Clinical science

12-month outcomes of photobiomodulation in dry age-related macular degeneration: a prospective multicentre randomised double-masked controlled clinical trial

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ABSTRACT

Background Dry age-related macular degeneration (dAMD) is the leading cause of irreversible vision loss in older adults, with no approved treatment to modify progression in early and intermediate stages. Photobiomodulation (PBM), which targets mitochondrial dysfunction and retinal inflammation, has shown promise in early studies. This study aims to evaluate the anatomical and functional efficacy of PBM in eyes with early and intermediate dAMD.

Methods In this 12-month, multicentre, randomised double-masked controlled trial, 138 eyes from 78 patients with early or intermediate dAMD were included. The primary outcome was change in mean drusen volume (MDV) from baseline to 12 months. Secondary outcomes included change in best-corrected visual acuity (BCVA) and adverse events. Multilevel mixed-effects regression was used to analyse treatment-time interactions.

Results MDV decreased significantly in the PBM group (–0.03±0.05 mm³) while increased in the sham group (+0.02 ± 0.04 mm³; p<0.001) at 12 months. The PBM group also showed a significant improvement in BCVA (+1.31 ± 6.7 letters) compared with a decline in the sham group (–2.62±7.1 letters), yielding a between-group difference of +3.75 letters (95% CI 1.16 to 6.34; p=0.0001). Female sex and higher Age-Related Eye Disease Study (AREDS) category were associated with MDV increase over time (p=0.030 and p=0.003; respectively), while older age was associated with MDV reduction (p=0.049). Four eyes in the sham group developed macular neovascularisation, compared with none in the PBM group (p=0.044), while one eye in the PBM group developed geographic atrophy (p=1.00). No cases of retinal phototoxicity were observed.

Conclusion PBM significantly reduced drusen burden and improved visual function in early and intermediate dAMD over 12 months, with an excellent safety profile. These findings support PBM as a promising therapeutic option for patients with non-neovascular age-related macular degeneration, despite further studies with longer follow-up are needed to confirm the role of PBM in potentially slowing the natural course of the disease.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Photobiomodulation (PBM) has shown potential benefits in early studies for treating dry age-related macular degeneration (dAMD), but robust clinical evidence from large, randomised controlled trials has been lacking.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that PBM significantly reduces drusen volume and improves visual acuity in early and intermediate dAMD, with no progression to neovascular age-related macular degeneration observed in treated eyes over 12 months.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings support PBM as a promising non-invasive therapeutic option for dAMD, warranting its integration into clinical practice and guiding future research on long-term disease modification.

INTRODUCTION

Age-related macular degeneration (AMD) remains the leading cause of irreversible vision loss in individuals over the age of 60 in developed countries. With an ageing global population, the burden of AMD continues to rise. Epidemiological data from large population-based studies estimate that the prevalence of early and intermediate AMD exceeds 10% in individuals aged 65 years and older, with projections indicating a doubling of cases by

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2050.[1–3] Dry AMD (dAMD), also known as non-neovascular AMD, accounts for approximately 85%–90% of all AMD cases and is characterised by progressive degeneration of the retinal pigment epithelium (RPE), accumulation of extracellular deposits (drusen) and in late stages, geographic atrophy (GA).[4]

Despite the growing clinical burden, treatment options remain limited. Complement inhibitors have been approved in some countries to slow the progression of late-stage dry AMD—specifically GA—but no therapies are currently available for earlier stages.[5 6] The pathogenesis of the disease is complex and multifactorial, involving oxidative stress, mitochondrial dysfunction, chronic inflammation and dysregulated autophagy within the RPE and overlying photoreceptors (PR).[7–9] Several seminal works have highlighted the pivotal role of mitochondrial injury in RPE senescence and degeneration, which subsequently impairs photoreceptor survival and function.[10–12]

In this context, photobiomodulation (PBM) has emerged as a promising non-invasive therapeutic strategy targeting the underlying cellular dysfunction in dAMD. PBM, also referred to as low-level light therapy (LLLT), employs specific wavelengths of visible and near-infrared light to stimulate biological processes at the mitochondrial level. The mechanism of action is based on the absorption of photons by cytochrome c oxidase (CCO), a key enzyme in the mitochondrial respiratory chain.[13–16] Preliminary animals and human trials, such as those by Merry *et al* and Ivandic *et al*,[17 18] have reported improvements in best-corrected visual acuity (BCVA) and contrast sensitivity in patients with early and intermediate AMD.[17 18] PBM treatment has been demonstrated to be safe and well tolerated among patients with dAMD; furthermore, both functional and anatomical data support the treatment's short-term efficacy.[19]

The present study reports the 12-month results of the DRUSEN trial (dry age-related macular degeneration: a prospective multicentre randomised controlled trial), evaluating efficacy and safety outcomes of PBM employed in patients with non-neovascular AMD.

MATERIALS AND METHODS

This was a multicentric, prospective, interventional, randomised, controlled, double-masked clinical trial comprising six European centres (University of Catanzaro, Catanzaro, Italy; University of Turin, Turin, Italy; University of Genoa, Genoa, Italy; University of Ferrara, Ferrara, Italy; University of Ankara, Ankara, Turkey; Istanbul Retina Institute, Istanbul, Turkey). Patients were recruited between June 2023 and April 2024. The study adhered to the guidelines of the Health Insurance Portability and Accountability Act and was performed in accordance with the tenets of the Declaration of Helsinki. The study was approved by Regione Calabria Ethics Committee and was prospectively registered on the clinicaltrial.gov. All participants provided written informed consent and were informed of their right to withdraw from the study at any time and for any reason. Patients were eligible for trial enrolment if they were at least 50 years old and had a diagnosis of stages 2–3 Age-Related Eye Disease Study (AREDS) category and were randomly assigned to either the treatment or sham group. The AREDS stage was ascertained based on colour fundus photography (CFP) and fundus autofluorescence (FAF) imaging.[20] In cases of bilateral disease, both eyes were included in the analysis and multilevel mixed-effects models were used to account for correlation between eyes within the same patient. Study subjects could use AREDS vitamin supplementation; however, no change in supplements 3 months before the study and during the entire study was allowed.

Exclusion criteria included: any history of neovascular AMD or presence of GA involving the fovea in the study eye, glaucoma or other concomitant retinal disorders, history of herpes infection, dense cataract not permitting high-quality imaging examinations. Additional exclusion criteria were concomitant epilepsy, neurological diseases, pregnancy and psychiatric comorbidities.

Treatment

Patients were randomly assigned in a 1:1 ratio to receive either PBM treatment using the eye-light device (Espansione Marketing S.p.A., Bologna, Italy) or sham treatment. To ensure double-masking, demo light mode with a very low level of energy not producing any therapeutic effect, simulating for both patient and operator a normal LLLT session, was used in patients belonging to sham. The treatment included two cycles: cycle 1 including 8 sessions, with 2 sessions per week over 4 weeks; cycle 2—conducted 6 months after cycle 1—comprised 6 sessions, with 2 sessions per week over 3 weeks. PBM was delivered through 2 distinct wavelengths, yellow (~590 nm; 25 mW/cm²) and red (~625 nm; 55 mW/cm²). Each session lasted 12 min in total: first 6 min through yellow light, followed by 6 min with red light. In detail, patient was instructed to keep his eyes closed for 5 min and opened for 1 min with both yellow-light and red-light masks. Patient compliance during the treatment was monitored by clinical staff to ensure correct adherence to the open/closed phases throughout the treatment. The sham device delivered <30% of the standard PBM output. Details regarding the sham mode and its biological inactivity have been discussed previously in prior publication.[21] Briefly, the sham device mimicked the appearance and operation of the active PBM system while the light intensity and fluence were below the established thresholds for photobiomodulation. While a minimal biological effect cannot be completely excluded, any such effect would, if present, reduce rather than exaggerate the difference observed between the active PBM and sham groups.

Ophthalmic examinations

All patients were evaluated at baseline (BL) and at 6 months (M6) after completion of the first treatment cycle. A second treatment cycle was administered 6 months after the first one. Following the second cycle, patients were evaluated at 12 months from the BL (M12). A complete ophthalmic examination was performed at BL, M6 and M12, including BCVA using Early Treatment for Diabetic Retinopathy Study (ETDRS) charts, slit lamp examination with lens opacity evaluation with the Lens Opacity Classification System (LOCS), fundus examination by indirect ophthalmoscopy, and intraocular pressure (IOP) measurement, CFP and FAF.

The BCVA was determined using the standard ETDRS protocol with modified ETDRS distance charts transilluminated with a chart illuminator (180 candela/m^2 Precision Vision) at 4 m. Visual acuity was scored as the total number of letters read correctly, calculated according to the ETDRS score method.

All patients were also evaluated using spectral-domain optical coherence tomography (SD-OCT) (Heidelberg Engineering, Heidelberg, Germany), using a 20×20 high dense volume scan (49 sections each). Only images with a signal strength of >20 decibels (dB) were used for the analysis. All scans were tracked with the follow-up function. Starting from the fovea, the central 1 mm (foveal) ETDRS ring was evaluated. The mean drusen volume (MDV) was assessed using Heidelberg software, followed by manual segmentation correction when necessary. The central

subfield thickness was measured using the automated measure provided by the Heidelberg software, and manual adjustments were adopted only in cases of segmentation errors. Drusenoid RPE detachments, defined as RPE elevations ≥350 µm, were also included in the drusen volume measurements. GA was defined as a round or oval area of atrophy of 175 µm or more as evaluated on FAF (Heidelberg Engineering, Heidelberg, Germany). Two independent masked imaging experts reviewed and graded all images confirming inclusion and exclusion criteria, and a third expert reader evaluated the optical coherence tomography (OCT) images in case of disagreement.

Adverse events (AEs) including dry eye-like symptoms, visual perseverations, warmth at the application site, or the onset of any macular neovascularisation (MNV) and foveal GA were evaluated at each follow-up visit. The tolerability of the treatment was measured at M12 through the Brief Ocular Discomfort Inventory (BODI) questionnaire,[22] an 11-point scale where 0 indicates no discomfort and 10 indicates extreme discomfort.

Outcomes

The primary endpoint of the study was the change in MDV over time in patients classified as AREDS 2 and AREDS 3, evaluated at BL, M6 and M12. The secondary endpoints included changes in BCVA assessed at the same time points.

Statistical analysis

Categorical variables are expressed as counts and percentages, whereas quantitative variables are expressed as mean±SD. The distribution of continuous variables was inspected graphically and then verified with the Shapiro-Wilk test. Given the lack of normal distribution, non-parametric tests were used when appropriate. Between-group comparisons were performed with either the Wilcoxon rank-sum (Mann-Whitney U) test or the Fisher's exact test according to variable type. The Friedman test was used to test for differences in repeated measures of MDV and BCVA in each group while the Wilcoxon signed-rank test for paired data was used to compare data from BL to M6 and from BL to M12 within the same patients' group (sham or PBM). Both eyes from individual patients were included in the study when eligible. To account for the correlation between eyes within the same patient, multilevel mixed-effects linear regression models were used to analyse the effect of PBM treatment over time on MDV and BCVA, adjusting for demographic and clinical covariates (age, sex and AREDS category). All statistical analyses were conducted using STATA version 18.0 (StataCorp, College Station, TX). A two-sided p value of <0.05 was considered statistically significant. Where appropriate, a Bonferroni-adjusted significance threshold of p<0.025 was applied to account for multiple comparisons.

RESULTS

A total of 138 eyes from 78 patients (mean age of 69.9±9.3 years) were included; 73.9% of participants were females. The baseline MDV was 0.39±0.11 mm³ and the mean BCVA was 81.14±6.26 ETDRS letters in the total cohort. No significant baseline differences were observed between the two treatment groups (table 1).

By month 12, 12 eyes from 6 patients were lost to follow-up due to lack of patients' adherence to the study. Consequently, 126 eyes were included in the final analyses (n=54 in the sham group; n=72 in the PBM group).

Mean drusen volume

MDV showed significant changes over time in both the sham and the PBM group (p<0.0001). Specifically, within the sham group, MDV increased significantly by +0.008 ± 0.02 mm³ at M6 (p=0.0059) and by +0.02 ± 0.04 mm³ at M12 (p<0.0001); conversely, within the PBM group, MDV decreased significantly by −0.025±0.05 mm³ at M6 (p<0.0001) and by −0.03±0.05 mm³ at M12 (p<0.0001, figure 1).

Multilevel mixed-effects model revealed a significant interaction between PBM treatment and time on MDV at both M6 (−0.03; p=0.017) and M12 (−0.05; p<0.001), along with a significant positive association with female sex (+0.04; p=0.030), AREDS category (+0.04; p=0.003) and a negative association with age (−0.002; p=0.049).

Table 1 Baseline clinical characteristics of the sham-treated and the photobiomodulation-treated groups

Parameter	Sham (eyes n=64)	PBM (eyes n=74)	P value
Age (years; mean±SD)	70.9±9.9	69.0±8.9	0.280
Sex (females; %)	67.2%	79.7%	0.120
Lens status (phakic; %)	81.3%	73%	0.313
AREDS (categories 2/3; %)	48.4 %/51.6%	47.3 %/52.7%	1.00
BCVA (ETDRS; mean±SD)	81.8±5.6	80.5±6.8	0.387
MDV (mm³; mean±SD)	0.38±0.10	0.39±0.12	0.887

AREDS, Age-Related Eye Disease Study; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; MDV, mean drusen volume; PBM, photobiomodulation.

Best-corrected visual acuity

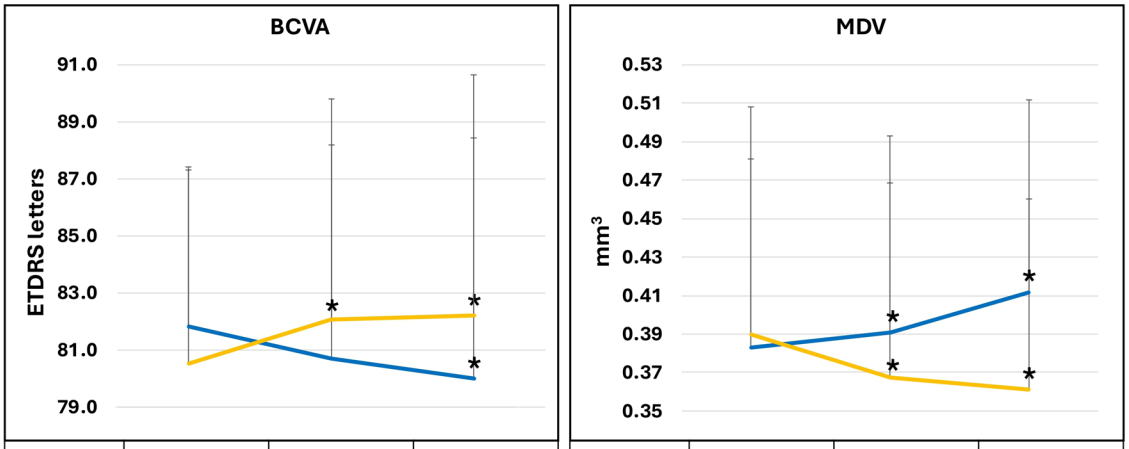
BCVA significantly changed over time in both the sham (p=0.025) and the PBM-treated groups (p=0.0008). In the PBM group, BCVA improvements were observed as early as 6 months post-treatment (p=0.017) and were sustained at M12 (p=0.006). In contrast, the sham group experienced a decline in BCVA at M12 (p=0.007). At M12, the PBM group showed a mean gain of 1.31±6.7 ETDRS letters (p=0.006), while the sham group showed a mean loss of −2.62±7.1 ETDRS letters (p=0.007), resulting in a between-group difference of 3.75 ETDRS letters (95% CI 1.16 to 6.34; p=0.0001, figure 1).

Multilevel mixed-effects linear regression model showed a marginally significant interaction between PBM treatment and time on BCVA at M6 (+2.38; p=0.058), which reached significance at M12 (+3.74; p=0.012). Additionally, there was a significant negative effect of time at M12 (−2.41; p=0.032) and of age (−0.23; p=0.001).

Safety outcomes

Overall, dry eye-like symptoms and visual perseverations each occurred in 8.7% of eyes (n=12), while warmth at the application site was reported in 18.1% (n=25). Four patients in the sham group developed macular neovascular membranes (0% in PBM; p=0.044), whereas one patient in the PBM group only developed geographic atrophy (0% in sham; p=1.00). At baseline, the eye developing GA was classified as AREDS 2 category, with an MDV of 0.27 mm³ and a BCVA of 80 ETDRS letters. Over the 12-month follow-up, BCVA declined by 25 letters, and foveal GA developed. This single occurrence did not affect the overall study outcomes and is consistent with the very low incidence reported in similar populations.

No signs of retinal phototoxicity were observed in either group. Table 2 provides a detailed summary of all ocular-specific AEs by group. The mean BODI score was 1.4±2.0 in the sham group and 1.6±2.5 in the PBM group, with no significant difference between groups (p=0.709).



	BL	M6	M12
Sham	81.8 ± 5.6	80.7 ± 7.5 p=0.846	80 ± 8.4 p=0.006
PBM	80.5 ± 6.8	82.1 ± 7.7 p=0.017	82.2 ± 8.4 p=0.006

	BL	M6	M12
Sham	0.38 ± 0.10	0.39 ± 0.10 p=0.0059	0.41 ± 0.10 p<0.0001
PBM	0.39 ± 0.12	0.37 ± 0.10 p<0.0001	0.36 ± 0.10 p<0.0001

Figure 1 Best-corrected visual acuity (BCVA) and mean drusen volume (MDV) at baseline (BL), month 6 (M6) and month 12 (M12) in sham-treated and photobiomodulation (PBM)-treated groups. P values indicate comparisons between BL and both M6 and M12 within each group. Adjusted significance threshold set at p<0.025. ETDRS, Early Treatment for Diabetic Retinopathy Study.

Representative cases of PBM effects on drusen volume are shown in figures 2 and 3.

DISCUSSION

This 12-month, prospective, multicentre, randomised, double-masked, controlled clinical trial was conducted to evaluate the efficacy and safety of PBM in patients with early and intermediate dAMD. Overall, the treatment proved to be safe and well tolerated. Notably, eyes receiving PBM showed statistically significant improvements, including a reduction in drusen volume and a gain in visual acuity.

The 12-month reduction in MDV in the PBM-treated group was modest, although significant, and it appeared to be consistent with the PBM proposed mechanism of action targeting mitochondrial dysfunction and drusen-associated inflammation, thus eventually leading to a reduction in drusen load.[10 17] Previous studies highlighted drusen volume as a key risk factor for disease progression. Abdelfattah *et al*[23] were among the first authors to use structural OCT to explore the association between drusen volume and progression to late AMD in individuals with early or intermediate disease. They found that patients with drusen volume exceeding 0.03 mm^3 had more than a four-fold increased risk of progressing to late AMD compared with those with lower volumes. Subsequently, Hirabayashi *et al*[24] used structural OCT to evaluate the prevalence of intermediate AMD (iAMD) biomarkers and their association with the development of complete RPE and outer retinal atrophy (cRORA) over 2 years. In a cohort of 330 eyes with iAMD, they confirmed that greater drusen volume was a risk factor for cRORA onset within the 24-month follow-up. More recently, Liu *et al*[25] conducted a longitudinal study of 171 iAMD eyes to inform clinical trial design for therapies targeting progression to GA. Using persistent choroidal hypertransmission defects (hyperTDs) as a surrogate endpoint, they demonstrated that drusen volume >0.25 mm^3 within a 5-mm fovea-centred area predicted the development of hyperTDs in approximately 68% of eyes within 12 months. Nonetheless, it is important to recognise that drusen volume is dynamic and may not exhibit a consistently progressive pattern over the course of the disease. In some cases, a reduction in drusen volume may precede the development of chorioretinal atrophy. Notably, in our study, the group of patients treated with PBM did not show an increased incidence of RPE atrophy at the 1-year follow-up. Nevertheless, we cannot exclude the possibility that atrophy may emerge at a later stage.

Another finding from our study was the average gain of 1.31 ETDRS letters that, compared with the mean loss of −2.62 in the sham group, resulted in a between-group difference of 3.75 letters. It is worth noting that baseline BCVA in the study population was consistent with previously reported values for iAMD,[26] with most eyes demonstrating relatively preserved vision and no major changes were expected over 12 months.[27 28] However, it is important to recognise that patients with iAMD typically do not experience significant visual acuity loss in early stages, and an average gain of 1.31 letters may not be clinically meaningful. More critically, since the primary concern in iAMD is progression to late-stage disease—which can severely impact vision—therapeutic strategies should prioritise reducing this risk.[28 29]

In addition to treatment effects, relevant demographic and clinical covariates were identified. Over the 12-month

Table 2 Ocular-specific adverse events in sham and photobiomodulation (PBM)-treated eyes

	Sham (n=64) n (%)	PBM (n=74) n (%)	Total (n=138) n (%)	P value
Dry eye-like symptoms	7 (10.9)	5 (6.8)	12 (8.7)	0.546
Visual perseverations	9 (14.1)	3 (4.1)	12 (8.7)	0.066
Warmth at the application site	16 (25)	9 (12.2)	25 (18.1)	0.075
Macular neovascular membrane	4 (6.3)	0 (0)	4 (2.9)	0.044
Geographic atrophy	0 (0)	1 (1.4)	1 (0.7)	1.00

P values represent between-group comparisons.

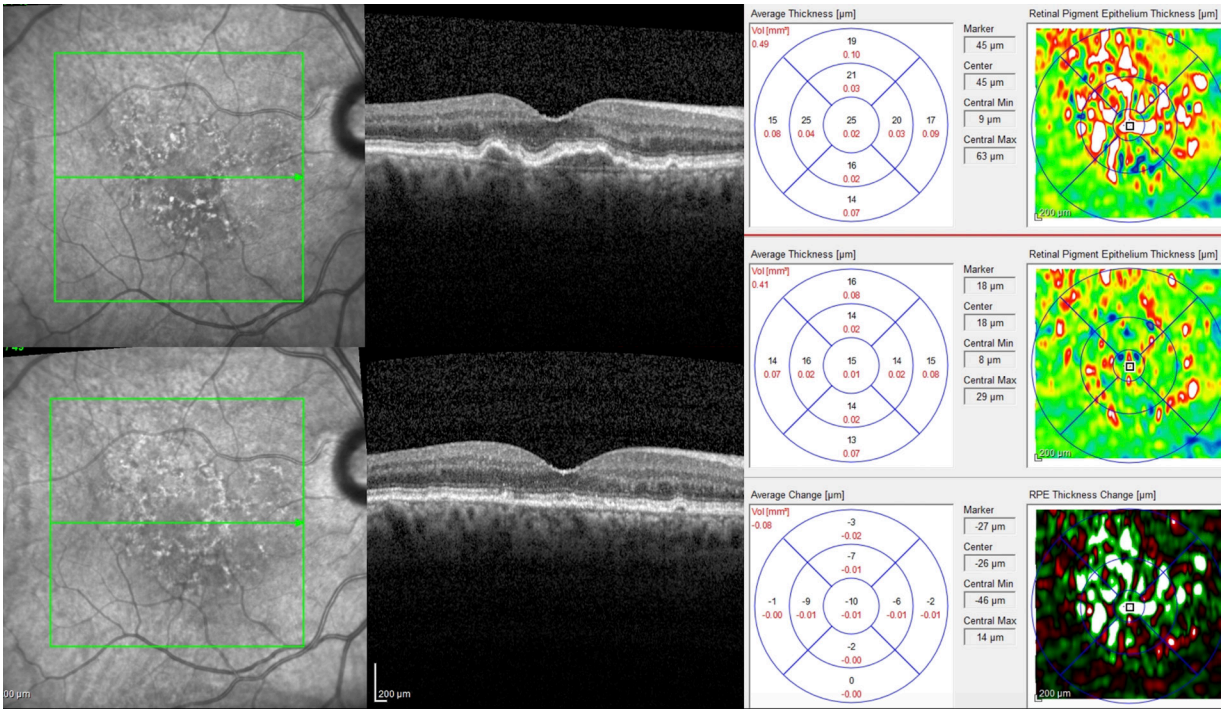


Figure 2 Representative imaging of macular drusen reduction in a PBM-treated eye. Baseline and 12-month tracked near infrared and spectral domain optical coherence tomography scans with corresponding drusen volume map showing a significant reduction of the drusen volume from 0.49 mm^3 to 0.41 mm^3 at 12 months. PBM, photobiomodulation; RPE, retinal pigment epithelium.

study period, female sex and higher baseline AREDS category were both associated with a statistically significant increase in MDV. These findings may reflect underlying biological or hormonal differences affecting drusen dynamics, or possibly a more active disease phenotype in these subgroups, rather than an enhanced therapeutic response. In contrast, older age was associated with a modest reduction in MDV over time, finding that could suggest either a slower rate of disease progression in older individuals or reduced responsiveness to PBM due to age-related declines in mitochondrial function and tissue repair capacity.

Importantly, an increase in MDV over time may indicate continued or accelerating disease activity and should not be interpreted as a positive outcome. These observations highlight the importance of patient stratification and reinforce

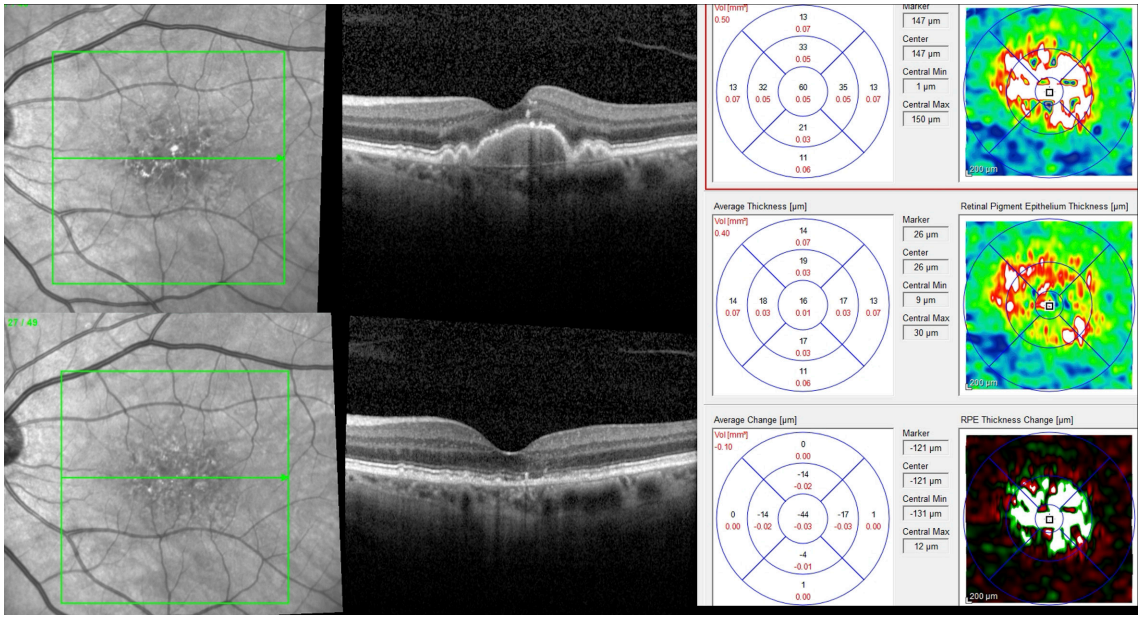


Figure 3 Representative imaging of macular drusen reduction in a PBM-treated eye. Baseline and 12-month tracked near infrared and spectral domain optical coherence tomography scans with corresponding drusen volume map showing a significant reduction of the drusen volume from 0.50 mm^3 to 0.40 mm^3 at 12 months. PBM, photobiomodulation; RPE, retinal pigment epithelium.

the need for early intervention—ideally before significant drusen accumulation and irreversible retinal damage occur.

Overall, results from the present study reinforce the biological plausibility of PBM in modulating mitochondrial function and retinal health and highlight the importance of personalised factors—such as age, sex and disease stage—when considering patient selection and treatment protocols.

Although the relationship between drusen volume and visual function remains a matter of debate,[30] our findings suggest that a reduction in MDV may be associated with functional (ie, visual acuity) improvement in selected cases. This observation potentially indicates that the treatment may confer functional benefits to the retina.

In terms of safety, PBM was well tolerated, with no evidence of retinal phototoxicity or treatment-related conversion to wet AMD. Intriguingly, all 4 cases of wet AMD occurred in the sham group. The overall incidence of ocular AEs was significantly lower in the PBM group, suggesting a favourable tolerability profile that supports its clinical applicability in an elderly population.

While these findings are encouraging, several limitations should be acknowledged. First, as mentioned above, the follow-up period, although adequate to capture short-term outcomes, may not fully reflect long-term disease-modifying effects of PBM. Second, while all participating centres adhered to standardised protocols, some degree of inter-centre variability cannot be excluded. Third, although the sample size was sufficient to detect significant differences in primary and secondary outcomes, larger-scale trials are needed to confirm these results and evaluate long-term efficacy, especially regarding progression to late-stage AMD (ie, GA or neovascular AMD). Moreover, drusen remodelling may spontaneously occur over time, and drusen reabsorption may be followed[31] or not[32] by retinal atrophy. Longer follow-up studies may be able to address this aspect. Limitations of the present study also include the use of BCVA as the sole functional endpoint, without incorporating additional assessments such as contrast sensitivity, low-luminance visual acuity, or microperimetry, or patient-reported outcomes such as vision-related quality-of-life measures. While BCVA provides a clinically meaningful assessment of visual function, these additional endpoints may be more sensitive to subtle changes in early and intermediate dAMD and could offer complementary insights. Future studies incorporating these measures would help to provide a more comprehensive evaluation of PBM therapy.

Despite these limitations, the DRUSEN trial represents, to date, one of the most robust investigations on PBM in non-neovascular AMD, offering compelling evidence for its clinical utility. The combination of statistically significant anatomical and functional benefits, along with favourable safety profile, positions PBM as a promising therapeutic option for early-intermediate dAMD, for which no approved disease-modifying treatments currently exist.

Future studies should aim to validate these findings in larger and more diverse populations, assess the optimal treatment frequency and duration, and explore potential synergies with nutritional or pharmacologic interventions. Moreover, the development of biomarkers predictive of treatment response may allow for more personalised therapeutic strategies in AMD management.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethics Committee 'Comitato Etico Regione Calabria' (approval number: 10/2024). It adheres to the tenets of the Declaration of Helsinki. Patients provided written informed consent prior to participation.

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