fast, and non-invasive. Although no adverse events have been reported thus far in the literature, the bright light can be uncomfortable and may cause a temporary reduction in the sensitivity of the eye to light, making it difficult to see and distinguish colors for a short period after the treatment is stopped (approximately 2 to 5 minutes). The participant may also experience a temporary afterimage that fades away in 2 to 5 minutes.

1.4.2 Known Potential Benefits

Previous small studies have reported improvement of DME, which could potentially result in preservation or improvement of visual acuity.

1.4.3 Risk Assessment

LED device has been deemed a non-significant risk device for treatment of eye disorders by the FDA during studies using it for treatment of laser eye injuries in military personnel. The dose of light falls well within the American National Standards Institute (ANSI) safety standards.

1.5 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP).

Details of the examination procedures are provided in study procedure manuals.

OCT technicians and visual acuity testers, including refractionists, will be masked to treatment group at outcome visits. Study participants will be masked to their treatment group assignment. Every effort will be made to keep investigators masked. Study coordinators who will be involved with training and compliance assessment will not be masked to treatment group.

Data will be directly collected in electronic case report forms, which will be considered the source data.

There is no restriction on the number of subjects to be enrolled by each site towards the overall recruitment goal.

The protocol does not meet the definition of a significant risk device study. A clinical investigation of a similar LED array device was designated a non-significant risk device study for treatment of eye disorders by the FDA. The current study device is:

- Not an implant
- Not used to support human life
- Not of substantial importance in treating disease (since there is no current standard care treatment for DME with good vision)
- Does not present potential for serious risk to the health, safety, or welfare of the subject.

Therefore, the protocol will follow the abbreviated requirements of 21 CFR 812.2(b).

CHAPTER 2: STUDY ENROLLMENT AND RANDOMIZATION

2.1 Participant Recruitment and Enrollment

A minimum of 134 eyes (one per participant) are expected to be randomized. Participants who have signed consent and started the screening process may be permitted to continue into the trial, if eligible, even if the randomization goal has been reached.

Study participants will be recruited from approximately 40 clinical centers in the United States. All eligible participants will be included without regard to gender, race, or ethnicity. There is no restriction on the number of participants to be enrolled by each site toward the overall recruitment goal.

2.1.1 Informed Consent and Authorization Procedures

Potential eligibility may be assessed as part of a routine-care examination. Before completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained.

The study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the Informed Consent Form to read. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study.

As part of the informed consent process, each participant will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review the study-specific information that will be collected and to whom that information will be disclosed. After speaking with the participant, questions will be answered about the details regarding authorization. A separate signature section will be used to collect whether or not the participant agrees to be randomly assigned to receive text message reminders (see section 3.2.1).

A participant is considered enrolled when the informed consent form has been signed. Once a study participant is randomized, that participant will be counted regardless of whether the assigned treatment is received. Thus, the investigator must not proceed to randomize an individual until he/she is convinced that the individual is eligible, will accept assignment to either of the two treatment groups, and will be compliant with device use.

2.2 Participant Inclusion Criteria

2.2.1 Patient-level Criteria

Inclusion

To be eligible for the randomized trial, the following inclusion criteria must be met:

1. Age ≥ 18 years
   - *Subjects <18 years old are not being included because DME is so rare in this age group that the diagnosis may be questionable.*
2. Diagnosis of diabetes mellitus (type 1 or type 2)
   - Any one of the following will be considered to be sufficient evidence that diabetes is present:
     - *Current regular use of insulin for the treatment of diabetes.*
     - *Current regular use of oral anti-hyperglycemia agents for the treatment of diabetes.*

- *Documented diabetes by American Diabetes Association and/or the World Health Organization criteria.*

3. At least one eye meets the study eye criteria listed in section 2.2.2.
4. Able and willing to provide informed consent.

Exclusion

A study participant is not eligible if any of the following exclusion criteria are present:

5. History of chronic renal failure requiring dialysis or kidney transplant.
6. A condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status that might preclude completion of follow-up).
7. Initiation of intensive insulin treatment (a pump or multiple daily injections) within 4 months prior to randomization or plans to do so in the next 4 months.
8. Participation in an investigational trial that involved treatment within 30 days of randomization with any drug/device that has not received regulatory approval for the indication being studied.
   - *Note: study participants cannot participant in another investigational trial that involves treatment with an investigational drug or device while participating in the study.*
9. Blood pressure > 180/110 (systolic above 180 or diastolic above 110).
   - *If blood pressure is brought below 180/110 by anti-hypertensive treatment, individual can become eligible.*
10. Systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomization.
    - *These drugs should not be used during the study.*
11. For women of child-bearing potential: pregnant or intending to become pregnant within the next 8 months.
    - *Women who are potential study participants should be questioned about the potential for pregnancy. Investigator judgment is used to determine when a pregnancy test is needed.*
12. Individual is expecting to move out of the area during the 8 months of the study.

2.2.2 Study Eye Criteria

To be eligible, the study participant must have at least one eye meeting all of the inclusion criteria and none of the exclusion criteria listed below.

A participant can have only one study eye. If a participant has two eligible eyes, the eye with the greatest central subfield will be selected as the study eye and the non-study eye will be followed to evaluate any potential contralateral effect.

The eligibility criteria for a study eye are as follows:

Inclusion

a. Best corrected E-ETDRS visual acuity letter score ≥ 79 (i.e., 20/25 or better)
b. Ophthalmoscopic evidence of central-involved DME, confirmed by CST on spectral domain OCT:

- Zeiss Cirrus: ≥290µm in women, and ≥305µm in men
- Heidelberg Spectralis: ≥305µm in women, and ≥320µm in men

c. Media clarity, pupillary dilation, and study participant cooperation sufficient for adequate OCT.

Exclusion

d. Macular edema is considered to be due to a cause other than DME.
   - *An eye should not be considered eligible if: (1) the macular edema is considered to be related to ocular surgery such as cataract extraction or (2) clinical exam and/or investigator assessment of OCT suggests that vitreoretinal interface abnormalities (e.g., a taut posterior hyaloid or epiretinal membrane) are contributing to the macular edema.*

e. An ocular condition is present such that, in the opinion of the investigator, any visual acuity loss would not improve from resolution of macular edema (e.g., foveal atrophy, pigment abnormalities, dense subfoveal hard exudates, nonretinal condition).

f. An ocular condition is present (other than DME) that, in the opinion of the investigator, might affect visual acuity during the course of the study or require intraocular treatment (e.g., vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, etc.)

g. Cataract is present that, in the opinion of the investigator, may alter visual acuity during the course of the study.

h. History of major ocular surgery (including cataract, scleral buckle, any intraocular surgery, etc.) within prior 4 months or major ocular surgery anticipated during the study period.

i. Any history of prior laser or other surgical, intravitreal, or peribulbar treatment for DME or DR (such as PRP, focal/grid macular photocoagulation, intravitreal or peribulbar corticosteroids, or anti-VEGF) within the prior 12 months.
   - *If treatment was given more than 12 months prior, no more than 4 prior intraocular injections*
   - *Enrollment will be limited to a maximum of 15% of the planned sample size with any history of anti-VEGF treatment and a maximum of 15% with any history of PRP.*

j. Anticipated need to treat DME or DR during the study period (Note: any DME treatment during the study must follow criteria in section 3.6).

k. History of topical steroid or NSAID treatment within 30 days prior to randomization.

l. History of YAG capsulotomy performed within 2 months prior to randomization

m. Any history of vitrectomy.

n. Aphakia

o. Uncontrolled glaucoma

2.2.3 Non-Study Eye

Subjects can have only one study eye. There are no eligibility or exclusion criteria with respect to the non-study eye.

2.3 Screening Evaluation

2.3.1 Historical Information

After informed consent has been signed, a potential participant will be evaluated for study eligibility through the elicitation of a medical history and performance of an ocular examination by study personnel to screen for exclusionary conditions.

Individuals who do not initially meet study eligibility requirements may be rescreened at a later date per investigator discretion.

All testing does not need to be completed on the same day provided it is within the windows specified below.

2.3.2 Screening Procedures

The following procedures are needed to confirm eligibility and/or serve as baseline measures for the randomized trial:

- If a procedure has been performed using the study technique and by study certified personnel as part of usual care, then it does not need to be repeated specifically for the study if it was performed within the defined time windows specified below.
- The testing procedures are detailed in the DRCR Retina Network procedures manuals. Visual acuity testing, ocular exam, and OCT will be performed by DRCR Retina Network certified personnel.
- OCTs meeting DRCR Retina Network criteria for manual grading will be sent to a reading center, but study participant eligibility is determined by the site (i.e., individuals deemed eligible by the investigator will be randomized without pre-randomization reading center confirmation).

1. Self-reported demographics (date of birth, sex, race and ethnicity)
2. Medical history (pre-existing medical conditions, concomitant medications, as well as ocular diseases, surgeries, and treatment)
    - Medical history will be obtained by medical charts if available at the enrolling site; otherwise, it will be self-reported
3. Electronic-ETDRS visual acuity testing at 3 meters using the Electronic Visual Acuity Tester (including protocol refraction) in study eye only *(within prior 14 days of randomization).*
4. Spectral-Domain OCT using Zeiss Cirrus or Heidelberg Spectralis in both eyes *(within prior 14 days of randomization).*
5. Ocular examination on each eye including slit lamp, measurement of intraocular pressure, lens assessment, and dilated ophthalmoscopy *(within prior 14 days of randomization)*.
6. OCT angiography on the study eye *(within prior 14 days of randomization).*
    - Only obtained by a subset of sites with OCT angiography capabilities.
7. Measurement of blood pressure.
8. Laboratory Testing- HbA1c.

- *HbA1c does not need to be repeated if available in the prior 3 months. If not available at the time of randomization, the individual may be enrolled but the test must be obtained within 3 weeks after randomization.*

2.4 Randomization of Eligible Subjects

1. Prior to randomization, the study participant's understanding of the trial, compliance with device use, willingness to accept the assigned treatment group, and commitment to the follow-up schedule will be reconfirmed.

2. Randomization is completed on the DRCR.net website.
   - Study participants will be assigned randomly (stratified by site and intravitreous treatment* in the non-study eye) with equal probability to one of two treatment groups:
     - Active treatment (670nm wavelength) device
     - Sham (broad spectrum white light) device

*Randomization will be stratified by site and recent (within 4 months) or planned intravitreous treatment in the non-study eye, including intravitreous anti-VEGF and steroid

3. For participants who consent, a second randomization will determine whether the participant will receive periodic text message reminders regarding device compliance.
   - Randomization is completed on the DRCR.net website and will be stratified by assigned treatment group.

Once a study participant is randomized, that participant will be counted regardless of whether the assigned treatment is received. Thus, the investigator must not proceed to randomize an individual until he/she is convinced that the individual is eligible and will accept whichever treatment group is assigned through randomization.

CHAPTER 3: RANDOMIZED TRIAL PROCEDURES

3.1 Study Device

3.1.1 Home Procedures

While a device is assigned, the study participant will be required to use the device twice daily (once in the morning and once before bed) for 90 seconds each. Participants will be provided with instructions to take home for proper device use and the required timing of treatments.

3.1.2 Primary Outcome Phase

Each participant will receive the type of device for home use based on their treatment group assignment (the participant will remain masked to whether the device is emitting active or sham treatment):

- Active treatment (670nm wavelength) device twice a day for 90 seconds
- Sham (broad spectrum white light) device twice a day for 90 seconds

The primary outcome phase will last until completion of the '4-month' visit, which could be up to 8 months post-randomization (see visit windows below). If the visit is not completed by 8 months, the participant will be instructed to discontinue device use, return the study device as soon as they are able, and study participation will be ended.

3.1.3 Post-Outcome Phase

At the 4-month visit, all participants will be unmasked to their treatment group assignment.

Participants originally assigned to Sham who have not already received alternative DME treatment (see section 3.6) will return the original device and have the option to receive the active treatment group device for the next 4 months.

Participants originally assigned to Active who have not received alternative treatment will return the original device and have the option to complete the remaining follow-up visits without device use.

3.1.4 Device Training

On the day of randomization, a device will be provided to the participant according to their randomized assignment. In order for investigators to remain masked, clinical site coordinators will instruct study participants regarding the proper use of the device. The eyelid must be closed for the duration of the treatment. The participant must turn the device on and it will stop automatically. The study participant will be asked to demonstrate proper use in the office, which will be considered the initial treatment. The participant will be instructed to complete the second treatment that day before bed.

3.2 Study Visits and Phone Contacts

A phone call is completed by site personnel within approximately one week of randomization (5 to 14 days) to emphasize compliance with device use and answer any questions.

Scheduled follow-up visits will occur at the following times (time from randomization unless otherwise noted):

Visit	Target Date	Target Window (around Target Date)	Allowable Window (around Target Date)
1 Month	4 weeks	± 1 week	± 2 weeks
2 Month	8 weeks	± 1 week	± 2 weeks
3 Month	12 weeks	± 1 week	± 2 weeks
4 Month/Primary Outcome Visit*	16 weeks	± 2 weeks	-4 weeks/+16 weeks
~6 Month/2-month post outcome	8 weeks after 4-Month visit	± 2 weeks	± 4 weeks
~8 Month/4-month post outcome	16 weeks after 4-Month visit	± 2 weeks	-8 weeks/+12 weeks

*Key visit

The goal will be for all participants to complete all scheduled visits. However, participants who (because of unforeseen circumstances) are unable or unwilling to return for all follow-up visits will be permitted to return for key visits only as an alternative to withdrawal from the study. Participants who are not using a device during the post-outcome phase but have not received alternative treatment will be given the option to continue study visits or end study participation early.

Additional phone contacts may be performed as needed.

3.2.1 Text Message Reminders

For participants randomly assigned to text message reminders, periodic messages will be sent by the Coordinating Center with a reminder to comply with the study device schedule.

3.3 Procedures at Study Visits

The following procedures will be performed in both groups at each visit, unless otherwise specified:

1. E-ETDRS visual acuity testing (best corrected) in each eye.
    - A protocol refraction in the study eye is required at each visit. Refraction in the non-study eye is only required at the 4 and 8 month visits. When a refraction is not performed, the most recently performed refraction is used for the testing.
2. Spectral-Domain OCT using Zeiss Cirrus or Heidelberg Spectralis in both eyes
    - The same machine type (Cirrus or Spectralis) used at baseline should be used during follow-up.
3. Ocular exam in the study eye, including slit lamp examination with lens assessment, measurement of intraocular pressure, and dilated ophthalmoscopy.
    - Required at Primary Outcome and 4-Month Post Outcome visits only. Otherwise, ocular exam is at investigator discretion. In general, an ocular exam should be completed if the OCT and/or visual acuity have worsened since baseline (e.g. more than 10% increase in CSF thickness or 5 letter loss in VA).

4. OCT angiography on the study eye if obtained at baseline (4 month/primary outcome visit only)
    - Only obtained by a subset of sites with OCT angiography capabilities.
    - *See procedure manual for more details on acquisition, including which fields to collect on a given OCT angiography system.*
5. Compliance assessment
    - The site personnel will download the compliance data and re-emphasize the importance of compliance with device use

All of the testing procedures do not need to be performed on the same day, provided that they are completed within the time window of a visit. If data from a testing procedure is unusable (ex. if OCT is ungradable), the participant may be asked to repeat the procedure during an additional visit, whether part of usual care or solely to repeat the procedure.

3.4 Early Termination Visit

Study participants who request to withdraw will be asked to have a final closeout visit at which the testing described for study visits will be performed.

3.5 Unscheduled Visits

Additional visits may occur as required for usual care of the study participant. Testing procedures at unscheduled visits are at investigator discretion. However, it is recommended that procedures that are performed should follow the standard DRCR Retina Network protocol for each procedure.

3.5.1 DME Treatment Initiation Visit

Participants for whom alternative treatment for DME is planned for the first time at an unscheduled visit (e.g. anti-VEGF or corticosteroid intravitreous injection, PRP, focal/grid laser, or vitrectomy) will be asked to complete the study procedures above before the treatment is administered. Usual care vision (e.g. Snellen charts) will be acceptable if the eye is already dilated when treatment is planned.

3.6 Alternative Treatment for CI-DME

Treatment for CI-DME must not be given unless one of the following criteria have been met or protocol chair approval is obtained:

- 1) at least 10 letter decrease in visual acuity from baseline <u>presumed to be from DME</u> at a single visit or
- 2) 5 to 9 letter decrease in visual acuity from baseline <u>presumed to be from DME</u> at two-consecutive visits at least 21 days apart.

Once criteria are met, alternative treatment is at the discretion of the investigator as part of usual care. If alternative treatment is given, study device use will be discontinued and participation in the study will be discontinued following the 4-month/primary outcome visit (or next study visit, if after 4 months).

3.7 Participant Access to Study Device at Study Closure

The study device is not commercially available and must be returned at the end of the study. Participants who withdraw from the study (or do not return for the final visit within the allowable window) will be asked to return the device as soon as possible.

CHAPTER 4: STUDY DEVICES

4.1 Description of the Investigational Device

The device to be evaluated is the PhotoOptx, LLC Retilux Eye Patch. It is worn as a single eye patch to maximize treatment effect. The active treatment version will emit light of 670nm at a dose of 4.5 J/cm^2 with an irradiance not greater than 50 mW/cm^2. The device includes a controller module to collect compliance data.

The sham version is identical, except that the light will be a broad spectrum white light at a low power.

The investigators have determined that use of the LED device in this protocol meets the criteria for the study to be classified as a non-significant risk device study as it does not meet any of the criteria from section 812.3 (m) of the FDA investigational device exemption regulation 21 CFR 812. As such an IDE is not required.

4.2 Study Device Accountability Procedures

Device accountability procedures will be detailed in the coordinator manual.

4.3 Safety Measures

The device includes an auto shut off after the desired treatment time.

CHAPTER 5: ADVERSE EVENTS, DEVICE ISSUES, AND STOPPING RULES

5.1 Adverse Events

5.1.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a study participant, irrespective of the relationship between the adverse event and the device(s) under investigation (see section 5.1.2 for reportable adverse events for this protocol)

Serious Adverse Event (SAE): Any untoward medical occurrence that:

- Results in death.
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening).
- Is a congenital anomaly or birth defect.
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).

In general, an ocular adverse event should be reported as serious (considered sight threatening) if it meets one of the following criteria:

1. It causes a decrease of $\geq$ 30 letters in visual acuity compared with the last visual acuity measurement prior to onset (e.g. central retinal artery occlusion)

2. In the opinion of the investigator, it requires prompt surgical intervention (e.g. vitrectomy, vitreous tap, intravitreous antibiotics) to prevent permanent loss of sight. Examples include endophthalmitis or rhegmatogenous retinal detachment.

Ocular adverse events that require eventual surgical intervention would not be considered serious. Ocular adverse events that do not have the potential to result in permanent loss of sight also would not be considered serious.

Unanticipated Adverse Device Effect (UADE): 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 protocol, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.3(s)).

Adverse Device Effect (ADE): Any untoward medical occurrence in a study participant which the device may have caused or to which the device may have contributed (Note that an Adverse Event Form is to be completed in addition to a Device Deficiency or Issue Form).

Device Complaints and Malfunctions: A device complication or complaint is something that happens to a device or related to device performance, whereas an adverse event happens to a

participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint.

A device malfunction is any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. (21 CFR 803.3). Note: for reporting purposes, sites will not be asked to distinguish between device complaints and malfunctions.

5.1.2 Reportable Adverse Events

For this protocol, a reportable adverse event includes any untoward medical occurrence that meets one of the following criteria:

1) An ocular adverse event in the study eye
2) A serious adverse event
3) An Adverse Device Effect as defined in section 5.1.1, unless excluded from reporting in section 5.2
4) A systemic adverse event occurring in association with a study procedure

All *reportable* Adverse Events—whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means—will be reported on an adverse event form online. Each adverse event form is reviewed by the Medical Monitor to verify the coding and the reporting that is required.

5.1.3 Relationship of Adverse Event to Study Device

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study device.

To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

<u>Yes</u>

There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon re-challenge.

<u>No</u>

Evidence exists that the adverse event has an etiology other than the study intervention (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study intervention.

5.1.4 Intensity of Adverse Event

The intensity of an adverse event will be rated on a three point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

- MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.
- MODERATE: Usually causes a low level of inconvenience or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.
- SEVERE: Interrupts a participant's usual daily activities and generally requires systemic drug therapy or other treatment.

5.1.5 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. Both the investigator's and Medical Monitor's assessments will be recorded. The Medical Monitor will have the final say in determining the causality.

Adverse events considered related to the study device that continue after the participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

5.1.6 Outcome of Adverse Event

The outcome of each reportable adverse event will be classified by the investigator as follows:

- COMPLETE RECOVERY/RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- ONGOING – An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
    - An ongoing outcome for which further improvement or worsening is possible will require follow-up by the site in order to determine the final outcome of the AE/SAE.
    - An ongoing outcome that is medically stable (further change not expected) will be documented as such and will not require additional follow-up.
    - The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.

If any reported adverse events classified as UADEs are ongoing with further improvement or worsening possible when a participant completes the study (or withdraws), the event will be followed until it is either resolved or medically stable, even after the subject has completed all applicable study visits/contacts. For all other adverse events, data collection will end at the time the participant completes the study. Note: participants should continue to receive appropriate medical care for an adverse event after their participation in the study ends.

5.2 Reportable Device Issues

All UADEs, ADEs, device complaints, and device malfunctions will be reported irrespective of whether an adverse event occurred, except in the following circumstances.

The following device issues are anticipated and will not be reported on a Device Issue Form but will reported as an Adverse Event if the criteria for AE reporting described above are met:

- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting
- Brightness of light
- Mild to moderate photo blanching or color distortion immediately following use that resolves

5.3 Pregnancy Reporting

If pregnancy occurs, device use will be discontinued immediately and participation in the study will be discontinued following the 4-month visit (or next study visit, if after 4 months). The occurrence of pregnancy will be reported on an AE Form.

5.4 Timing of Event Reporting

SAEs and UADEs must be reported to the Coordinating Center within 24 hours via completion of the online adverse event form.

The Coordinating Center will notify all participating investigators of any adverse event that is serious, related, and unexpected. Notification will be made within 10 days after the Coordinating Center becomes aware of the event.

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee.

Upon receipt of a UADE report, JCHR will investigate the UADE and if indicated, report the results of the investigation to the sites' IRBs, and the FDA within 10 working days of JCHR becoming aware of the UADE per 21CFR 812.46(b) (2). The Medical Monitor must determine if the UADE presents an unreasonable risk to participants. If so, the Medical Monitor must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than 5 working days after the Medical Monitor makes this determination and no later than 15 working days after first receipt notice of the UADE.

In the case of a device malfunction, it should be reported to JCHR by site personnel and the information will be forwarded to PhotoOptx, LLC, to be handled by their complaint management system.

5.5 Stopping Criteria

5.5.1 Participant Discontinuation of Study Device

Rules for discontinuing study device use are described below.

- The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety
- The participant requests that the treatment be stopped
- Participant pregnancy

Even if the study device system is discontinued, the participant will be encouraged to remain in the study through the 4-month primary outcome visit. Participants who are not using a device during the post-outcome phase but have not received alternative treatment will be given the option to continue study visits or end study participation early.

5.5.2 Criteria for Suspending or Stopping Overall Study

Study activities could be suspended if the manufacturer of the study device requires stoppage of device use for safety reasons (e.g. product recall). The affected study activities may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

The Data and Safety Monitoring Committee (DSMC) will be informed of any unanticipated adverse device events that occur during the study and will review compiled safety data at periodic intervals. The DSMC will request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

The study may be discontinued by the Executive Committee (with approval of the DSMC) prior to the preplanned completion of follow-up for all study participants.

5.6 Independent Safety Oversight

A DSMC will approve the protocol, template informed consent form, and substantive amendments and provide independent monitoring of adverse events. Cumulative adverse event data are tabulated semi-annually for review by the DSMC. Following each DSMC data review, a summary will be provided to IRBs. A list of specific adverse events to be reported expeditiously to the DSMC will be compiled and included as part of the DSMC Monitoring Plan document.

5.7 Risks

While no known adverse events have been reported thus far in the literature, the bright light can be uncomfortable and may cause a temporary reduction in the sensitivity of the eye to light, making it difficult to see and distinguish colors for a short period after the treatment is stopped. The participant may also experience a temporary afterimage that should fade away.

Many of the testing procedures in this study are part of daily ophthalmologic practice in the United States and pose few if any known risks.

- Dilating eye drops will be used as part of the exam. There is a small risk of inducing a narrow-angle glaucoma attack from the pupil dilation. However, all participants will have had prior pupil dilation usually on multiple occasions and therefore the risk is extremely small.

Additional risks are minor and/or infrequent and include:

- Pain, bruising, redness, or infection from baseline blood draw
- Loss of confidentiality

CHAPTER 6: MISCELLANEOUS CONSIDERATIONS

6.1 Prohibited Medications, Treatments, and Procedures

Alternative treatment for DME will not be permitted unless protocol criteria in section 3.6 are met or treatment is discussed with and approved by the Protocol Chair or Coordinating Center designee.

6.2 Treatment in Non-study Eye

Treatment of DR or DME in the non-study eye is at investigator discretion.

6.3 Diabetes Management

Diabetes management is left to the study participant's medical care provider.

6.4 Participant Compensation

Participant compensation will be specified in the informed consent form.

6.5 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. If a study participant is considering withdrawal from the study, the principal investigator should personally speak to the individual about the reasons and every effort should be made to accommodate him or her.

The goal for the study is to have as few losses to follow-up as possible. The Coordinating Center will assist in the tracking of study participants who cannot be contacted by the site. The Coordinating Center will be responsible for classifying a study participant as lost to follow-up. For participants who withdraw, their data up until the time of withdrawal will be used.

6.6 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. De-identified participant information may also be provided to research sites involved in the study.

6.6.1 Contact Information Provided to the Coordinating Center

The Coordinating Center will be provided with contact information for each study participant. Permission to obtain such information will be included in the Informed Consent Form. The contact information will be maintained in a secure database and will be maintained separately from the study data.

Phone contact from the Coordinating Center will be made with each study participant in the first month after enrollment. Additional phone contacts from the Coordinating Center will be made if necessary to facilitate the scheduling of the study participant for follow-up visits. A participant-oriented newsletter and a study logo item may be sent once. For participants randomly assigned to text message reminders, periodic messages will be sent by the Coordinating Center with a reminder to comply with the study device schedule.

824 Study participants will be provided with a summary of the study results in a newsletter format after
825 completion of the study by all study participants.

CHAPTER 7: STATISTICAL CONSIDERATIONS

7.1 Statistical and Analytical Plans

The approach to sample size calculation and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the first review of study outcome data by the Data and Safety Monitoring Committee. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan.

7.2 Statistical Hypotheses

A test of superiority will be used in evaluating the following hypotheses for the primary outcome:

Null Hypothesis (H_0): There is no difference in the mean change in CST from baseline to 4 months between photobiomodulation (PBM) and sham groups.

Alternative Hypothesis (H_a): There is a difference in the mean change in CST from baseline to 4 months between PBM and sham groups.

Similar hypothesis tests will be conducted for all secondary, exploratory, and safety outcomes.

7.3 Sample Size

7.3.1 Outcome Projections:

To estimate the standard deviation (SD) of change in OCT CST, data from the DRCR Retina Network Protocol A (Treatment for Central-Involved Diabetic Macular Edema in Eyes with Very Good Visual Acuity) was used. The Protocol A cohort of eyes with 20/25 baseline visual acuity and central subfield thickening treated with modified-ETDRS laser was used for the estimation. In protocol A, 42 eyes in the modified-ETDRS laser group completed a visit within 4 months of randomization. The SD of change in CST adjusted for baseline CST in these eyes was 50 microns (personal communication, Adam Glassman). The mean change in CST was -2 microns.

The expected change and standard deviation of CST in an untreated group is unknown at this time.

7.3.2 Sample Size Estimates

Table 1 shows total sample size estimates under several scenarios. These calculations assume a Type I error rate of 5%, 90% power, and a two-sided test of superiority (see Section 7.6) with a null hypothesis of no difference between the groups (see Section 7.2).

Table 1: Total Sample Size Under Various Assumptions for True Mean Change and Standard Deviation

Mean Treatment Group Difference, microns	Change in Central Subfield Standard Deviation, microns (adjusted for baseline)			
	40	**50**	**60**	**70**
20	172	266	382	518
30	78	120	172	232
40	46	68	98	132

Assuming an effective standard deviation of 50 microns and a true difference in mean CST of 30 microns, the required total sample size is 120 eyes to achieve 90% power. Sample size will be increased to 134 eyes to account for 10% lost to follow-up.

7.4 Outcome Measures Phase 1 (Baseline to completion of the 4-Month/Primary outcome visit)

Primary Efficacy Endpoint(s): Mean change in CST from baseline

Secondary Efficacy Endpoint(s):

- Mean change in retinal volume from baseline
- Percentage of eyes with CST below OCT machine and gender-specific threshold for DME
- Percentage of eyes receiving alternative treatment for DME*
- Percentage of eyes with a 5-letter loss in visual acuity from baseline
- Mean change in visual acuity from baseline*
- Patient compliance*

*Outcomes marked with an asterisk will include descriptive statistics only and not statistical comparisons of treatment groups

To ensure that statistical outliers do not have undue impact on analyses of continuous outcomes, change in continuous outcomes from baseline will be truncated to ± 3 standard deviations based on the overall mean and standard deviation at primary outcome visit from both treatment groups combined. Analyses to be conducted on these outcomes are detailed in Section 7.8.

7.5 Analysis Cohorts

- Intention-To-Treat (ITT) Analysis Cohort: all randomized participants irrespective of treatment received, analyzed according to treatment assignment
- Safety Analysis Cohort: all randomized participants irrespective of treatment received, analyzed according to treatment assignment

- Per-Protocol Analysis Cohort: participants who complete primary outcome visit, 70% or more of prescribed sessions of treatment, and do not receive an alternative treatment for DME

The primary analysis will follow the intention-to-treat principle. It will include all randomized participants. The data from the ITT cohort will be analyzed according to the group to which the participants were assigned through randomization, regardless of treatment actually received.

A per-protocol analysis will be performed to provide additional information regarding the magnitude of the treatment effect. The per-protocol analysis will only be performed if more than 10% of randomized participants would be excluded by these criteria. The intention-to-treat analysis is considered primary and if the results of the per-protocol analysis and intention-to-treat give inconsistent results, exploratory analyses will be performed to evaluate possible factors contributing to the differences.

7.6 Analysis of the Primary Efficacy Endpoint(s)

The primary outcome of mean change in CST on OCT is a continuous variable. The primary analysis will consist of a treatment group comparison of mean change in CST from baseline using analysis of covariance, with adjustment for baseline CST and randomization stratification factor. Eyes that receive treatment for DME (see section 3.6) will have the last OCT measurement prior to treatment used for the primary analysis. OCTs can be obtained from either Spectralis or Cirrus images. Values from these machines cannot be used interchangeably. OCT values will be converted to a common value for reporting and analyses. The estimated treatment-group difference, 95% confidence interval and 2-sided *P* value will be obtained using robust variance estimation. The assumptions of linearity, normality, and homoscedasticity will be verified using graphical methods. Serious violations may be addressed by transformation of dependent and/or independent variables, non-parametric transformation, categorizing continuous covariates, and/or excluding covariates. Transformation of the dependent variable will be used to obtain valid p-values while ensuring statistical model assumptions are met. However, mean treatment group differences, rather than results based on transformed outcomes will be reported for clinical interpretation. Change in CST will be truncated at ±3 SD to improve robustness of the treatment comparison to CST change outliers.

Markov chain Monte Carlo (MCMC) multiple imputation will be used to handle missing data for eyes not treated with an alternative DME treatment. The imputation model will be stratified by treatment group and include the CST measured at randomization visit and change in CST from baseline at all monthly interim visits up to the primary outcome visit along with the randomization stratification factor of recent or planned intravitreous treatment in the non-study eye. MCMC imputation will be used to estimate treatment group differences, 95% confidence intervals, and *P* values; observed data will be used to estimate within treatment group changes.

A sensitivity analysis including observed data from participants completing the primary outcome visit (no imputation of missing data) also will be conducted (i.e., complete-case analysis). In addition, a sensitivity analysis including observed data from participants completing the primary outcome visit within -4 weeks and +8 weeks of the target date will be conducted. Status of intravitreous treatment in the non-study eye (recent or planned versus none) will be included as a covariate because it is a randomization stratification factor. Eyes that receive an alternative treatment for DME will be handled in the same manner as in the primary analysis. If the analyses

of imputed and observed data differ substantially, then exploratory analyses will be performed to evaluated factors that may have contributed to the differences. A separate sensitivity analysis will be conducted where no data truncation on outlying values for change in CST will be performed.

7.7 Sensitivity Analysis

An additional sensitivity analysis will be performed, where OCT measurements taken after an eye receives an alternative treatment for DME will be considered as missing and will be imputed using multiple imputation stratified by treatment group. The imputation model will include an additional variable indicating whether the eye receives an alternative treatment, in addition to all variables specified in the primary imputation model.

7.8 Analysis of the Secondary Endpoint(s)

The ITT analysis cohort will be used for all secondary outcomes unless otherwise specified. Eyes that receive treatment for DME (see section 3.6) will have the last measurement prior to treatment used for the secondary analysis unless otherwise specified. Unless otherwise specified, missing data will be imputed with multiple imputation. The imputation model will be stratified by treatment group and include the baseline value of the outcome, the randomization stratification factor, and change in the outcome for the available time points.

Change in retinal volume from baseline is a continuous variable and will be analyzed using analysis of covariance. The analysis will include adjustment for baseline CST, baseline retinal volume, and the randomization stratification factor. The estimated treatment-group difference, 95% confidence interval and 2-sided *P* value will be presented. The assumptions of linearity, normality, and homoscedasticity will be verified using graphical methods. Serious violations may be addressed by transformation of dependent and/or independent variables, non-parametric methods, categorizing continuous covariates, and/or excluding covariates.

The percentage of eyes with CST below OCT machine and gender-specific threshold for DME at the primary outcome visit is a binary variable that will be analyzed with logistic regression with robust variance estimation. Baseline CST and the randomization stratification factor will be included as covariates.

The percentage of eyes receiving an alternative treatment for DME before the primary outcome visit will be reported. Only participants receiving alternative treatment or completing the primary outcome visit without receiving alternative treatment will be included. Statistical comparison between treatment groups will not be performed.

The percentages of eyes with 5-or-more-letter decrease from randomization at primary outcome visit is a binary variable that will be compared between treatment groups using logistic regression with robust variance estimation. Baseline visual acuity and randomization stratification factor will be included as covariates. The mean change in visual acuity will also be reported; however, statistical comparison between treatment groups for the mean change will not be performed.

For each logistic regression analysis, the odds ratio for the treatment group effect, 95% confidence interval, and *P* value will be presented.

7.9 Safety Analyses

All reportable adverse events will be categorized as study eye or systemic. All events will be tabulated by treatment group in a listing of each reported Medical Dictionary for Regulatory Activities (MedDRA) term and summarized over each MedDRA System Organ Class. All randomized participants will be included in safety analyses.

Since there are no known risks of the device, there are no pre-specified safety outcomes of interest. However, the frequency of each ocular adverse event occurring at least once per eye and each systemic event occurring at least once per participant will be calculated.

In addition, the following will be tabulated by treatment group:

- For each MedDRA System Organ Class, percentage of participants with at least one serious event
- Number of adverse events thought by investigator to be related to treatment

No formal statistical comparisons will be performed for reported adverse events.

7.10 Outcome Measures Phase 2 (4 Months Post-Outcome)

The following post-switch effects on DME from completion of the 4-month/primary outcome visit to the final visit will be tabulated separately within each treatment group:

- Duration of effect on DME after active treatment is stopped
    - Mean change in CST between 4-month and the final visit
    - Mean change in retinal volume between 4-month and the final visit
    - Percentage of eyes with CST below OCT machine and gender-specific threshold for DME at final visit
- Effect on DME in eyes previously receiving sham that switch to active
    - Mean change in CST between 4-month and the final visit
    - Mean change in retinal volume between 4-month and the final visit Percentage of eyes with CST below OCT machine and gender-specific threshold for DME at the final visit
- Patient compliance

For continuous outcomes, median and interquartile ranges and/or means and standard deviations will be reported to describe the data. Only participants with available CST at the primary outcome visit that did not already receive alternative DME treatment will be included. No statistical comparisons will be performed in Phase 2 to compare treatment groups.

7.11 OCT Angiography Ancillary Study

At a subset of sites with OCT angiography capabilities, images will be taken at baseline and 4 months to explore whether there are changes in any features evident on OCT angiography.

7.12 Intervention Adherence

For the primary analyses at the end of Phase 1, adherence will be defined as compliance with device use during the primary outcome phase. An exploratory dose response analysis will be

performed to evaluate whether there appears to be an association of compliance (defined as the total number of sessions of the study device use during the primary outcome phase) versus magnitude of treatment effect (defined as the change in OCT CST from baseline at primary outcome visit). The distribution of the total number of sessions will be described using summary statistics and graphical methods. A scatter plot with a regression line will be constructed to examine for evidence of dose-response, separately for each treatment group. If there is evidence of a dose-response effect in either or both groups, an analysis of covariance will be performed including treatment, compliance, and the interaction between treatment group and compliance to test for evidence that the dose-response effect is limited to the active treatment group. If the interaction between compliance and treatment group is significant, a stratified analysis will be performed to evaluate the potential association between compliance and treatment effect within each treatment group. Model assumptions will be checked, and transformation or categorization of compliance will be used if there is evidence of non-linearity in the dose response. It is recognized that the study is not powered to detect a definitive dose-response association existing only in the active treatment group and that lack of significance is not necessarily an indication that the association does not exist. It is also recognized that compliance may be affected by both measured and unmeasured post-randomization factors, including efficacy of masking and perceived effects of the treatment; hence, the observed dose-response associations may be biased.

If compliance lessens over time during the primary outcome phase, an exploratory analysis will investigate whether there appears to be any association of compliance versus magnitude of treatment effect over those months.

For Phase 2, adherence will be evaluated in a similar fashion for those using the device to assess whether compliance affects the post-switch effect within group, specifically:

- For the initial treated group, whether there is an association between compliance during phase 1 and duration of treatment effect in phase 2.
- For the initial sham group, whether there is an association between compliance during phase 2 and treatment effect in phase 2.

In addition, for each phase the effect of text message reminders will be evaluated by assessing compliance within each treatment group. Compliance will be defined as the total number of sessions of the study device use during each phase divided by the total number of possible treatment sessions. This analysis will consist of a comparison between those receiving texts and those not received texts of mean compliance using analysis of covariance, with adjustment for treatment. Only participants who have been randomly assigned to receive or not receive text messages will be included in this analysis.

7.13 Protocol Adherence and Retention

Protocol deviations and visit completion rates (excluding deaths) will be tabulated for each treatment group.

7.14 Baseline Descriptive Statistics

Baseline characteristics will be tabulated by treatment group and summary statistics appropriate to the distribution will be reported.

7.15 Device Issues

Number of reported device issues will be tabulated by treatment group.

7.16 Planned Interim Analyses

There is no formal interim analysis planned for this study. The Data and Safety Monitory Committee (DSMC) will review tabulated safety and outcome data approximately every 6 months while the study is ongoing.

7.17 Subgroup Analyses

Subgroup analyses/assessments of effect modification (interaction) will be conducted for the primary outcome. Since there is no strong prior rationale for potential subgroup effects, these analyses will be considered exploratory and hypothesis generating, rather than definitive. It is recognized that the study is not powered to detect subgroup effects and that lack of significance is not necessarily an indication that subgroup effects do not exist. Additionally, interpretation of the analyses will depend on whether the primary analysis demonstrates a significant treatment group difference; in the absence of such a difference, subgroup analyses will be interpreted with caution. The general approach for these exploratory analyses will be to add an interaction term for the subgroup factor by treatment into the primary analysis model.

Subgroup analyses will use observed data (no imputation) from participants who complete the primary outcome visit without missing CST data. Exploratory subgroup analysis will evaluate the effects of the following baseline factors:

- Prior DME treatment: yes vs. no
- Intravitreous treatment in non-study eye: recent (within 4 months) or planned
- Lens status: phakic vs. pseudophakic
- Baseline CST: continuous and categorical (dichotomized based on a clinically relevant cut point or an approximate median value)
- Hemoglobin A1c: continuous and $<7.5\%$ vs. $\geq 7.5\%$
- Iris color: blue, brown, or other

Subgroup analyses will only be conducted if there are at least 20 eyes in each subgroup for each treatment group. There are no data to suggest that the treatment effect will vary by sex or race/ethnicity. However, both of these factors will be evaluated in exploratory subgroup analyses as mandated by NIH guidelines. Subgroup factors will be analyzed as continuous/ordinal variables where possible.

7.18 Multiple Comparisons/Multiplicity

Due to the large number of outcomes evaluated, only $P < .05$ will be considered of interest and warranting further exploration. It is recognized that this does not completely control the Type I error rate. There will be no other adjustments made for multiple comparisons or multiple testing.

7.19 Additional Tabulations and Analyses

To evaluate the potential contralateral effect, visual acuity, OCT measurements, and treatment for DME in non-study eyes will be tabulated at primary outcome visit by the treatment group assigned to the study eye. These outcomes will be analyzed and presented similarly to the primary and secondary analyses as specified above for the study eyes, with the exception that no imputation will be performed for missing data.

This pilot study is being conducted to determine whether the conduct of a pivotal trial has merit based on an anatomic outcome and to provide information on outcome measures needed to design a pivotal trial. If the results of this study support proceeding with a pivotal trial after evaluation of all the data and discussion within DRCR, information from this study will contribute to designing the pivotal trial. The standard deviation of the difference in visual acuity will be used in the sample size calculation of the pivotal trial. Patient compliance (for example, the proportion of enrolled participants that are randomized and the proportion of randomized participants who comply with the use of the study device post-randomization) will also aid in the design of the pivotal trial.

CHAPTER 8: DATA COLLECTION AND MONITORING

8.1 Case Report Forms and Device Data

The main study data are collected through electronic case report forms (CRFs). Compliance data are collected via electronic device data files obtained from the study device. When data are directly collected in electronic case report forms, this will be considered the source data. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

8.2 Study Records Retention

Study documents should be retained for a minimum of 3 years following the NIH grant cycle for which the last visit was completed (expected to be December 31, 2026) or 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, whichever is later. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of JCHR, if applicable. It is the responsibility of JCHR to inform the investigator when these documents no longer need to be retained.

8.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812.

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the RBM plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of the key site data. Elements of the RBM may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Device accountability
- Communications with site staff

- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

Coordinating Center representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study.

8.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the monitoring plan.

CHAPTER 9: ETHICS/PROTECTION OF HUMAN PARTICIPANTS

9.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

9.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

9.3 Informed Consent Process

9.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their family members and their personal physicians(s) or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the JCHR and their agents. This confidentiality is extended to cover biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the JCHR.

The study monitor, other authorized representatives of the JCHR, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but

not limited to, and medical records (office, clinic, or hospital). The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Separately from any research data, the coordinating center for the study, the Jaeb Center for Health Research (JCHR) in Tampa, Florida, will be provided with participant contact information to aid in study retention efforts. Study participant's contact information will be securely stored and will be destroyed at the end of the study.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at JCHR. This will be stored separately from the participant's contact or direct identifying information. For research purposes, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by JCHR research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at JCHR.

To further protect the privacy of study participants, a Certificate of Confidentiality is available from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

9.3.3 Future Use of Stored Data

Data collected for this study will be analyzed and stored at the Jaeb Center for Health Research. After the study is completed, the de-identified, archived data will be made publicly available, for use by other researchers including those outside of the study. Permission for future use of the data will be included in the informed consent.

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