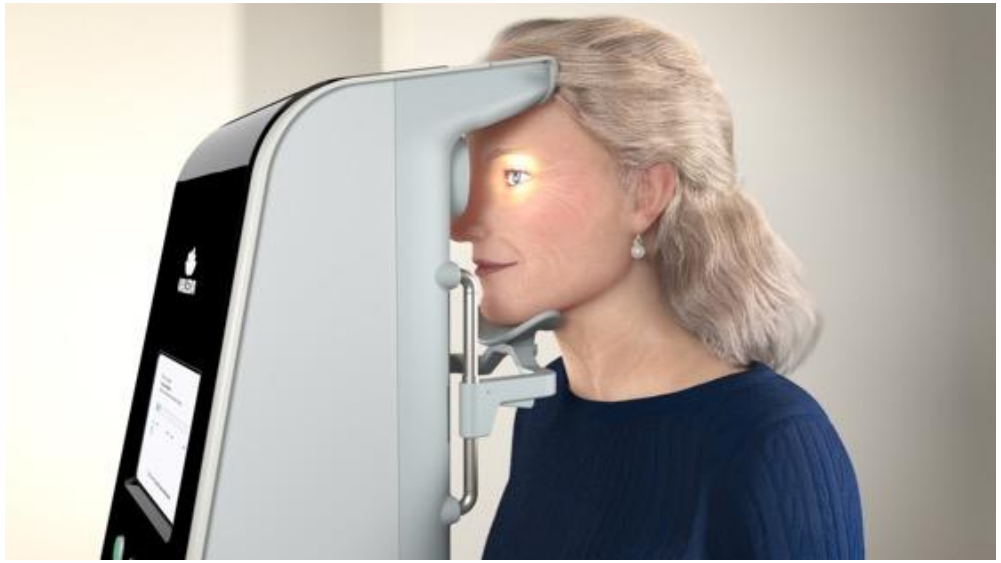
LIGHTSITE III: US Pivotal 24-Month Study

The LIGHTSITE III study was an FDA, IDE-approved, prospective, double-masked, randomized, sham-controlled, parallel group, multi-center study to assess the safety and efficacy of photobiomodulation (PBM) in subjects with dry age-related macular degeneration (AMD)

Valeda® Light Delivery System

Parameter	Specification
Size	530 mm height x 300 mm width x 330 mm depth (20.8” x 11.8” x 13”)
Weight	10.8 Kg (23.8 lbs.)
Light sources	Light Emitting Diodes (LEDs)
Light emission	590 nm output: 5 mW/cm^2 660 nm output: 65 mW/cm^2 850 nm output: 8 mW/cm^2
Beam diameter	30 mm (nominal) at treatment plane
Treatment exposure time	A total of 250 seconds (4 minutes 10 seconds). There are 4 phases: • Phase 1: 590 and 850 nm pulsed: 35 seconds • Phase 2: 660 nm continuous waveform: 90 seconds • Phase 3: 590 and 850 nm pulsed: 35 seconds • Phase 4: 660 nm continuous waveform: 90 seconds



Valeda® Light Delivery System

Valeda Overview

- Valeda treatment delivery very similar to many ophthalmology office diagnostic and treatment devices
- Implementation support available from LumiThera Customer Success Team
- Treatment is simple to learn and easy to train for operators
- No pupil dilation required
- Nine (9) flexible treatment sessions delivered over 3–4 weeks
- 2-3 treatment cycles per annum

Photobiomodulation Delivery Specifications

- Valeda delivers eye safe photobiomodulation treatment using LEDs
- The eye is uniquely accessible to PBM treatment. No other tissue or bone interferes with treatment directed to the eye
- Valeda is NOT a LASER. Valeda delivers a non-coherent, homogenized, light beam produced by LEDs
- Valeda meets all requirements set forth by ANSI Z80.36 and IEC 62471for light exposure safety
- Valeda does not deliver thermal treatment or produce local cellular damage
- No dilation required for PBM treatment
- No phototoxicity or serious adverse events considered related to PBM treatment have been reported in Valeda clinical trials

LIGHTSITE III: Principal Investigators

Clinical Sites		
Principal Investigator	**Clinic**	**Location**
Diana Do	Byers Eye Institute, Stanford University	Palo Alto, CA
Richard Rosen	New York Ear and Eye Infirmary of Mount Sinai	New York, NY
David Boyer	Retina Vitreous Associates Medical Group	Beverly Hills, CA
Victor Gonzalez	Valley Retina Institute	McAllen, TX
Samantha Xavier	Florida Eye Clinic	Altamonte Springs, FL
Allen Hu	Cumberland Valley Retina Consultants	Hagerstown, MD
David Warrow	Cumberland Valley Retina Consultants	Chambersburg, PA
Eleonora Lad	Duke Eye Center	Durham, NC
Todd Schneiderman	Retina Center NorthWest	Silverdale, WA
Allen Ho	Mid Atlantic Retina	Cherry Hill, NJ

LIGHTSITE III: Clinical Trial Design

Key Study Criteria:

Inclusion

- Diagnosis of Dry AMD
- BCVA between 20/32 to 20/100

Exclusion

- Current or history of neovascular maculopathy
- Presence of center involving geographic atrophy (GA) within central ETDRS 1 mm diameter
- Visually significant disease in any ocular structure apart from dry AMD

Study Duration: 24-Months; Focus on Month 13, Month 21 (Final Tx series), and Month 24 (3 months after final Tx series) timepoints
Randomization: 2:1 randomized into PBM:Sham treatment groups
Sham Control (Active low dose control): 10-100x reduction of 590 and 660 nm; Removal of 850 nm
Masking: Triple masked (subjects, sites, sponsor)
Outcome measures: Best corrected visual acuity (BCVA); Low Luminance BCVA (LLBCVA); MARS Contrast sensitivity (CS); Radner Reading; Visual Function Questionnaire 25 (VFQ-25, Quality of Life); D-15 Color Vision; Perimetry; OCT/FAF/Fundus photo imaging (Heidelberg Spectralis, Duke Reading Center)

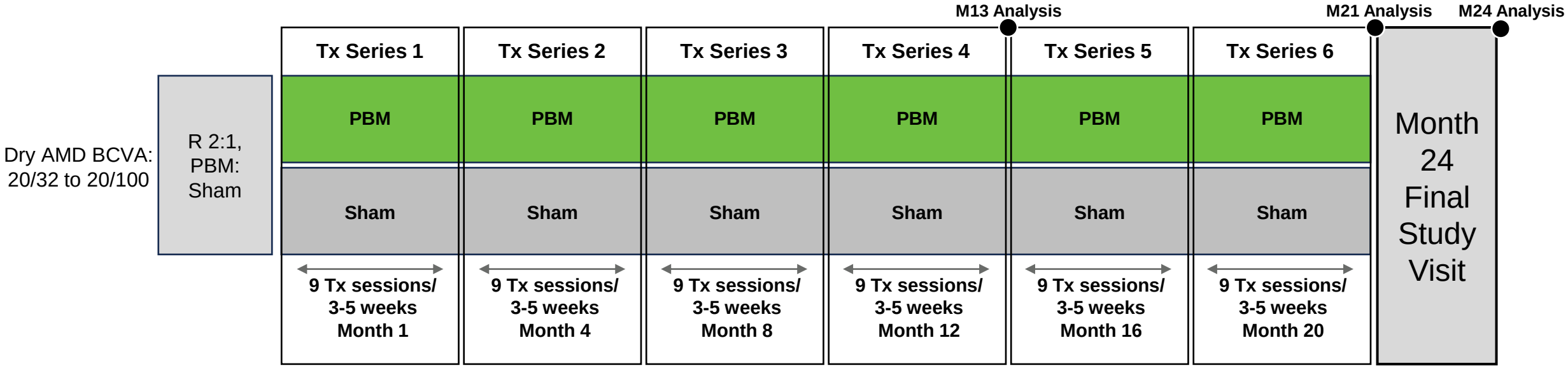
Boyer D. et al., Retina, 2024

LIGHTSITE III: Clinical Trial Design

A double-masked, randomized, sham-controlled, parallel group, multi-center study to assess the safety and efficacy of PBM in subjects with dry AMD

PBM Tx: 590, 660 and 850 nm

Sham: 10x and 100x reduction of 590 and 660 nm; Removal of 850 nm



Primary Endpoint: *BCVA change from baseline at Month 13 or Month 21. Comparison between the PBM and Control arms to demonstrate statistical superiority of the PBM treatment, (α of 0.025 to control for multiple testing), at both Month 13 and 21 with Month 13 tested first.*

Secondary and Exploratory Endpoints: *BCVA, MARS CS, Radner Reading, LLBCVA, Quality of Life (VFQ-25), and anatomical outcomes via OCT/FAF/Fundus photo imaging were conducted at selected timepoints over 24-months with a focus on Month 13, 21 (Final Tx series), and 24 (3 months after final Tx series).*

Boyer D. et al., Retina, 2024

LIGHTSITE III: Subject Baseline Characteristics

LIGHTSITE III Baseline Characteristics	
Subjects	100
Eyes	148 (2:1 randomized into PBM and Sham Treatment groups)
Race	99% Caucasian, 1% Black/African American
Gender	32 M (32%), 68 F (68%)
Age	Mean 75.0 years
BCVA BL Letter Score	PBM: 70.7 (SD 5.2) Sham: 70.1 letters (SD 4.3)
Clinical Classification (Beckman*)	Early: 32 (21.6%); Intermediate: 105 (71.0%); Late: 11 (7.4%)
AREDS Categories	AREDS II: 19 eyes (13%); AREDS III: 129 eyes (87%)
Risk Factors for AMD progression^	
Low Risk (1-2 risk factors)	48 eyes (32.4%)
Moderate to High Risk (3-4 risk factors)	100 eyes (67.6%)
Time from Diagnosis	Mean 4.9 years
AREDS supplements	86 (86%) Yes 14 (14%) No

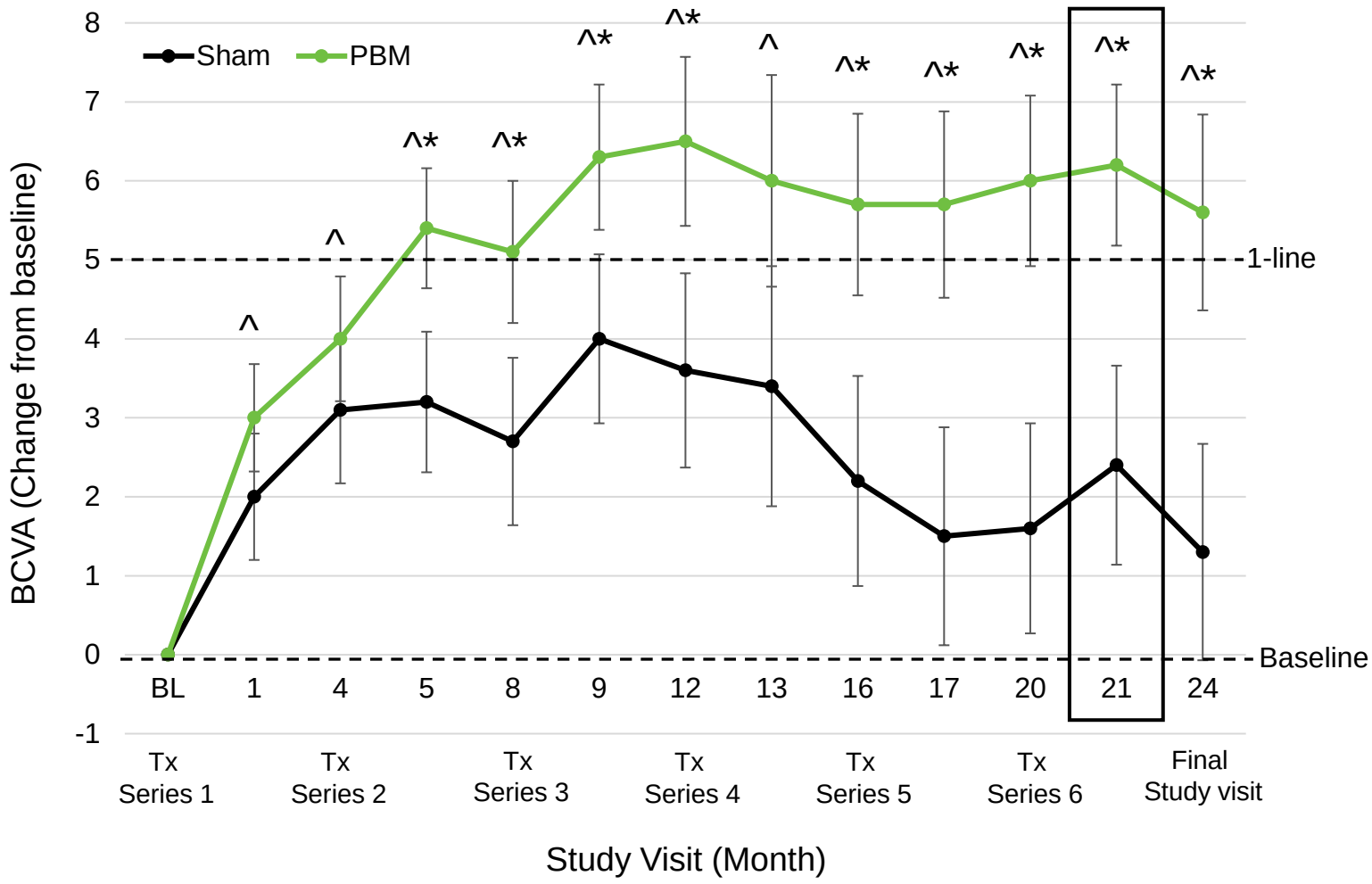
**Ferris FL 3rd, Wilkinson CP, Bird A, et al. Clinical classification of age-related macular degeneration. Ophthalmology. 2013;120(4):844-851. doi:10.1016/j.ophtha.2012.10.036. ^A modified Ferris risk factor scoring system was used to identify the total risk factors for each eye indicating potential risk for further progression of disease (max of 4 points for high risk).*

Boyer D. et al., Retina, 2024

LIGHTSITE III: Primary BCVA Efficacy Endpoint Met

Trial Design

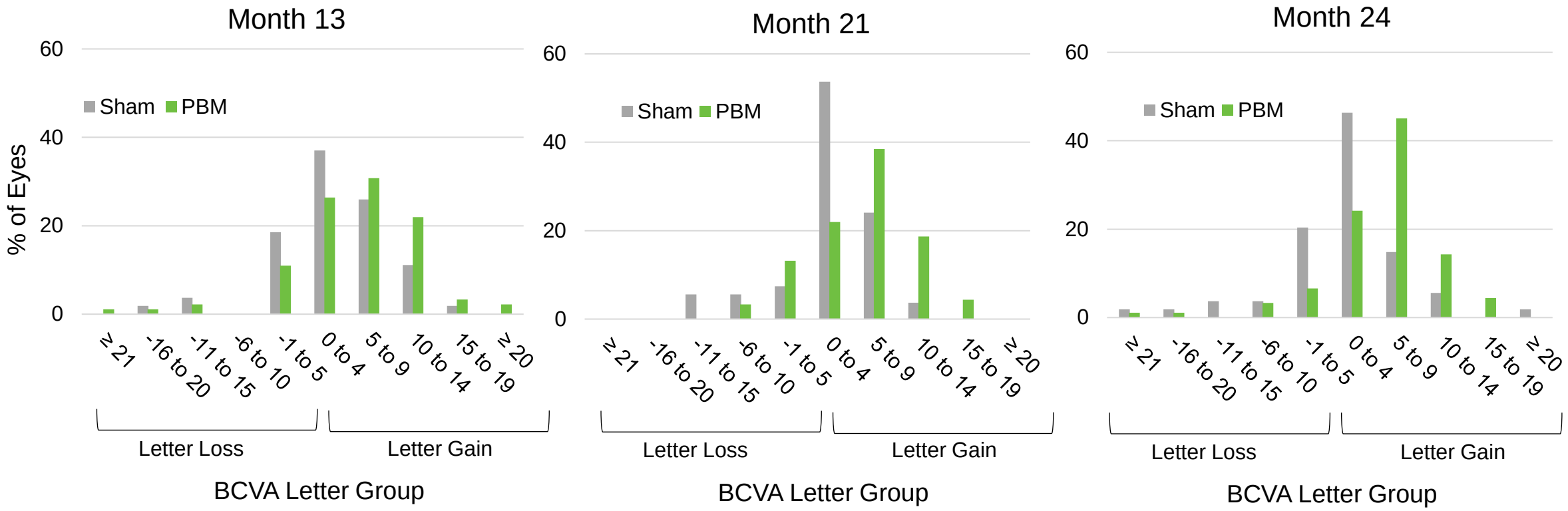
- The study met the predetermined primary efficacy BCVA endpoint at Month 21 (p = 0.0036) with a gain of 6.2 letters in the PBM group (mean letter difference of 3.8 letters between Tx groups)
- A mean letter gain of 5.6 letters in the PBM group was maintained at Month 24 (mean letter difference of 4.3 letters between Tx groups, p = 0.0024)



*LS mean presented with multiple imputation. *, p < 0.05 between groups; ^, p<0.0001 within group. Do, D. et al., Photobiomodulation for Dry AMD. Presented at the American Academy of Ophthalmology, Chicago, IL, USA. October 20, 2024.*

LIGHTSITE III: BCVA Letter Distribution

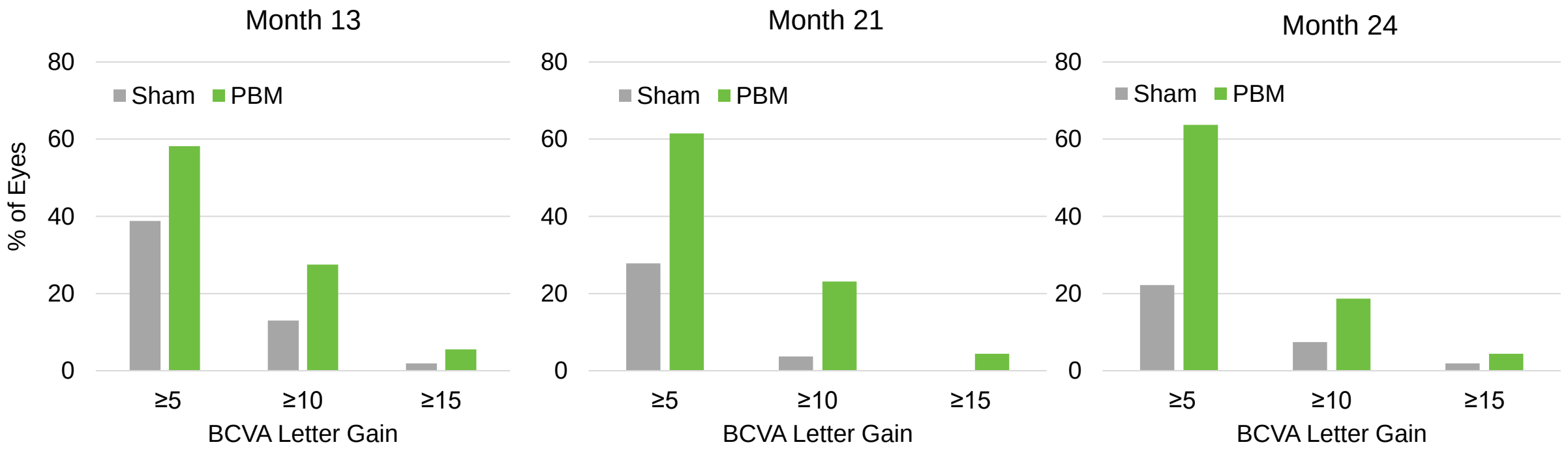
At Month 24, the PBM group showed maintained vision improvements in ~60% of patients of > 5 letter benefits while BCVA letter loss increased in the Sham group



Data presented with multiple imputation. *Do, D. et al., Photobiomodulation for Dry AMD. Presented at the American Academy of Ophthalmology, Chicago, IL, USA. October 20, 2024.*

LIGHTSITE III: BCVA Letter Gain Distribution

The PBM group showed a higher frequency of ≥ 5 letter, ≥ 10 letter, and ≥ 15 BCVA letter gains compared to the Sham group at Months 13, 21, and 24.

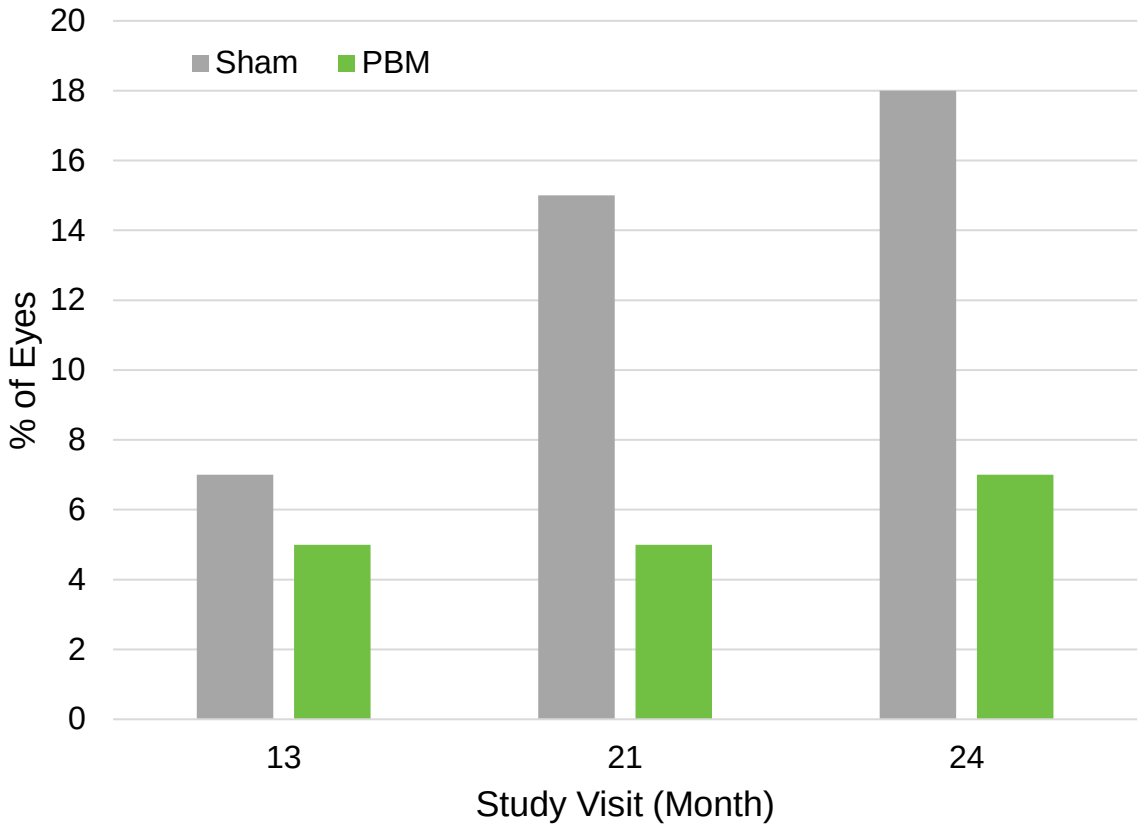


Data presented with multiple imputation. ***Do, D. et al., Photobiomodulation for Dry AMD. Presented at the American Academy of Ophthalmology, Chicago, IL, USA. October 20, 2024.***

LIGHTSITE III: Percentage of BCVA Loss (> 5 Letters)

PBM reduced the % of eyes with vision loss of >5 letters compared to the Sham group over 24 Months

Timepoint	Sham	PBM
Month 13	7%	5%
Month 21	15%	5%
Month 24	18%	7%

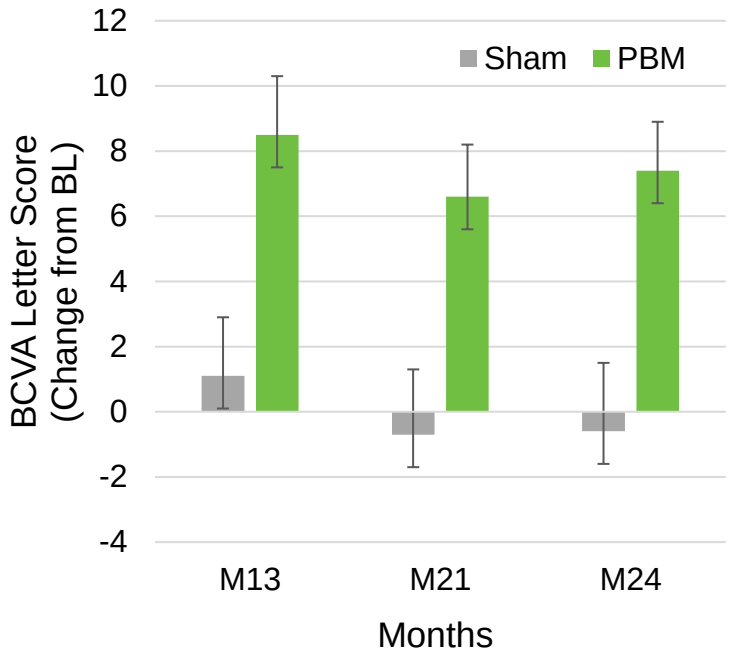


Data presented with actual values. ***Do, D. et al., Photobiomodulation for Dry AMD. Presented at the American Academy of Ophthalmology, Chicago, IL, USA. October 20, 2024.***

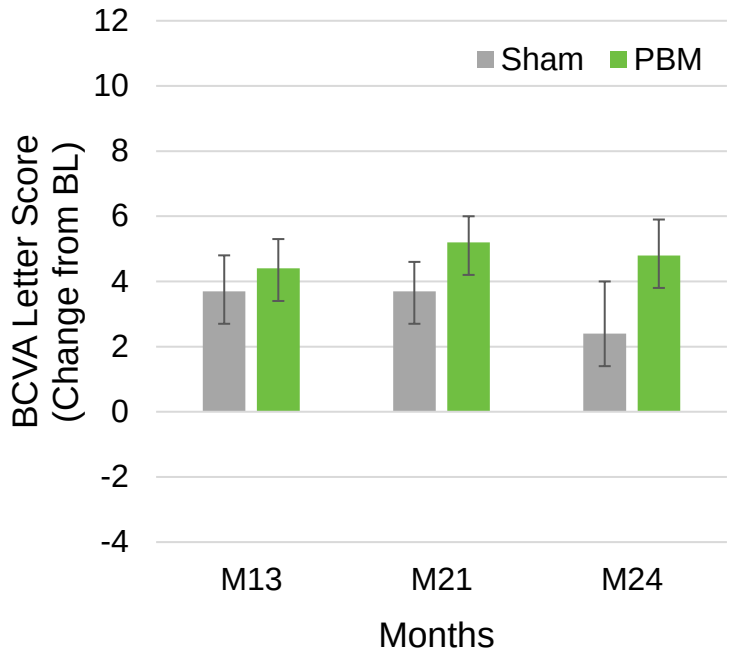
LIGHTSITE III: BCVA Change Stratified by Baseline Acuity

- Eyes with worse baseline BCVA show larger visual gains
- At baseline, 30.0% of eyes (n=45) had BCVA <70 letters; 70.0% of eyes (n=103) had BCVA ≥ 70 letters (mean of 72.4 letters - near normal/ mild visual impairment)
- Eyes with baseline BCVA between 61-70 letters showed more robust increases in acuity following PBM compared to eyes with baseline letter scores ≥ 70 letters

Baseline BCVA:
61-70 Letters
(20/63 – 20/40 Snellen)



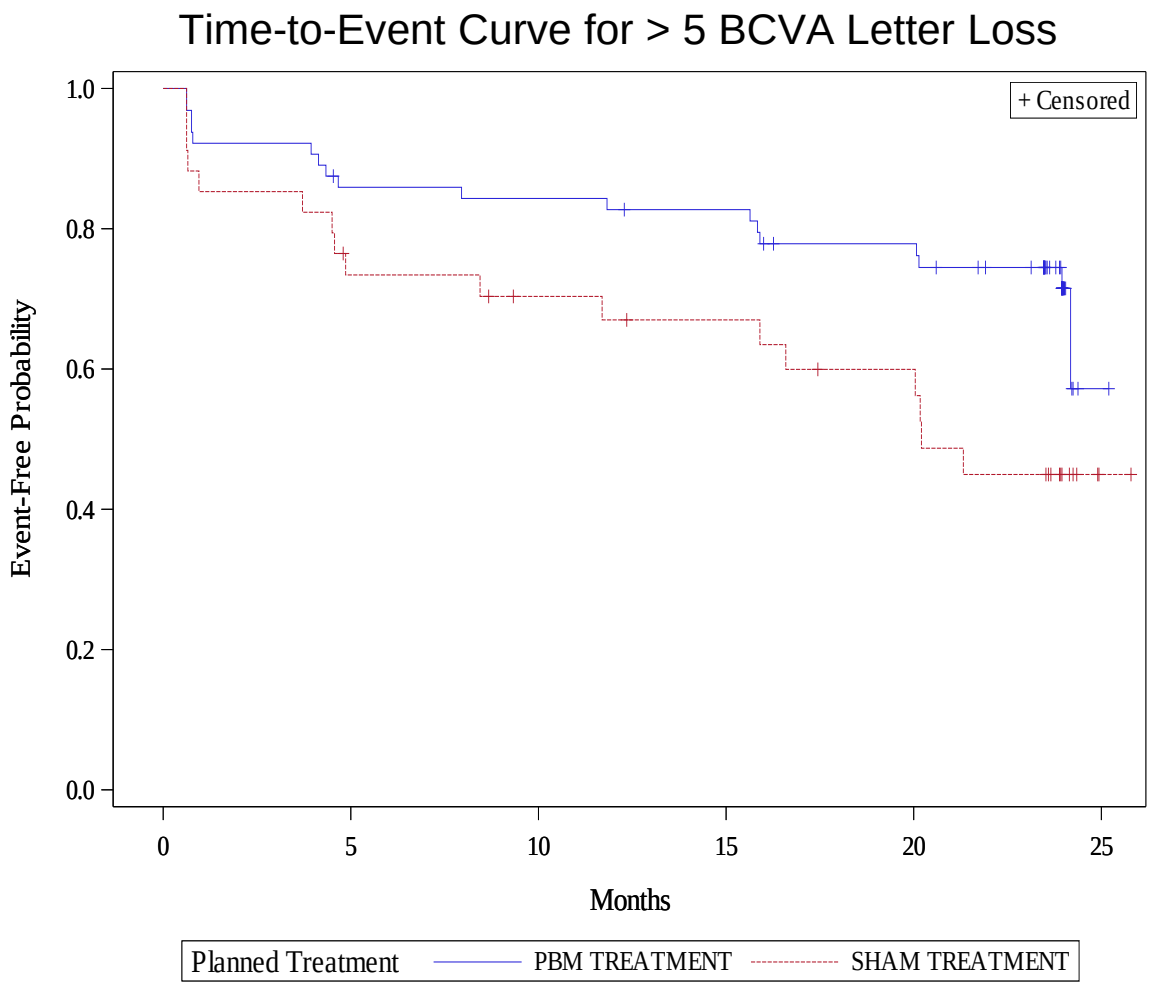
Baseline BCVA:
>70 Letters
(>20/40 Snellen)



Data presented with last observation carried forward (LOCF). ***Do, D. et al., Photobiomodulation for Dry AMD. Presented at the American Academy of Ophthalmology, Chicago, IL, USA. October 20, 2024.***

LIGHTSITE III: Reduced Risk of BCVA Loss

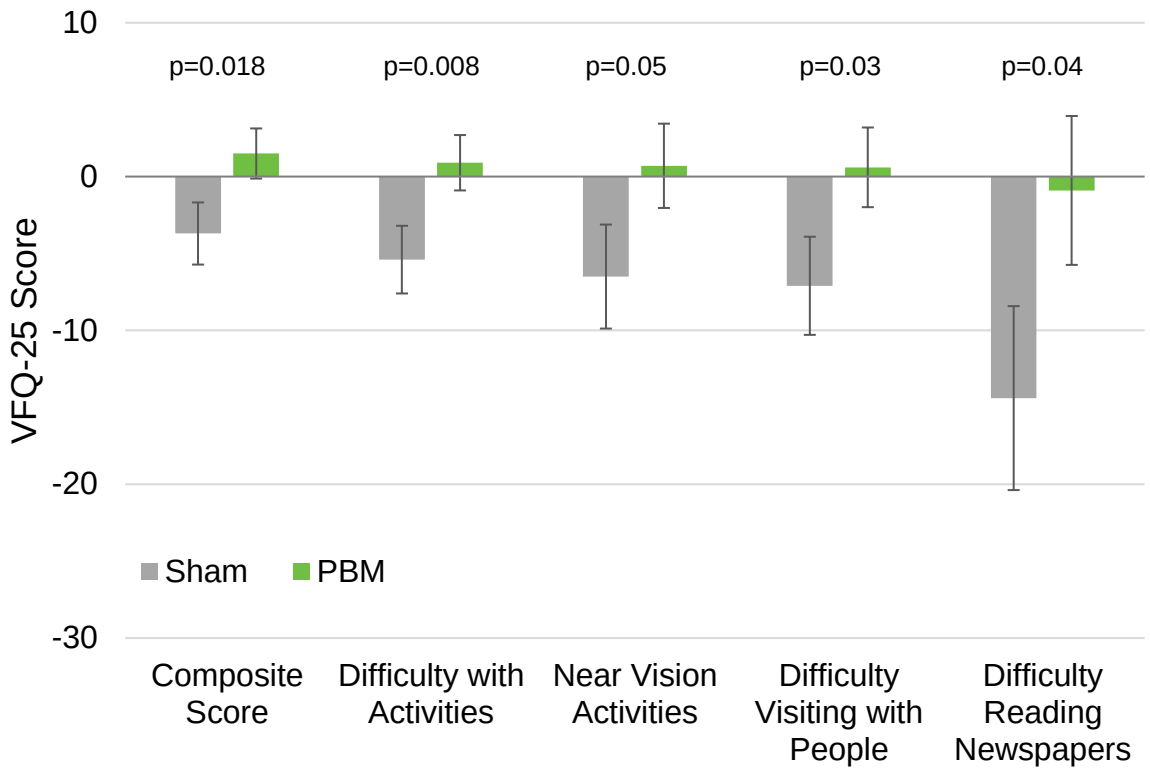
- A post-hoc Cox proportional hazards model was performed to evaluate the time to event hazard ratio of BCVA loss > 5 ETDRS letters
- The hazard ratio for BCVA with a > 5 letter loss was 0.47, ($p < 0.02$) which indicated a statistically significant 53% reduction in onset of vision loss of > 5 letters for subjects that received PBM versus Sham treatment over 24-months



Do, D. et al., Photobiomodulation for Dry AMD. Presented at the American Academy of Ophthalmology, Chicago, IL, USA. October 20, 2024.

LIGHTSITE III: Quality of Life Improvement

- Additional Clinical outcome measures for Quality of life (QoL, VFQ-25)
- Significant improvement in overall VFQ-25 QoL Composite Score (p = 0.018)
- At Month 21, PBM-treated subjects showed improvement in overall VFQ-25 composite score and subscore assessments of difficulty with activities, near vision activities, difficulty visiting with people, and difficulty reading newspapers compared to deterioration observed in the Sham group



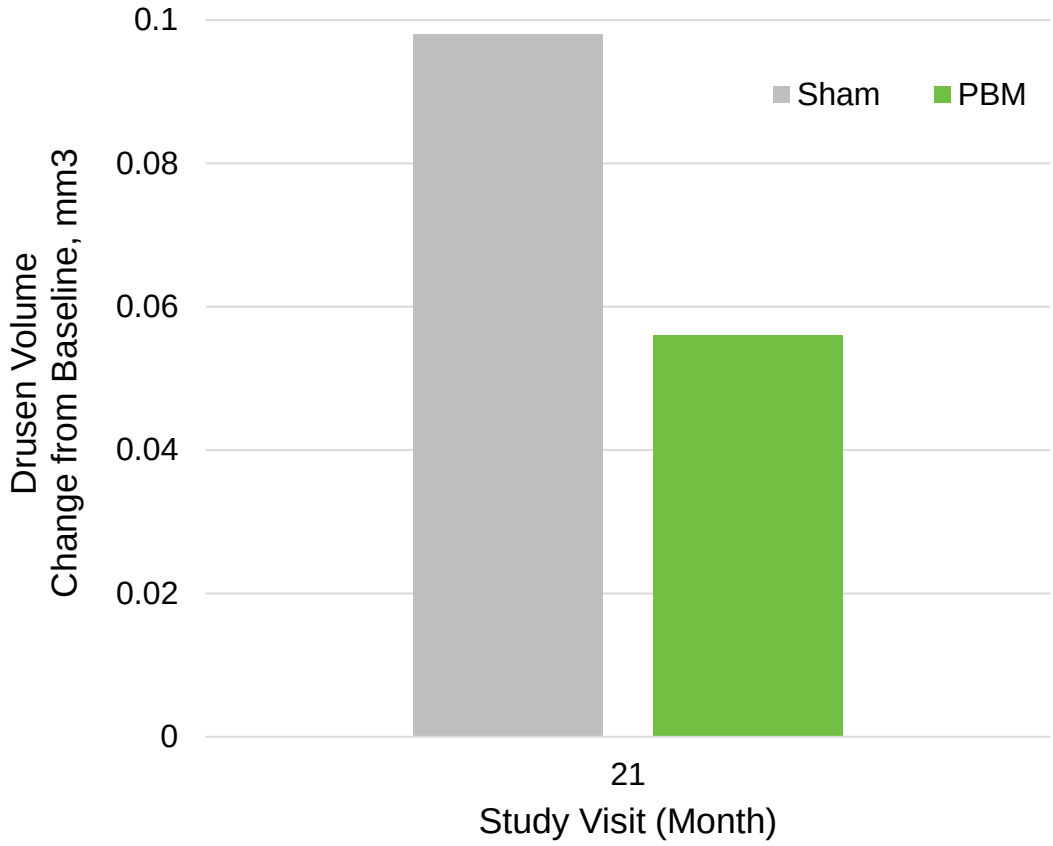
Data presented with actual values. *Do, D. et al., Photobiomodulation for Dry AMD. Presented at the American Academy of Ophthalmology, Chicago, IL, USA. October 20, 2024.*

LIGHTSITE III: Macular Drusen Volume

Baseline drusen volume levels:

- Sham: 0.947 mm^3
- PBM: 0.973 mm^3

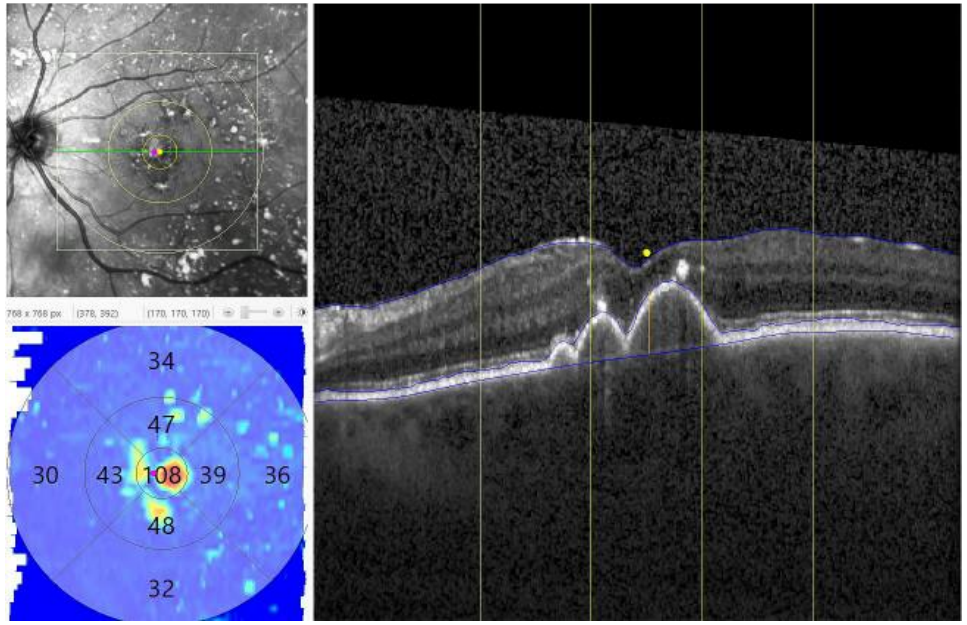
- A greater numerical increase (~2x) in change from baseline macular drusen volume was observed in Sham vs. PBM-treated eyes at Month 21



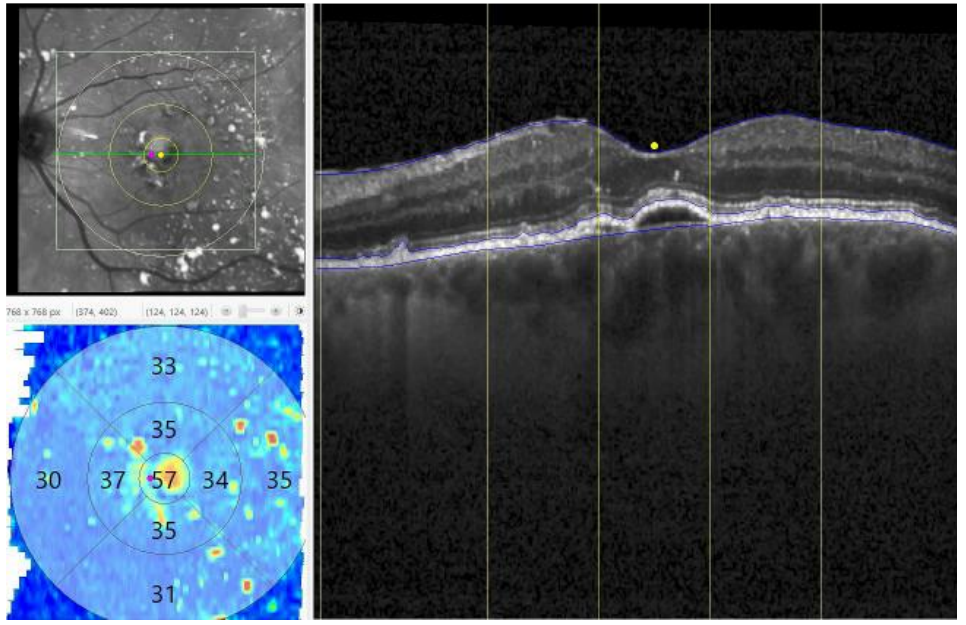
Data presented with multiple imputation. ***Do, D. et al., Photobiomodulation for Dry AMD. Presented at the American Academy of Ophthalmology, Chicago, IL, USA. October 20, 2024.***

LIGHTSITE III: Macular Drusen Volume Reduction

Visit 1, Screening Visit



Visit 60, Month 21 Visit (After 6 series of PBM)



Representative OCT imaging from a 77-year-old female subject showing a significant reduction in macular drusen volume after the final series of PBM treatment at Month 21 without loss of photoreceptor or retinal pigment epithelium visible.

Starting BCVA: 75 letters

Month 13 BCVA (4 series of PBM): 79 letters; 4 letter gain

Month 21 BCVA (6 series of PBM): 84 letters; 9 letter gain

Month 24 BCVA (3 months after final PBM Tx): 82 letters; 7 letter gain

LIGHTSITE III: Incident Geographic Atrophy

Disease progression to incident GA significantly higher in the Sham group vs PBM group at Month 24

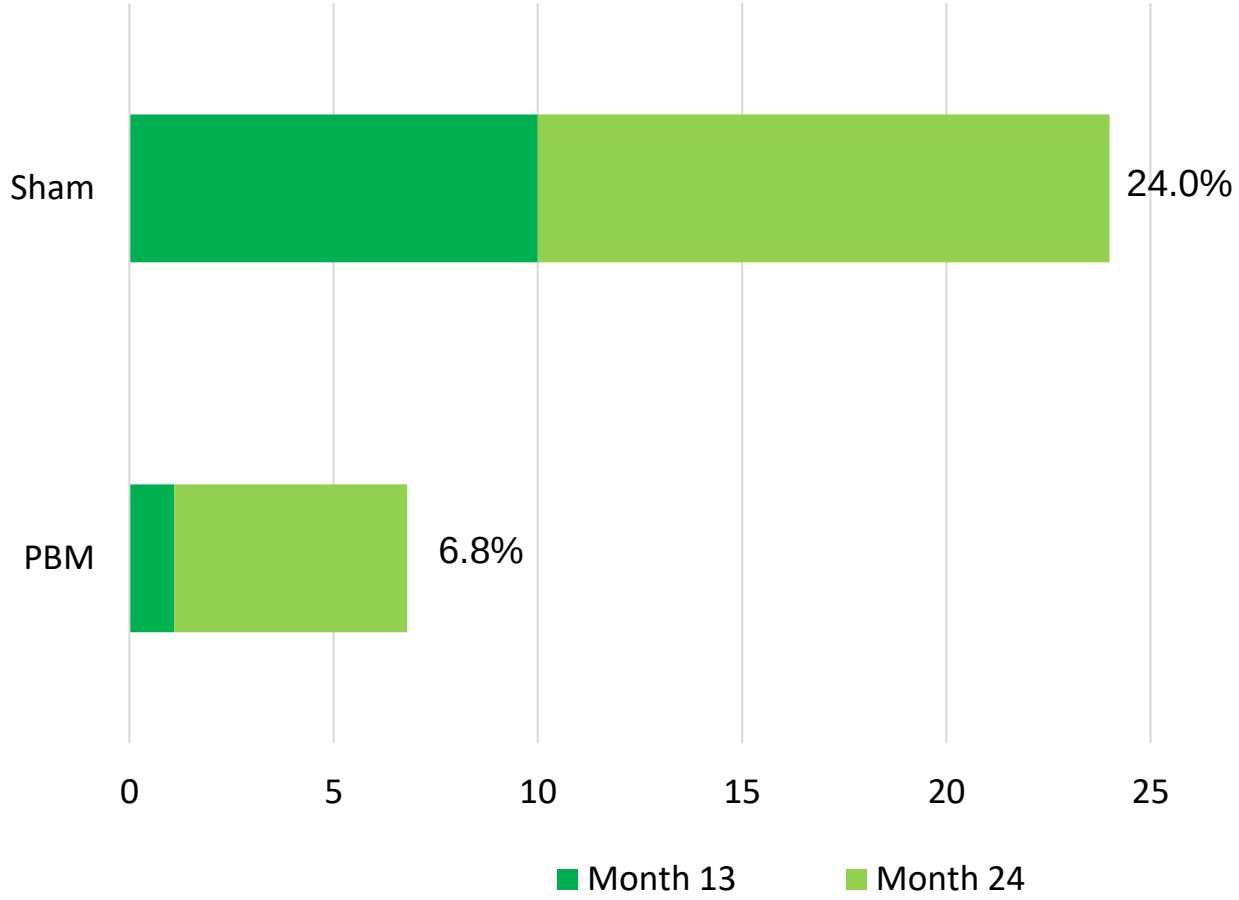
Incidence of New GA:

Month 13 (M13), p = 0.024

- Sham group: 5/50 (10.0%)
- PBM group: 1/87 (1.1%)

Month 24 (M24), p = 0.007

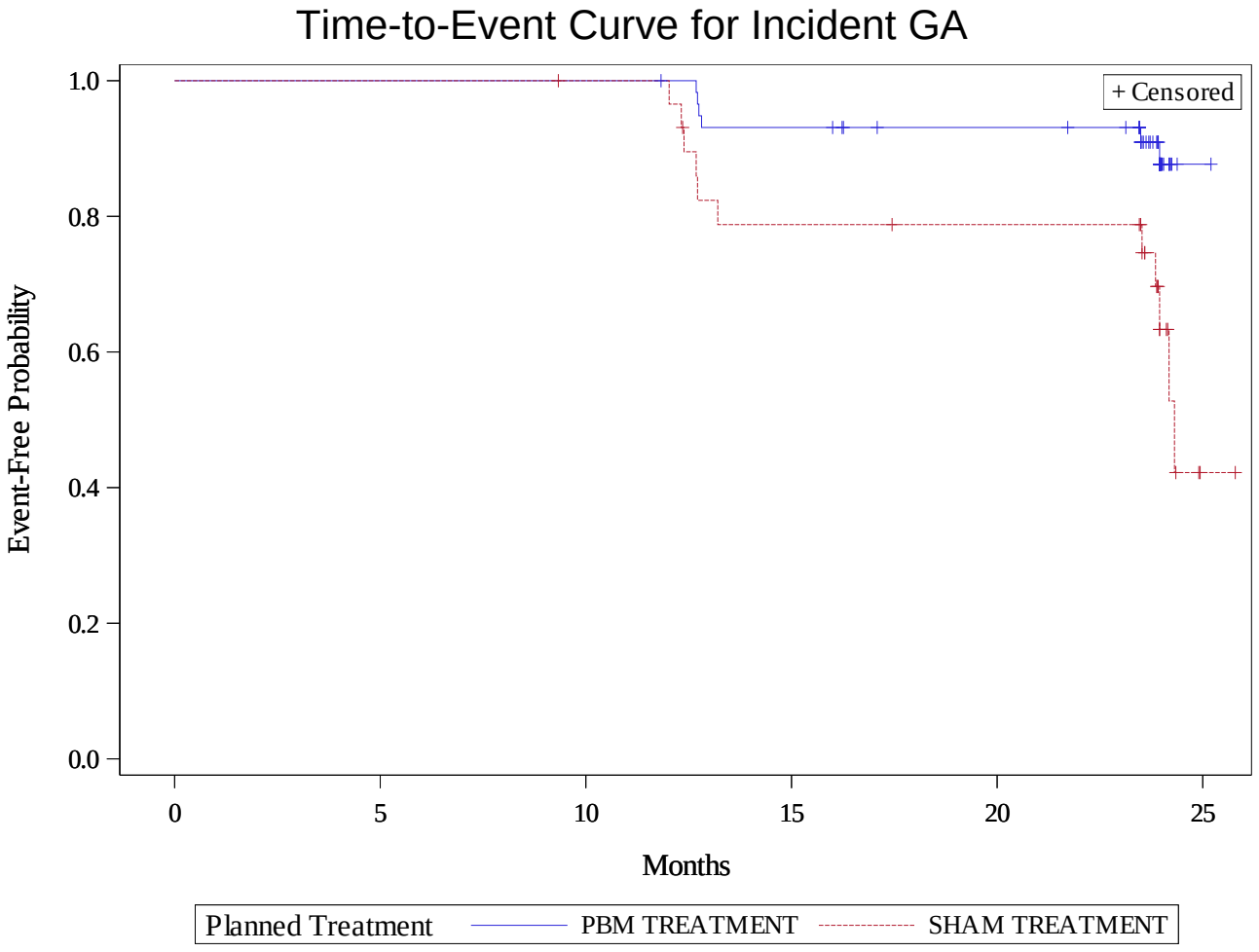
- Sham group: 12/50 (24.0%)
- PBM group: 6/87 (6.8 %)



Data presented with actual values. ***Do, D. et al., Photobiomodulation for Dry AMD. Presented at the American Academy of Ophthalmology, Chicago, IL, USA. October 20, 2024.***

LIGHTSITE III: Reduction of Incident GA

- A post-hoc Cox proportional hazards model time to event hazard ratio of GA incidence
- The hazard ratio (HR) for GA incidence was 0.27, ($p < 0.006$) indicating a statistically significant risk reduction of 73% to new incident GA over 24-months with PBM vs. Sham treatment



Do, D. et al., Photobiomodulation for Dry AMD. Presented at the American Academy of Ophthalmology, Chicago, IL, USA. October 20, 2024.

LIGHTSITE III: Incident iRORA

Reduced incidence of new iRORA in eyes with absence of prior iRORA and cRORA at screening

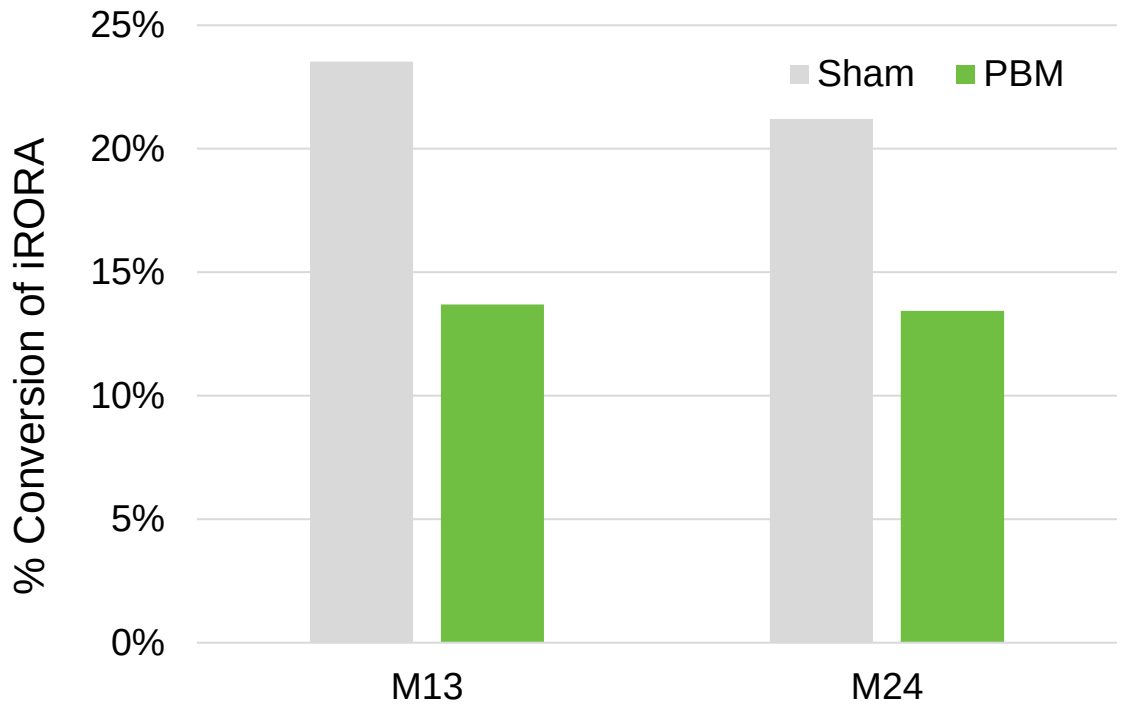
Incidence of iRORA at Month 13:

- 8 of 34 (23.5%) Sham eyes
- 10 of 73 (13.7%) PBM eyes

Incidence of iRORA at Month 24:

- 7 of 33 (21.2%) Sham eyes
- 9 of 67 (13.4%) PBM eyes

Conversion to iRORA in Eyes with absence of prior iRORA and cRORA



Data presented with actual values. Composite of all imaging modalities as confirmed by Duke Imaging center. Do, D. et al., Photobiomodulation for Dry AMD. Presented at the American Academy of Ophthalmology, Chicago, IL, USA. October 20, 2024.

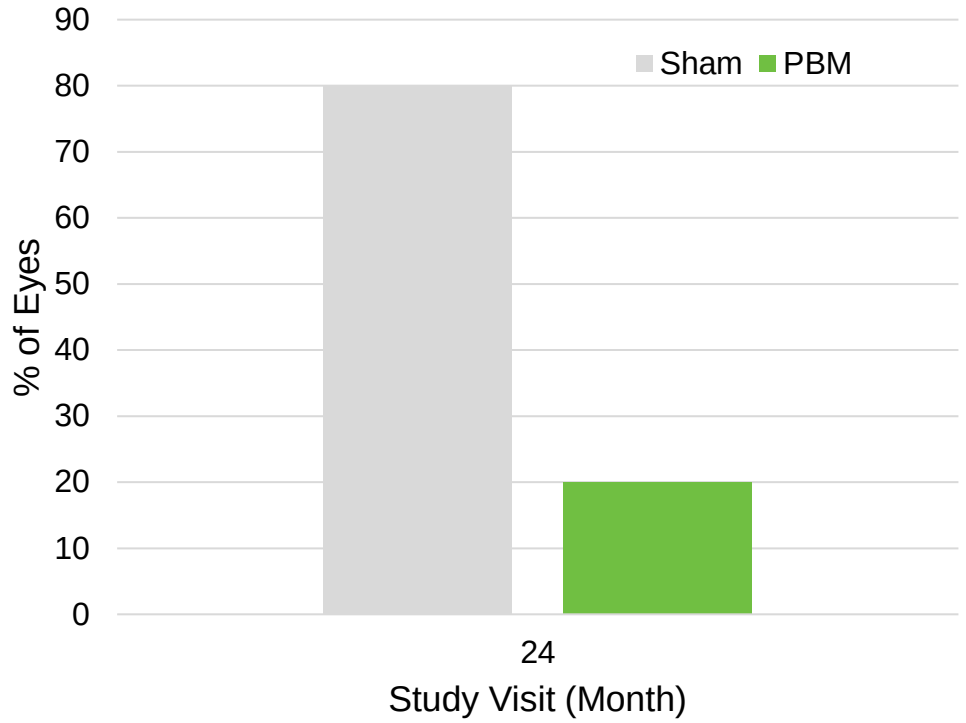
LIGHTSITE III: Conversion to GA/cRORA

Reduced incidence of new GA with iRORA present at screening

Occurrence of GA with iRORA at Month 24:

- 4 of 5 (80.0%) Sham eyes
- 1 of 5 (20.0 %) PBM eyes

% Eyes that Converted to GA with iRORA at Screening



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LIGHTSITE III: Adverse Event Reporting

System Organ Class Preferred Term	Sham (N = 55) n (%)	PBM (N = 93) n (%)	Total (N = 148) 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 Haemorrhage	0 (00.0)	2 (2.2)	2 (1.4)
Conjunctivitis Allergic	0 (00.0)	2 (2.2)	2 (1.4)
Cystoid Macular Oedema	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)
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)

**Prevalence of High-Risk Eyes (companion eye with nAMD at Baseline) was 3x higher (12:4) in the PBM group vs. Sham group - when Sham is normalized to the higher rate, development frequency would be estimated at 7.3%.*

LIGHTSITE III: Adverse Event Reporting

System Organ Class Preferred Term	Sham (N = 55) n (%)	PBM (N = 93) n (%)	Total (N = 148) n (%)
Adverse Events (Continued)			
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)

LIGHTSITE III: Safety Summary

- Similar frequencies of adverse events (AE) (Sham, 25.5%; PBM, 25.8%) and ocular-specific AEs (Sham, 20.0%; PBM, 22.6%) observed between treatment groups
- Three subjects had ocular-specific AEs considered related to the procedure: punctate keratitis (Sham; n = 2; 3.6%), visual perseveration (after image) (Sham; n = 1; 1.8%), and application site warmth (PBM; n = 1; 1.1%). No ocular-specific AEs led to study discontinuation.
- Seven (7.5%) ocular-specific serious adverse events (SAE) of nAMD were reported in the PBM group and three (5.5%) ocular-specific SAEs (2 nAMD, 1 cystoid macular edema) were reported in the Sham group. No SAEs were considered associated to the treatment by the primary investigator.
- Severity of AEs reported were mostly mild/moderate in both treatment groups
- No signs of phototoxicity
- No adverse effect on color vision or perimetry

LIGHTSITE III: Study Summary

LIGHTSITE III study results show significant effect on clinical and anatomical outcomes that support vision improvement and disease modifying effects

- LIGHTSITE III met the primary efficacy endpoint with a statistically significant improvement in BCVA in the PBM versus the Sham group
- Eyes with worse BCVA at baseline showed larger magnitude gains in BCVA
- Increased rate of > 5, 10, and 15 letter BCVA gains following PBM compared to BCVA loss in the Sham group
- Cox proportional analyses showed a significant reduction in the hazard ratios for BCVA vision loss and incident GA in PBM vs Sham treatment groups
- Reduced occurrence of incident GA and other exploratory markers of disease progression
- Reduced macular drusen volume
- Improved QoL in VFQ-25 Composite score and select subscales
- A favorable safety profile was observed with no signs of phototoxicity and no deterioration in other visual outcomes including contrast sensitivity, low luminance BCVA, Radner reading, perimetry, or color vision observed