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Effect of Transcranial Near-Infrared Light 1068 nm Upon Memory Performance in Aging Healthy Individuals: A Pilot Study

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Abstract

Background: We present a pilot study of near-infrared (NIR) 1068 nm transcranial photobiomodulation therapy (PBM-T). Impact upon motor function, memory, and processing speed in healthy individuals, older than 45 years of age, was evaluated.
Methods: PBM-T was performed at home using a transcranial phototherapy device, a helmet that comprised 14 air cooled light emitting diode panel arrays, with a peak wavelength of 1068 nm, full width at half maximum bandwidth of 60 nm and total average optical output power of 3.8 W. The device was used for 6 min twice daily on age-matched middle-aged subjects with normal intellectual function. The US Food and Drug Administration (FDA)-approved computerized assessment tool Automated Neuropsychological Assessment Metrics (ANAM) was adopted to quantify a series of cognitive and motor activities in the participating groups.
Results: A significant improvement in motor function, memory performance, and processing speed was observed in healthy individuals with PBM-T compared to the placebo group. No adverse effects were reported.
Conclusions: PBM-T may be a promising new approach to improve memory in healthy middle-aged individuals. ClinicalTrials.gov ID: NCT04568057.

Keywords: aging, photobiomodulation, transcranial, near-infrared light

Introduction

Photobiomodulation therapy (PBM-T) refers to the use of nonthermal light to achieve a therapeutic outcome, and can apply to a variety of light-emitting devices of various wavelengths. Interest in recent advances in the use of light-emitting diodes (LEDs) has led to their clinical application for a variety of medical and cosmetic uses.[1] Distinct wavelengths, blue (415 nm), red (633 and 660 nm), and near-infrared (830, 850, and 1060–1080 nm), have demonstrated efficacy for multiple therapeutic applications.[2] A previous laboratory research study[3] has shown that human lymphocytes preirradiated with 1072 nm light are resistant against subsequent ultraviolet light toxicity.

Further studies have shown that this wavelength, when applied transcranially, demonstrated a beneficial effect on spatial memory performance, with no deleterious effects on anxiety or motor performance, in a mouse model of premature aging.[4] Further, this wavelength was shown to elicit a range of positive effects upon cellular stress, leading to reduced β-amyloid and phosphor-tau in a mouse model of Alzheimer's disease (AD).[5] The mechanisms of action for red and near-infrared (NIR) light is believed to involve photon absorption in the mitochondria electron-transport chain (cytochrome c oxidase) and quasi-crystalline exclusion zone (EZ water), as photoreceptors, respectively, together with upregulation of ATP production,[2] iNOS,[3] and selective neuroprotective and protein folding chaperone genes, including hsp70.[5]

A recent double blind, placebo-controlled study provided the first evidence for the utility of the 1060–1080 nm wavelength range in treating age-dependent neurodegenerative diseases.[6] In this study, 28 daily 6-min exposures (6 active, 3 controls) improved executive functions, as measured by clock-drawing, praxis memory, visual attention, and task switching, in patients with dementia. A subsequent study

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indicated that transcranial near-infrared (tNIR) light treatments demonstrated safety and positive cognitive improvements in patients with dementia.[7]

At the molecular level, there is a distinction between Age-Related Memory Impairment and AD.[8] In healthy individuals, a recent study has identified age-dependent volume reductions across the entire cortex and in 48 regions of interest.[9] Cortical reductions in the healthy 55- to 90-year age group were extensive after only 1 year, especially evident in temporal and prefrontal cortices, where the annual decline was 0.5%. All subcortical and ventricular regions, except caudate nucleus and the fourth ventricle, changed significantly over 1 year and atrophy accelerated with age.[10]

High-resolution magnetic resonance imaging was utilized to investigate gray and white matter aging in the major lobes of the cerebrum (frontal, parietal, temporal, and occipital) and the major sectors of the temporal lobe (temporal pole, superior temporal gyrus, inferotemporal region, parahippocampal gyrus, amygdala, and hippocampus).[11] For the cerebrum in general, the gray matter was shown to reduce in volume linearly with age, resulting in a decline of about 9.1–9.8% between the ages of 30 and 70 years, and a decline of 11.3–12.3% by the age of 80. In contrast, white matter volume increased until the mid-50s, after which it declined at an accelerated rate.

At 70 years, white matter volume was only 5.6–6.4% less than at 30 years, but by age 80, a cubic regression model predicted that the decrease would be 21.6–25.0%. Multivariate analyses indicate that the frontal gray matter was most strongly associated with age, while occipital gray matter and white matter were least associated. No gender differences in aging were found for any regions of interest.[11]

The loss of intellectual and motor function is not only related to atrophy, but also to changes of functional connectivity (FC), as well as regional atrophy.[11] The anterior mid-cingulate cortex showed exclusive age-related decoupling from the anterior cingulate motor area.[12] FC decrease, in addition to gray matter atrophy within the striatum, may provide a substrate for the declining motor control in the elderly.[13] Age-related FC changes in both the network for movement initiation as well as the network for motor execution is not explained by regional atrophy in the healthy aging brain.[14]

The brain requires 20% of the body basal oxygen to fulfil its function, the mitochondria being the source of the energy for the brain. Brain aging is marked by a range of issues, including decreased antioxidant defences, increased oxidative stress, and deficits in mitochondrial oxidative phosphorylation.[15]

NIR transcranial PBM-T presents itself as an intervention that could improve neuronal cell function and may well improve cell connectivity and, hence, intellectual function. In this present study, we explored the potential for the beneficial effects' of 1068 nm PBM-T upon normal, healthy, middle-aged individuals, aged between 45 and 70 years.

1068 nm NIR transcranial PBM-T device

An air-cooled LED helmet with a peak wavelength of 1068 nm, full width at half-maximum bandwidth of 60 nm, with a 6-min internal timer was used. The average optical power output of the combined arrays was 3.8 W, each module delivering 12 mw/cm^2. The total energy delivered to the cranium was 1368 J (3.8×360) per treatment session. The plan of the device with positions of the LED panels is shown in Fig. 1. The fan speed for air-cooling of each module was microprocessor-controlled to maintain the module temperature close to ambient temperature. Each device had an internal counter, which increased each time the device was turned on and completed a treatment cycle.

Study question

Does twice daily 1068 nm NIR transcranial phototherapy have any effect upon memory in healthy middle-aged individuals?

Inclusion criteria

Participants with normal cognitive function for their age, free of any significant pathology of any kind, in essence healthy individuals.

Exclusion criteria

Potential participants with any significant health issues such as systemic cancer, cerebrovascular disease, epilepsy, diabetes, depression, anxiety, substance misuse, minor cognitive impairment, or any neurodegenerative disorder were excluded.

Recruitment

Recruitment was over 2 years, using age-matched participants (active group mean of age 57 ± 10 years; placebo group mean age of 57 ± 8 years) from local medical clinicians, medical support staff, and their relatives residing in the north of England. A total of 27 participants completed the study. Recruitment was facilitated by word of mouth and by posts on social media.

Blinding

NIR light is invisible to the human eye, thus determining whether the device was active or placebo was not possible by external viewing of the device. The external workings of the device were the same in both the active and placebo

FIG. 1. The 1068 nm LED helmet showing positions of the LED modules. LED, light emitting diode.

units. The control electronics used on both active and placebo units were identical in appearance and function; all external appearances of the active and placebo devices were identical. The placebo device had LEDs, which did not emit any NIR light. All participants were requested to wear the helmet twice daily. The LEDs in contact with the skin are poor thermal conductors giving a sensation of warmth, with both the active and placebo devices.

Randomization

A computer-generated randomzation table was adopted. The odd numbers were assigned to individuals in the placebo group, and the even numbers were assigned to individuals in the active group.

Assessment tools

The US Food and Drug Administration (FDA)-approved computerized assessment test Automated Neuropsychological Assessment Metrics (ANAM)[16–20] was used in this study.

The ANAM assessment tool identified 16 different modalities:

(1) composite score (overall performance),
(2) simple reaction time (SRT 1),
(3) code substitution (learning),
(4) procedural reaction time,
(5) mathematical processing (working memory 1),
(6) matching to sample (spatial working memory),
(7) code substitution—delayed (delayed memory),
(8) simple reaction time (SRT 2),
(9) Go/no-go (inhibition),
(10) logical relationships (reasoning),
(11) spatial processing,
(12) tower puzzle (problem solving),
(13) tapping R hand (motor speed),
(14) tapping L hand (motor speed),
(15) two-choice reaction time (attention/processing speed),
(16) running memory (working memory 2).

The outputs of the ANAM assessment tool are derived using the first assessment as baseline, which gives a unitless composite score.[21] The comparison with norms scores[21] is calculated based on a combination of percentiles for Mean Reaction Time for Correct Responses, Percent Correct, and Throughput.[22] All outputs from the ANAM assessment tool are unitless.

Methods

Interested participants were either sent information via e-mail or given a participant information sheet to read before their first interview with an assessor. All assessors held a registered qualification and maintained compliance with protocol. Each participant was given the opportunity to ask questions and seek clarity regarding the requirements of the study before participation. Participants signed a consent form, a loan agreement form, and provided base line data on their medication and general health; there were no exclusions based upon this information. The participants were then assigned to an intervention according to a computer-generated randomization table to receive either an active or placebo device. Each participant was assessed on 3 separate days before receiving the treatment device and assessed on 3 separate days after using the treatment device for at least 28 days to minimize the impact of day-to-day variations in intellectual performance.

The participants were shown a transcranial phototherapy device and given the appropriate instructions on how to use the device. All participants were requested to use the phototherapy device for at least 28 days; the device was to be used twice daily until reassessment on three separate occasions. A total of six assessments were conducted on each participant.

Statistical evaluation

For each participant and each modality, pre- and posttreatment, the mean of all source data was calculated. These basic mean scores formed the data units for the analysis. Pre- and posttreatment mean values (of basic mean score) across participants were calculated for the active group and for the placebo group, but the focus of the analysis was on the change in basic mean score relative to pretreatment.

Within the active and placebo groups separately, mean values of change across participants were calculated, with corresponding p-values from paired-comparison t-tests. Counts were also made of participants with results better after treatment and of those with results worse after treatment, and associated p-values were evaluated from the sign test of the null hypothesis that a better result and a worse result are equally likely. Mean values of change (in basic mean score) across participants were also compared between the active and placebo groups by means of the two-sample t-test and the Wilcoxon rank-sum test.

The issue of multiple comparisons was addressed by means of the Benjamini-Hochberg procedure, which requires independence or positive dependence among statistical tests. This was checked by computing and assessing an intermodality correlation matrix of change in basic mean score relative to pretreatment, for each of the active and placebo groups. Coefficients were compared to the minimum absolute value significant at the 5% level for a bivariate normal population (0.497 for $n=16$).

Results

Thirty-five participants were recruited and were assessed using the ANAM assessment tool, where $n=27$ completed the tasks and took part in follow-up (14 active and 13 placebo participants). Five participants opted out because they found the assessments too challenging, and three participants changed their mind. Due to workload and clinical commitments, some participants were only available over a limited period for reassessment, therefore the interval between test assessments was variable between individuals; because of participant time constraints, seven of the participants did not have three posttreatment assessments, but only had two posttreatment assessments (four in the active group and three in the placebo group). All participants completed reassessments between 35 and 55 days after initiating the intervention. Age and gender distributions were similar in the two groups. In the active group, there were 11 right-handed and 3 left-handed individuals, and in the placebo group there were 11 right-handed and 2 left-handed individuals.

Compliance with the treatment protocol was confirmed by accessing the internal counter in the device,

Table 1. Comparison Between the Pretreatment and Posttreatment Scores Together with a Comparison Between the Active and Placebo Groups for the First 8 Components of the ANAM Assessment Tool (Modalities 1–8)

	Composite score	*Simple reaction Time 1*	*Learning*	*Maths process Speed*	*Work memory*	*Spatial memory*	*Delayed memory*	*Simple reaction Time 2*
Active								
Mean pre-Tx*	0.22	0.060	0.67	–0.61	0.27	0.30	–0.187	0.27
Mean post-Tx	0.72	0.22	0.98	0.086	0.84	0.55	0.48	0.14
Mean change	0.50	0.16	0.31	0.70	0.57	0.25	0.67	–0.13
p (*t*-Test)	0.00053	0.28	0.076	0.013	0.0042	0.11	0.000084	0.31
Number >0	13	9	10	11	12	10	13	5
Number <0	1	5	4	3	2	4	1	9
p (Sign test)	0.0018	0.42	0.18	0.057	0.013	0.18	0.0018	0.42
Placebo								
Mean pre-Tx	–0.51	–0.16	0.45	–0.39	0.37	0.045	0.14	0.33
Mean post-Tx	–0.47	–0.21	0.66	–0.14	0.41	–0.2	0.35	0.36
Mean change	0.04	–0.047	0.21	0.25	0.03	–0.26	0.21	0.037
p (*t*-Test)	0.79	0.61	0.28	0.20	0.82	0.27	0.13	0.90
Number >0	8	7	8	6	7	5	8	6
Number <0	5	6	5	7	6	8	5	7
p (Sign test)	0.58	1.0	0.58	1.0	1.0	0.58	0.58	1.0
Active versus placebo								
p (*t*-Test)	0.020	0.23	0.67	0.15	0.039	0.069	0.015	0.58
p (Wilcoxon)	0.012	0.33	0.59	0.19	0.020	0.11	0.020	0.48

*Pretreatment.
Underlined "*p*" value indicates statistically significant difference.

and checking the device was used twice daily for the duration of the intervention. All participants missed at least two treatments; however, no participants missed more than six treatments. The average compliance was 93% in the placebo group and 94% in the active group.

Analysis was conducted on all participants as compliance in all participants was >85%.

The statistical analysis of the outcome assessment is presented in Tables 1 and 2, in which positive values indicate improvements and *p*-values lower than the conventional 5% significance level are underlined.

Table 2. Comparison Between the Pretreatment and Posttreatment Scores Together with a Comparison Between the Active and Placebo Groups for the Second 8 Components of the ANAM Assessment Tool (Modalities 9–16)

	Inhibition	*Reasoning*	*Spatial process*	*Problem solve*	*Motor speed R*	*Motor speed L*	*Attention process speed*	*Working memory 2*
Active								
Mean pre-Tx*	0.11	0.57	0.26	0.38	–0.046	0.10	0.35	0.30
Mean post-Tx	0.16	0.71	0.19	0.54	0.57	0.38	0.34	0.57
Mean change	0.052	0.14	–0.069	0.16	0.61	0.28	–0.010	0.27
p (*t*-Test)	0.76	0.35	0.70	0.34	0.010	0.052	0.92	0.039
Number >0	8	8	9	10	11	9	8	11
Number <0	6	6	5	4	2	5	6	3
p (Sign test)	0.79	0.79	0.42	0.18	0.022	0.42	0.79	0.092
Placebo								
Mean pre-Tx	0.41	0.42	0.35	0.25	0.46	0.24	0.68	0.24
Mean post-Tx	0.35	0.35	0.15	0.15	0.53	0.28	0.32	0.17
Mean change	–0.065	–0.07	–0.20	–0.092	0.063	0.034	–0.36	–0.068
p (*t*-Test)	0.75	0.67	0.33	0.57	0.64	0.86	0.028	0.66
Number >0	7	6	5	6	9	9	2	8
Number <0	6	7	8	7	3	4	11	5
p (Sign test)	1.0	1.0	0.58	1.0	0.092	0.27	0.022	0.58
Active versus placebo								
p (*t*-Test)	0.66	0.34	0.62	0.27	0.034	0.29	0.054	0.088
p (Wilcoxon)	0.54	0.47	0.81	0.21	0.021	0.17	0.033	0.29

*Pretreatment.
Underlined "*p*" value indicates statistically significant difference.

TABLE 3. STATISTICAL SUMMARY FOR 4 SELECTED MODALITIES OF THE ANAM TEST, ACTIVE GROUP

	Baseline				*Change from baseline*			
	Mean	*SE*	*LCL*	*UCL*	*Mean*	*SE*	*LCL*	*UCL*
Composite score (overall performance)	0.22	0.22	–0.22	0.66	0.50	0.11	0.29	0.71
Mathematical processing (working memory)	0.27	0.15	–0.016	0.56	0.57	0.17	0.25	0.90
Code substitution (delayed memory)	–0.19	0.13	–0.45	0.072	0.67	0.12	0.44	0.90
Tapping—right hand (motor speed R hand)	–0.046	0.18	–0.40	0.31	0.61	0.21	0.21	1.02

LCL, lower 95% confidence limit; SE, standard error of mean; UCL, upper 95% confidence limit.

In the active group, six measures showed significantly improved performance by paired *t*-tests, of which these four were also deemed significant by the sign test:

(1) Composite score (measurement of overall performance)
(2) Mathematical processing (Working memory)
(3) Code substitution—delayed (delayed memory)
(4) Tapping—right hand (motor speed R hand)

In the placebo group, none of the mean changes from baseline was statistically significant, except for processing speed where deterioration in performance was observed.

Comparisons of changes in basic mean scores between the active and the placebo groups were assessed using two-sample *t*-tests and Wilcoxon rank-sum tests. For five modalities, the superiority of the active group was found to be statistically significant by the Wilcoxon test and four of these, the modalities listed above, were supported by significant *p*-values from the *t*-tests. Superiority of the active group was also demonstrated by the numbers of modalities where more than half of the subjects improved. In the active group, this occurred in 15 of the 16 modalities, compared to 9 of the 16 modalities in the placebo group.

For each of the active and placebo groups, the intermodality correlation matrix consisted of 120 correlation coefficients of change in basic mean score and these indicated low levels of intermodality correlation. For the active group, the numbers of positive and negative coefficients exceeding the 0.497 criterion were 1 and 7, respectively, and for the placebo group the corresponding numbers were 4 and 8. The numbers of positive coefficients for the active and placebo groups were 67 (56%) and 73 (61%), respectively.

Using a false discovery rate of 10%, the Benjamini-Hochberg procedure was applied to the *p*-values for the 16 Wilcoxon tests, comparing the active and placebo groups, and the statistical significance of the four modalities identified above was confirmed.

Additional statistics relating to these modalities are presented in Tables 3 and 4, including 95% confidence intervals for the baseline mean values. Although differences in the baseline mean values between the active and placebo groups are apparent, it can also be seen that the 95% confidence intervals overlap for each of the four modalities.

Discussion

The multi-mechanistic positive biological effects of PBM-T 1068 nm provide a sound rationale for maintaining healthy aging.[2–5] The main research question posed was to identify whether the 1068 nm PBM-T affected memory, irrespective of the duration of the intervention. The results, herein reported, suggest that transcranial LED stimulation with 1068 nm LED PBM-T improves examples of motor function, as well as working and delayed memory performance, and may, therefore, have potential for delaying or even preventing deficits resulting from normal healthy aging or neuropsychological disorders, such as Parkinson's, Alzheimer's or motor neuron disease.[5,23]

This present study also concurs with recent studies,[24] which reported that transcranial laser stimulation with 1064 nm, localized to prefrontal cortex, enhanced sustained attention and short-term memory in young adult humans (undergraduate students, mean age 20). This was extended recently to show enhanced executive function; transcranial laser stimulation enhanced performance in the Wisconsin Card Sorting Task (gold-standard of executive function), often compromised in normal aging and several neuropsychological disorders.[25] Further, in another study, AD participants who received 1068 nm LED treatment made fewer errors and showed improved set-shifting ability and changes in executive functioning (clock drawing, immediate recall, praxis memory, visual attention, and task switching), relative to placebo controls, as well as a trend to improved

TABLE 4. STATISTICAL SUMMARY FOR 4 SELECTED MODALITIES OF THE ANAM TEST, PLACEBO GROUP

	Baseline				*Change from baseline*			
	Mean	*SE*	*LCL*	*UCL*	*Mean*	*SE*	*LCL*	*UCL*
Composite score (overall performance)	–0.51	0.26	–1.0	0.01	0.04	0.15	–0.25	0.33
Mathematical processing (working memory)	0.37	0.14	0.09	0.65	0.04	0.18	–0.31	0.39
Code substitution (delayed memory)	0.14	0.19	–0.24	0.51	0.21	0.13	–0.04	0.46
Tapping—right hand (motor speed R hand)	0.46	0.15	0.16	0.76	0.06	0.13	–0.19	0.32

LCL, lower 95% confidence limit; SE, standard error of mean; UCL, upper 95% confidence limit.

electroencephalogram (EEG) amplitude and connectivity measures.[6] A follow-up study of patients with dementia over a 2-month intervention period identified a significant improvement in Mini-Mental State Examination (MMSE), Logical Memory Tests and Boston Naming Test as well improved sleep, reduced anxiety, and improved energy. These effects were noted from 7 to 21 days after commencement of the intervention.[7]

In this present study, the follow-up assessment and period of treatment was variable, ranging from 35 to 55 days, which introduced an unwanted confounder. Recruiting busy professionals into research was associated with time restraints for reassessment, resulting in this unwanted and unintended variable. Further, a review of the initial scores of the active and placebo groups in this present study indicated that the groups were not balanced when reviewing the initial values of the parameters that achieved a significantly improved score compared to placebo, it was found that the groups were not balanced. The composite score in the active group pretreatment was 0.22, whereas the pretreatment score in the placebo group was –0.51, however, for working memory, the pretreatment score in the active group was 0.27 and 0.37 in the placebo group; for delayed memory, the pretreatment score in the active group was –0.187 and 0.14 in the placebo group; and for motor speed right hand, the pretreatment score in the active group was –0.046 and 0.46 in the placebo group. This may be as a result of small numbers in the study, which was an unanticipated confounder. The results were derived from comparing performance before and after intervention, which had the result of negating the effect of the difference in the initial scores in the placebo and active groups. From a physiological perspective, lower scoring of the participants as noted in participants would not have any effect upon assessment of efficacy, given that the device demonstrated a positive effect upon patients with dementia.[7] This concept is supported in this study where the pretreatment active score was 0.52 lower than the pretreatment placebo score for the motor speed right hand, suggesting that an initial lower score in any parameter does not impact the overall outcome.

Possible relevant well-established mechanisms of action of the PBM-T 1068 in aging are via upregulation of nitric oxide (blood flow)[3] and intracellular HSP70,[5] which provides protective effects against hypoxia and excess oxygen radicals (oxidative stress), as well as proteostasis in aging.

The duration of the effect of the PBM-T requires evaluation to identify how long the effect lasts once the intervention has been halted. Nizamutdinov et al.[7] demonstrated that the benefits of the PBM-T declined after the treatment was withdrawn. Twenty percent of the participants of this study who were allocated the active intervention opted to continue treatment for a further 3 months. This cohort was retested monthly using the ANAM assessment tool. This small cohort continued to make small improvements over the 3-month follow-up period suggesting the maximum potential of PBM-T is yet to be fully evaluated. Further unpublished effects of PBM-T 1068 include upregulation of surface α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, cAMP response element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF), indicative of enhanced neuroplasticity and repair, may account for these long-term positive effects (unpublished).

Many biopsychosocial interventions have the capacity to slow the rate of age-related cognitive decline, including exercise[26] and meditation.[27] PBM-T 1068 may provide an additional modality to improve cognitive function with advancing years.

Conclusions

Overall, this present study provides further evidence supporting the beneficial effects of 1068 nm PBM-T upon aging and age-related memory, worthy of further exploration in larger cohort balanced group studies. The effect of long-term treatment with transcranial PBM-T 1068 requires further evaluation.

Ethics Approval and Consent to Participate

The study design was submitted to the North East-York Research Ethics Committee, REC reference: 16/NE/300. The Ethical decision was reached on October 21, 2016. The Committee stated that the study did not require ethical review by National Health Service (NHS) REC for the following reasons: (1) the study does not involve the use of a medical device for treatment or assessment of a medical condition; (2) the study involves only healthy volunteers; and (3) the study does not involve NHS patients. ''Furthermore, after discussion with the HRA, we assessed that the project did not require HRA approval, as healthy volunteers were consented and seen at private non-NHS premises.'' The Health Research Authority (HRA) stated ''we are of the view that the project would more appropriately be classified and managed as service evaluation, rather than research intervention.'' Informed consent was obtained from all individual participants included in the study.

Consent to Publish

Not applicable; there is no participant identifiable information in the article.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. A previous version of this article was submitted to Research Square.

Authors' Contributions

G.D. is responsible for the supervision, study design, and article composition of the study. Both P.L.C. and A.E. are equally responsible for study design, article composition, and editing of the study.

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Author Disclosure Statement

G.D. is a majority shareholder in Maculume Ltd. All other authors have no competing financial interests.

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