Conclusion.

- **2008** paper 203 patients, both dry and wet
- Ten controls
- 780nm transconjunctival irradiation 40 seconds
- LLLT group improved vision (P<0.000001)
- Metamorphopsia, scotoma decreased.
- Maintained for 3 – 36 months.
- Control group unchanged.
- No side effects.

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Low-Level Laser Therapy Improves Vision in Patients with Age-Related Macular Degeneration

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Abstract

Objective: The objective of this study of a case series was to examine the effects of low-level laser therapy (LLLT) in patients with age-related macular degeneration (AMD).

Background Data: AMD affects a large proportion of the elderly population; current therapeutic options for AMD are limited, however.

Patients and Methods: In total, 203 patients (98 men and 113 women; mean age 63.4 ± 5.5 y) with beginning ("dry") or advanced ("wet") forms of AMD (n = 348 eyes) were included in the study. One hundred ninety-three patients (mean age 64.6 ± 4.5 y; n = 328 eyes) with cataracts (n = 182 eyes) or without cataracts (n = 146 eyes) were treated using LLLT four times (twice per week). A semiconductor laser diode (780 nm, 7.5 mW, 292 Hz, continuous emission) was used for transconjunctival irradiation of the macula for 40 sec (0.3 J/cm^2) resulting in a total dose of 1.2 J/cm^2. Ten patients (n = 20 eyes) with AMD received mock treatment and served as controls. Visual acuity was measured at each visit. Data were analyzed retrospectively using a *t*-test.

Results: LLLT significantly improved visual acuity ($p < 0.00001$ versus baseline) in 162/182 (95%) of eyes with cataracts and 142/146 (97%) of eyes without cataracts. The prevalence of metamorphopsia, scotoma, and dyschromatopsia was reduced. In patients with wet AMD, edema and bleeding improved. The improved vision was maintained for 3–36 mo after treatment. Visual acuity in the control group remained unchanged. No adverse effects were observed in those undergoing therapy.

Conclusion: In patients with AMD, LLLT significantly improved visual acuity without adverse side effects and may thus help to prevent loss of vision.

Introduction

AGE-RELATED MACULAR DEGENERATION (AMD) is the predominant cause of irreversible loss of vision in the elderly. AMD affects 30–50% of individuals 60 years or older.[1,2] AMD-related disability and poor quality of life are likely to increase the socioeconomic burden in the elderly living in industrialized countries.[3]

AMD results from defects in the choriocapillaris, Bruch's membrane, and the retinal pigmented epithelium (RPE) underneath the macula. The epitheliopathy diminishes lysosomal activity and phagocytosis of the outer photoreceptors and disrupts the transportation of cell debris through the RPE to the choriocapillaris.[4] The resulting accumulation of cell debris in Bruch's membrane leads to thickening and hydrophobic charging of the membrane.[5] This suffocates the photoreceptors and promotes fibrovascular proliferation and the formation of subretinal exudates. Ultimately, the decay of the retina results in loss of vision.[6]

Current therapeutic approaches aim to stabilize the remaining vision because photoreceptor function appears to be irreversibly lost. Treatment options, such as photodynamic therapy, laser photocoagulation, transpupillary thermotherapy, ionizing radiation, and surgery have been applied with limited success in cases of exudative, advanced AMD.[7–9] These treatments may also produce collateral damage of the foveal neurosensory retina and impair visual function further. At present, antioxidant and mineral dietary supplements as well as anti-angiogenetic drugs are being discussed as alternative treatment options.[10–12]

LLLT represents a novel therapeutic method that, other than surgical laser applications, does not damage tissues. In this study of a case series we investigated the effects of LLLT in patients with AMD of all forms and stages, and varying degrees of vision impairment.

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PHOTOBIOMODULATION THERAPY FOR LARGE SOFT DRUSEN AND DRUSENOID PIGMENT EPITHELIAL DETACHMENT IN AGE-RELATED MACULAR DEGENERATION

A Single-Center Prospective Pilot Study

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Purpose: To evaluate visual acuity and morphologic changes after photobiomodulation (PBM) for patients affected with large soft drusen and/or drusenoid pigment epithelial detachment associated with dry age-related macular degeneration.

Method: Twenty eyes with large soft drusen and/or drusenoid pigment epithelial detachment age-related macular degeneration were included and treated using the LumiThera Valeda Light Delivery System. All patients underwent two treatments per week for 5 weeks. Outcome measures included best-corrected visual acuity, microperimetry-scotopic testing, drusen volume, central drusen thickness, and quality of life score at baseline and month 6 (M6) follow-up. Data of best-corrected visual acuity, drusen volume, and central drusen thickness were also recorded at week 5 (W5).

Results: Best-corrected visual acuity significantly improved at M6 with a mean score gain of 5.5 letters ($P = 0.007$). Retinal sensitivity decreased by 0.1 dB ($P = 0.17$). The mean fixation stability increased by 0.45% ($P = 0.72$). Drusen volume decreased by 0.11 mm^3 ($P = 0.03$). Central drusen thickness was reduced by a mean of 17.05 μm ($P = 0.01$). Geographic atrophy area increased by 0.08 mm^2 ($P = 0.07$) over a 6-month follow-up, and quality of life score increased by 3.07 points on average ($P = 0.05$). One patient presented a drusenoid pigment epithelial detachment rupture at M6 after PBM treatment.

Conclusion: The visual and anatomical improvements in our patients support previous reports on PBM. PBM may provide a valid therapeutic option for large soft drusen and drusenoid pigment epithelial detachment age-related macular degeneration and may potentially slow the natural course of the disease.

RETINA 43:1246–1254, 2023

Age-related macular degeneration (AMD) accounts for approximately 10% of blindness in developed countries.[1] Disease progression unavoidably leads to significant visual loss and severely affects quality of life (QoL).[1] Early stages of AMD are characterized by accumulation of membranous lipidoproteic debris, including lipofuscin, extracellular material, and complement deposition.[1] The advanced late-stages of AMD are usually divided into exudative AMD (also called wet AMD) or geographic atrophy (GA) (also called dry AMD).[2] Dry AMD is characterized by complete or incomplete retinal pigment epithelium (RPE) and complete or incomplete outer retinal atrophy.[1,3] The pathogenesis of AMD is mainly genetically driven but remains partly understood.[2] Nevertheless, there is evidence that RPE dysfunction is involved in dry

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None of the authors has any financial/conflicting interests to disclose.

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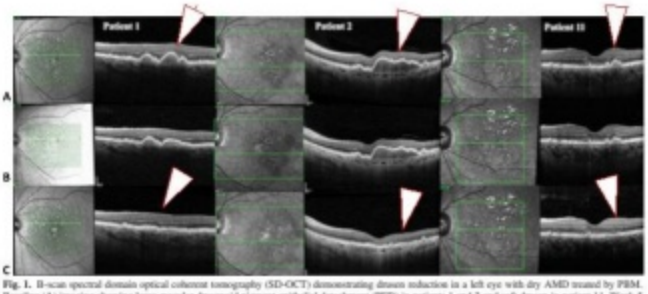

Fig. 1. B-scan spectral domain optical coherent tomography (SD-OCT) demonstrating drusen reduction in a left eye with dry AMD treated by PBM. Baseline (**A**) imaging showing large macular drusenoid pigment epithelial detachment (PED) in patients 1 and 2 and soft drusen in patient 11. Week 5 (**B**) B-scan SD-OCT showing drusen volume evolution with a main reduction at the time points between week 5 and month 6. Month 6 (**C**) imaging illustrates the complete reduction of the drusenoid PED and soft drusen after a series of 10 photobiomodulation (PBM) treatments.

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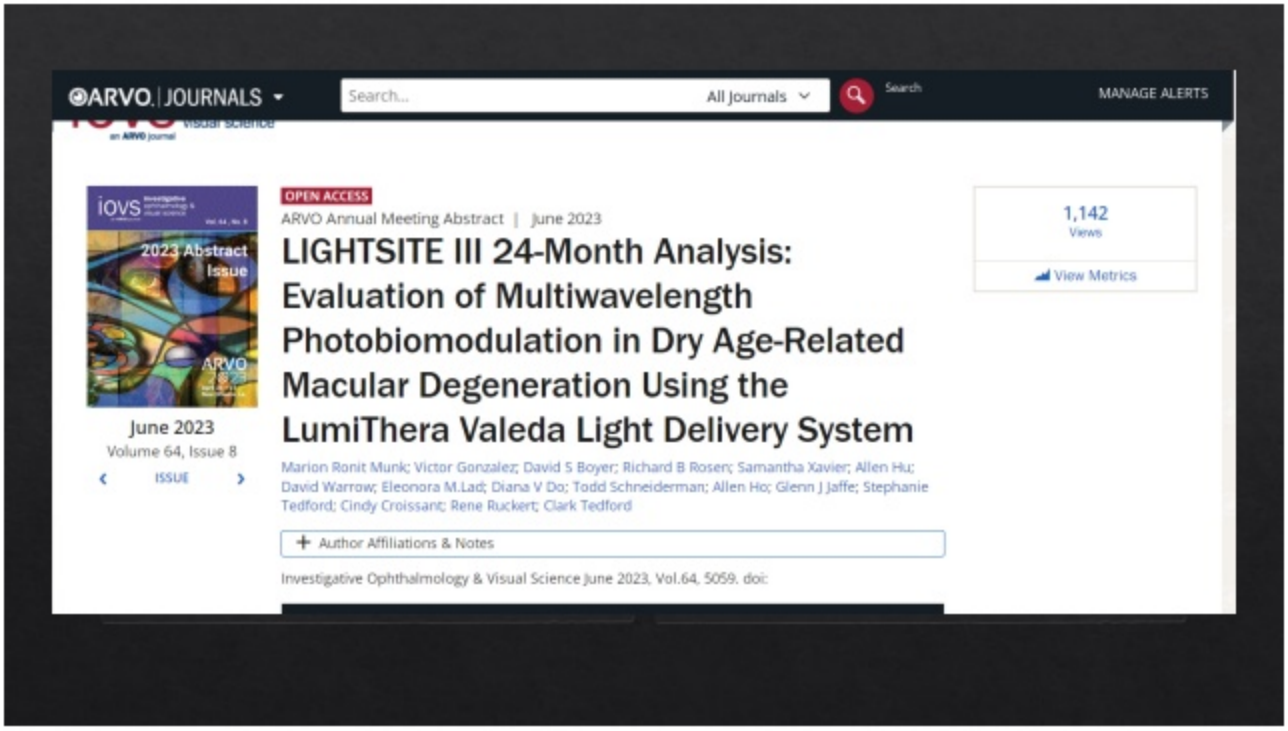
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ARVO Annual Meeting Abstract | June 2023
LIGHTSITE III 24-Month Analysis: Evaluation of Multiwavelength Photobiomodulation in Dry Age-Related Macular Degeneration Using the LumiThera Valeda Light Delivery System
Marion Ronit Munk; Victor Gonzalez; David S Boyer; Richard B Rosen; Samantha Xavier; Allen Hu; David Warrow; Eleonora M.Lad; Diana V Do; Todd Schneiderman; Allen Ho; Glenn J Jaffe; Stephanie Tedford; Cindy Croissant; Rene Ruckert; Clark Tedford
Author Affiliations & Notes
Investigative Ophthalmology & Visual Science June 2023, Vol.64, 5059. doi:
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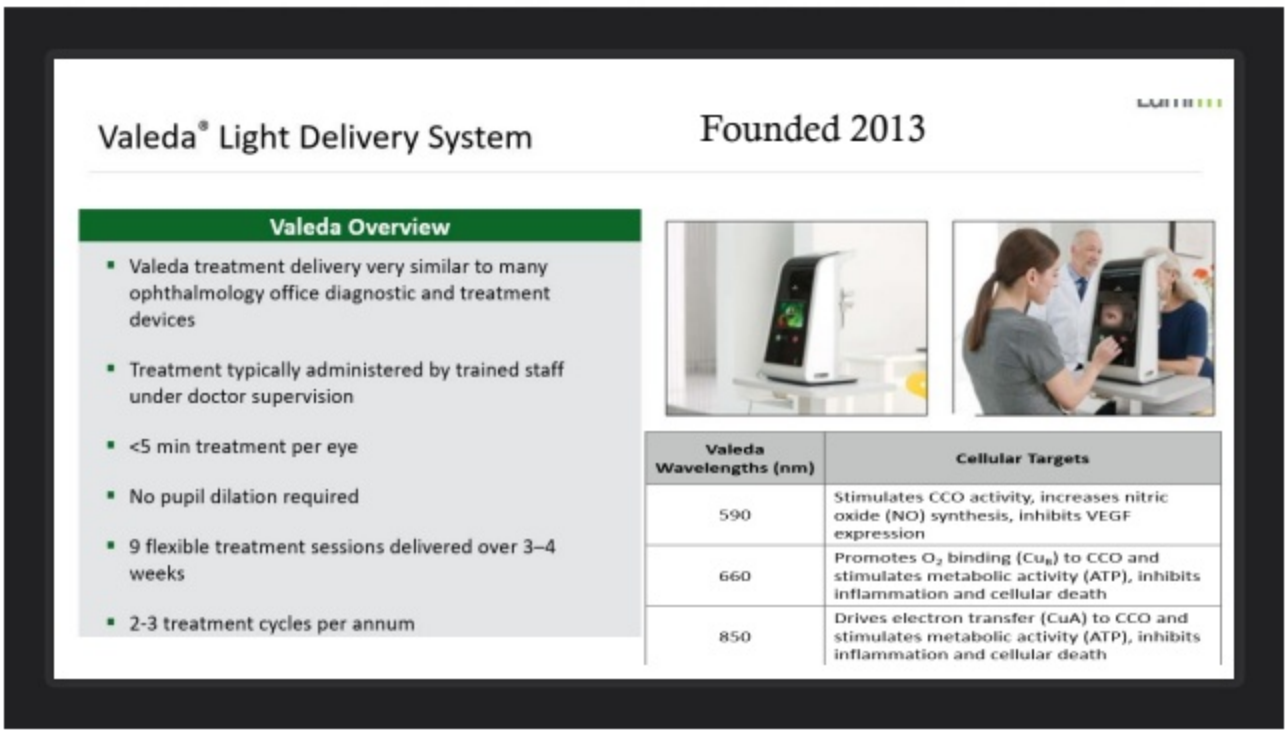
Valeda® Light Delivery System
Founded 2013
Valeda Overview
Valeda treatment delivery very similar to many ophthalmology office diagnostic and treatment devices
Treatment typically administered by trained staff under doctor supervision
<5 min treatment per eye
No pupil dilation required
9 flexible treatment sessions delivered over 3–4 weeks
2-3 treatment cycles per annum
Valeda Wavelengths (nm)
Cellular Targets
590
Stimulates CCO activity, increases nitric oxide (NO) synthesis, inhibits VEGF expression
660
Promotes O_2 binding (Cu_B) to CCO and stimulates metabolic activity (ATP), inhibits inflammation and cellular death
850
Drives electron transfer (CuA) to CCO and stimulates metabolic activity (ATP), inhibits inflammation and cellular death

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OPEN

A DOUBLE-MASKED, RANDOMIZED, SHAM-CONTROLLED, SINGLE-CENTER STUDY WITH PHOTOBIOMODULATION FOR THE TREATMENT OF DRY AGE-RELATED MACULAR DEGENERATION

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Purpose: The LIGHTSITE I study investigated the efficacy and safety of photobiomodulation (PBM) treatment in subjects with dry age-related macular degeneration.

Methods: Thirty subjects (60 eyes) were treated with the Valeda Light Delivery System, wherein subjects underwent two series of treatments (3× per week for 3–4 weeks) over 1 year. Outcome measures included best-corrected visual acuity, contrast sensitivity, microperimetry, central drusen volume and drusen thickness, and quality of life assessments.

Results: Photobiomodulation-treated subjects showed a best-corrected visual acuity mean letter score gain of 4 letters immediately after each treatment series at Month 1 (M1) and Month 7 (M7). Approximately 50% of PBM-treated subjects showed improvement of >5 letters versus 13.6% in sham-treated subjects at M1. High responding subjects (>5-letter improvement) in the PBM-treated group showed a gain of 8 letters after initial treatment ($P < 0.01$) and exhibited earlier stages of age-related macular degeneration disease. Statistically significant improvements in contrast sensitivity, central drusen volume, central drusen thickness, and quality of life were observed ($P < 0.05$). No device-related adverse events were reported.

Conclusion: Photobiomodulation treatment statistically improved clinical and anatomical outcomes with more robust benefits observed in subjects with earlier stages of dry age-related macular degeneration. Repeated PBM treatments are necessary to maintain benefits. These pilot findings support previous reports and suggest the utility of PBM as a safe and effective therapy in subjects with dry age-related macular degeneration.

RETINA 40:1471–1482, 2020

Age-related macular degeneration (AMD) is a retinal disease that results in irreversible, severe loss of vision, including legal blindness. Disease progression inevitably leads to significant visual dysfunction and serious compromises in quality of life (QoL). The prevalence of AMD is projected to affect 196 million by the year 2020 with an expected growth rate to 288 million in 2040.[1]

Progression of AMD is characterized by accumulation of membranous debris, lipofuscin, and extracellular material and complement deposition. The advanced late-stage dry form of AMD, which accounts for 80% to 90% of the cases, is characterized by retinal pigment epithelium (RPE) and outer retinal atrophy, whereas only 10% to 20% develop the exudative, wet late-stage form, with choroidal neovascularization (CNV) as a hallmark of respective disease.[2] Contributing factors to RPE cell degeneration include mitochondrial dysfunction, oxidative stress, inflammation, and genetic disposition.[3]

Treatment is available for wet AMD through periodic intravitreal injections of anti-vascular endothelial growth factor compounds. The more frequent dry form of AMD has limited treatment options available other than lifestyle changes and the use of vitamin supplements, demonstrating a significant unmet clinical need for alternate treatment plans for an expanding population base.[4,5]

Ophthalmol Ther (2023) 12:955–968
https://doi.org/10.1007/s40123-023-00640-6

ORIGINAL RESEARCH

LIGHTSITE II Randomized Multicenter Trial: Evaluation of Multiwavelength Photobiomodulation in Non-exudative Age-Related Macular Degeneration

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ABSTRACT

Introduction: Photobiomodulation (PBM) represents a potential treatment for non-exudative age-related macular degeneration (AMD). PBM uses wavelengths of light to target components of the mitochondrial respiratory chain to improve cellular bioenergetic outputs. The aim of this study was to further investigate the effects of PBM on clinical, quality of life (QoL) and anatomical outcomes in subjects with intermediate stage non-exudative AMD.

Methods: The multicenter LIGHTSITE II study was a randomized clinical trial evaluating safety and efficacy of PBM in intermediate non-exudative AMD. The LumiThera Valeda® Light Delivery System delivered multiwavelength PBM (590, 660 and 850 nm) or sham treatment 3 × per week over 3–4 weeks (9 treatments per series) with repeated treatments at baseline (BL), 4 and 8 months. Subjects were enrolled with 20/32 to 20/100 best-corrected visual acuity (BCVA) and no central geographic atrophy (GA) within the central fovea (500 µm).

Results: LIGHTSITE II enrolled 44 non-exudative AMD subjects (53 eyes). PBM-treated eyes showed statistically significant improvement in BCVA at 9 months ($n = 32$ eyes, $p = 0.02$) with a 4-letter gain in the PBM-treated group versus a 0.3-letter gain in the sham-treated group (ns, $p < 0.1$) for patients that received all 27 PBM treatments ($n = 29$ eyes). Approximately 35.3% of PBM-treated eyes showed ≥ 5-letter improvement at 9 months. Macular drusen volume was not increased over time in the PBM-

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LIGHTSITE I on PBM for Eye Diseases summary

- 1. Safety and Tolerability: establish the safety and tolerability of PBM therapy in patients with eye conditions, showing minimal adverse effects.
- 2. Visual Acuity Improvements: improvements in visual acuity or the stabilization of vision in patients with AMD, indicating that PBM could help slow the progression of vision loss.
- 3. Retinal Changes: Imaging studies (such as OCT) might show structural changes in the retina that suggest reduced degeneration or improved integrity of the retinal layers after PBM treatment.
- 4. Functional Improvements: Beyond structural changes, functional improvements, such as enhanced contrast sensitivity and visual fields, can be reported, suggesting overall benefits to visual function.
- 5. Mechanisms of Action: discuss the potential mechanisms by which PBM exerts its effects, including enhanced ATP production, reduced inflammation, and downregulation of apoptotic pathways in retinal cells.
- 6. Longevity and Treatment Protocols: Findings may also address the longevity of treatment effects and optimal protocols for PBM application, including frequency and duration of treatment sessions.

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LIGHTSITE III Protocol Recap Increased from 2 treatments per year to 3

- ETDRS BCVA between 20/32 and 20/100
- Intermediate drusen and/or GA, confirmed by Duke Imaging
- Wet AMD excluded
- Geographic Atrophy (GA) in central fovea 1 mm excluded
- Treatment randomized 2:1 PBM to Sham - triple masked (Subjects/Sites/Imaging Center)
- Six rounds of treatment every 4 months (24-month study participation/61 visits)
- Primary efficacy analysis: BCVA Change from BL at Month 13 and Month 21 between PBM and Sham
- Safety analyses at Month 24: AEs, BCVA, CS, D-15, perimetry and color fundus
- Sites performed: BCVA, LLBCVA, CS, Radner, D-15, VFQ-25, Perimeter, Eye Exams, OCT, FAF and Color Fundus Photos

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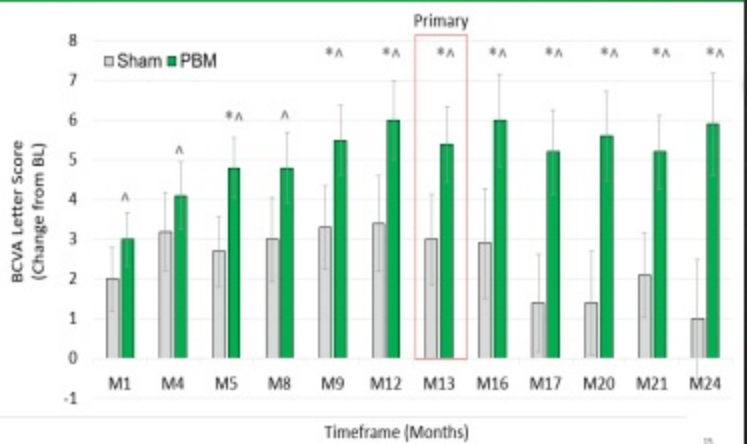
US Pivotal Study Design (LIGHTSITE III - Primary Efficacy Met)

LIGHTSITE III

Trial Design

- 100 subjects (148 eyes) from 10 leading retinal centers throughout the US
- Topline data showed a statistically significantly difference between the PBM and Sham groups at month 13 ($p = 0.02$) and Month 24 ($p = 0.0015$)
- PBM provided a sustained and improved BCVA with a mean 5.5 letter change from BL gain at month 13 ($p < 0.0001$) and mean 5.9 letter change from BL at month 24 ($p < 0.0001$)



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LIGHTSITE III Study Design

The LIGHTSITE III study is a double-masked, randomized, sham-controlled, parallel group, multi-center study to assess the safety and efficacy of photobiomodulation (PBM) in subjects with dry age-related macular degeneration

LIGHTSITE III enrolled 100 subjects (148 eyes)

PBM Tx: 590, 660 and 850 nm

Sham Tx: (50x and 100x reduction of 590 and 660 nm; no 850 nm)

Month 13 Analysis

		Tx Series 1	Tx Series 2	Tx Series 3	Tx Series 4	Tx Series 5	Tx Series 6
Intermediate dry AMD BCVA 20/32 to 20/100	R 2:1	PBM	PBM	PBM	PBM	PBM	PBM
	PBM: Sham	Sham	Sham	Sham	Sham	Sham	Sham
		9 Tx sessions/ 3-5 weeks	9 Tx sessions/ 3-5 weeks	9 Tx sessions/ 3-5 weeks	9 Tx sessions/ 3-5 weeks	9 Tx sessions/ 3-5 weeks	9 Tx sessions/ 3-5 weeks

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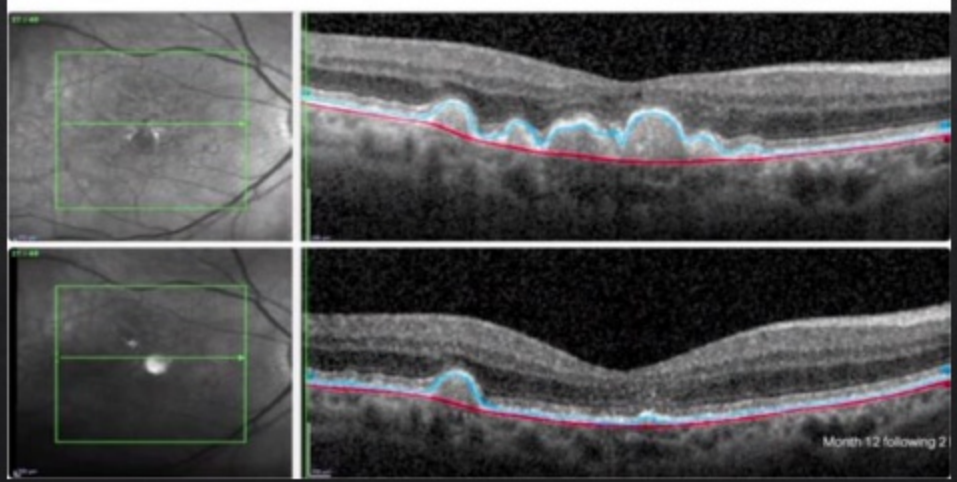
Dry Age-Related Macular Degeneration (AMD)
Reduced Drusen



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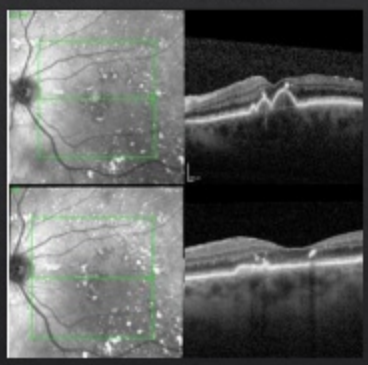
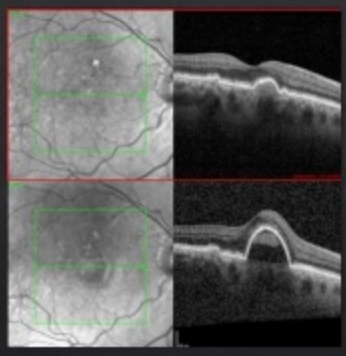
Examples of Patients

Treated Patient PBM



Control Sham



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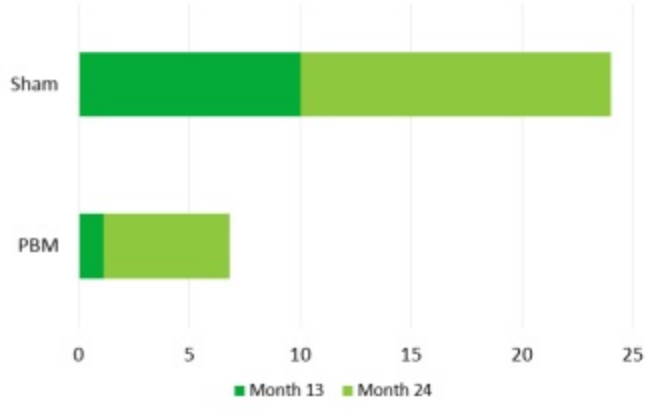
Valeda Treatment Benefit on New Onset GA Occurrence

LIGHTSITE III

Occurrence of new GA in LIGHTSITE III:

- Month 13
  - 5 of 50 (10.0%) of Sham eyes
  - 1 of 87 (1.1%) of PBM eyes
- The occurrence of new GA was significantly higher in the Sham group than in the PBM group (*p = 0.024, Fisher exact test, odds ratio 9.4*)
- Month 24
  - 12 of 50 (24.0%) of Sham eyes
  - 6 of 87 (6.8 %) of PBM eyes
- The occurrence of new GA was significantly higher in the Sham group than in the PBM group (*p = 0.007, Fisher exact test, odds ratio 4.2*)



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Dry Age-Related Macular Degeneration (AMD)
Reduced New Geographic Atrophy

Dry AMD leading cause of blindness in the developed world projected to affect 196 million by 2020

100 patients (145 eyes)
Randomised 2:1
A 10-site multi-center RCT

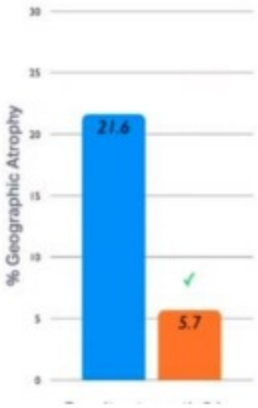
Early to intermediate dry AMD
Treated with the Lumithera Valeda PBM system
Active PBM vs Low dose PBM
Primary endpoint Best Corrected Visual Acuity (BCVA)

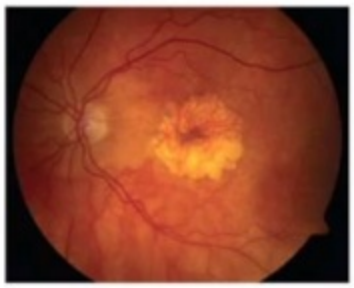
Treatment three times a week for three weeks
Every 4 months
Last treatment month 21
Follow-up at month 24

GA RESULTS 24 MONTHS FOLLOW UP
11 of 51 (21.6%) of Sham eyes
5 of 88 (5.7 %) of PBM eyes
Developed new Geographic Atrophy
p = 0.003, Fisher exact test, odds ratio 4.5

SUMMARY OF FIVE STUDIES
Total 298 eyes total

RESULTS:
- Improved visual acuity (up to 16.6 letter gain)
- Reduced drusen
- Reduced geographic atrophy
- [illegible] contrast sensitivity
- [illegible] retinal fluid and





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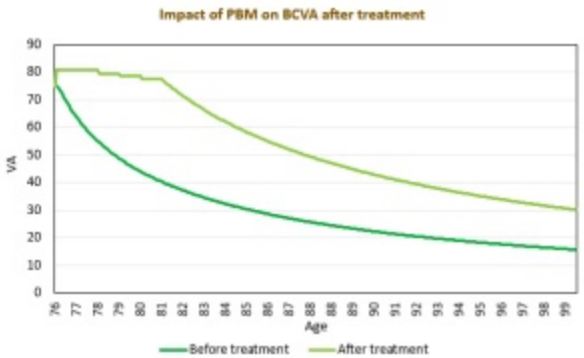
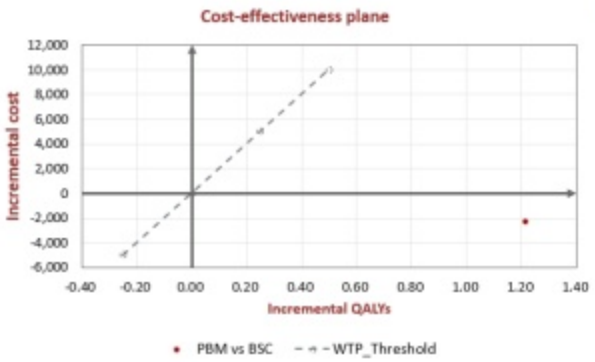
Reimbursement QALYs Analysis

PBM dominates basic standard care in the treatment of dry AMD in NHS health care model

Impact of PBM Treatment on BCVA



QALYs Improvement with PBM



Note: Patients starting at 75 years of age and receiving a 5.9 letter gain in 24 months of PBM and diminishing benefits over the next 4 years

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