Title: 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 (AMD) (LIGHTSITE III)

NCT: NCT04065490

Date of Document: January 14, 2025

STUDY PROTOCOL & METHODOLOGY

Study Participants

Subjects were enrolled if they were ≥ 50 years of age, had a diagnosis of dry AMD (each eye independently assessed for enrollment) as defined by the presence of drusen that were intermediate in size or larger (63 µm or larger in diameter) with at least a few (3) being regular drusen and not pseudodrusen and/or GA, and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) letter scores between 50 and 75 (Snellen equivalent: 20/32 to 20/100). Excluded eyes had a history of neovascular maculopathy, presence of central 1 mm ETDRS grid-involving GA, or other significant retinal disease. Detailed inclusion/exclusion criteria are available in in the inclusion/exclusion section.

Subjects were enrolled across 10 centers throughout the United States. Institutional Review Board (IRB) approval was obtained for all sites and written informed consent was obtained from all subjects in this study. This study was conducted in compliance with the protocol, Good Clinical Practice guidelines, the guidelines of the Declaration of Helsinki, and all other applicable regulatory requirements.

Study Design

LIGHTSITE III was a double-masked, randomized, sham-controlled, parallel-group, multicenter, prospective study. Randomized subjects (2:1 into PBM and Sham treatment groups, respectively) underwent PBM or Sham treatment using the Valeda® Light Delivery System [Valeda] (LumiThera, Inc., Poulsbo, WA, USA). The current report details study results through 24-months, which extended three months beyond treatment completion to assess carryover effect. Sham subjects were not allowed to crossover in the event of advancing disease.

Evaluated Parameters

The study was powered for the BCVA endpoint which evaluated the difference in BCVA (change from baseline) between PBM and Sham groups. Secondary and exploratory clinical outcome measures included BCVA at other timepoints, low luminance BCVA (LLBCVA), contrast sensitivity (CS, Mars Perceptrix letter charts), reading ability (Radner reading charts), color vision (Farnsworth-Munsell D-15 dichotomous color test), and vision-related quality of life (QoL) (Visual Function Questionnaire-25, [VFQ-25]). Anatomical data was assessed throughout the 24-month trial. All eyes were individually assessed for AMD stage, drusen, GA, and nAMD by a masked central reading center (Duke Reading Center, Durham, NC, USA) for inclusion in the study. Images were subsequently obtained at multiple pre-determined study visits following treatment. Fundus autofluorescence (FAF) images (Heidelberg Engineering, Heidelberg, Germany) were acquired at high speed, 30°x30°, 488-nm wavelength. Spectral-domain optical coherence tomography (SD-OCT) volume scans were acquired at high resolution, 20°x20°. Modified 3-field color fundus photographs were obtained with a white flash fundus camera. The RPE drusen complex volume was measured automatically with manual segmentation correction from the inner aspect of the RPE to Bruch's membrane with custom in-house-developed 21-CFR-compliant software (Duke OCT Retina Analysis Program [DOCTRAP]). Total RPE drusen complex was assessed

within the entire 20°x20° OCT scan area. The mean central subfield RPE-drusen complex thickness was analyzed within the central 1 mm ETDRS subfield. GA was initially identified as complete RPE and outer retinal atrophy (cRORA) on OCT and quantified using a multimodal approach. GA was measured on FAF with RegionFinder software (Heidelberg Engineering, Heidelberg, Germany) supplemented by near infrared (NIR), fundus photos, and OCT to help define GA boundaries.

Safety information was collected at all timepoints through Month 24. The Month 13 (primary endpoint), Month 21 (final treatment visit), and Month 24 (final study visit – 3 months follow-up after final treatment) study visits are described in the present report. Not all outcome measures were collected at both the Month 21 and Month 24 visits and therefore the visit timepoint collected is noted for each assessment.

Photobiomodulation Treatment with the Valeda® Light Delivery System

Valeda delivers three wavelengths in the yellow (590 nm; 4 mW/cm^2; 2 x35s), red (660 nm; 65 mW/cm^2; 2 x 90s), and NIR (850 nm; 0.6 mW/cm^2; 2 x35s) range. The Sham treatment (an active control) delivered a 10x and 100x reduction in treatment fluence of the visible 590 and 660 nm wavelengths, respectively, and removed the non-visible 850 nm wavelength. Subjects received either PBM or Sham treatment; no subjects received mixed treatments if both eyes were enrolled to prevent unmasking in the double-masked design. Subjects were exposed to 6 treatment series delivered every 4 months over the 24-month study (**Figure 1**). Each treatment series consisted of 9 sessions delivered over a 3–5-week period.

STATISTICAL ANALYSIS PLAN

The study was powered for the primary BCVA endpoint. Allowing for a 10.0% dropout rate, assuming an average of 1.5 eligible eyes per subject, and potentially smaller effect size and larger standard deviation (SD), a sample size of at least 96 subjects (144 eyes) was planned. Of the 100 subjects enrolled, a total of 148 eyes were eligible and included in the intent-to-treat (ITT)/safety population analyses. The modified ITT (mITT) analyses included all subjects in the safety/ITT set that had at least one post-baseline efficacy measurement. A total of 145 eyes were included in the modified ITT (mITT) analyses, which were conducted across all outcomes and study timepoints. Linear mixed model analyses were based on individual eyes, and subjects, as indicated. OCT and FAF imaging data conducted at the screening visit (prior to study enrollment) were used as baseline measures for subsequent analyses and referred to as baseline throughout. Statistics were performed using R (version 3.4.4) and SAS (SAS Institute, Cary, North Carolina, USA).

The previous 13-month manuscript performed analyses using actual values and last observation carried forward (LOCF) datasets. The current manuscript expands analyses through a supplemental statistical analysis plan (SAP) to include multiple imputation (MI) analyses as agreed upon during FDA regulatory review that led to USA approval. MI analyses further established robustness of the treatment effect through parametric analysis with random imputation criteria. MI analyses used baseline age group (<70, ≥70), gender, use of AREDS supplements and number of eyes treated (1 eye vs 2 eyes) as covariates and 25 simulations per timepoint. Summary results were

based on the average of all 25 simulations, rounded to the nearest integer. In datasets where MI and LOCF analyses were both performed, MI-based analyses are primarily discussed. The method of data analysis is indicated for each outcome and timepoint. In the MI analyses, all available data was used including those that were considered treatment protocol violations. Those included eyes that may have undergone partial treatments or completed treatments outside the treatment window or had discontinued the study prior to completion of all 6 series of treatment but had available BCVA data prior to discontinuation. Out of window eyes included in the MI analysis for the primary Month 13 and Month 21 timepoints were 1/145 eyes and 2/145 eyes, respectively.

The primary efficacy endpoint was the mean BCVA change from baseline to Month 13 or Month 21. Comparison was to be made between the PBM and Control groups to demonstrate statistical superiority of the PBM treatment. Type 1 error was controlled for by assessing the Month 13 result first and then Month 21. Mean and least squares (LS) means are presented with change from baseline following treatment using linear mixed effects models that accounted for correlation between eyes within subject. The LS mean estimation is based on a linear mixed effects model with eye nested within subject and use of AREDS supplements as a covariate. A Fisher exact test was used to analyze incident GA between treatment groups.