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LONG-TERM EFFICACY AND SAFETY OF PHOTOBIOMODULATION IN DRY AGE-RELATED MACULAR DEGENERATION (LIGHTSITE III: 24-MONTH ANALYSIS)

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Purpose: To evaluate the safety and efficacy of multiwavelength photobiomodulation (PBM) in nonexudative (dry) age-related macular degeneration (AMD).

Methods: LIGHTSITE III used a double-masked, randomized, sham-controlled, parallel-group, prospective study design. Subjects were enrolled with a diagnosis of dry AMD and treated with multiwavelength PBM (Valeda Light Delivery System; 590, 660, and 850 nm) or sham treatment. A treatment series included 9 PBM or sham treatments delivered 3x/week over 3 to 5 weeks every 4 months (M) for 24M.

Results: A total of 148 eyes (100 subjects) with dry AMD were randomized into the study. LIGHTSITE III met the prespecified primary BCVA efficacy end point at M21 with a significant difference between treatment groups ($P = 0.0036$) and a +6.2 letter gain after PBM. At M21, 61.5% of PBM-treated eyes showed ≥5, 23.1% showed ≥10, and 4.4% showed ≥15 letter gains. A favorable safety profile was observed with no signs of phototoxicity. Disease progression to Geographic Atrophy (GA) showed a significant decrease in incidence (Sham, 24.0% vs. PBM, 6.8%; $P = 0.007$) after PBM treatment at M24. Significant benefit in vision QoL was observed.

Conclusion: Multiwavelength PBM represents an interventional therapy that restores visual function and has potential disease-modifying effects in intermediate dry AMD.

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Photobiomodulation (PBM) delivers light wavelengths in the 500 to 1,000 nm range from a laser or light-emitting diode (LED) applied directly to target tissues for cellular effect.[1,2] The primary proposed mechanism is mitochondrial photoacceptor activation that produce a biological response resulting in energy production, stabilization of metabolic function, and cytoprotection.[3,4] Retinal tissue has one of the highest energy demands in the body.[5] Mitochondrial dysfunction is known to play a role in degenerative eye disease. From a mechanistic standpoint, PBM therapy is an attractive treatment strategy for degenerative ocular disorders.[6]

Positive benefits after PBM treatment are observed in a variety of disease states including degenerative pathologies.[7–11] Recent ophthalmologic clinical trials have explored PBM effect in multiple conditions, including AMD.[12] The LIGHTSITE I and II studies provide foundational evidence for the benefit of multiwavelength PBM on aspects of visual function, anatomy, and safety in dry AMD.[13–15] The LIGHTSITE III trial further investigated the effects of multiwavelength PBM treatment in dry AMD over a 24-month (M) duration. Positive data from the 13M analysis have previously been reported.[16] The current report details the long-term efficacy and safety findings of

multiwavelength PBM on the full data set extending to 24M.

Methods

LIGHTSITE III study methodology (ClinicalTrials.gov Registration: NCT04065490) has been previously described.[16]

Study Participants

Subjects were enrolled if they were 50 years and older, had a diagnosis of dry AMD as defined by the presence of drusen that were intermediate in size or larger ($\geq$63 μm) with at least a few (3) being regular drusen and not pseudodrusen and/or geographic atrophy (GA), and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) letter scores between 50 and 75 (Snellen equivalent: 20/32-20/100). Excluded eyes had neovascular AMD (nAMD), presence of central 1-mm ETDRS grid-involving GA, or other significant retinal disease. Detailed inclusion/exclusion criteria are available in **Table**, **Supplemental Digital Content 3**, http://links.lww.com/IAE/C882. Individual eye risk for AMD progression was estimated using a modified Ferris Simplified Scoring System (**Table**, **Supplemental Digital Content 3**, http://links.lww.com/IAE/C882).[17]

Subjects were enrolled across 10 centers throughout the United States. Institutional Review Board approval and written informed consent were obtained from all study subjects. 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, multicenter, prospective study. Randomized subjects (2:1 into PBM and Sham treatment groups, respectively) underwent PBM or sham treatment with the Valeda Light Delivery System [Valeda] (LumiThera, Inc., Poulsbo, WA).

Evaluated Parameters

The study was powered for BCVA and evaluated the difference between treatment groups. Secondary and exploratory clinical outcome measures included low luminance BCVA (LLBCVA), contrast sensitivity (CS, Mars Perceptrix letter charts), reading ability (Radner reading charts), color vision (Farnsworth-Munsell D-15 dichotomous color test), and vision-related quality of life (QoL) (Visual Function Questionnaire-25, [VFQ-25]). Imaging was obtained at predetermined study visits after treatment and evaluated by a masked central reading center (Duke Reading Center, Durham, NC). Detailed imaging methodology is provided in the supplement (see **Table**, **Supplemental Digital Content 3**, http://links.lww.com/IAE/C882). The 13M and 21M (coprimary end points) and 24M (final study visit—3 months follow-up after the final treatment) study visits are described in this report.

Subjects received either multiwavelength PBM (590, 660, and 850 nm) or Sham (reduced dose) treatment using Valeda. Subjects were exposed to six treatment series delivered every 4 months over the 24M study (Figure 1). Each treatment series consisted of nine sessions delivered over a 3–5-week period (see **Table**, **Supplemental Digital Content 3**, http://links.lww.com/IAE/C882).

Statistical Analysis

The primary BCVA end point evaluated change from baseline at M13 and/or M21. Comparison was

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This study involved human subjects, was approved by the Institutional Review Board for each participating site, and adhered to the tenets of the Declaration of Helsinki.

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

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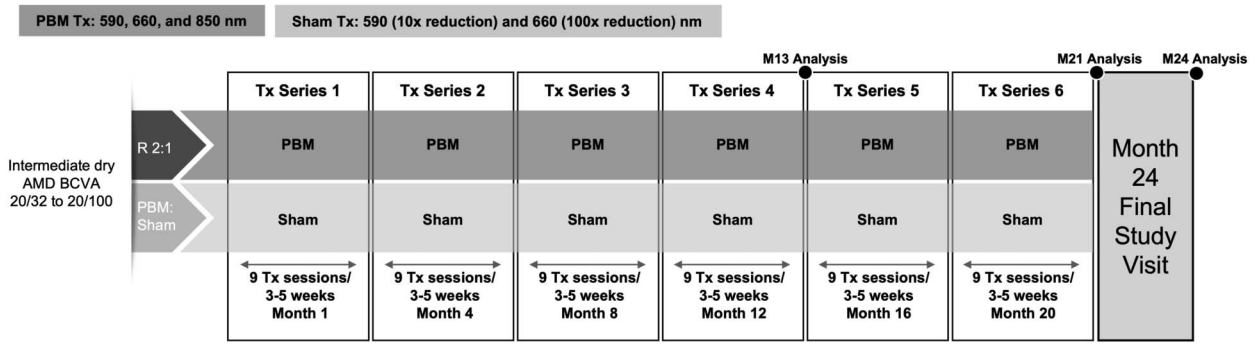

Fig. 1. LIGHTSITE III study design. Subjects were randomized in a 2:1 fashion (PBM: Sham) and followed for 24M. Data analyses were planned for M13, M21, and M24 timepoints. The PBM mode delivered 590, 660, and 850 nm multiwavelength treatment. The sham mode (active control) delivered a 10x reduction of the 590 nm and a 100× reduction of the 660 nm wavelengths; the 850 nm was omitted. BL, baseline; M, month; PBM, photobiomodulation; R, randomized; Tx, treatment.

made between the PBM and sham group to demonstrate statistical superiority of PBM. Mean and least squares (LS) means are presented with change from baseline using linear mixed-effects models (LME) that accounted for correlation between eyes within subject. The LS mean estimation was based on a LME model with eye nested within subject and use of AREDS supplements as a covariate. A Fisher exact test analyzed incident GA between treatment groups and is regarded as a descriptive statistic (not multiplicity-controlled). Analyses are preferably presented using multiple imputation (MI) and were based on individual eyes or subjects, as indicated. Imaging data conducted at the screening visit were used as baseline measures for subsequent analyses and referred to as baseline throughout. Statistics were performed using R (version 3.4.4) and SAS (SAS Institute, Cary, NC). Amendments to the previously described statistical analysis plan to include MI are summarized in **Table**, **Supplemental Digital Content 3**, http://links.lww.com/IAE/C882.[18]

Results

Participants

A total of 100 subjects and 148 eyes were randomized in a 2:1 treatment ratio (93 PBM:55 Sham) into the study. **Table**, **Supplemental Digital Content 3**, http://links.lww.com/IAE/C882, summarizes detailed reasons for nonstudy eye exclusion. During the 24M duration, 20 subjects discontinued (12 PBM; 8 sham) (see **Figure**, **Supplemental Digital Content 1**, http://links.lww.com/IAE/C880). Subject characteristics are summarized in Table 1. Of the 100 subjects enrolled, 52 subjects had one eye enrolled (OD: 24 subjects; OS: 28 subjects) and 48 subjects had bilateral eye enrolment (OU). Most eyes enrolled were categorized as intermediate AMD (71.0%). At baseline, 70.0% of eyes had a BCVA letter score $\geq$ 70 letters (20/40 Snellen or better). Most eyes enrolled (67.6%) were of moderate-to high-risk for disease progression (see **Table**, **Supplemental Digital Content 3**, http://links.lww.com/IAE/C882). Groups were statistically balanced for age and baseline BCVA scores ($P > 0.05$). No impact of baseline cataracts, age, eye laterality, or worse eye status on clinical outcomes were observed ($P > 0.05$).

Efficacy Assessments

Clinical outcomes. ***Primary BCVA end point.*** The prespecified primary BCVA efficacy end point showed a statistically significant difference between treatment groups at M21 ($P = 0.0036$) with a +6.2 letter gain after PBM, which was maintained at M24 (+5.6 letter gain, $P = 0.0024$) (MI analysis). Significant improvements in BCVA were observed at all study visits after PBM (within group analyses, $P < 0.05$) and between treatment groups ($P < 0.05$) at most timepoints assessed (Table 2, Figure 2). At M21, 61.5% of PBM-treated eyes showed a $\geq$5 letter gain (mean of 9.0 letters), 23.1% of PBM-treated eyes showed a $\geq$10 letter gain (mean of 12.8 letters), and 4.4% of PBM-treated eyes responded with a $\geq$15 letter gain (mean of 15.5 letters). The PBM group showed increased BCVA gains compared with sham which also showed a higher percentage of eyes that lost vision over time (Table 2, Figure 2). Previous analyses using LOCF were consistent with MI analyses showing significant BCVA improvements in between groups at most timepoints including M13 ($P = 0.0204$), M21 ($P = 0.0054$), and M24 ($P = 0.003$) (see **Table**, **Supplemental Digital Content 3**, http://links.lww.com/IAE/C882). Stratification by baseline BCVA for those with $>$ or $\leq$70 letters showed improvements with larger

Table 1. Demographics and Baseline Characteristics

Variable	PBM (N = 65 Subjects/93 Eyes*) n (%)	Sham (N = 35 Subjects/55 Eyes*) n (%)	Total (N = 100 Subjects/148 Eyes*) 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)
Cataracts*			
Yes	52 (55.9)	21 (38.2)	73 (49.3)
No	41 (44.1)	34 (61.8)	75 (50.7)
AREDS category*			
II	11 (12.0)	8 (15.0)	19 (13.0)
III	82 (88.0)	47 (85.0)	129 (87.0)
IV	0 (0.0)	0 (0.0)	0 (0.0)
Clinical categories*			
Early	23 (24.7)	9 (16.4)	32 (21.6)
Intermediate	64 (68.1)	41 (74.5)	105 (71.0)
Late	6 (6.5)	5 (9.1)	11 (7.4)

Data presented from all subjects/eyes enrolled.
*Number of eyes analyzed.

magnitude BCVA gains afforded in the 61 to 70 letter baseline subgroup [(M13, 8.5 letters (SE, 1.8); M21, 6. 6 letters (SE 1.6); M24, 7.4 letters (SE 1.5)] (Table 2, Figure 2).

Secondary and exploratory end points. Improved vision-related QoL measures were achieved after PBM at M21. A statistically significant improvement in the VFQ-25 composite score ($P = 0.02$) in the PBM compared with the sham group was observed. While the PBM group maintained QoL at M24, the sham group showed a significant decline which was mirrored in select VFQ-25 subscales at M24 (Table 3, see **Figure**, **Supplemental Digital Content 2**, http://links.lww.com/IAE/C881).

Normal or near-normal visual function was observed for secondary and exploratory evaluations of CS, perimetry, color vision, and reading ability at baseline. Outcome measures remained stable through the 24M timepoint in all treatment groups (Table 3; see **Table**, **Supplemental Digital Content 3**, http://links.lww.com/IAE/C882).

Anatomical outcomes. Subjects were enrolled with anatomical deficits that included drusen deposition and a limited number of eyes with noncentral GA at baseline as determined for study inclusion (sham, n = 3; PBM, n = 4 using FAF imaging only). A nonsignificant greater increase (~2x) in macular drusen volume was observed in sham-treated eyes at M21 ($P = 0.65$). The decrease in drusen volume was not reflective of GA formation (Table 3, Figure 3).

A significant reduction in incident GA after PBM was observed at M13 ($P = 0.024$) and M24 ($P = 0.007$). At M24, 24.0% (n = 12/50) of sham-treated eyes showed development of incident GA compared with 6.8% (n = 6/87) of PBM-treated eyes (Table 3, Figure 4). Most eyes that converted to GA in the PBM group showed development of noncentral GA (n = 5/6, 83.3%) versus an increased development of central-involving GA (n = 7/12, 58.3%) in the sham group. Stratification of BCVA outcomes at M24 by eyes with GA versus those with no GA showed a larger benefit in eyes with no GA at M24 after PBM (No GA (n = 63), +6.1 letters; Noncentral GA at baseline (n = 5), +5.4 letters; incident GA (n = 5), −0.2 letters) (data not shown).

Exploratory analysis showed the development of incomplete retinal pigment epithelium (RPE) and outer retinal atrophy (iRORA) observed in 13.4% (n = 9/67)

Table 2. Clinical Analyses

Primary End Point: BCVA	PBM (N = 91)	Sham (N = 54)
Mean baseline BCVA score, letters (SD)	70.7 (5.23)	70.1 (4.29)
Change in BCVA from baseline*		
Month 13		
ETDRS letters, LS mean (SE)	6.0 (1.34)	3.4 (1.52)
95% CI	3.3, 8.6	0.4, 6.4
Within group comparison	$P < 0.0001$	$P = 0.03$
Between group comparison		$P = 0.05$
Month 21		
ETDRS letters, LS mean (SE)	6.2 (1.02)	2.4 (1.26)
95% CI	4.2, 8.2	−0.1, 4.9
Within group comparison	$P < 0.0001$	$P = 0.0567$
Between group comparison		$P = 0.0036$
Month 24		
ETDRS letters, LS mean (SE)	5.6 (1.24)	1.3 (1.37)
95% CI	3.2, 8.0	−1.4, 3.9
Within group comparison	$P < 0.0001$	$P = 0.36$
Between group comparison		$P = 0.0024$
Letter gain distribution*		
Month 13		
No. of eyes BCVA ≥ 5 letter improvement, n (%)	53 (58.2)	21 (38.8)
ETDRS letters, mean (SE)	9.7 (0.5)	8.6 (0.7)
No. of eyes BCVA ≥ 10 letter improvement, n (%)	25 (27.5)	7 (13.0)
ETDRS letters, mean (SE)	13.0 (0.6)	12.1 (0.7)
No. of eyes BCVA ≥ 15 letter improvement, n (%)	5 (5.5)	1 (1.9)
ETDRS letters, mean (SE)	17.6 (1.2)	15.0 (−)
Month 21		
No. of eyes BCVA ≥ 5 letter improvement, n (%)	56 (61.5)	15 (27.8)
ETDRS letters, mean (SE)	9.0 (0.5)	8.0 (0.5)
No. of eyes BCVA ≥ 10 letter improvement, n (%)	21 (23.1)	2 (3.7)
ETDRS letters, mean (SE)	12.8 (0.4)	11.5 (1.5)
No. of eyes BCVA ≥ 15 letter improvement, n (%)	4 (4.4)	0.0 (0.0)
ETDRS letters, mean (SE)	15.5 (0.5)	—
Month 24		
No. of eyes BCVA ≥ 5 letter improvement, n (%)	58 (63.7)	12 (22.2)
ETDRS letters, mean (SE)	8.8 (0.4)	9.8 (0.3)
No. of eyes BCVA ≥ 10 letter improvement, n (%)	17 (18.7)	4 (7.4)
ETDRS letters, mean (SE)	12.8 (0.6)	13.8 (2.8)
No. of eyes BCVA ≥ 15 letter improvement, n (%)	4 (4.4)	1 (1.9)
ETDRS letters, mean (SE)	16.3 (0.9)	22.0 (−)
Subgroup analysis: BCVA letter gain by baseline Measures†		
Baseline > 70 letters subgroup		
Month 13		
Change in BCVA from baseline		
ETDRS letters, mean (SE)	4.4 (0.9)	3.7 (1.1)
Month 21		
Change in BCVA from baseline		
ETDRS letters, mean (SE)	5.2 (0.8)	3.7 (0.9)

(*continued on next page*)

Table 2. (*Continued*)

Primary End Point: BCVA	PBM (N = 91)	Sham (N = 54)
Month 24		
Change in BCVA from baseline ETDRS letters, mean (SE)	4.8 (1.1)	2.4 (1.6)
Baseline 61–70 letters subgroup		
Month 13		
Change in BCVA from baseline ETDRS letters, mean (SE)	8.5 (1.8)	1.1 (1.8)
Month 21		
Change in BCVA from baseline ETDRS letters, mean (SE)	6.6 (1.6)	−0.7 (2.0)
Month 24		
Change in BCVA from baseline ETDRS letters, mean (SE)	7.4 (1.5)	−0.6 (2.1)

*Data presented using multiple imputation from the mITT group analyses.

†Data presented using actual values for subgroup analyses. Months 13, 21, and 24 timepoints presented. Note: n = Number of eyes with data available.

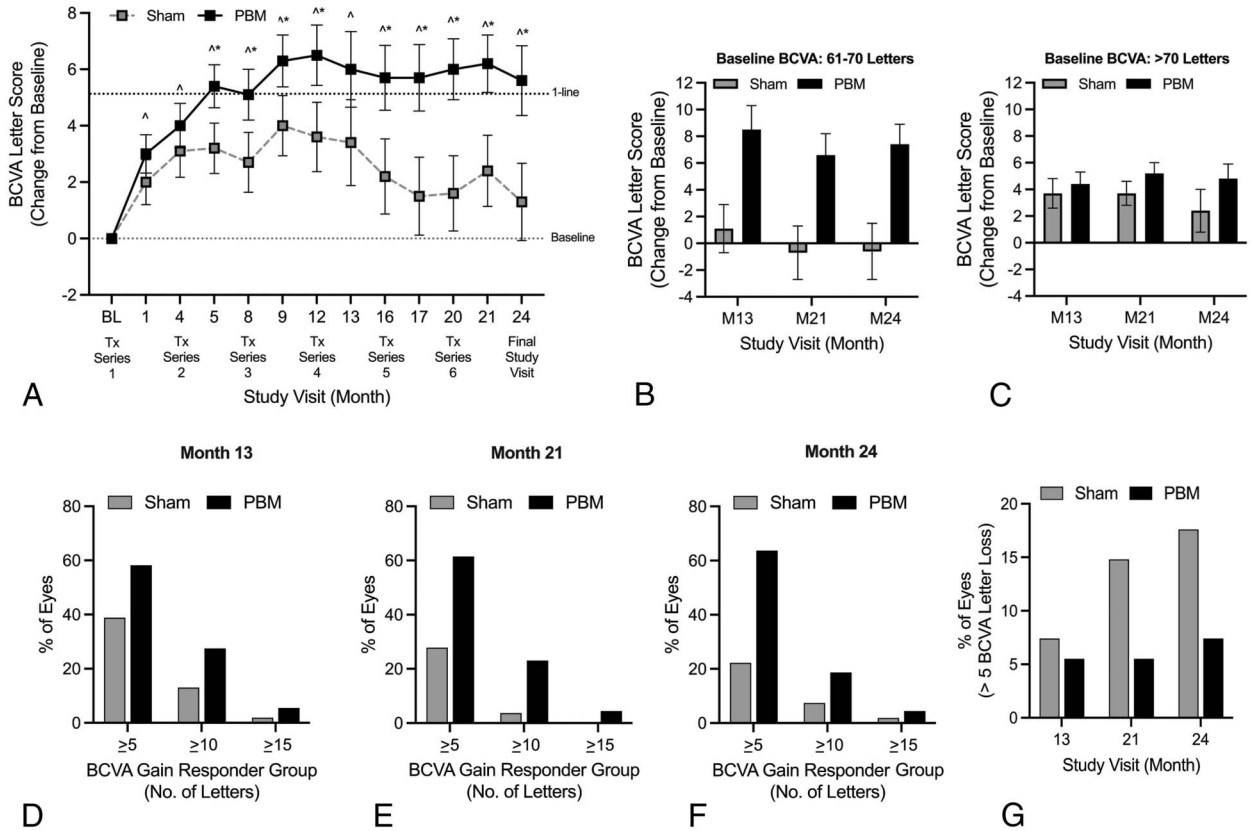

Fig. 2. Restoration of BCVA after photobiomodulation treatment. Subjects received PBM or sham treatment at baseline and 4, 8, 12, 16, and 20-month timepoints. **A.** †Significant improvements in BCVA were observed through M24 after PBM treatment. ^Within PBM group comparison, $P < 0.0001$; *PB*M* versus sham between group comparison, $P < 0.05$. **B.** ††Eyes with worse vision (≤70 letters) were afforded larger BCVA magnitude gains compared with (**C**) those with better vision (>70 letters). **D–F.** †A higher percentage of PBM-treated eyes showed ≥5, ≥10, and ≥15 BCVA letter gains compared with sham-treated eyes at all timepoints. **G.** ††A higher percentage of sham-treated eyes showed BCVA letter loss compared with PBM-treated eyes at each study timepoint. LS, least squares; M, month; PBM, photobiomodulation; SEM, standard error of the mean; Tx, treatment. † Data presented with multiple imputation. ††Data presented with actual values.

Table 3. Secondary and Exploratory End Points

Secondary and Exploratory End Points	PBM (N = 91)	Sham (N = 54)
LLBCVA†		
Mean baseline LLBCVA (SE)	54.0 (1.18)	49.3 (1.40)
Month 21		
ETDRS letters, LS mean (SE)	3.6 (1.68)	5.9 (1.88)
95% CI	0.3, 6.9	2.2, 9.6
Within group comparison	$P = 0.0314$	$P = 0.0019$
Between group comparison		$P = 0.29$
Low luminance deficit††		
Mean baseline low luminance deficit (SE)	16.7 (1.10)	20.8 (1.43)
Month 21		
LS mean (SE)	85.0 (5.78)	59.5 (6.82)
95% CI	73.6, 96.4	46.1, 73.0
Within group comparison	$P < 0.0001$	$P < 0.0001$
Between group comparison		$P = 0.0003$
Macular drusen volume (mm^3)**		
Mean baseline macular drusen volume (SE)	0.941 (0.02)	0.973 (0.04)
Month 21		
Mean (SE)	0.056 (0.01)	0.098 (0.1)
LS mean (SE)	0.03 (0.08)	0.07 (0.07)
95% CI	−0.122, 0.177	−0.084, 0.221
Within group comparison	$P = 0.72$	$P = 0.38$
Between group comparison		$P = 0.65$
Contrast sensitivity (40 cm)**		
Mean baseline contrast sensitivity (SE)	1.35 (0.02)	1.27 (0.03)
Month 21		
Mean (SE)	−0.011 (0.02)	−0.001 (0.04)
LS mean (SE)	−0.029 (0.03)	−0.021 (0.03)
95% CI	−0.085, 0.027	0.086–0.043
Within group comparison	$P = 0.30$	$P = 0.52$
Between group comparison		$P = 0.82$
Geographic atrophy‡‡		
Incident geographic atrophy, No. of events*		
No. of eyes at baseline, # (%)	6 (6.5)	5 (9.1)
Month 13		
No. of events	1 (1.1)	5 (10.0)
Between group comparison		$P = 0.024$
Month 24		
No. of events	6 (6.8)	12 (24.0)
Between group comparison		$P = 0.007$
Two-sided CI for difference between rates		3.1–31.6
New iRORA**		
Month 13		
No. of events	10/73 (13.7)	8/34 (23.5)
Month 24		
No. of events	9/67 (13.4)	7/33 (21.2)
iRORA conversion to GA/cRORA‡		
Month 13		
No. of events	0/5 (0.0)	4/5 (80.0)
Month 24		
No. of events	1/5 (20.0)	4/5 (80.0)
Geographic atrophy lesion area (mm^2)§		
No. of eyes**	4	3
Mean baseline GA lesion area (SE)	1.25 (0.41)	0.24 (0.09)
Month 21		
Change from baseline, LS mean (SE)	2.06 (0.64)	2.53 (0.91)
95% CI	0.27, 3.9	0.002, 5.1
Within group comparison	$P = 0.03$	$P = 0.05$
Between group comparison		$P = 0.63$

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Table 3. (*Continued*)

Secondary and Exploratory End Points	PBM (N = 91)	Sham (N = 54)
Geographic atrophy lesion area (square root Analysis)††		
No. of eyes¶	4	3
Mean baseline square root GA (SE)	1.07 (0.19)	0.47 (0.10)
Month 21		
Change from baseline, mean (SE)	0.62 (0.17)	0.83 (0.29)
Mean % change from baseline (SE)	68.12 (20.39)	194.63 (70.27)
Between group comparison		0.52
Quality of life (VFQ-25 Questionnaire)††		
Mean baseline VFQ-25 (SE)	79.59 (1.94)	79.53 (1.90)
Month 21		
Composite score		
LS mean (SE)	1.5 (1.63)	−3.7 (2.02)
95% CI	−1.7, 4.8	−7.7, 0.3
Within group comparison	$P = 0.35$	$P = 0.073$
Between group comparison		$P = 0.0182$
VFQ-25 subscores/subscales		
Difficulty with activities		
LS mean (SE)	0.99 (1.77)	−5.4 (2.2)
95% CI	−2.53, 4.52	−9.72, −1.02
Within group comparison	$P = 0.57$	$P = 0.016$
Between group comparison		$P = 0.0078$
Near vision		
LS mean (SE)	0.65 (2.74)	−6.52 (3.38)
95% CI	−4.81, 6.12	−13.26, 0.22
Within group comparison	$P = 0.81$	$P = 0.0576$
Between group comparison		$P = 0.0503$
Difficulty reading newspapers		
LS mean (SE)	−0.9	−14.4
95% CI	−10.5, 8.8	−26.3, −2.5
Within group comparison	$P = 0.86$	$P = 0.019$
Between group comparison		$P = 0.038$
Difficulty visiting with people		
LS mean (SE)	0.6 (2.6)	−7.1 (3.19)
95% CI	−4.5, 5.8	−13.4, −0.7
Within group comparison	$P = 0.80$	$P = 0.03$
Between group comparison		$P = 0.03$
Radner reading speed††		
Maximum reading speed		
Mean baseline maximum reading speed	177.6 (5.68)	174.4 (8.05)
Month 21		
Change from baseline, LS mean (SE)	−1.4 (9.50)	0.6 (11.17)
95% CI	−20.1, 17.4	−21.5, 22.7
Within group comparison	$P = 0.30$	$P = 0.49$
Between group comparison		$P = 0.12$
Reading acuity score		
Mean baseline reading acuity score	0.75 (0.02)	0.78 (0.01)
Month 21		
Change from baseline, LS mean (SE)	0.001 (0.02)	0.011 (0.02)
95% CI	−0.04, 0.04	−0.00, 0.01
Within group comparison	$P < 0.0001$	$P < 0.0001$
Between group comparison		$P = 0.78$
Critical print size		
Mean baseline critical print size		
Month 21	0.4 (0.03)	0.4 (0.03)
Change from baseline, LS mean (SE)	0.0 (0.04)	0.0 (0.05)
95% CI	−0.1, 0.1	−0.1, 0.1
Within group comparison	$P < 0.0001$	$P < 0.0001$
Between group comparison		$P = 0.73$

Table 3. (*Continued*)

Secondary and Exploratory End Points	PBM (N = 91)	Sham (N = 54)
Reading score Log 0.5		
Mean baseline reading score Log 0.5	0.5 (0.0005)	0.5 (0.0001)
Month 21		
Change from baseline, LS mean (SE)	0.00 (0.001)	0.001 (0.001)
95% CI	−0.002, 0.003	−0.002, 0.004
Within group comparison	*P* = 0.93	*P* = 0.31
Between group comparison		*P* = 0.25

The low luminance deficit was calculated by subtracting LLBCVA from BCVA at each time point.
*Eyes included at baseline removed; eyes with GA at baseline determined using multimodal imaging confirmed through Duke.
†Eyes with absence of prior iRORA and cRORA at baseline.
‡Eyes with iRORA at baseline.
§Eyes with GA at baseline determined through FAF imaging.
¶Multiple imputation analysis.
**LOCF analysis.
††Actual values analysis.

of PBM-treated eyes compared with 21.2% (n = 7/33) of sham-treated eyes over the 24M study. In a small number of eyes, iRORA was present at baseline (n = 10); conversion of iRORA to complete RPE and outer retinal atrophy (cRORA) was observed in 20.0% (n = 1/5) of PBM-treated eyes and 80.0% (n = 4/5) of sham-treated eyes (Table 3).

At M21, a nonsignificant greater increase in GA lesion area growth was observed in the sham (2.53 mm^2, SE 0.91) compared with PBM (2.06 mm^2, SE 0.64) group ($P = 0.63$). Square root analysis of GA lesion area showed growth at most timepoints for each group with a larger rate observed in the sham group (M5, $P = 0.02$; M9, $P < 0.001$; Pre-M12, $P = 0.03$) (data not shown). At M21, a 68.1% increase in lesion area was noted in the PBM group compared with a 194.6% increase in the sham group (nonsignificant, $P = 0.52$) (Table 3).

Safety and Compliance Outcomes

The primary safety end point evaluated BCVA decline in both treatment groups. PBM reduced the % of eyes with vision loss of >5 letters compared with the sham group [(M13: PBM (5%), sham (7%); M21: PBM (5%), sham (15%); M24, PBM (7%), sham (18%)]. Sham-treated eyes lost vision due to progression of disease; all eyes with >5 letter loss at M24 progressed to GA.

At least one ocular-specific AE was observed in 38 study eyes (25.7%) from 32 subjects (21.6%). The number of eyes with at least one AE was similar between groups (sham, 25.5%; PBM, 25.8%). Four ocular-specific AEs (2.7%) were considered related to the treatment (sham: n = 3; PBM: n = 1). These AEs included dry eye (sham: n = 2, 5.7%), punctate keratitis (Sham: n = 2, 5.7%), visual perseveration (persistence or the reappearance of the visual image) (sham; n = 1, 2.9%), and application site warmth (PBM; n = 1, 1.5%). No ocular-specific AEs led to study discontinuation. A total of 7 (7.5%) ocular-specific serious AEs (SAE) of nAMD were reported in the PBM treatment group and 3 (5.5%) ocular-specific SAEs (2 nAMD; one cystoid macular edema) were reported in the sham treatment group. In the

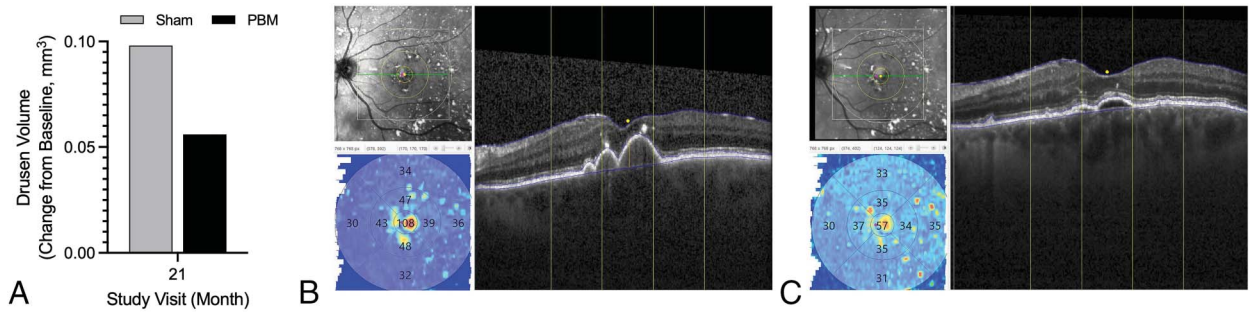

Fig. 3. Reduction in macular drusen volume after photobiomodulation treatment. **A.** A reduction in macular drusen volume was observed in the PBM versus sham group at M21 (data presented using multiple imputation). **B.** Baseline and C. M21 representative imaging (exploratory) from a single subject showing a significant reduction in macular drusen volume after the final series of PBM treatment (6 series) at M21 without loss of photoreceptor or retinal pigment epithelium visible. A 9-letter increase in BCVA was observed from 75 letters to 84 letters.

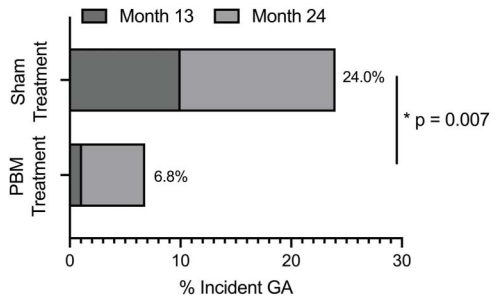

Fig. 4. Reduced incident GA after PBM treatment. At M24, 24.0% of sham-treated eyes showed development of incident GA compared with 6.8% of PBM-treated eyes ($P = 0.007$).

nonstudy group, three ocular-specific SAEs of nAMD (8.3%) were reported. No SAEs were considered associated to the treatment. The number of subjects with ocular-specific AEs was similar between sham (20.0%) and PBM (22.6%) subjects (Table 4).

Nine study eyes progressed to later-stage nAMD during the 24M study: 2 sham-treated eyes (3.6%) and 7 PBM-treated eyes (7.5%). In addition, three nonstudy eyes (8.3%) progressed to nAMD. A total of 16 subjects were randomized with the fellow, nonstudy eye that had nAMD at screening. However, the prevalence of these high-risk eyes was 3-fold higher (12:4) in the PBM versus sham group. Of the study eyes that converted to nAMD, 66.7% (n = 6/9 study eyes) were at high risk for conversion (i.e., the companion nonstudy eye had nAMD). On average, conversion to nAMD occurred 78.9 (SE 10.0) days after the last PBM treatment and 54.4 (SE 38.5) days after the last sham treatment. No dose-dependent increase of risk to nAMD conversion was observed after each additional PBM Tx series delivered.

Overall, 72.7% of sham and 87.1% of PBM subjects were greater than or equal to 75% compliant with study treatments. In the PBM group, 82.8% of subjects were 100% compliant with all treatment sessions.

Discussion

The LIGHTSITE III study met the primary efficacy end point with a significant difference in BCVA between PBM and sham treatment groups. The 24M analysis demonstrated positive clinical outcomes with improvements after PBM observed in BCVA letter gain, QoL enhancement, and anatomical outcomes such as a reduction in incident GA, suggesting a disease-modifying effect.

Improvements in BCVA were noted at all timepoints after PBM with a +6.2 letter gain at M21. Factors such as age, cataracts, and eye laterality between treatment groups had no impact on clinical outcomes and were nonsignificant. Most eyes were enrolled with baseline BCVA scores of 70 letters (20/40 Snellen) or better. These scores are consistent with mild vision loss and accompanied by anatomical deficits.[17,19] Subgroup analyses by baseline vision demonstrated larger gains afforded to eyes with worse vision. These findings are consistent with anti-VEGF trials showing that worse acuity at baseline predicts larger gains in vision and that patients presenting with good acuity are affected by a ceiling effect.[20,21]

The sham group is an active control group that received a reduced fluence of the PBM treatment. The loss of effect over the 24M duration reflects worsening of visual status in sham eyes and not a regression to the mean. All sham-treated eyes with >5 letter loss at M24 progressed to GA. The PBM arm showed immediate BCVA improvement from baseline on completion of the first series of treatment (M1, 3.0 letters). After treatment, eyes continued to improve over time as evidenced at the beginning of the second series (M4, 4.0 letters) and third series (M8, 5.1 letters). BCVA stabilization was seemingly observed after completion of the third treatment series which showed a mean 6.3 letter gain from baseline in the PBM group, and was maintained to M24 with repeat PBM therapy at 4-month intervals.

The higher frequency of >5 letter BCVA gains in the PBM group and greater loss of >5 letters in the sham group over time highlight that PBM promotes vision recovery and also reduces progressive decline. Both are important components of treating a degenerative disease such as AMD for which a loss of 2 to 3 letters per year (intermediate AMD) and development of GA with irreversible loss of retinal tissue is projected.[22–24] Interventions targeted to the earlier disease stages focused at preventing disease progression and resulting vision loss are valuable.

Baseline scores for other vision tests such as CS, reading ability, and color vision were near-normal and limited the ability to detect any change after PBM treatment. The stability of these scores over 24M supports the safety of PBM and the potential for PBM to prevent progressive decline in various aspects of visual function. Vison-related QoL demonstrated significant benefits in the PBM group and clinically meaningful deterioration in the sham group, supporting parallel QoL benefits with PBM along with BCVA and anatomical benefits. For the NEI-VFQ-25, an MCID is generally considered to be a 4–6-point change in the composite and subscale scores.[25] The sham group showed a significant deterioration of approximately 4 to 14 points in the composite score and subscales whereas the PBM group maintained QoL over the 24M duration.

Table 4. Ocular Adverse Events by System Organ Class and Preferred Term in Study Eyes

System Organ Class	Sham	PBM (N = 93)	Total
	(N = 55)	(N = 93)	(N = 148)
Preferred Term	n (%)	n (%)	n (%)
Serious adverse events	3 (5.5)	7 (7.5)	10 (6.8)
nAMD	2 (3.6) [7.3%]*	7 (7.5)	9 (6.1)
Cystoid macular edema	1 (1.8)	0 (0.0)	1 (0.7)
Adverse events	14 (25.5)	24 (25.8)	38 (25.7)
Vitreous floaters	4 (7.3)	1 (1.1)	5 (3.4)
Dry eye	2 (3.6)	1 (1.1)	3 (2.0)
Punctate keratitis	2 (3.6)	1 (1.1)	3 (2.0)
Vitreous detachment	1 (1.8)	2 (2.2)	3 (2.0)
Blepharitis	0 (00.0)	2 (2.2)	2 (1.4)
Conjunctival hemorrhage	0 (00.0)	2 (2.2)	2 (1.4)
Conjunctivitis allergic	0 (00.0)	2 (2.2)	2 (1.4)
Cystoid macular edema	2 (3.6)	0 (00.0)	2 (1.4)
Eye pain	0 (00.0)	2 (2.2)	2 (1.4)
Foreign body sensation in eyes	0 (00.0)	2 (2.2)	2 (1.4)
Lacrimation increased	0 (00.0)	2 (2.2)	2 (1.4)
Lamellar macular Hole	0 (00.0)	2 (2.2)	2 (1.4)
Photopsia	0 (00.0)	2 (2.2)	2 (1.4)
Posterior capsule opacification	1 (1.8)	1 (1.1)	2 (1.4)
Abnormal sensation in eye	1 (1.8)	0 (00.0)	1 (0.7)
Amaurosis fugax	0 (00.0)	1 (1.1)	1 (0.7)
Angle closure glaucoma	1 (1.8)	0 (00.0)	1 (0.7)
Cataract	1 (1.8)	0 (00.0)	1 (0.7)
Diplopia	0 (00.0)	1 (1.1)	1 (0.7)
Eye discharge	1 (1.8)	0 (00.0)	1 (0.7)
Eye irritation	0 (00.0)	1 (1.1)	1 (0.7)
Eye pruritus	0 (00.0)	1 (1.1)	1 (0.7)
Open-angle glaucoma	1 (1.8)	0 (00.0)	1 (0.7)
Photophobia	0 (00.0)	1 (1.1)	1 (0.7)
Retinal vein occlusion	0 (00.0)	1 (1.1)	1 (0.7)
Visual perseveration	1 (1.8)	0 (00.0)	1 (0.7)
Vitreous degeneration	0 (00.0)	1 (1.1)	1 (0.7)
General disorders and administration site conditions	0 (00.0)	1 (1.1)	1 (0.7)
Application site warmth	0 (00.0)	1 (1.1)	1 (0.7)
Infections and infestations	0 (00.0)	1 (1.1)	1 (0.7)
Hordeolum	0 (00.0)	1 (1.1)	1 (0.7)
Vascular disorders	1 (1.8)	0 (00.0)	1 (0.7)
Retinopathy Hypertensive	1 (1.8)	0 (00.0)	1 (0.7)

A total of 38 ocular-specific AEs were observed in the study eyes. Overall, a limited number of ocular-specific AEs were observed with low frequencies.

N = Number of eyes in treatment group. n = Number of eyes with reported event. Percentages are based on the number of eyes treated in the group. If there was more than one adverse event in a category was reported for a study subject, it was counted only once in that category.

*Prevalence of high-risk eyes (companion eye with nAMD at baseline) was 3x higher (12:4) in the PBM group versus sham group—when sham is normalized to the higher rate, development frequency would be estimated at 7.3%.

A greater increase in drusen volume, a higher rate of incident GA, increased GA lesion area growth, higher incidence of iRORA, and conversion from iRORA to cRORA were all observed in the sham group compared with the PBM group. While exploratory, these anatomical outcomes are suggestive of a disease-modifying PBM effect that warrants further investigation.

The LIGHTSITE III trial results are in keeping with the clinical and anatomical results from the previous LIGHTSITE I and II trials.[13,15] These findings are further supported by other reports of positive PBM effect on AMD disease correlates. Le et al[14] report stabilization of reticular pseudodrusen (RPD) and reductions in Stages 2 and 3 RPD after PBM with Valeda. Similarly, Benlahbib et al[26] show drusen volume

and thickness reductions, improved QoL measures, and >5 letter BCVA improvements after PBM treatment with Valeda in patients with large soft drusen and/or drusenoid pigment epithelial detachment AMD. Nassisi et al[27] report a significant ~5 letter improvement in BCVA, improvement in LLBCVA and CS, reduced drusen volume, and decreased scotopic microperimetry retinal sensitivity after PBM in early/intermediate dry AMD. Exploratory reports also support clinical improvements with Valeda in other ocular conditions suggesting translation of retinal health benefits to other disorders.[28–30]

PBM was well-tolerated with a limited number of AEs and showed high levels of patient compliance. These findings are consistent with the safety of PBM treatment across a myriad of medical indications with low rates of AEs.[31–34] This favorable safety profile is further highlighted among the >30 published ophthalmic studies using PBM with no reports of safety concerns.[13,15,35] A lower or comparable rate of nAMD conversion was observed compared with other recently completed dry AMD trials.[36,37] Future studies should continue to monitor this important safety outcome.

The study design has inherent limitations. The sham treatment served as an active control delivering a low fluence (dose) of PBM. Even with a significant fluence reduction, sham treatment activates photoacceptors and is anticipated to produce a small biologic effect paralleling a high dose/low dose study design within the treatment groups.[13,15] Moderate effects observed in the sham group reduced over time, with a ~1-letter change from baseline observed at M24. Subject sensitivity may account for enhanced response variability at lower-dose PBM.

The LIGHTSITE III study is the first clinical trial to assess long-term effects of multiwavelength PBM in dry AMD. Data from this analysis show statistically significant improvements in BCVA immediately after the first series of PBM treatment which were maintained through the 24M trial. Safety data show a strong profile with AEs consistent with the patient population and no signs of phototoxicity. A significant reduction in progression to GA and other anatomical biomarkers of disease status are suggestive of pathological benefits. For patients with early/intermediate dry AMD, BCVA improvement and/or maintained BCVA (i.e., no further decline or projected decline), and disease-modifying impact on the underlying etiology (not just late-stage growth of scar, once tissue is lost) represents clinically meaningful benefits. Slowing progression of vision loss can change the trajectory of the disease and provide immediate improvement in QoL, delay permanent vision loss, and reduce overall health care costs.

Key words: photobiomodulation, multiwavelength, age-related macular degeneration, mitochondria, ocular disease, vision, retina, nonexudative macular degeneration, light therapy, Valeda.

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