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LETTER

Letter to the Editor Regarding "LIGHTSITE II Randomized Multicenter Trial: Evaluation of Multiwavelength Photobiomodulation in Non-exudative Age-Related Macular Degeneration"

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Dear Editors,

We read with great interest the article related to the LIGHTSITE II clinical study [1] on the efficacy of photobiomodulation (PBM) with the LumiThera™ Valeda Light Delivery System in patients with non-exudative age-related macular (AMD) degeneration.

After the sobering Cochrane report [2] referring the LIGHTSITE I clinical trial [3], we were very excited to see the results of the follow-up study.

A major limitation of the first study was the small number of patients ($n = 30$) and eyes ($n = 46$) included, suggesting underpowering for its primary outcome and therefore no meaningful clinical difference for BCVA (best corrected visual acuity) [2].

Unfortunately, in the current LIGHTSITE II study only 27 subjects (29 eyes) received the complete treatment as planned. Furthermore, treatment and control groups in this trial were not homogeneous. At baseline the percentage of eyes in the advanced AMD stages 3 and 4 (based on AREDS categories) was much lower in the PBM group (67.6%) compared to the sham group (94.7%). This marked difference in the distribution of disease severty in the treatment and control arms is relevant for the interpreta-

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tion of the results. Additionally, the presence and amount of drusen do not appear to be reflected by the higher percentage of the advanced disease stages in the control group compared to the PBM group. The macular drusen volume (mm^3) at baseline is quite the same in both groups (sham 0.59 ± 0.22, 0.58 ± 0.27 PBM), though the percentage of advanced disease categories in the sham group was much higher. After 9 months, the macular drusen volume in the sham group increased by a modest 0.03 mm^3, whereas the volume remaining in the PBM group was suggested to remain stable. A known phenomenon in AMD is that drusen progression and regression may occur even without external intervention. Interestingly, in the LIGHTSITE I trial drusen regressed after two series of interventions [3], whereas drusen in the LIGHTSITE II study remained stable after an additional third series. Anyway, there is a more serious flaw that needs to be mentioned. Assuming that the examples provided in Fig. 4 are the most representative for this study, it is obvious that the OCT segmentation lines are incorrectly positioned in some areas. In the treated patient (Fig. 4a, b), drusen confining lines are correctly positioned at baseline, but underestimating some drusen in the post-treatment situation, therefore falsely contributing to a stable situation. In the sham patient (Fig. 4c, d), the confining OCT segmentation lines at baseline are underestimating some drusen but are positioned correctly 9 months later, therefore falsely contributing to an increasing drusen volume.

Regarding the primary endpoint, which is best corrected visual acuity, again the heterogeneity of disease stages is not reflected by the BCVA at baseline. This applies to both all patients (PBM vs. sham, 70.06 ± 5.76 vs 70.53 ± 5.02) and the subgroups (PBM vs. sham, 70.65 ± 4.94 vs 70.53 ± 5.02) receiving the complete protocol. Within this context, it is quite amazing that mean BCVA and standard deviation in the sham group with all (n = 19) eyes included are identical (70.53 ± 5.02) to those of the smaller group of eyes (n = 12) receiving the full protocol. Additionally, trusting that BCVA measurements were performed correctly and that BCVA at baseline was equal in both groups, we may have at least expected a distinct progression dependent of the baseline severity (AREDS category).

Another point of interest is the effect of PBM on geographic atrophy (GA). Though the presented results are based on a very small number of eyes (n = 8 for each group) and therefore highly underpowered and not suitable for any conclusions, more flaws have been introduced in measurements and the interpretations. Mean area (mm^2) of GA at baseline is larger in the sham group (6.65 mm^2) compared to the PBM group (4.86 mm^2). The way progression is measured and how progression is expected to occur within the natural course will have a major influencing impact on the results. As synthesized by Fleckenstein et al. [4], progression rate of GA is dependent on the size at baseline. Figure 5 shows representative fundus autofluorescence images of GA at baseline and after 9 months in treated (Fig. 5a, b) and untreated (Fig. 5c, d) eyes. The small GA lesions in the PBM treated eye at baseline (0.58 mm^2) seem correctly measured. After 10 months, however, apparently a few lesions have been missed (Fig. 5b). Nevertheless, the lesion size after 10 months is reported to be 0.78 mm^2. In the figure legend the authors declare "Following PBM treatment, the difference in lesion area was 0.16 mm^2." The correct difference, however, is 0.2 mm^2 and not 0.16 mm^2. Though this might be seen a small mistake that was overseen by the authors and the reviewers of the manuscript, it raises further doubts on the correctness of the measurements. In addition, GA growth rate depends on baseline lesion size [4]. For example, in the observational study by Sunness et al., lesions measuring < 1.3 mm^2, 1.3–8.3 mm^2, and ≥ 8.3 mm^2 had progression rates of 0.8 mm^2/year, 2.1 mm^2/year, and 3.0 mm^2/year, respectively [5]. Since the mean lesion size at baseline in the sham group is significantly larger than that in the PBM group, a confounding systematic factor, conceivably leading to false results, was introduced.

In conclusion, we totally agree with the authors of the LIGHTSITE II study that efficient treatment options are warranted for the millions of people worldwide suffering from AMD. However, clinical trials and the interpretation

of their results must meet the high standards of evidence-based medicine. The way this study was conducted is likely to have introduced errors in the results. We have very little confidence in the evidence suggested by the LIGHTSIDE II study. We hope that the forthcoming data from the LIGHTSITE III study will avoid these aforementioned limitations and provide scientifically profound results that can serve the scientific progress in ophthalmology and, most importantly, our patients.

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Declarations

Conflict of Interest. Salvatore Grisanti, Karl-Ulrich Bartz-Schmidt, Heinrich Heimann, Albrecht Lommatzsch, Peter Walter, and Thomas Ach 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.

REFERENCES

1. Burton B, Parodi MB, Jürgens I, Zanlonghi X, Hornan D, Roider J, Lorenz K, Munk MR, Croissant CL, Tedford SE, Walker M, Ruckert R, Tedford CE. LIGHTSITE II randomized multicenter trial: evaluation of multiwavelength photobiomodulation in non-exudative age-related macular degeneration. Ophthalmol Ther. 2023;12(2):953–68.

2. Henein C, Steel DHW. Photobiomodulation for non-exudative age-related macular degeneration. Cochrane Database Syst Rev. 2021. https://doi.org/10.1002/14651858.CD013029.pub2.

3. Markowitz SN, Devenyi RG, Munk MR, Croissant CL, Tedford SE, Rückert R, Walker MG, Patino BE, Chen L, Nido M, Tedford CE. A double-masked, randomized, sham-controlled, single-center study with photobiomodulation for the treatment of dry age-related macular degeneration. Retina. 2020;40(8):1471–82.

4. Fleckenstein M, Mitchell P, Freund KB, Sadda S, Holz FG, Brittain C, Henry EC, Ferrara D. The progression of geographic atrophy secondary to age-related macular degeneration. Ophthalmology. 2018;125(3):369–90.

5. Sunness JS, Margalit E, Srikumaran D, Applegate CA, Tian Y, Perry D, Hawkins BS, Bressler NMI. The long-term natural history of geographic atrophy from age-related macular degeneration: enlargement of atrophy and implications for interventional clinical trials. Ophthalmology. 2007;114:271–7.