



# Letter to the Editor Regarding “Multiwavelength Photobiomodulation Improves Multiple Aspects of Visual Function in Early-Stage Dry Age-Related Macular Degeneration”

Christina Karakosta · Robert E. MacLaren

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To the Editor,

We read with interest the recent report by Küçükerdönmez and Tedford evaluating multiwavelength photobiomodulation (PBM) in a real-world clinical setting for early-stage non-exudative age-related macular degeneration (AMD) [1]. As one of the first non-randomized, single-center assessments of the LumiThera Valeda® Light Delivery System (LumiThera, Inc., Poulsbo, WA, USA) outside a controlled trial, this study offers valuable insight into the translational potential of PBM. However, the modest visual acuity gains reported—particularly in the absence of a control or masking—may reflect test–retest variability or learning effects rather than true physiological improvement. A closer

analysis of the methodology and results raises important questions regarding the clinical relevance and robustness of the findings. Below, we outline several key concerns.

## MODEST VISUAL GAINS OF UNCERTAIN SIGNIFICANCE

The study reports a statistically significant mean best-corrected visual acuity (BCVA) gain of +1.1 and +1.8 letters in cohort 1 and 2, respectively, 3 months after PBM treatment. While these findings suggest short-term visual function enhancement, the magnitude of change falls below the conventional threshold for clinical relevance—typically considered  $\geq 5$  letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale.

A similar issue was observed in the larger LIGHTSITE III randomized trial, where the PBM group showed a +5.4 letter gain versus +3.0 letters in the sham group at 13 months—a between-group difference of only 2.4 letters, which, although statistically significant ( $p=0.02$ ), also challenges the clinical meaningfulness of the treatment [2].

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C. Karakosta · R. E. MacLaren (✉)  
Oxford Eye Hospital, Oxford University Hospitals  
NHS Trust, Oxford, UK  
e-mail: enquiries@eye.ox.ac.uk

R. E. MacLaren  
Nuffield Department of Clinical Neuroscience,  
University of Oxford, Oxford, UK

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## ABSENCE OF CONTROL GROUP AND RISK OF PLACEBO EFFECTS

The lack of a control group or masking in the Küçükerdönmez and Tedford study precludes differentiation between treatment effects and potential placebo responses or learning effects from repeated visual testing. This is especially relevant in early AMD, where patients may retain good central acuity and can improve with familiarization alone. An attempt was made in the LIGHTSITE III trial to address this using a low-intensity sham device that emitted light at 1–2% intensity of the active device, but concerns remain about whether masking was successful or perceptible to participants, as no masking validation was reported.

## SHORT-TERM FOLLOW-UP AND UNCLEAR DURABILITY

Most patients in Küçükerdönmez and Tedford's real-world study were followed only for 3 months, limiting insight into the durability of PBM's effects. Interestingly, patients in cohort 2 who received repeated treatment cycles showed BCVA gains that were similar but slightly reduced compared with those in their first cycle (+2.2 letters at 1 month and +1.8 letters at 3 months after treatment), raising questions about whether improvements reflect transient functional enhancement rather than lasting structural change or disease modification.

In the LIGHTSITE III study, a longer-term follow-up revealed a decline in visual gains after 9 months despite repeated treatments, highlighting the importance of sustained follow-up in understanding PBM's role.

## NO STRUCTURAL CORRELATES TO FUNCTIONAL IMPROVEMENT

It is unclear why retinal thickness was not assessed in Küçükerdönmez and Tedford's real-world study even though optical coherence

tomography (OCT) was performed. The authors mentioned that no signs of phototoxicity were observed, but no specific definition for those signs is given in the Methods section. The authors reported no significant changes in choroidal thickness; however, retinal thickness was not assessed, which could have provided an indirect estimate of drusen volume. The rationale for prioritizing choroidal thickness as a structural outcome remains unclear.

This disconnect between structural and functional findings also mirrors the LIGHTSITE III study, which showed no significant change in drusen volume or other anatomical endpoints. Although some post hoc correlations between BCVA and drusen load were reported in LIGHTSITE III, these were exploratory and not powered to demonstrate causality.

The absence of consistent structure–function correlation weakens the mechanistic plausibility of PBM as a disease-modifying therapy, raising the possibility that observed effects may be due to neuroadaptive or neuromodulatory processes rather than true anatomical restoration.

## MECHANISTIC GAPS AND LACK OF BIOMARKER VALIDATION

It is hypothesized that PBM improves mitochondrial function and reduces oxidative stress, but Küçükerdönmez and Tedford's study provides no mechanistic data or biomarker evidence to support these claims. As in LIGHTSITE III trial, the reliance on speculative preclinical models without human validation of underlying biological effects limits confidence in the proposed therapeutic mechanism.

## STUDY DESIGN CONSIDERATIONS AND GENERALIZABILITY

The retrospective nature of Küçükerdönmez and Tedford's study, coupled with a small sample size and potential selection bias restricts generalizability. Moreover, the authors included both eyes from the same patients in the analysis,

which introduces data dependency. It is unclear whether the statistical methods appropriately accounted for this intra-subject correlation, raising questions about the validity of the reported significance levels.

More standardized treatment criteria and prospective protocols will be necessary to evaluate PBM consistently in broader clinical populations.

## CONCLUSION

The study by Küçükerdönmez and Tedford provides real-world data suggesting that PBM may offer modest short-term functional benefits in patients with early and intermediate AMD. However, the absence of a control group, short duration of follow-up, lack of anatomical change, and very modest visual gains echo concerns raised in the LIGHTSITE III trial and underscore the need for caution in interpreting these findings.

To fully understand the clinical role of PBM, larger-scale, independently funded, sham-controlled, and mechanistically informed trials with multimodal imaging and functional endpoints will be essential. Until such evidence emerges, PBM should be considered an investigational therapy, not yet ready for routine clinical adoption.

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**Data Availability.** Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

## Declarations

**Conflict of Interest.** Christina Karakosta and Robert E. MacLaren have nothing to disclose.

**Ethical Approval.** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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