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LIGHTSITE III: 13-Month Efficacy and Safety Evaluation of Multiwavelength Photobiomodulation in Nonexudative (Dry) Age-Related Macular Degeneration Using the LumiThera Valeda Light Delivery System

Abbreviated Title: PBM Improves Clinical Outcomes in AMD

Authors: Boyer, David, MD[1]; Hu, Allen, MD[2]; Warrow, David, MD[3]; Xavier, Samantha, MD[4]; Gonzalez, Victor, MD[5]; Lad, Eleonora, MD, PhD[6]; Rosen, Richard B., MD[7]; Do, Diana, MD[8;] Schneiderman, Todd, MD[9]; Ho, Allen, MD[10]; Munk, R. Marion, MD, PhD[11]; Jaffe, Glenn, MD[12]; Tedford,Stephanie E., PhD[13]; Croissant, Cindy L., MBA[13]; Walker, Michael, PhD[14]; Rückert, Rene, MD, MBA[13]; Tedford, Clark E., PhD[13]

Affiliations:

1 Retina Vitreous Associates Medical Group, Beverly Hills, CA, USA;

2 Cumberland Valley Retina Consultants, Hagerstown, MD, USA;

3 Cumberland Valley Retina Consultants, Chambersburg, PA, USA;

4 Florida Eye Clinic, Altamonte Springs, FL, USA;

5 Valley Retina Institute, McAllen, TX, USA;

6 Department of Ophthalmology, Duke University Medical Center, Durham, NC, USA;

7 New York Ear and Eye Infirmary of Mount Sinai, New York, NY, USA;

8 Byers Eye Institute, Stanford University, Palo Alto, CA, USA;

9 Retina Center NorthWest, Silverdale, WA USA;

10 Mid Atlantic Retina, Cherry Hill, NJ, USA;

11 Department of Ophthalmology, Inselspital University Hospital Bern, Bern, Switzerland;

12 Duke Reading Center, Duke University School of Medicine, Durham, NC, USA;

13 LumiThera, Inc., Poulsbo, WA, USA;

14 Walker Biosciences, Carlsbad, CA, USA;

Corresponding Author:

Stephanie E. Tedford, PhD

Phone: (360) 536-5122

Email: Setedford@lumithera.com

Address: 19578 10th Ave NE, Poulsbo, WA 98370

Summary Statement: (50 words)

Photobiomodulation (PBM) targets mitochondrial signalling systems to improve cellular bioenergetic processes. Age-related macular degeneration (AMD) shows mitochondrial dysfunction contributing to disease pathology. Multiwavelength PBM improved clinical and anatomical outcomes in early-intermediate nonexudative (dry) AMD. PBM offers a novel treatment with a unique mechanism and mode of delivery for dry AMD.

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Informed consent: Written informed consent was obtained from all subjects in this study.

Abstract (maximum 200 words)

Purpose: The LIGHTSITE III study evaluated multiwavelength photobiomodulation (PBM) therapy in nonexudative (dry) AMD using the LumiThera Valeda® Light Delivery System.

Methods: LIGHTSITE III is a randomized, controlled trial to assess the safety and effectiveness of PBM in dry AMD. Subjects were treated with multiwavelength PBM (590, 660 and 850 nm) or Sham treatment delivered 9 treatments over 3-5 weeks every four months over 24 months. Subjects were assessed for efficacy and safety outcomes. Data from the 13-month analysis are presented in this report.

Results: A total of 100 subjects (148 eyes) with dry AMD were randomized. LIGHTSITE III met the primary efficacy BCVA endpoint with a significant difference between PBM (n = 91 eyes) and Sham (n = 54 eyes) groups (Between group difference: 2.4 letters (SE 1.15), CI: -4.7 - -0.1, p = 0.02)(PBM alone: 5.4 letters (SE 0.96), CI: 3.5 - 7.3, p < 0.0001; Sham alone: 3.0 letters (SE 1.13), CI: 0.7 - 5.2, p < 0.0001). The PBM group showed a significant decrease in new onset GA (p = 0.024, Fisher exact test, odds ratio 9.4). A favorable safety profile was observed.

Conclusions: LIGHTSITE III provides a prospective, randomized controlled trial showing improved clinical and anatomical outcomes in intermediate dry AMD following PBM.

Key Words: Photobiomodulation, multiwavelength, age related macular degeneration, mitochondria, ocular disease, vision, retina, nonexudative macular degeneration, light therapy

INTRODUCTION

Age-related macular degeneration (AMD) is a retinal disease that causes irreversible, severe loss of vision and blindness. AMD is classified into two categories: exudative (wet) and nonexudative (dry) AMD. Dry AMD affects 90% of AMD patients characterized by accumulation of extracellular material under the retinal pigment epithelium (RPE). Geographic atrophy (GA) results from atrophy of the RPE cell layer which leads to vision loss secondary to death of macular photoreceptors.[1] Global prevalence of AMD is expected to reach 288 million by 2040. In the USA, it is estimated that 18.34 million individuals (11.64%) are living with early-stage AMD and 1.49 million (0.94%) are living with late-stage AMD (choroidal neovascularization (CNV)/ neovacular AMD (nAMD) and/or GA).[2, 3] There are currently no approved treatments for dry AMD in early to intermediate-stages beyond antioxidant supplementation which only delay progression in 20%–25% of eyes.[1, 4]

Photobiomodulation (PBM) is an established biotechnology that involves light from the visible spectrum to near infrared (NIR) (500-1000 nm) applied to selected tissue to produce beneficial cellular effect.[5-8] The mechanism of PBM is ascribed to stimulation of mitochondrial respiratory chain components resulting in stabilization of metabolic function and initiation of signaling cascades promoting cellular proliferation and cytoprotection. Cytochrome C oxidase (CCO) is recognized as a key photoacceptor of light in the far red to NIR spectral range.[9-12] CCO activation enhances electron transport pathway function and promotes ATP production, the cell's major source of energy.[10, 13-16]

Collectively, studies across multiple indications show improvements in clinical and anatomical outcomes following PBM treatment. Recent ophthalmologic clinical trials including LIGHTSITE I and II evaluated the effect of multiwavelength PBM using the Valeda® light delivery system and found improvement in clinical vision outcomes and anatomical correlates of the disease.[17-19] LIGHTSITE III further investigates the effects of PBM treatment in early to intermediate dry AMD.

METHODS

Study Participants

Subjects were eligible for enrollment (NCT04065490) if they were at least 50 years of age, had a diagnosis of dry AMD defined by the presence of drusen and/or non-foveal center geographic atrophy (GA) with best-corrected visual acuity (BCVA) scores determined by Early Treatment Diabetic Retinopathy Study (ETDRS) between 50 and 75 (snellen equivalent: 20/32 to 20/100) (Supplementary Table S1, http://links.lww.com/IAE/C119). Subjects were excluded with a history of CNV, presence of center involving GA, or other significant retinal disease. Each eye was individually assessed for drusen, GA and CNV by a central reading center (Duke Reading Center, Durham, NC, USA).[19]

Subjects were enrolled across 10 centers throughout the United States. This study was conducted in compliance with the protocol, Good Clinical Practice guidelines, the guidelines of the Declaration of Helsinki and all other applicable regulatory requirements.

Study Design

LIGHTSITE III was a double-masked, randomized, sham-controlled, parallel group, multi-center prospective study. Subjects who met the inclusion criteria, had none of the exclusion criteria, and provided their informed consent underwent PBM or Sham treatment randomized in a 2:1 ratio. Subjects were treated with the Valeda® Light Delivery System (LumiThera, Inc., Poulsbo, WA, USA) and received treatment for a series of 9 sessions over a 3-5 week period. The 24-month study included 6 series of treatment delivered every 4 months. A pre-specified primary analysis was conducted at Month 13 after 4 series of treatments. Data was collected during 61 visits over

the 24-month study with a 13-month analysis (Figure 1). The study has been completed; 24-month data is under analysis.

Evaluated Parameters

Clinical classification of disease stage followed Beckman's categorization.[20] The prespecified primary endpoint was the 13-month difference in BCVA (change from baseline) between the PBM and Sham groups. A second primary endpoint was the 21-month data if the study did not achieve statistical significance at 13-months. A statistically significant difference was defined with a p-value threshold of p = 0.025 for both the primary endpoints (accounting for both possible endpoints). The ETDRS BCVA examination was employed pre-and post-treatment series. The BCVA evaluation included a thorough protocol refraction and visual acuity examination with certified equipment and examination rooms. Subjects were also assessed for low luminance BCVA (LLBCVA), Mars letter contrast sensitivity (CS), Radner reading speed, Farnsworth-Munsell D-15 dichotomous color vision testing, and completed the Visual Function Questionnaire-25 (VFQ-25) at selected timepoints. Certifications for clinical outcomes were performed by specialists (Global Eye Trials, London, UK). Subjects were assessed with 20 x 20 mm high-speed SD-optical coherence tomography (OCT) volume scans, fundus autofluorescence (FAF) and fundus photo imaging (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) as described previously.[17, 19] An independent, masked imaging center reviewed and graded all images. Safety information was collected at all timepoints through the Month 13 visit.

Photobiomodulation treatment with Valeda Light Delivery system

Subjects were treated with Valeda using three distinct wavelengths in the yellow (590 nm; 4 mW/cm^2; 2x 35s), red (660 nm; 65 mW/cm^2; 2x 90s), and NIR (850 nm; 0.6 mW/cm^2; 2x 90s) range. A complete masked control is not possible (i.e., a true Sham would deliver zero light fluence which would be observable to patients and study staff). Therefore, the Sham treatment consisted of an active control which delivered a lower fluence of selected wavelengths. The Sham mode delivered a 50x and 100x reduction in treatment fluence compared with the PBM mode of the 590 and 660 nm wavelengths, respectively; the 850 nm wavelength was omitted.

Statistical Analysis

Statistical analyses were performed using SAS or R version 3.4.4 (SAS Institute, Cary, North Carolina, USA).[21] Based on previous studies, a within group standard deviation (SD) of 5.0 in BCVA change from baseline was assumed. A total of 119 eyes (40 sham, 79 PBM) completing the study provided power of 0.84 to detect a difference of 3.18 between groups in BCVA with a two-sided alpha of 0.025. Allowing for a 10.0% dropout, assuming an average of 1.5 eligible eyes per subject, and potentially smaller effect size and larger SD, a sample size of at least 96 subjects, giving 144 eyes, was planned.

All analyses are based on individual eyes, rather than subjects, unless otherwise indicated. All subjects enrolled (n = 144 eyes) and modified intent-to-treat (n = 142 eyes) analyses were conducted across outcomes and study timepoints. Non-study eye analyses included companion eyes that were not enrolled in the study and did not receive treatment. Analyses of change from baseline following treatment and the treatment effect on the change

from baseline used linear mixed effects models that account for correlation between eyes within subject. Efficacy analyses were implemented using (i) the measured value of each outcome and (ii) the rank value of each outcome. For each efficacy analysis, the model residuals from the measured values were examined using the Anderson-Darling test for normality. If the residuals were not normally distributed ($p < 0.05$), the analysis using the rank values was considered the principal analysis, with the measured values analysis considered to be a sensitivity analysis.

RESULTS

Participants

A total of 178 subjects were screened for the study with 100 subjects (56.2%) eligible for randomization. At Month 13, a total of 17 subjects discontinued the study (9 PBM; 8 Sham): 10 withdrew consent, 3 were unable to return to the facility and 4 discontinued due to adverse events (AEs) not considered related to the treatment (Figure 2). Baseline characteristics are provided in Table 1. Subjects were enrolled with Baseline BCVA scores between 50 and 75 letters. At Baseline, 45/148 eyes (30.0%) had baseline BCVA < 70 letters (20/100 to 20/40 Snellen) and 103/148 eyes (70.0%) have a baseline BCVA between 70 and 75 letters (20/40 to 20/32 Snellen). AREDs category and clinical classification of subjects in the MITT group showed a majority enrolled in an AREDS 3 category (86.9%) and classification of intermediate AMD (72.0%). A total of 13.1% (n = 19) of subjects were AREDS category 2 and 86.9% (n = 126) were AREDS category 3. A total of 20.0% (n = 29) of subjects were categorized as early-stage AMD, 72.0% (n = 105) were intermediate-stage AMD, and 8.0% (n = 11) were late-stage AMD (GA, no CNV).

Efficacy Assessments

At Month 13 (4 series of treatment), the average change from Baseline in BCVA was an increase of 5.4 letters (SE 0.96; SD 9.15) in PBM and 3.0 letters (SE 1.13; SD 8.30) in Sham-treated eyes. The BCVA change from Baseline to Month 13 was not normally distributed (Anderson-Darling p-value = 0.04), therefore, the rank analysis was considered the principal analysis, giving the

rank p-value of 0.0204 for the primary analysis comparing PBM and Sham groups at Month 13 (Table 2; Figure 3). Approximately 55.0% of PBM eyes showed ≥ 5 letter gain compared to 40.8% of Sham, 26.4% of PBM eyes showed ≥ 10 letter gain compared to 14.9% of Sham, and 5.5% of PBM eyes showed ≥ 15 letter gain compared to 1.9% of Sham. Sham-treated eyes showed a two-fold decrease in BCVA letter count and an increased number of eyes with a letter loss ≥ 10 at each visit compared to PBM-treated eyes. A significant difference in BCVA between PBM and Sham groups was also observed at Months 5, 9 and 12. A significant difference in PBM-treated subjects was observed within the group at all time points assessed ($p < 0.05$) (Table 2; Figure 4).

Secondary and exploratory evaluation of LLBCVA, CS, Radner reading charts, and the VFQ-25 showed normal or near normal visual outcomes at baseline which were stable through the 13-month timepoint in both groups (Supplementary Table S2).

Anatomical Outcomes

A total of 138 eyes were enrolled with drusen at baseline (PBM, n = 86; Sham, n = 52). No change in subRPE macular drusen volume was seen in PBM-treated eyes (0.006 mm^3), however, an increase was seen in the Sham group (0.049 mm^3) (Figure 5). At Month 13, a statistically significant correlation was observed for measured BCVA scores and measured macular drusen volume in PBM-treated eyes. Subjects with higher BCVA scores showed lower values for macular drusen volume in the PBM group ($p = 0.004$). Representative images are presented in Figures 6-7.

Development of advanced AMD

A very small number of eyes presented with non-center involving GA at baseline (PBM, n = 6; Sham, n = 5). Using FAF analysis, a numerical trend showed an increase in GA lesion area in Sham (1.48, SE 0.94; SD 1.62) compared to PBM-treated eyes (1.16, SE 0.66; SD 1.32, p = 0.75) eyes at Month 13 (change from Baseline) (Table 2; Figure 5). The occurrence of new GA over the course of 13 Months was observed in 6 additional eyes. A total of 10.0% (n = 5/50) of new onset GA was seen in Sham and 1.1% (n = 1/87) were seen in PBM groups. The occurrence of new GA was significantly higher in the Sham vs. PBM group (p = 0.024, Fisher exact test, odds ratio 9.4) (Table 2; Figure 5).

A total of 1 Sham eye (1.8%), 5 PBM eyes (5.4%) and 3 non-study eyes (8.3%) converted to nAMD by Month 13. A total of 16 subjects were randomized with one non-study eye that had nAMD. Of the 16 eyes with the non-study companion eye with nAMD, 12/16 (75.0%) were in the PBM group providing a higher risk proportion for conversion to nAMD. The single Sham eye that converted was at high risk and 4/5 (80.0%) of the PBM-treated eyes were high risk eyes.

Safety and Compliance Outcomes

A total of 33 study eyes (22.3%) presented with at least one ocular-specific AE. Four ocular-specific AEs were considered related to the treatment (none led to study discontinuation and

were mild or moderate in intensity). Only 1 ocular-specific SAE was reported and was not considered related to the treatment. No ocular-specific AE was reported at a frequency of over 5%. A total of 3 device-related AEs were reported. All device-related AEs were Dry Eye and considered possibly or probably related to the device. A total of 3 subjects had non-ocular SAEs that resulted in death. All SAEs were considered not related to the treatment (Table 3). No significant changes were observed in perimetry or color vision assessment. The majority of subjects were compliant with all treatment visits. At Month 13, 88.2% of eyes receiving PBM and 74.5% of eyes receiving Sham treatment were fully compliant with the treatment protocol.

DISCUSSION

The current report provides details the 13-month analysis of the LIGHTSITE III 24-month study. The study met the predetermined primary efficacy endpoint with a statistically significant difference in BCVA between the PBM vs. Sham treatment groups. A mean letter gain $\geq$ 5 letters was observed following PBM. Furthermore, 55.0% of PBM-treated eyes showed $\geq$ 5 letter gain and 26.4% showed $\geq$ 10 letter gain. A total of 92.0% of eyes were categorized as early/intermediate dry AMD and showed limited visual impairment at study enrollment. BCVA letter scores of 60 to 70 letters (Snellen 20/40 to 20/64) are considered mild vision loss/near-normal vision and 40-60 letters (Snellen 20/64 to 20/160) considered moderate visual impairment, or moderate low vision. The majority of eyes enrolled in this study had an initial BCVA letter score consistent with very mild or near-normal vision.[20, 22] Earlier stage dry AMD patients with better vision are not capable of large magnitude gains as seen in later stage patients with worse BCVA. Subjects that were enrolled had good vision with 70.0% of eyes showing a Baseline BCVA of 70-75 letters (20/40 to 20/32 Snellen) which made these improvements in BCVA more noteworthy. Stabilization of BCVA, i.e., a reduction in further decline, is also of critical consideration in degenerative disease. Treatment with PBM showed a reduction in the number of treated eyes that lost BCVA letters in the treated study eye. The non-study eye subgroup with good vision (> 75 letters) further documents the loss of BCVA over time with a 2.3 letter loss. This BCVA letter loss per year is consistent with natural history studies of earlier/intermediate dry AMD.[23]

A loss of 2-3 ETDRS letters per year in intermediate dry AMD has been shown to increase to > 5 letters per year, followed by development of GA and irrevisible loss of viable retinal tissue.[23, 24] This decline in vision impacts on patient independence and quality of life. Clinical outcomes such as CS, color vision, VFQ-25 and reading speed are also of interest to provide a well-rounded assessment of visual function. Secondary outcomes included these measures and showed normal to near normal vision scores at baseline. These values did not allow sufficient room to determine beneficial effect, however, no decreases in outcome scores were observed supporting safety of PBM and potential to prevent progressive decline in visual function. However, central fovea mediated improvements in BCVA were statistically significant with a mean increase of nearly two lines in 55.0% of PBM-treated eyes demonstrating high impact of PBM effect on BCVA in early/intermediate dry AMD subjects with better vision.

Drusen, a hallmark pathology for AMD, provides a risk factor for the development of inflammation, ischemia and further complications of AMD. Previous studies show progression rates to advanced AMD (CNV and GA over 5 years) of 1.3% with many small or few medium drusen, 18% if many medium or any large drusen and 43% if unilateral advanced AMD is present.[25, 26] Higher frequency and larger drusen deposits are indicative of disease progression. Pegcetacoplan is the only approved treatment for GA having recently received FDA-approval indicated for GA secondary to AMD. The Pegcetacoplan studies show slowing of GA lesion progression with no impact on other clinical outcomes such as BCVA.[27, 28] Anatomical markers such as GA and drusen represent appealing treatment targets in AMD. After GA onset, central GA is observed at 2.5 years accompanied by a BCVA loss of 3.7 letters; a 22 letter loss is expected at 5 years.[29] The current study showed the occurrence of new GA in 9.8% of Sham eyes and 1.1% of PBM-treated eyes, demonstrating a statistically significant reduction in new onset

GA in the PBM group. A numerical trend showed an increase in GA lesion area in Sham compared to PBM-treated eyes. No macular drusen volume increase was observed in PBM-treated eyes whereas the volume showed trends for increase over time in Sham-treated eyes. These effects support the potential disease-modifying effects of PBM on dry AMD pathology. Slowing of drusen and/or GA lesion growth or progression should be recognized as important to delay disease progression, and any improvement in vision or visual stabilization should be considered clinically important. Recently (2022), a retrospective observational case series published by Le et. al. assessed the impact of multiwavelength PBM using Valeda in subjects with reticular pseudodrusen (RPD). PBM treatment showed stabilization of RPD and reductions in stage 2 and 3 RPD following PBM. No progression of RPD into greater stages was observed.[18]

PBM was well tolerated, with a favorable safety and compliance profile. Compliance rates for both PBM and Sham groups were high throughout each treatment series with a higher rate noted in the PBM group. Similar to previous clinical PBM studies, subjects showed a positive benefit-risk profile with high subject compliance rates and a low rate of AEs.[17, 19, 30]

Study limitations include masking of the study. A Sham arm was included to ensure masking and emitted a reduced light dose compared to the PBM mode. A 50-100x reduction in light fluency parameters was assumed to provide a significant reduction in the biological effect being studied. While reduced, these wavelengths still produce a treatment that is visible to the eye and activates photoacceptors, thus could be anticipated to activate CCO and other cellular targets that may produce a small biologic effect. The Sham arm in this study could therefore be considered an active control arm which also showed moderate improvements in BCVA that were inferior to the full PBM active dose. In support for this limitation, non-study eyes with no other

ocular variable and good vision (> 75 letters at Baseline) lost 2.3 letters at Month 13. This loss is consistant with published literature in intermediate dry AMD studies.[23] Change from Baseline within groups provides a secondary measure of improvements in BCVA letter score following PBM or Sham treatments over time and confirmed the BCVA improvements. These Sham effects are consistent with prior reports from the LIGHTSITE I and II studies which used the same fluency doses.[17, 19] The study required extensive visits from subjects (i.e., 40 visits over 13-months). Regardless of this burden, subject compliance was 100% in the majority of subjects (PBM: 88.2%; Sham: 74.5%). While study visits were extensive (and took place during the COVID-19 pandemic), treatment visits were < 5 minutes per eye and subjects were motivated to attend.

The LIGHTSITE III 13-month analysis evaluating multiwavelength PBM in subjects with early-intermediate stage dry AMD showed statistically significant improvements in BCVA across time points collected during the first four treatment series. Improvements in clinical and anatomical endpoints following PBM treatment suggest disease modifying effects. Safety data shows a strong profile with AEs consistent with the patient population and no signs of phototoxicity. Multiwavelength PBM therapy may offer a new treatment strategy with a unique mechanism and modality for subjects with dry AMD. Additonal data will be reported on the 24-month outcomes in a secondary report.

REFERENCES

1. Fernandes AR, Zielińska A, Sanchez-Lopez E, et al. Exudative versus Nonexudative Age-Related Macular Degeneration: Physiopathology and Treatment Options. Int J Mol Sci 2022;23(5).

2. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health 2014;2(2):e106-16.

3. Pennington KL, DeAngelis MM. Epidemiology of age-related macular degeneration (AMD): associations with cardiovascular disease phenotypes and lipid factors. Eye Vis (Lond) 2016;3:34.

4. Evans J. Antioxidant supplements to prevent or slow down the progression of AMD: a systematic review and meta-analysis. Eye (Lond) 2008;22(6):751-60.

5. Chung H, Dai T, Sharma SK, et al. The Nuts and Bolts of Low-level Laser (Light) Therapy. Ann Biomed Eng 2011.

6. Hashmi JT, Huang YY, Osmani BZ, et al. Role of low-level laser therapy in neurorehabilitation. PM R 2010;2(12 Suppl 2):S292-S305.

7. Tata DB, Waynant RW. Laser Therapy: A review of its mechanism of action and potential medical applications. Laser and Photonics Reviews 2010;5(1):1-12.

8. Rojas JC, Gonzalaz-Lima F. Low level light therapy of the eye and brain. Dovepress 2011;2011(3):49-67.

9. Grossman N, Schneid N, Reuveni H, et al. 780 nm low power diode laser irradiation stimulates proliferation of keratinocyte cultures: involvement of reactive oxygen species. Lasers Surg Med 1998;22(4):212-8.

10. Karu T, Pyatibrat L, Kalendo G. Irradiation with He-Ne laser increases ATP level in cells cultivated in vitro. J Photochem Photobiol B 1995;27(3):219-23.

11. Karu TI, Kolyakov SF. Exact action spectra for cellular responses relevant to phototherapy. Photomed Laser Surg 2005;23(4):355-61.

12. Wong-Riley MT, Liang HL, Eells JT, et al. Photobiomodulation directly benefits primary neurons functionally inactivated by toxins: role of cytochrome c oxidase. J Biol Chem 2005;280(6):4761-71.

13. Oron U, Ilic S, De TL, Streeter J. Ga-As (808 nm) laser irradiation enhances ATP production in human neuronal cells in culture. Photomed Laser Surg 2007;25(3):180-2.

14. Silveira PC, Silva LA, Fraga DB, et al. Evaluation of mitochondrial respiratory chain activity in muscle healing by low-level laser therapy. J Photochem Photobiol B 2009;95(2):89-92.

15. Passarella S, Casamassima E, Molinari S, et al. Increase of proton electrochemical potential and ATP synthesis in rat liver mitochondria irradiated in vitro by helium-neon laser. FEBS Lett 1984;175(1):95-9.

16. Mochizuki-Oda N, Kataoka Y, Cui Y, et al. Effects of near-infra-red laser irradiation on adenosine triphosphate and adenosine diphosphate contents of rat brain tissue. Neurosci Lett 2002;323(3):207-10.

17. Burton B, Parodi MB, Jürgens I, et al. LIGHTSITE II Randomized Multicenter Trial: Evaluation of Multiwavelength Photobiomodulation in Non-exudative Age-Related Macular Degeneration. Ophthalmology and Therapy 2023.

18. Le HM, Mehanna CJ, De Rosa I, et al. Effects of Photobiomodulation in Patients Presenting with Reticular Pseudodrusen: A Retrospective Observational Case Series Study. Medicina (Kaunas) 2022;58(11).

19. Markowitz SN, Devenyi RG, Munk MR, et al. A DOUBLE-MASKED, RANDOMIZED, SHAM-CONTROLLED, SINGLE-CENTER STUDY WITH PHOTOBIOMODULATION FOR THE TREATMENT OF DRY AGE-RELATED MACULAR DEGENERATION. Retina 2020;40(8):1471-82.

20. Ferris FL, 3rd, Wilkinson CP, Bird A, et al. Clinical classification of age-related macular degeneration. Ophthalmology 2013;120(4):844-51.

21. 2.33 RCTR. A language and environment for statistical computing. R Foundation for Statistical Computing 2022; Vienna, Austria.

22. Low Vision and Legal Blindness Terms and Descriptions. American Foundation for the Blind 2023.

23. Thompson AC, Luhmann UFO, Stinnett SS, et al. Association of Low Luminance Questionnaire With Objective Functional Measures in Early and Intermediate Age-Related Macular Degeneration. Invest Ophthalmol Vis Sci 2018;59(1):289-97.

24. Holekamp N, Wykoff CC, Schmitz-Valckenberg S, et al. Natural History of Geographic Atrophy Secondary to Age-Related Macular Degeneration: Results from the Prospective Proxima A and B Clinical Trials. Ophthalmology 2020;127(6):769-83.

25. Chew EY, Clemons TE, Agrón E, et al. Ten-year follow-up of age-related macular degeneration in the age-related eye disease study: AREDS report no. 36. JAMA Ophthalmol 2014;132(3):272-7.

26. Joachim N, Mitchell P, Burlutsky G, et al. The Incidence and Progression of Age-Related Macular Degeneration over 15 Years: The Blue Mountains Eye Study. Ophthalmology 2015;122(12):2482-9.

27. Apellis Announces Top-Line Results from Phase 3 DERBY and OAKS Studies in Geographic Atrophy (GA) and Plans to Submit NDA to FDA in the First Half of 2022.

28. Holz FG, Sadda SR, Busbee B, et al. Efficacy and Safety of Lampalizumab for Geographic Atrophy Due to Age-Related Macular Degeneration: Chroma and Spectri Phase 3 Randomized Clinical Trials. JAMA Ophthalmol 2018;136(6):666-77.

29. Lindblad AS, Lloyd PC, Clemons TE, et al. Change in area of geographic atrophy in the Age-Related Eye Disease Study: AREDS report number 26. Arch Ophthalmol 2009;127(9):1168-74.

30. Kim JE, Glassman AR, Josic K, et al. A Randomized Trial of Photobiomodulation Therapy for Center-Involved Diabetic Macular Edema with Good Visual Acuity (Protocol AE). Ophthalmol Retina 2021.

FIGURE LEGENDS

Figure 1. LIGHTSITE III Study Design. Subjects were randomized in a 2:1 fashion (PBM: Sham treatment) and followed for 24 Months. Data analyses were planned for Month 13 and Month 24. The PBM mode delivered 590, 660 and 850 nm multiwavelength treatment. The Sham mode delivered a 50x reduction of the 590 nm and a 100x reduction of the 660 nm wavelengths; the 850 nm was omitted. *BCVA, best-corrected visual acuity; BL, baseline; M, month; PBM, photobiomodulation; R, randomized; Tx, treatmemt.*

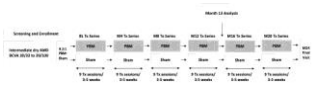


Figure 2. Diagram of LIGHTSITE III Subject Enrollment. A total of 100 subjects and 148 eyes were enrolled into the study.

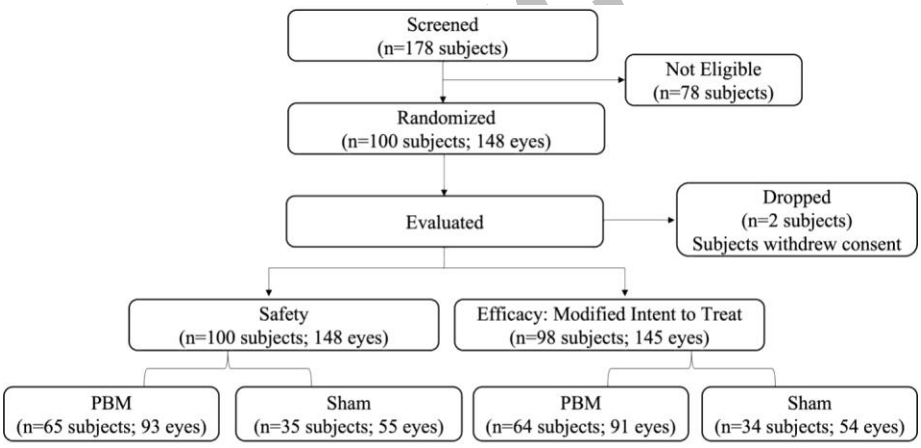


Figure 3. Photobiomodulation Improves BCVA in Early to Intermediate Stage Dry AMD.

A. Subjects received PBM or Sham treatment at Baseline, Month 4, Month 8 and Month 12 timepoints. Significant improvements in BCVA were observed through Month 13 following PBM treatment. B. At Month 13, Non-study eyes showed a mean letter loss of 2.3 letters, Sham-treated eyes showed a mean letter gain of 3.0 letters and PBM-treated eyes showed a mean letter gain of 5.4 letters. * *within group (PBM) comparison, p < 0.005, ^ PBM vs Sham between group comparison, p < 0.05. BCVA, best-corrected visual acuity; BL, baseline; M, month; PBM, photobiomodulation.*

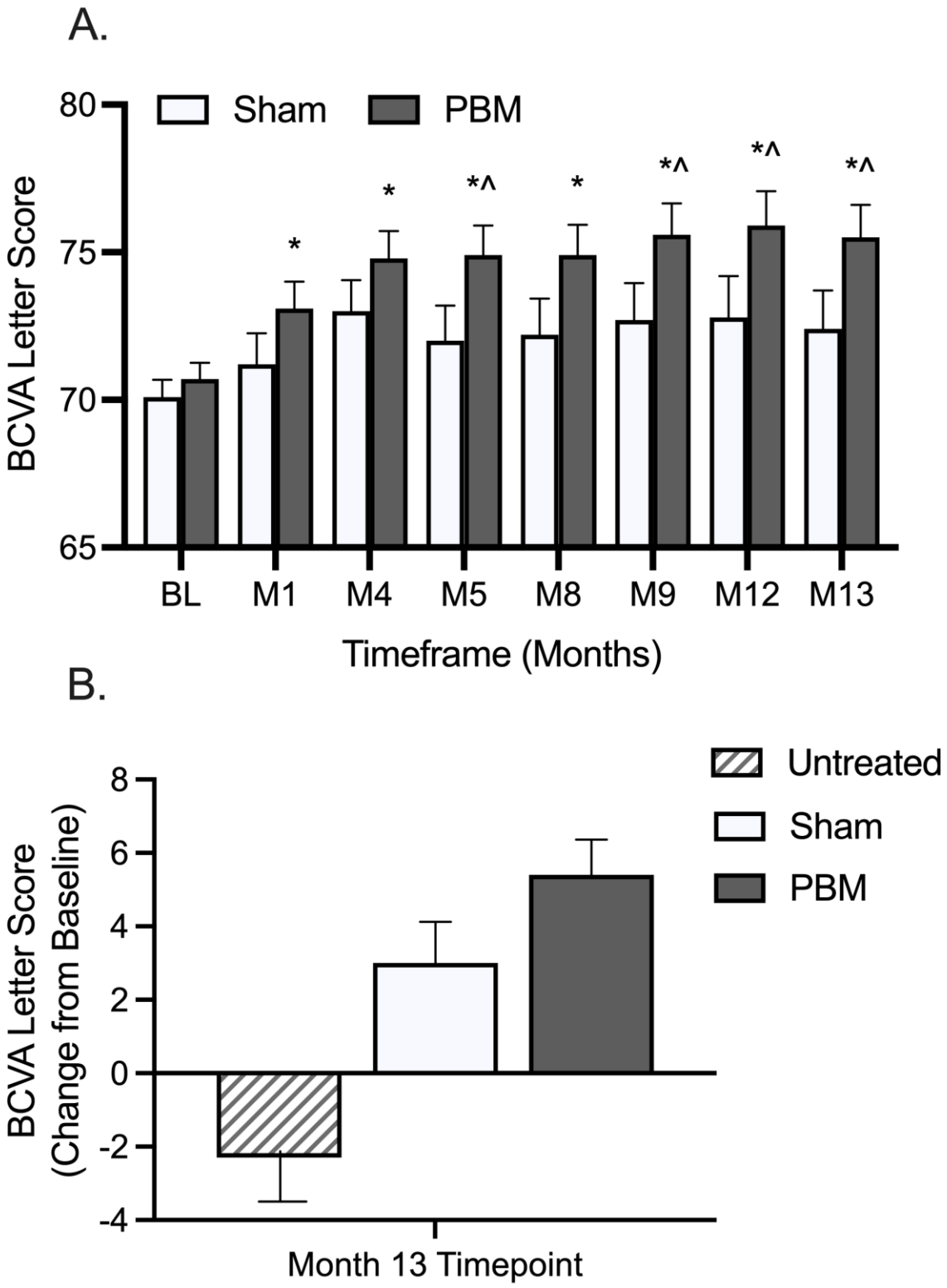


Figure 4. Distribution of BCVA Letter Gain and Loss by Group at Month 13. A. Approximately 55.0% of PBM-treated eyes showed ≥ 5 letter gain (mean of 9.7 letters, SD 3.7) compared to 40.8% of Sham, 26.4% of PBM-treated eyes showed ≥ 10 letter gain (mean of 12.8 letters, SD 2.7) compared to 14.9% of Sham, and 5.5% of PBM eyes showed ≥ 15 letter gain compared to 1.9% of Sham. B. A higher number of Sham-treated and Non-study eyes showed BCVA letter losses compared to PBM as noted in the -11 to -15, -6 to -10, and -1 to -5 letter loss groups. A higher number of PBM-treated eyes showed BCVA letter gains in the 5-9, 10-14, 15-19 and ≥ 20 letter gain groups. ** Patient had vision loss due to worsening of posterior capsule opacity. BCVA, best-corrected visual acuity; BL, baseline; PBM, photobiomodulation.*

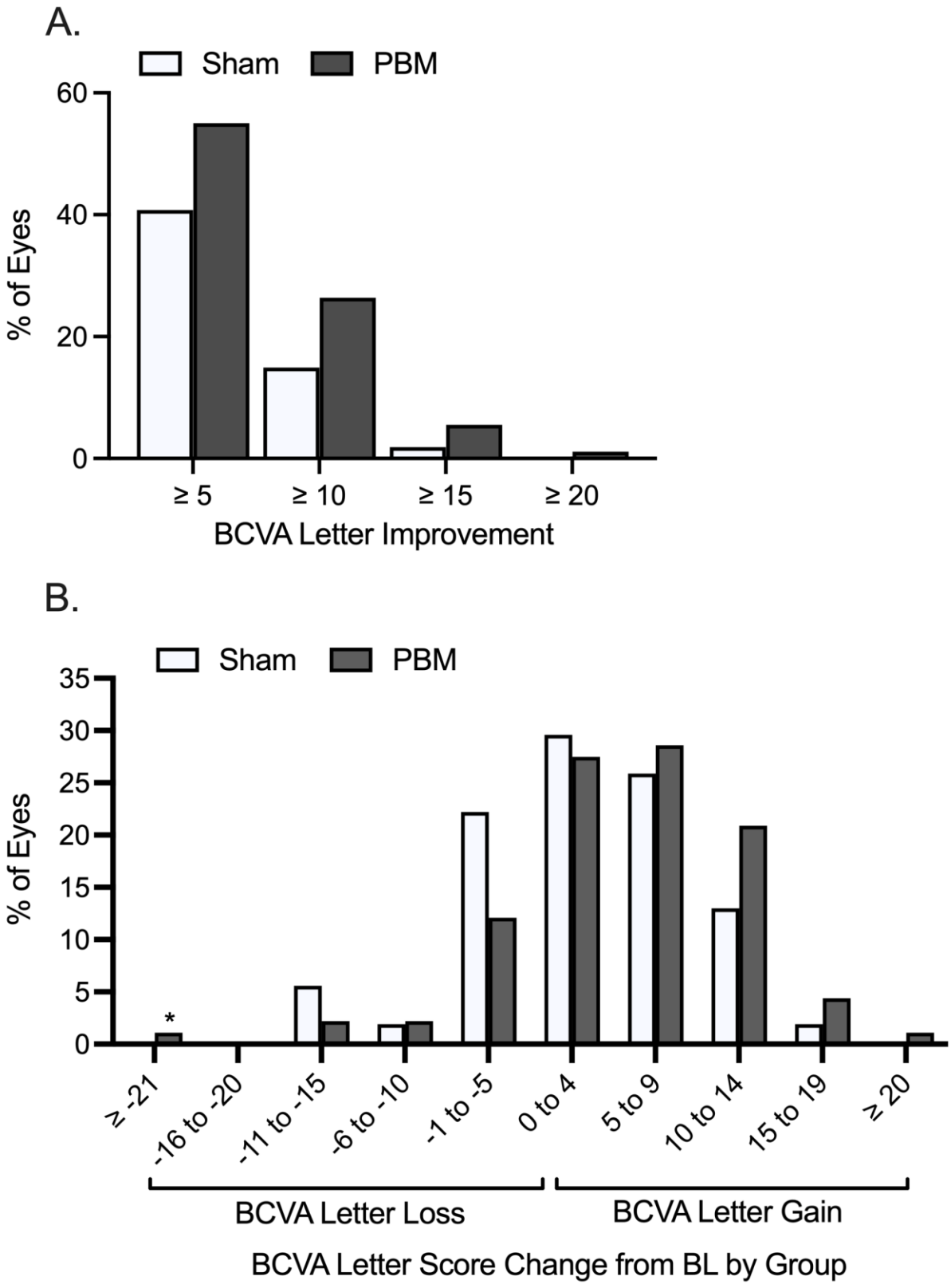
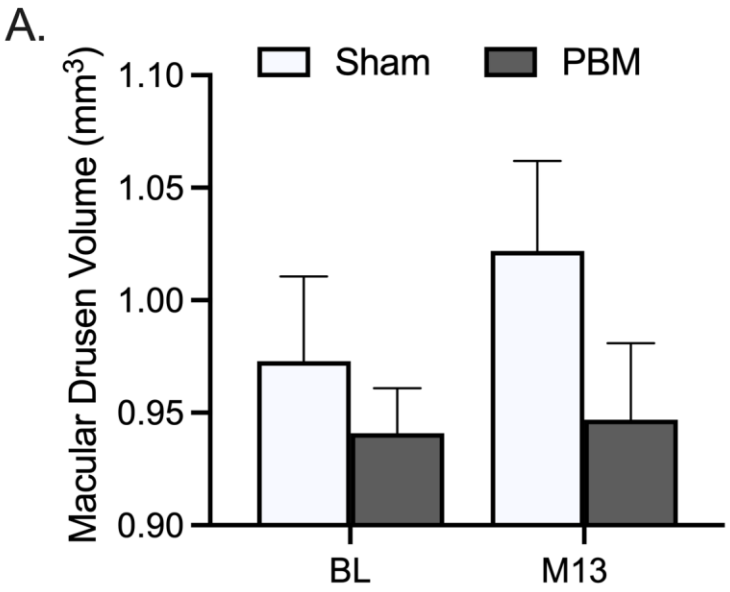
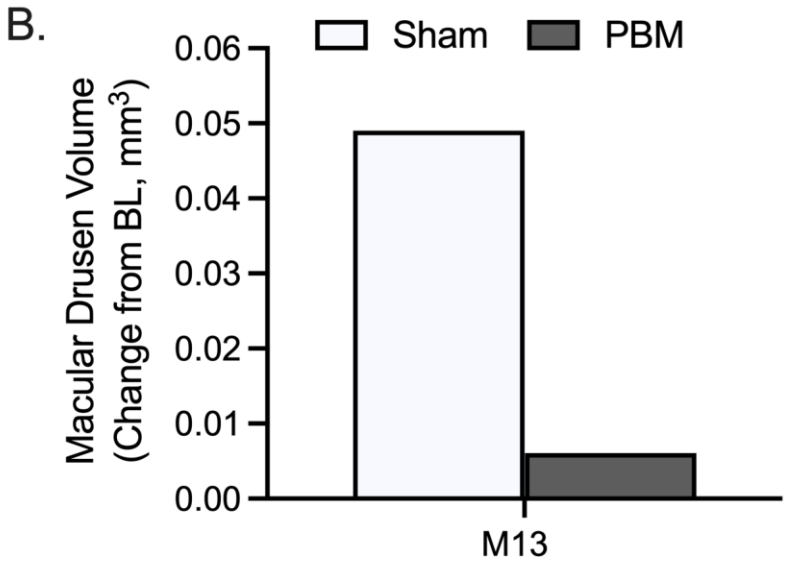


Figure 5. Impact of Photobiomodulation on Anatomical Outcomes. A. A numerical increase in macular drusen volume was observed in Sham-treated eyes, ns, $p > 0.05$. B. Macular drusen volume increased 0.049 mm^3 in Sham-treated eyes and 0.006 mm^3 in PBM-treated eyes. The ocurrence of new GA was observed in 5/51 (9.8%) of Sham-treated eyes and 1 of 88 (1.1%) of PBM-treated eyes. C. The occurrence of new GA in eyes with intermediate dry AMD was significantly higher in the Sham group than in the PBM group ($p = 0.025$, Fisher exact test, odds ratio 9.3). *BL, baseline; GA, geographic atrophy; M, month; ns, non-significant.*





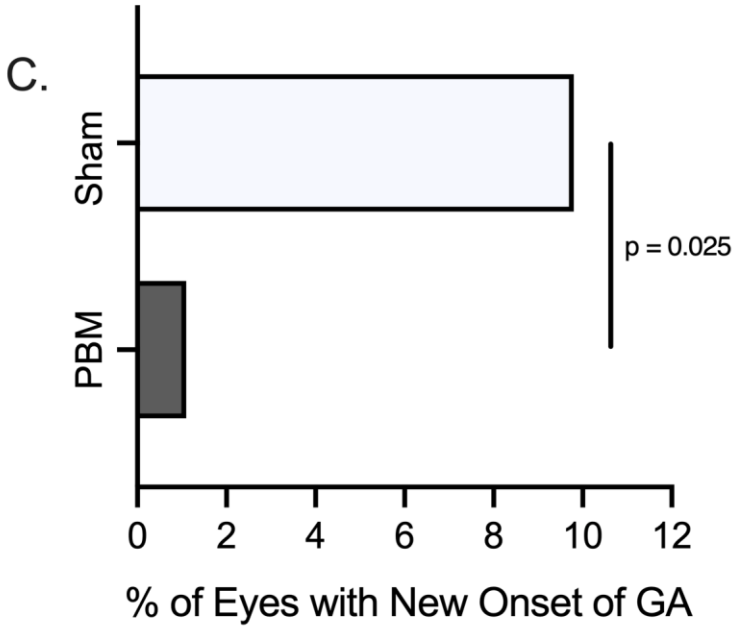


Figure 6. Representative Imaging of Macular Drusen Reduction Following Photobiomodulation Treatment. A significant reduction in macular drusen volume was observed following four series of PBM treatment without loss of photoreceptor or retinal pigment epithelium visible. A 4-letter increase in BCVA was observed from 75 letters to 79 letters at Month 13. *PBM, photobiomodulation.*

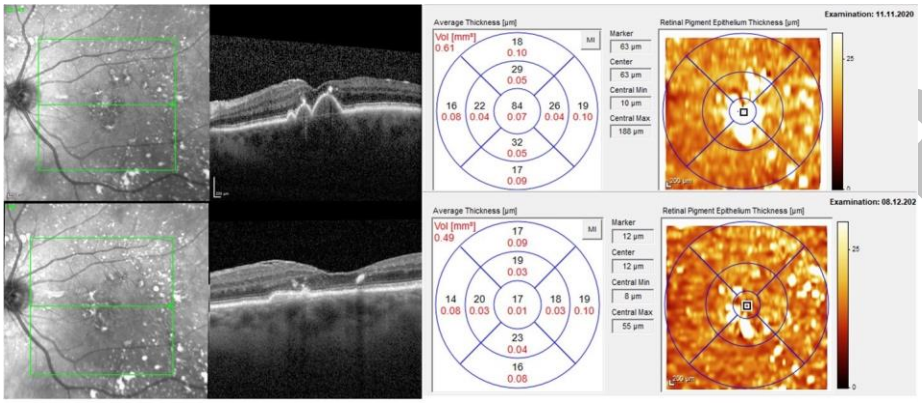
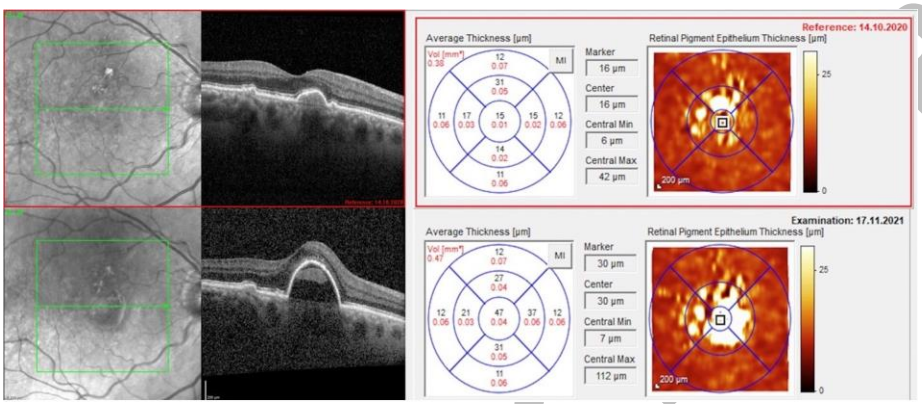


Figure 7. Representative Imaging of Macular Drusen Increase Following Sham Treatment.

A significant increase in macular drusen volume was observed following four series of Sham treatment with confluent drusen that further developed into large retinal pigment epithelial detachments. A 3-letter decrease in BCVA was observed from 72 letters to 69 letters at Month 13. The subject subsequently converted to nAMD.



Supplementary Tables

Table S1. Inclusion/ Exclusion Criteria

Table S2. Other Clinical Outcomes at Month 13

Variable	PBM (N = 65) n (%)	Sham (N = 35) n (%)	Total (N = 100) n (%)
Age (years)			
Mean (SD)	74.4 (7.3)	77.1 (6.2)	75.4 (7.1)
Min - Max	53 - 91	66 - 88	53 - 91
Gender			
Female	46 (70.8)	22 (62.9)	68 (68.0)
Male	19 (29.2)	13 (37.1)	32 (32.0)
Ethnicity			
Hispanic or Latino	3 (4.6)	3 (8.6)	6 (6.0)

Not Hispanic or Latino	62 (95.4)	32 (91.4)	94 (94.0)
Race			
Black or African American	0 (0.0)	1 (2.9)	1 (1.0)
White	65 (100)	34 (97.1)	99 (99.0)
AREDS Supplementation			
Yes	57 (87.6)	29 (82.8)	86 (86.0)
No	8 (12.3)	6 (17.2)	14 (14.0)
Eye Color			
Blue	24 (36.9)	9 (25.7)	33 (33.0)
Green	8 (12.3)	3 (8.6)	11 (11.0)
Brown	18 (27.7)	15 (42.9)	33 (33.0)
Hazel	14 (21.5)	7 (20.0)	21 (21.0)
Other	1 (1.5)	1 (2.9)	2 (2.0)
Diabetes			
Yes	2 (5.7)	7 (10.8)	9 (9.0)
Type I	0 (0.0)	1 (1.5)	1 (1.0)
Type II	2 (5.7)	6 (9.2)	8 (8.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
No	33 (94.3)	58 (89.2)	91 (91.0)
Hypertension			
Yes	23 (65.7)	32 (49.2)	55 (55.0)

No	12 (34.3)	33 (50.8)	45 (45.0)

Table 1. Demographics and Baseline Characteristics.

Presented data is from subjects and not eyes.

Table 2. Clinical Outcomes

Clinical Parameter	**PBM (N = 91)***	**Sham (N = 54)***
Best-Corrected Visual Acuity (BCVA)		
Mean Baseline BCVA Score, letters (SE) [SD]	70.7 (0.55) [5.23]	70.1 (0.58) [4.29]
Primary BCVA Endpoint^		
Change in BCVA from Baseline at Month 13		
ETDRS Letters, LS mean (SE) [SD]	5.4 (0.96) [9.16]	3.0 (1.13) [8.30]
95% CI	3.5 - 7.3	0.7 - 5.2
Within group comparison	p < 0.0001	p = 0.0094
Between group comparison		p = 0.0204
Secondary and Exploratory BCVA Endpoints		
No. of Subjects BCVA ≥ 5 Letter Improvement, n	50 (54.9)	22 (40.7)
(%)	24 (25.8)	8 (15.1)
No. of Subjects BCVA ≥ 10 Letter Improvement, n	4 (4.4)	1 (1.9)
(%)	9.7 (0.5) [3.7]	8.7 (0.7) [3.1]
No. of Subjects BCVA ≥ 15 Letter Improvement, n	12.8 (0.5) [2.7]	11.9 (0.6) [1.8]

(%)		
BCVA ≥ 5 Mean Letter Improvement, mean (SE) [SD]		
BCVA ≥ 10 Mean Letter Improvement, mean (SE) [SD]		
Secondary and Exploratory Endpoints		
Change from Baseline, mean (SE) [SD]		
Month 1	3.0 (0.68) [6.49]	2.0 (0.80) [5.88]
PBM within group comparison		p < 0.0001
Between group comparison		p = 0.22
Month 4	4.1 (0.85) [8.1]	3.2 (0.98) [7.20]
PBM within group comparison		p < 0.0001
Between group comparison		p = 0.37
Month 5	4.8 (0.75) [7.15]	2.7 (0.89) [6.54]
PBM within group comparison		p < 0.0001
Between group comparison		p = 0.027
Month 8	4.8 (0.9) [8.59]	3.0 (1.06) [7.79]
PBM within group comparison		p < 0.0001
Between group comparison		p = 0.08
Month 9	5.5 (0.88) [8.39]	3.3 (1.04) [7.64]
PBM within group comparison		p < 0.0001
Between group comparison		p = 0.045

Month 12	6.0 (1.01) [9.63]	3.4 (1.20) [8.82]
PBM within group comparison		p < 0.0001
Between group comparison		p = 0.04
Secondary and Exploratory Endpoints		
Macular Drusen Volume		
Baseline, mean (SE) [SD]	0.941 (0.02)	0.973 (0.04)
Month 13	[0.22]	[0.27]
Within group comparison	0.947 (0.03)	1.02 (0.04) [0.29]
PBM vs Sham difference in means	[0.29]	p = 0.36
	p = 0.57	p = 0.36
New Onset Geographic Atrophy, No. of events (%) ^		
No. of subjects at baseline	6 (6.5)	5 (9.1)
No. of new onset subjects at Month 13	1 (1.1)	5 (10.0)
Between group comparison		p = 0.024

*Note: n = Number of eyes with data available. LS mean = Least Squares estimation of mean based on a liner mixed effect model with eye nested within subject, and use of AREDS supplements as a covariate. * MITT population analysis. ^ The Anderson-Darling test for normality indicated that the model residuals from measured values were not normally distributed (p = 0.04), which lead to rank assessment. ^ Subject eyes included at screening/baseline removed.*

Table 3. Ocular Adverse Events by System Organ Class and Preferred Term in Study Eyes.

A total of 33 ocular-specific AEs categorized as eye disorders were observed in study eyes. In total, no ocular specific AE was reported at a frequency of over 5% in study eyes.

	Study Eyes			Non-Study Eyes
Preferred Term	**PBM (N = 93) n (%)**	**Sham (N = 55) n (%)**	**Total (N = 148) n (%)**	**Total (N = 52) n (%)**
Eye Disorders	21 (22.6)	12 (21.8)	33 (22.3)	18 (34.6)
Neovascular Age-Related Macular Degeneration	5 (5.4)	1 (1.8)	6 (4.1)	3 (8.3)*
Vitreous Floaters	1 (1.1)	4 (7.3)	5 (3.4)	0 (0.0)
Dry Eye	1 (1.1)	2 (3.6)	3 (2.0)	2 (3.8)
Punctate Keratitis	1 (1.1)	2 (3.6)	3 (2.0)	0 (0.0)
Vitreous Detachment	2 (2.2)	1 (1.8)	3 (2.0)	0 (0.0)
Blepharitis	2 (2.2)	0 (0.0)	2 (1.4)	1 (1.9)
Conjunctival Haemorrhage	2 (2.2)	0 (0.0)	2 (1.4)	0 (0.0)
Conjunctivitis Allergic	2 (2.2)	0 (0.0)	2 (1.4)	0 (0.0)
Eye Pain	2 (2.2)	0 (0.0)	2 (1.4)	0 (0.0)
Foreign Body Sensation In Eyes	2 (2.2)	0 (0.0)	2 (1.4)	0 (0.0)
Lacrimation Increased	2 (2.2)	0 (0.0)	2 (1.4)	0 (0.0)
Photopsia	2 (2.2)	0 (0.0)	2 (1.4)	1 (1.9)
Posterior Capsule Opacification	1 (1.1)	1 (1.8)	2 (1.4)	0 (0.0)

	Study Eyes			Non-Study Eyes
Preferred Term	**PBM (N = 93) n (%)**	**Sham (N = 55) n (%)**	**Total (N = 148) n (%)**	**Total (N = 52) n (%)**
Abnormal Sensation In Eye	0 (0.0)	1 (1.8)	1 (0.7)	0 (0.0)
Amaurosis Fugax	1 (1.1)	0 (0.0)	1 (0.7)	0 (0.0)
Angle Closure Glaucoma	0 (0.0)	1 (1.8)	1 (0.7)	1 (1.9)
Cataract	0 (0.0)	1 (1.8)	1 (0.7)	3 (5.8)
Cataract Subcapsular	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.8)
Cystoid Macular Oedema	0 (0.0)	1 (1.8)	1 (0.7)	0 (0.0)
Diplopia	1 (1.1)	0 (0.0)	1 (0.7)	0 (0.0)
Eye Discharge	0 (0.0)	1 (1.8)	1 (0.7)	0 (0.0)
Eye Irritation	1 (1.1)	0 (0.0)	1 (0.7)	2 (3.8)
Eye Pruritus	1 (1.1)	0 (0.0)	1 (0.7)	0 (0.0)
Macular Hole	1 (1.1)	0 (0.0)	1 (0.7)	0 (0.0)
Open Angle Glaucoma	0 (0.0)	1 (1.8)	1 (0.7)	1 (1.9)
Photophobia	1 (1.1)	0 (0.0)	1 (0.7)	1 (1.9)
Retinal Vein Occlusion	1 (1.1)	0 (0.0)	1 (0.7)	0 (0.0)
Retinopathy Hypertensive	0 (0.0)	1 (1.8)	1 (0.7)	0 (0.0)
Vitreous Degeneration	1 (1.1)	0 (0.0)	1 (0.7)	0 (0.0)
Vitreous Hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.8)
Diplopia	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.8)

	Study Eyes			Non-Study Eyes
Preferred Term	**PBM (N = 93) n (%)**	**Sham (N = 55) n (%)**	**Total (N = 148) n (%)**	**Total (N = 52) n (%)**
Amaurosis Fugax	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Chalazion	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
General Disorders and Administration Site Conditions	3 (3.2)	0 (0.0)	3 (2.0)	0 (0.0)
Pain	2 (2.2)	0 (0.0)	2 (1.4)	0 (0.0)
Application Site Warmth	1 (1.1)	0 (0.0)	1 (0.7)	0 (0.0)
Infections And Infestations	1 (1.1)	0 (0.0)	1 (0.7)	0 (0.0)
Hordeolum	1 (1.1)	0 (0.0)	1 (0.7)	0 (0.0)

*Note: N = Number of eyes treated in the group; n = Number of eyes reported such event. Percentages are based on the number of eyes treated in the group. * 16 non-study eyes presented with neovascular AMD at study enrollment so were removed from the total number of eyes for development of new neovascular AMD.*