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LETTER

A Response to: Letter to the Editor Regarding "Safety, Tolerability, and Short-Term Efficacy of Low-Level Light Therapy for Dry Age-Related Macular Degeneration"

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Dear Editor,

We appreciate the thoughtful comments of Drs. Augustin and Koss [1] on our recent article [2]. We especially value their letter given their recognized expertise and extensive experience with photobiomodulation (PBM) technology in patients with age-related macular degeneration (AMD), which makes their observations particularly insightful.

First, the authors raised a question regarding the power and energy density of the wavelengths employed in our study, where PBM treatment was administered using the EYE-LIGHT® device (Espansione Group, Funo, Italy). The parameters were 55 mW/cm^2 ± 20% for the red light (625 nm ± 40 nm) and 25 mW/cm^2 ± 20% for the yellow light (590 nm ± 40 nm). We regret any lack of clarity on this aspect and appreciate the opportunity to provide further details.

The second point raised concerns the sham mode used in our study, which delivered < 30% of the standard output. While it cannot be excluded that such low power may have some biological effect, we would like to provide several clarifications. The authors cited two papers to support the notion that lower power levels may still be biologically active. The first is by Boyer et al. [3] who reported the 13-month results of the LIGHTSITE III trial evaluating PBM therapy in nonexudative AMD (i.e., both intermediate AMD and geographic atrophy [GA]) using the LumiThera Valeda Light Delivery System. In this study, the sham arm received a 50- to 100-fold reduction in treatment fluence compared with the PBM arm. Importantly, the latter study was

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not designed or powered to determine the biological activity of the sham mode, as it lacked a third "no-treatment" control group. We assume Drs. Augustin and Koss refer to the modest gain of + 3.0 letters (SE 1.13; SD 8.30) in the sham group as evidence of biological effect. However, as shown in the supplemental material (http://links.lww.com/IAE/C119), most other functional outcomes—including low luminance best-corrected visual acuity (BCVA), VFQ-25 Composite Score, and Radner Maximum Reading Speed—did not improve in the sham group. The second cited study assessed low-fluence light stimulation emitted by a light-emitting diode (LED) with a peak wavelength of 630 nm and a corneal irradiance of 15 µW [4]. However, this investigation lacked randomization, presented significant baseline differences in retinal sensitivity between groups, and included patients with GA rather than intermediate AMD as in our study. Taken together, we believe these two studies do not provide convincing evidence that lower power levels lead to meaningful functional improvements. That said, we acknowledge that a minimal biological effect in the sham group cannot be completely excluded. If this is the case, this would reinforce our findings, as the observed difference between PBM and sham groups would likely be even greater in the presence of a small sham effect.

Regarding the third point, efficacy was not a primary endpoint since, as the authors correctly noted, no published data were available on this treatment, and our initial aim was therefore to obtain safety data. However, modifications in visual acuity were among the study outcomes, although our report was focused on short-term outcomes (i.e., 4 months after treatment initiation), which might be too early to detect meaningful changes in visual function. While the difference observed between groups (less than two letters) was statistically significant, we agree that this might not be clinically relevant. It is important to note, however, that patients with intermediate AMD generally do not exhibit substantial visual acuity loss. The main concern in this disease stage is the risk of progression to late AMD, which carries major visual consequences. Accordingly, therapeutic strategies should prioritize reducing this progression risk. Future research will be essential to determine whether PBM can slow or prevent advancement to late AMD. Despite this, we emphasize that this is a novel therapeutic approach and that these early studies are seminal in shaping our understanding of its efficacy. Even if the visual gains are not clinically meaningful at this stage, they remain important as they may signal a biological effect on disease progression. In addition, we would like to provide the information requested by Drs. Augustin and Koss: a lower percentage of eyes treated with PBM lost one or more ETDRS letters compared with sham-treated eyes (28% versus 41%), although this difference was not statistically significant ($p = 0.130$). We agree that including this information improves transparency regarding vision changes in both groups.

Finally, Drs. Augustin and Koss noted errors in the tables and results, which—as they correctly pointed out—stemmed from mistakes in the manuscript compilation. In details, values were mistakenly reported without the decimal point due to a formatting error. This does not alter the results or conclusions. We apologize for this oversight and will submit a correction to address these errors. We also confirm that some patients had missing data; therefore, for certain metrics, the number of patients analyzed was smaller than the total study cohort.

Once again, we thank Drs. Augustin and Koss for raising these important considerations.

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Declarations

Conflict of Interest. Enrico Borrelli, Giulia Coco, Vincenzo Scorcia, Adriano Carnevali, Michele Reibaldi, and Giuseppe Giannaccare 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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