DE NOVO CLASSIFICATION REQUEST FOR

VALEDA LIGHT DELIVERY SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Light based device for dry age-related macular degeneration**. A light based device for dry age-related macular degeneration device is a prescription device intended for use in the application of non-coherent light energy to the eye. The device treats or improves visual acuity in patients with dry age-related macular degeneration.

NEW REGULATION NUMBER: 21 CFR 886.5520

CLASSIFICATION: II

PRODUCT CODE: SDE

BACKGROUND

DEVICE NAME: Valeda Light Delivery System

SUBMISSION NUMBER: DEN230083

DATE OF DE NOVO: December 14, 2023

SPONSOR INFORMATION:

LumiThera, Inc.
Lori Holder
19578 10th Ave. NE
Poulsbo, Washington 98370

INDICATIONS FOR USE

The Valeda Light Delivery System is intended to provide improved visual acuity in patients with best-corrected visual acuity of 20/32 through 20/70 and who have dry age-related macular degeneration (AMD) characterized by:

- The presence of at least 3 medium drusen (> 63 μm and ≤ 125 μm in diameter), or large drusen (> 125 μm in diameter), or non-central geographic atrophy, AND
- The absence of neovascular maculopathy or center-involving geographic atrophy.

After about two years, the Valeda Light Delivery System treatment provides improved mean visual acuity of approximately one line of visual acuity (ETDRS) compared to those not receiving the treatment.

LIMITATIONS

The sale, distribution, and use of Valeda Light Delivery System are restricted to prescription use in accordance with 21 CFR 801.109.

The following contraindications and precautions apply to the Valeda Light Delivery System:

Contraindication

- As a precaution, patients have not been tested and should not be treated with Valeda if they have any known photosensitivity to yellow light, red light or near-infrared radiation (NIR), or if they have a history of light activated central nervous system disorders (e.g., epilepsy, migraine). In addition, patients should not receive treatment within 30 days of using photosensitizing agents (e.g., topicals, injectables) that are affected by 590, 660, and/or 850 nm light before consulting with their physician.

Precautions

- Safety and effectiveness in patient populations and/or conditions excluded from the clinical study has not been established. This includes the following: patients under the age of 50, pregnant or nursing women, current or history of neovascular maculopathy, presence of center involving geographic atrophy (GA) within the central 1 mm diameter, media opacities, including cataracts, which might interfere with visual acuity or imaging in the eye, posterior capsule opacification, which might interfere with visual acuity or imaging in the eye, ocular disorder or disease that partially or completely obstructs the pupil, any visually significant disease in any ocular structure apart from dry AMD.

- There is limited safety and effectiveness in patients with best-corrected visual acuity (BCVA) worse than 20/70 or better than 20/32, and have been excluded from the Indications for Use. If the eyecare practitioner wishes to treat these patients who are not considered in the intended population, he/she should consider that the safety and effectiveness have not been demonstrated in these groups.

- No non-white subjects received treatment with the device in the study and the clinical performance of the device in non-white patients is unknown. There is limited safety and effectiveness data in subjects of Hispanic or Latino origin. The eye care practitioner should consider the benefit/risk of treating patients outside of the study population.

- An analysis of the primary effectiveness endpoint (mean BCVA change from baseline for the PBM arm – the mean BCVA change in the Sham arm) showed the following differences

between arms for the subgroup of pivotal study patients with early AMD (Beckman Clinical Category Classification):

- At Month 13: +1.90 letters;
- At Month 21: -0.10 letters;
- At Month 24: +0.29 letters.

The eyecare practitioner should consider the observed benefit/risk profile for this sub-population, when contemplating treatment of patients with this classification of Early AMD.

- It is possible that treatment benefit may not persist significantly after treatment is stopped. The eyecare practitioner should inform patients of this potential.

- The clinical study provided no significant data concerning the safety and effectiveness of the device should treatments be applied more frequently than described in this manual, or if more than 54 total treatments are delivered per eye. The eyecare practitioner should inform patients of this information.

- Twelve (12) eyes (12.9%) in the PBM group and 4 eyes (7.3%) in the sham group had a fellow eye that had neovascular AMD (nAMD). Of these 5 (41.7%) of 12 eyes in the PBM-treated group converted to nAMD, and 1 (25.0%) of the 4 eyes in the Sham group converted to nAMD. The eye care practitioner should consider the benefit/risk profile in this sub-population and should closely monitor patients whose fellow eye has nAMD.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Valeda Light Delivery System is a benchtop instrument emitting non-coherent light in the wavelengths of 590 nm (amber), 660 nm (red), and 850 nm (near infrared, i.e., NIR) from three light emitting diodes (LEDs), respectively. The system projects a beam spot with a diameter of approximately 30 mm at the corneal plane of the patient for each of the three wavelengths. The system is to be used by eye care professionals to treat certain population of patients with dry AMD as defined in the Indications for Use (IFU).
That
The operator interface (Operator View in Figure 1) consists of a touchscreen, start and stop buttons and a joystick to center the beam on the patient's eye. A USB port is used to load treatment credits into the system. The patient interface (Patient View in Figure 1) consists of a fixed forehead rest, the light aperture (exit window) and an adjustable chin rest.

Figure 1. The operator view and patient view of Valeda Light Delivery System

Each treatment takes a total of 250 seconds and consists of four phases as described below.

1) Open Eye: Pulsed amber (590 nm, 3 Hz) and NIR (850 nm, 3 Hz) LEDs are turned on for 35 seconds.
2) Closed Eye: Continuous red LED (660 nm) is turned on for 90 seconds.
3) Open Eye: Pulsed amber (590 nm, 3 Hz) and NIR (850 nm, 3 Hz) LEDs are turned on for 35 seconds.
4) Closed Eye: Continuous red LED (660 nm) is turned on for 90 seconds.

For each treatment series, the patient receives 3 treatments each week for a total of 9 treatments over a period of 3-5 weeks.

The device's LED outputs for treatment beams at the patient's corneal plane are the follows.

Amber LED (590 nm): 4 mW/cm^2, pulse rate - 3 Hz, duty cycle - 71%
Red LED (660 nm): 65 mW/cm^2, continuous
NIR LED (850 nm): 0.57 mW/cm^2, pulse rate - 3 Hz, duty cycle - 71%

The device also includes an additional amber LED (590 nm) for the aiming purpose to help align the device with the center of the eye. The size of the aiming beam at the corneal plane is about 30 mm with an irradiance of about 0.3 mW/cm^2.

SUMMARY OF NONCLINICAL/BENCH STUDIES

Test	*Purpose*	*Method*	*Acceptance Criteria*	*Results*
Beam diameter measurement	To ensure a relatively constant beam size (red and amber treatment and sham beams, IR treatment beam)	Measured the beam sizes projected on a screen at the corneal plane	Between (b) (4) and (b) (4) mm	7 of the 7 tested devices passed; Average ~ 31 mm
Treatment beam divergence angle measurement	To ensure a relatively constant beam divergence angle (red and amber treatment and sham beams, IR treatment beam)	Measured the beam sizes at different planes and calculated divergence angle	(b) (4) degrees	7 of the 7 tested devices passed; Average ~ 13 deg
Treatment beam irradiance measurement	To ensure a relatively constant irradiance at the corneal plane	Measured the power at the corneal plane and calculated the irradiance	Red: (b) (4) Amber: (b) (4) IR: (b) (4)	7 of the 7 tested devices passed
Long-term stability of device output testing (all treatment beams)	To ensure the long-term stability of device outputs (devices tested 9 months to 5 years after the previous calibration)	Measured the devices' power outputs at various time points	Calibrated power output at factory (b) (4)	Passed

OPTICAL RADIATION SAFETY

Light hazard assessment was performed to ensure that the Valeda Light Delivery System delivers acceptable optical radiation to the eye, in accordance with the following standard:

- ANSI Z80.36-2021: *American National Standard for Ophthalmics — Light hazard protection for ophthalmic instruments*

The test report for ANSI Z80.36:2021 included descriptions of all the light sources and their optical paths along with functions and technical specifications of these light sources. Measurement procedures, equipment used for measurements, raw data and formulas used for calculations were provided and were found to be acceptable. A justification was provided to explain why the worst-case scenarios were considered in the assessment of optical radiation safety.

BIOCOMPATIBILITY/MATERIALS

The patient contacting components in the device are the chin rest and forehead rest. These components are manufactured from BayBlend M301 FR, a flame-retardant polycarbonate + acrylonitrile butadiene styrene (PC+ABS) blend used for medical applications. The material was tested by the supplier in accordance with International Standard Organization (ISO) 10993-1:2018 *Biological evaluation of medical devices-Part 1: Evaluation and testing within a risk management process* and following FDA Guidance: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" - Guidance for Industry and Food and Drug Administration Staff (fda.gov). This evaluation was found to be acceptable.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

Electrical safety testing and electromagnetic compatibility (EMC) testing were performedper the following recognized consensus standards and the results support electrical safety and electromagnetic compatibility.

- IEC 60601-1: 2005, A1:2012, A2: 2020 Medical electrical equipment — Part 1: General requirements for basic safety and essential performance, including US National Deviations.
- IEC 60601-1-2:2020: Medical electrical equipment-Part 1-2: General requirements for basic safety and essential performance-Collateral standard: Electromagnetic disturbances-Requirements and tests

SOFTWARE AND CYBERSECURITY

The Valeda Light Delivery System is a cyber device per 524B(c) of the Food, Drug & Cosmetic Act. LumiThera, Inc. has followed the recommendations in the Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions guidance document (September 27, 2023). FDA reviewed the cybersecurity documentation provided and found it acceptable.

The software documentation provided in the De Novo request is consistent with the intended use of the device and recommendations identified according to FDA Guidance Document Content of Premarket Submissions for Device Software Functions (issued June 14, 2023).

A detailed description of all firmware (v4.06) and software (v4.12) inputs and outputs was provided, along with description of all software modules and interactions with device hardware. All components of the device are controlled/monitored by software, which is responsible for the functionality, user interface, hardware start-up checks. The submission describes verification and validation testing to address the potential hazards with satisfactory results. Software documentation and testing, including cybersecurity information, demonstrates that the software will operate in a manner described in the specifications. All testing and results were adequate.

SUMMARY OF CLINICAL INFORMATION

The LIGHTSITE III was a double-masked, sham-controlled, parallel design, prospective, multi-site study. The target enrollment was up to 96 subjects, to be recruited in order to achieve 144 evaluable eyes, in up to 15 centers in the United States, randomized at a 1:2 ratio into 2 treatment groups: PBM (active) or Sham (control).

Each eye was independently qualified for the study. Both eyes, if eligible, received the same treatment (PBM or Sham) throughout the study. If only one eye qualified, it received either PBM or Sham treatment and the non-qualifying eye received no treatment. .

For the sham treatment, the device's outputs at the corneal plane were the follows. The IR LED was turned off for the sham treatment.

Red (660 nm): visible and $\leqslant$ 0.68 mW/cm^2
Amber (590 nm): visible and $\leqslant$ 0.48 mW/cm^2

Each group received 3 treatments per week over a period of 3 to 5 weeks for a total of 9 treatments (one treatment series). Starting at Baseline (Month 0) and starting again at Months 4, 8, 12, 16 and 20, the study participants received a total of 6 treatment series. One hundred (100) subjects were enrolled in the study at 10 of 11 participating clinical study sites. Sixty-five subjects (65.0%) received PBM (active) treatment. Thirty-five subjects (35.0%) received Sham (control) treatment.

The primary efficacy endpoint was the mean best corrected visual acuity (BCVA) change from baseline to Month 13 or Month 21. Comparison was to be made between the PBM and Control arms to demonstrate statistical superiority of the PBM treatment, using an alpha value of 0.025 to control for multiple testing, with the Month 13 result tested first and then Month 21.
Secondary effectiveness endpoints included:

1) Mean BCVA change from baseline to Month 13 or Month 21 among the PBM-treated subjects.
2) Mean changes in low light best corrected visual acuity (LLBCVA) from baseline to Month 13 or Month 21. Comparisons were conducted between the sham-treated and the PBM-treated subjects.
3) Mean changes in macular drusen volume and central subfield drusen thickness from baseline to Month 13 or Month 21. Comparisons were conducted between the sham-treated and the PBM treated subjects.
4) Mean changes in contrast sensitivity at 40 cm from baseline to Month 13 or Month

The primary safety endpoint/analysis was the mean change from baseline to Month 13 or Month 24. Comparison was to be made between the PBM and Sham arms to demonstrate statistical non-inferiority of the PBM treatment. Non-inferiority test was performed to determine if PBM is non-inferior to the Sham with a non-inferiority margin of 2 (two) letters No secondary safety endpoints were specified in the protocol, however the protocol stated "additional safety

analyses" included frequency and severity of the reported adverse events, and descriptive statistics for BCVA, color vision testing, color fundus images, perimetry and contrast sensitivity.

Key Inclusion Criteria included:

- Male or female at least 50 years of age at Screening visit
- Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA letter score between 50* and 75* (Snellen equivalent of 20/100 to 20/32). *If the subject met this criterion at the Screening Visit, but the Baseline BCVA letter score was between 48 and 77, the subject could be entered in the study as long as the difference in score between Screening and Baseline was not more than 3 letters.
- Diagnosis of dry AMD as defined by the presence of the following:
  - 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 geographic atrophy (GA) visible on two of the following: color fundus images, optical coherence tomography (OCT) and/or fundus autofluorescence (FAF), as confirmed by the reading center

Key Exclusion Criteria included:

- Current or history of neovascular maculopathy that included any of the following (as confirmed by the reading center):
  - Choroidal neovascularization (CNV) defined as pathologic angiogenesis originating from the choroidal vasculature that extended through a defect in Bruch's membrane
  - Serous and/or hemorrhagic detachment of the neurosensory retina or retinal pigment epithelial (RPE)
  - Retinal hard exudates (a secondary phenomenon resulting from chronic intravascular leakage)
  - Subretinal and sub-RPE fibrovascular proliferation
  - Disciform scar (subretinal fibrosis)
- Presence of center involving GA within the central ETDRS 1 mm diameter at Screening, as confirmed by the reading center
- Media opacities, including cataracts, which might interfere with visual acuity or imaging in the study eye(s). Subjects should not have been entered if there was likelihood that they would require cataract surgery in the study eye in the next 24 months.
- Posterior capsule opacification, which might interfere with visual acuity or imaging in the study eye(s). Subjects should not have been entered if there was a likelihood that they would require surgery in the study eye in the next 24 months.
- Invasive eye surgery (e.g., cataract, capsulotomy) on a qualifying eye within three 3 months prior to Screening
- Ocular disorder or disease that partially or completely obstructed the pupil (e.g., posterior synechia in uveitis)
- Visually significant disease in any ocular structure apart from dry AMD (e.g., diabetic macular edema, glaucoma (using >2 eye drop medications, uncontrolled intraocular pressure (IOP) and/or central/paracentral visual field loss), glaucoma surgery, active uveitis, active vitreous disease, intraocular tumor, retinal vascular diseases)
- Ocular disorder or disease other than dry AMD that could cause drusen (glomerulonephritis Type 2, Autosomal dominant drusen), GA (North Carolina dystrophy) or mitochondrial diseases (parafoveal petaloid GA, Stargardt disease)

- Presence or history of disease or condition affecting functional vision without obvious structural abnormalities (e.g., amblyopia, stroke, nystagmus)
- Presence or history of known light sensitivity to yellow light, red light, or near infrared radiation (NIR), or if they had a history of light activated central nervous system disorders (e.g. epilepsy, migraine)
- Use of any photosensitizing agent (e.g., topicals, injectables, oral) within 30 days of treatment without consulting subject's physician

Study Population Demographics and Baseline Parameters:

The overall mean age at screening was 75.4 years (Standard Deviation (SD) 7.1) with a higher distribution of females (n = 68; 68.0%) than males (n = 32; 32.0%). The median age was 75.0 years. The majority of subjects were Caucasian/white (n = 99; 99.0%). Most eyes were of blue (n = 33; 33.0%) or brown color (n = 33, 33.0%). The majority of subjects were on AREDS supplements (n = 86; 86.0%). Groups were statistically balanced for age (p = 0.07) and baseline BCVA scores (p = 0.39). Distribution was similar for baseline demographics in Sham and PBM groups.

The average baseline BCVA score was 70.1 letters for Sham-treated eyes and 70.7 letters for PBM-treated eyes. The majority of eyes at Baseline (n = 79; 53.4%) had a BCVA between 71-75 letters. Table 1 provides a cross reference between ETDRS used in the study and Snellen and LogMAR VA measurements.

Table 1 Cross reference for ETDRS, Snellen and LogMAR VA measurements

ETDRS Letter Score	Snellen	LogMAR
50	20/100	0.7
55	20/80	0.6
60	20/64	0.5
65	20/50	0.4
70	20/40	0.3
75	20/32	0.2
80	20/25	0.1
85	20/20	0
90	20/16	-0.1
95	20/12.5	-0.2
100	20/10	-0.3

A modified Ferris risk factor scoring system was used to identify the total risk factors for each eye indicating potential risk for further progression of disease. A risk factor score of 1 was assigned to each study eye for each of the following: a) at least 3 medium drusen or 1 large drusen; b) pigmentary changes. If the eye had non-central GA, a risk factor score of 2 was assigned (maximum score could not exceed a score of 2). The fellow eye was then evaluated and assigned a risk factor score of 1 for each of the following: a) at least 3 medium drusen or 1 large drusen; b) pigmentary changes. If the fellow eye had nAMD or GA (central or non-central) a risk factor score of 2 was assigned (maximum score could not exceed a score of 2). Finally, the score for

the eye and fellow eye were added together to obtain the total risk factor for the study eye, which had a maximum possible score of 4. Table 2 provides an overview of the stratification of risk factors for subjects enrolled in the study.

Table 2 Stratification of Risk Factors for Progression of Dry AMD

	Sham (n=55)	**PBM (n=93)**	**Total (n=148)**
# of Risk Factors	N (%)	N (%)	N (%)
1 Risk Factor	0 (0.0)	1 (1.0)	1(0.7)
2 Risk Factors	11 (20.0)	36 (38.7)	47 (31.8)
3 Risk Factors	13 (23.6)	23 (24.7)	36 (24.3)
4 Risk Factors	31 (56.4)	33 (35.5)	64 (43.2)
Low-Risk Group (1-2 Risk factors)	11 (20.0)	37 (39.8)	48 (32.4)
Moderate to High-Risk Group (3-4 risk factors)	44 (80.0)	56 (60.2)	100 (67.6)

In the current study, 65% of the study eyes (89/136) that had not progressed to GA at baseline had a factor of 3 or 4 putting them at least at a 25 - 50% risk for potential disease progression. For 28% of the subjects, the fellow eye had nAMD and/or GA.

Clinical classification of eyes (Table 3) showed a total of 20.3% (n = 30) of eyes categorized as early-stage AMD, 72.3% (n = 107) were intermediate-stage AMD, and 7.4% (n = 11) were late-stage AMD (GA, no CNV).

Table 3 Beckman Clinical Category Classification (all subjects enrolled)

Clinical Category	Sham n = 55 n (%)	PBM n = 93 n (%)	Total n = 148 n (%)
Early AMD	9 (16.4)	23 (24.7)	32 (21.6)
Intermediate AMD	41 (74.5)	64 (68.1)	105 (71.0)
Late Stage	5 (9.1)	6 (6.5)	11 (7.4)

Reference: Ferris FL 3rd, et al. Clinical classification of age-related macular degeneration. Ophthalmology. 2013;120(4):844-851. doi:10.1016/j.ophtha.2012.10.036

Accountability

At the time of database lock, of 100 patients enrolled in the study, 80% (n=80) patients were available for analysis at the completion of the study, the 24-month visit.

Table 4 Subject/Eyes Disposition (All Subjects/Eyes Enrolled)

Disposition	Sham n (%) Subjects/Eyes	PBM n (%) Subjects/Eyes	Total n (%) Subjects/Eyes
Screened			178
Randomized (ITT Population)	35 / 55	65 / 93	100 / 148
Treated	35 / 55	65 / 93	100 / 148
Study Completed [1]	27 (77.1) / 43 (78.2)	53 (81.5) / 78 (83.9)	80 (80.0) / 121 (81.8)

Study Discontinued [1]	8 (22.9) / 12 (21.8)	12 (18.5) / 15 (16.1)	20 (20.0) / 27 (18.2)
Safety Population	35 / 55	65 / 93	100 / 148
mITT Population	34 / 54	64 / 91	98 / 145
Primary Reason for Discontinuation [2]			
Screening/Baseline failure			78
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal of consent	4 (50.0) / 5 (41.7)	8 (66.7) / 9 (60.0)	12 (60.0) / 14 (51.9)
Subject unable to return to facility	2 (25.0) / 3 (25.0)	2 (16.7) / 2 (13.3)	4 (20.0) / 5 (18.5)
Adverse events [3]	2 (25.0) / 4 (33.3)	2 (16.7) / 4 (26.7)	4 (20.0) / 8 (29.6)
Other	0 (0.0)	0 (0.0)	0 (0.0)

Notes: n = Number of subjects/eyes.
ITT (Intent-to-Treat) Population: All subjects who have signed the Informed Consent Form and are randomized to treatment.
mITT (Modified Intent-to-Treat) Population: All subjects randomized to treatment who receive at least one treatment and have at least one post-baseline efficacy measurement.
[1] Percentages are based on the number of subjects/eyes treated in the group.
[2] Percentages are based on the number of subjects/eyes discontinued in the group.
[3] All non-ocular adverse events unrelated to the study device or procedure.

Table 5 illustrates the number of eyes with BCVA data at baseline and Months 13, 21, and 24. The table reflects mITT study results using multiple imputation and used all available data from subject visits that were seen outside the protocol visit window.

Table 5 Number of Eyes with BCVA Data at Baseline, Month 13, 21 and 24

Eyes With BCVA Data Available	# Eyes in Study	Baseline (Visit 2)	Visit 40 (Month 13)	Visit 60 (Month 21)	Visit 61 (Month 24)
Total Number of Eyes with BCVA data Available	148	148	126	114	101
Percentage of Eyes Available		100%	85.14%	77.03%	68.24%
Eyes With Missing BCVA Data:		0	22	34	47
# Discontinued from BCVA Collection		0	19	29	35
# Missing at Scheduled Visit but Seen Outside Window*		0	1	2	12
# Not Seen but Accounted For (missed visit but still in study)		0	2	3	0
# Lost to follow-up		0	0	0	0
PBM Number of Eyes with BCVA data Available	93	93	82	76	67
Percentage of Eyes Available		100%	88.17%	81.72%	72.04%
Eyes With Missing BCVA Data:		0	11	17	26
# Discontinued from BCVA Collection		0	9	15	20

# Missing at Scheduled Visit But Seen Outside Window*		0	1	2	6
# Not Seen But Accounted For (missed visit but still in study)		0	1	0	0
# Lost to follow-up		0	0	0	0
Sham Number of Eyes with BCVA data Available	55	55	44	38	34
Percentage of Eyes Available		100%	80.00%	69.09%	61.82%
Eyes With Missing BCVA Data:		0	11	17	21
# Discontinued rom BCVA Collection		0	10	14	15
# Missing at Scheduled Visit but Seen Outside Window*		0	0	0	6
# Not Seen but Accounted For (missed visit but still in study)		0	1	3	0
# Lost to follow-up		0	0	0	0

** The presentation and analyses of BCVA-related study results used all available data from subject visits that occurred either within or outside the protocol visit window.*

Effectiveness Results

Primary Effectiveness Endpoint/Analysis

The analysis of effectiveness was based on the mITT patient population consisting of all subjects' eyes in the Safety set that received at least one post-baseline efficacy measurement. The primary endpoint/analysis was the BCVA mean change from baseline to Month 13 or Month 21. Comparison was made between the PBM and Control arms to demonstrate statistical superiority of the PBM treatment, using an alpha value of 0.025 to control for multiple testing, with the Month 13 result tested first, followed by Month 21. The null hypothesis was that the difference between the arms in terms of the mean BCVA change from baseline was equal to zero. (Month 24 was pre-defined only as the primary safety endpoint (3 months after last treatment) but is included with the effectiveness data for comparison.)

Using multiple imputation analysis with the mITT dataset (PBM: n = 91, Sham: n = 54), the study met the predetermined primary effectiveness BCVA endpoint at Month 21 with the following results.

- At Month 13: The mean PBM result was 2.6 letters better than the mean Sham result (p=0.0548; non-significant);
- At Month 21: The mean PBM result was 3.8 letters better than the mean Sham result (p=0.0036; significant). The 95% confidence interval on the difference between the mean BCVA changes from baseline was: 1.2 to 6.3 letters.

Additional Analyses Concerning Comparisons between arms for Mean BCVA Changes from Baseline

The PBM arm maintained a mean letter difference of 4.3 letters at Month 24. (95% confidence interval: 1.5 to 7.2 letters) However, as shown in Table 5, above, a substantial proportion of eyes

did not have BCVA data at Month 24; this is particularly true for the Sham arm for which nearly 40% of eyes had no BCVA data.

At Month 13, the mean BCVA increase from baseline was 6.0 letters in the PBM arm vs. 3.4 letters in the Sham arm, a difference of 2.6 letters. At Month 21, the mean increase from baseline was 6.2 letters in the PBM arm vs. 2.4 letters in the Sham, a difference of 3.8 letters. At Month 24, the increase from baseline was 5.6 letters in the PBM arm compared to 1.3 letters in the sham, a difference of 4.3 letters.

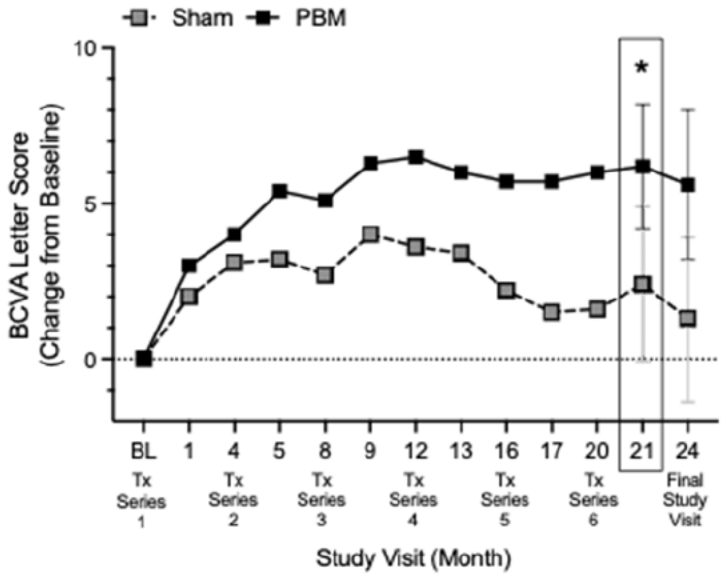

Figure 3 Mean Change of BCVA from Baseline with 95% Confidence Intervals (CI) Shown at Month 21 and to Month 24 (Final Visit). (Calculated for mITT population using multiple imputation for missing data)

Table 6 Mean BCVA Letter Change from Baseline I from Month 1 to Month 24

	Sham LS Mean (SD)	**PBM LS Mean (SD)**
Month 1	2.0 (9.6)	3.0 (8.1)
Month 4	3.1 (11.1)	4.0 (9.4)
Month 5	3.2 (10.6)	5.4 (9.1)
Month 8	2.7 (12.6)	5.1 (10.7)
Month 9	4.0 (12.8)	6.3 (11.0)
Month 12	3.6 (14.7)	6.5 (12.8)
Month 13	3.4 (18.2)	6.0 (16.0)
Month 16	2.2 (15.9)	5.7 (13.8)
Month 17	1.5 (16.6)	5.7 (14.1)
Month 20	1.6 (16.0)	6.0 (13.0)
Month 21	2.4 (15.1)	6.2 (12.2)
Month 24	1.3 (16.3)	5.6 (14.8)

At Month 13, approximately 58.2% of PBM-treated eyes showed a ≥ 5 letter gain (mean of 9.7 letters) compared to 38.8% of Sham-treated eyes (mean of 8.6 letters), 27.5% of PBM-treated eyes showed a ≥ 10 letter gain (mean of 13.0 letters) compared to 13.0% of Sham-treated eyes (mean of 12.1 letters) and 5.5% of PBM-treated eyes showed a ≥ 15 letter gain (mean of 17.6 letters) compared to 1.9% of Sham-treated eyes (mean of 15.0 letters).

At Month 21, approximately 61.5% of PBM-treated eyes showed a ≥ 5 letter gain (mean of 9.0 letters) compared to 27.8% of Sham-treated eyes (mean of 8.0 letters), 23.1% of PBM-treated eyes showed a ≥ 10 letter gain (mean of 12.8 letters) compared to 3.7% of Sham-treated eyes (mean of 11.5 letters) and 4.4% of PBM-treated eyes responded with a ≥ 15 letter gain (mean of 15.5 letters) compared to 0.0% of Sham-treated eyes.

At Month 24, approximately 63.7% of PBM-treated eyes responded with a ≥ 5 letter gain (mean of 8.8 letters) compared to 22.2% of Sham-treated eyes (mean of 9.8 letters), 18.7% of PBM-treated eyes responded with a ≥ 10 letter gain (mean of 12.8 letters) compared to 7.4% of Sham-treated eyes (mean of 13.8 letters) and 4.4% of PBM-treated eyes responded with a ≥ 15 letter gain (mean of 16.3 letters) compared to 1.9% of Sham-treated eyes (mean of 22.0 letters).

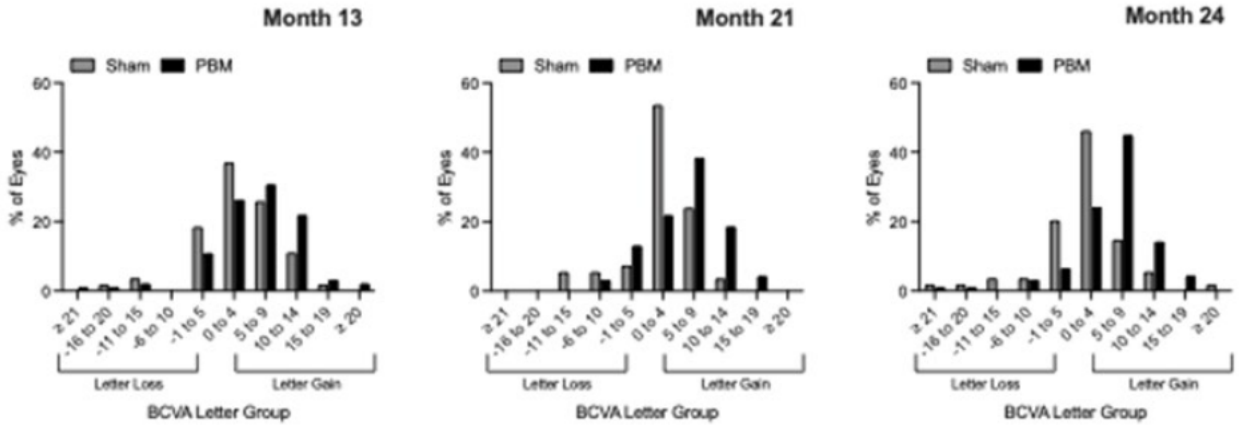

Figure 4 Distribution of BCVA Letter Gain or Loss, PBM versus Sham, by Follow-up Month

The distribution of BCVA letter scores indicated a higher number of Sham-treated eyes showed BCVA letter losses compared to PBM as noted in the -11 to -15, -6 to -10, and -1 to -5 letter loss groups indicative of AMD disease progression over the course of the 24 Month study. The Sham group showed a larger number of eyes with a decrease in BCVA letter count of 10 or greater at each visit compared to the PBM group.

Table 7 Mean BCVA Change from Baseline Using Beckman Clinical Category Classification with the mITT Population on Actual Data (No Imputation Used)

Mean BCVA Change from BL mITT Population, actual data	Sham		PBM		Net change between PBM and Sham
	mean	n	mean	n	
BL BCVA Letter Score	69.33	9	70.90	21	

Early	Month 13 Δ from BL	4.57	7	6.48	21	1.90
	Month 21 Δ from BL	6.50	6	6.40	20	-0.10
	Month 24 Δ from BL	6.71	7	7.00	19	0.29
Intermediate	BL BCVA Letter Score	70.23	40	70.63	64	
	Month 13 Δ from BL	2.31	32	5.54	56	3.22
	Month 21 Δ from BL	1.68	28	5.43	53	3.76
	Month 24 Δ from BL	0.46	28	5.10	49	4.64
Late	BL BCVA Letter Score	70.00	5	71.50	6	
	Month 13 Δ from BL	2.60	5	1.83	6	-0.77
	Month 21 Δ from BL	-2.75	4	3.40	5	6.15
	Month 24 Δ from BL	-1.40	5	5.40	5	6.80

Table 7 lists the baseline stratification of subjects by Early, Intermediate and Late dry AMD using the Beckman Clinical Classification. The mITT population mean change from baseline BCVA values are provided and the difference between the PBM-treated and Sham-treated eyes. The PBM-treated groups had an increase in BCVA letters from baseline of 6.40, 5.43 and 3.4 letters, respectively in the early, intermediate and late-stage groups at Month 21. The sham-treated groups had an increase of 6.50, 1.68 and -2.75 letters, respectively in the early, intermediate and late-stage groups at Month 21. The net change between groups was 0.10, 3.76 and 6.15 letters between the early, intermediate and late-stage groups at Month 21. Early-stage subjects responded with an increase in BCVA letter scores from baseline equally between PBM and Sham subjects. The largest net changes were in the intermediate dry AMD group across all time points. Late-stage dry AMD patients were small in number but showed >6 letter difference at Months 21 and 24.

Secondary Effectiveness Endpoints/Analyses

The following secondary effectiveness endpoints were pre-defined for the study:

1) Mean BCVA change from baseline to Month 13 or Month 21 among the PBM-treated subjects.
2) Mean changes in low light best corrected visual acuity (LLBCVA) from baseline to Month 13 or Month 21. Comparisons were conducted between the sham-treated and the PBM-treated subjects.
3) Mean changes in macular drusen volume and central subfield drusen thickness from baseline to Month 13 or Month 21. Comparisons were conducted between the sham-treated and the PBM-treated subjects.
4) Mean changes in contrast sensitivity at 40 cm from baseline to Month 13 or Month 21.

The analysis was to be performed at the same timepoint as the initial success on the primary effectiveness endpoint. These were evaluated using statistical hypothesis tests using a hierarchical testing procedure to control for multiplicity.

Best-Corrected Visual Acuity (BCVA) within PBM Group Analysis

Using multiple imputation with the mITT group, the within group analysis showed improved BCVA with a mean > 5 letter gain in PBM eyes from Baseline at Month 13 (LS mean 6.0 letters) (p = < 0.0001), Month 21 (LS mean 6.2 letters) (p < .0001) and maintained at Month 24 (LS mean 5.6 letters).

Low Luminance Best Corrected Visual Acuity (LLBCVA)
No significant difference was observed between the Sham and PBM groups at Month 13 and Month 21 in LLBCVA.

OCT/FAF Anatomical Outcomes
No significant difference was observed between the Sham and PBM groups at Month 21 in macular drusen volume or macular drusen thickness. Eyes from the Sham-treated macular drusen volume change from baseline group increased to 0.098 mm^3 at Month 21. Eyes from the PBM-treated macular drusen volume change from baseline group increased to 0.056 mm^3 at Month 21.

Mars Contrast Sensitivity (CS)
No significant difference was observed between the Sham and PBM groups at Month 13 and Month 21 in Mars Contrast Sensitivity at 40 cm.

Safety Results
The analysis of safety was based on the safety cohort of 100 subjects/148 eyes. Any patient randomized into the study who received at least one study treatment was considered part of the safety population.

Primary Safety Endpoint
The primary safety endpoint was to rule out inferiority for the difference between PBM and Sham groups in the mean BCVA changes from Baseline to Month 13 or Month 24. (Month 13 was to be used only if primary effectiveness was demonstrated at this timepoint, which was not the case.) Statistically significant improvements in BCVA letter changes between the PBM and Sham groups were observed at Month 21 (p = 0.0036) with maintained BCVA improvement out to Month 24 (p = 0.0024). Thus, with superiority achieved, inferiority was ruled out at Month 24. Subject data from out of window visits was included in this multiple imputation analysis. At Month 24, BCVA data was available for 67 of the 93 subject eyes enrolled in the PBM group (72.04%), and for 34 of the 55 subject eyes enrolled in the sham group (61.82%), as shown in Table 5.

A lower percentage of PBM-treated eyes showed BCVA letter losses (>5 letters) compared to Sham over the 24 Month study. A total of 5% of the PBM subjects lost >5 letters at Month 13 and remained at 5% at Month 21 which increased to 7% at Month 24. In contrast, 7% of the Sham subjects lost >5 letters at Month 13 which increased to 15% at Month 21 and 18% at Month 24.

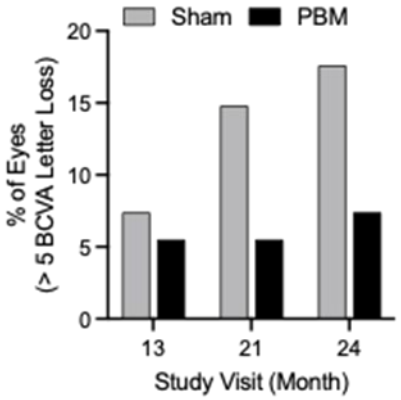

Figure 6 Number of Actual Eyes Used for Percentage of >5 Letter Loss

Note: Prior to the initiation of the study, FDA indicated that it believed that this outcome based upon mean BCVA change from baseline, was an inappropriate primary safety endpoint. Among the reasons for this was that it was based upon the same parameter as the primary effectiveness endpoint, and that it was much more appropriate to have a primary safety endpoint based upon rates of adverse events or adverse effects seen in the study.

Additional Safety Analyses

Within the clinical study protocol, no secondary safety endpoints were specified. However, additional safety analyses are included in the following section. These include eyes with >10 letter loss, color vision testing, color fundus images, perimetry and contrast sensitivity, conversion from dry to neovascular AMD, occurrence of incident GA, frequency and severity of the reported adverse events, and non-study eye adverse events.

Study Eyes with >10 letter loss

A total of 8 study eyes (5 Sham; 3 PBM) showed a BCVA letter loss of greater than 10 letters at the last subject visit. Seven of the 8 study eyes completed the 24-month protocol. None of the 8 eyes were considered high-risk for conversion to nAMD (i.e., other companion eye had nAMD at Screening). None of the 8 eyes converted to nAMD during the study or had ocular surgery. Natural progression of AMD was identified as contributing factor for 4 subjects (3 Sham, 1 PBM); these subjects were classified as AREDS III at study initiation but progressed to AREDS IV due to development of central geographic atrophy during the study. Two Sham-treated subjects had concurrent ocular conditions unrelated to the study device or procedures affecting their BCVA outcomes. A clinical rationale for the BCVA loss was not identified for1 PBM subject and 1 PBM subject's last BCVA test was incomplete.

Valeda Impact on Color Vision

The majority of Sham-treated eyes showed normal color vision testing at Baseline (94.4%), Month 13 (97.7%) and Month 21 (97.7%). The majority of PBM-treated eyes showed normal color vision testing at Baseline (100.0%), Month 13 (98.8%) and Month 21 (98.7%). Results support comparability between groups.

Color Fundus Imaging

Color fundus photography was performed at screening, Month 13, and Month 24. Evaluations included presence of drusen by size, pigmentary changes, geographic atrophy (central or non-central), and neovascular maculopathy. The changes over time are reflective of AMD progression and were used to support OCT imaging results, with an overall increased percentage of eyes with medium or large drusen, pigmentary changes, geographic atrophy, and neovascular maculopathy.

Perimetry Testing

No significant changes in Perimetry outcomes (PSD and Mean Deviation of Retinal Sensitivity) were observed in either treatment group at Month 13 or Month 24.

Mars Contrast Sensitivity

No significant difference was observed between the Sham and PBM groups at Month 13 and Month 21 in Mars Contrast Sensitivity at 40 cm.

Conversion from Dry to Neovascular AMD

A total of 9 eyes converted to neovascular AMD (nAMD) during the 24-month study: 2 Sham-treated eyes (3.6%) and 7 PBM-treated eyes (7.5%). A total of 16 subjects were randomized with the fellow, non-study eye that had neovascular AMD. Of the study eyes that converted to neovascular AMD, the majority of eyes were at high risk for conversion (i.e., the fellow, non-study eye had preexisting nAMD). Twelve (12) of 93 eyes (12.9%) in the PBM group were high-risk and 4 of 55 eyes (7.3%) in the sham group were high risk. Overall, conversion to nAMD occurred 78.9 (SE 10.0) days following the last PBM treatment and 54.4 (SE 38.5) days following the last Sham treatment.

Table 10 Conversion of Dry to Neovascular AMD

	Sham (N = 55) n (%)	**PBM (N = 93) n (%)**
New Development of Neovascular AMD	2 (3.6)	7 (7.5)
Total # of high-risk eyes that developed neovascular AMD	1	5

Occurrence of Incident GA

Review of OCT and FAF images along with fundus photos determined that new onset GA occurred at a higher incidence in the Sham vs. PBM group. The minimum lesion size used to make the determination of the progression to geographic atrophy was 0.049 mm2 on FAF which corresponds to a diameter of 250 microns on OCT, as defined by Classification of Atrophy Meetings (CAM) criteria[1-3]. GA was determined on spectral domain optical coherence tomography (SD-OCT) 97-line high resolution volume scans.

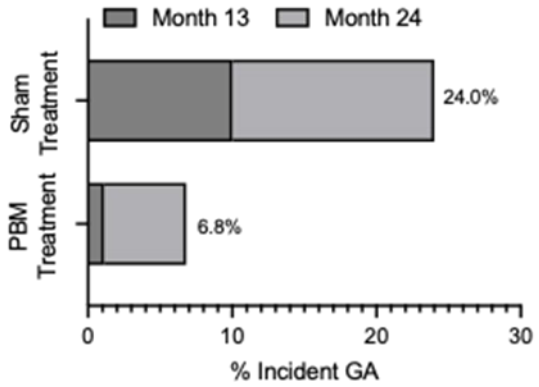

Figure 7 Percent Occurrence of Incident GA by Treatment Group[1]

[1]*One patient (one eye) included in the Sham group that progressed to GA prior to month 13 had Best Disease. This patient's enrollment was due to a major protocol deviation. When this eye is excluded, 11/49 eyes (22.4%) of sham eyes developed new GA by month 24.*

By Month 13, 5/50 (10.0%) Sham eyes and 1/87 (1.1%) PBM eyes developed incident GA. By Month 24, a total of 12/50 (24.0%) Sham eyes and 6/87 (6.8 %) PBM eyes developed incident GA during the course of the study. Non-study eyes were not evaluated. It is unclear if this outcome is related to the investigational treatment as development of new GA was not a pre-specified endpoint. The study and the pre-specified endpoints were not designed to assess whether the treatment could slow the rate of progression to GA, the incidence of GA, or the rate of growth of GA lesion.

Adverse Events That Occurred in the Clinical Study

A total of 38 study eyes (25.73%) from 32 subjects (21.6%) presented with at least one ocular-specific adverse event (AE). The number of eyes with at least one AE reported was similar between groups (Sham, 25.5%; PBM, 25.8%). Seven (7.5%) ocular-specific serious adverse events (SAE) of nAMD were reported in the PBM treatment group and three (5.5%) ocular-specific SAEs, 2 nAMD, 1 cystoid macular edema, were reported in the sham treatment group. No SAEs were considered associated to the treatment by the primary investigator. The number of patients with ocular-specific AEs reported was similar between Sham (20.0%) and PBM (22.6%) groups.

The severity of AEs reported was mostly mild/moderate in both treatment groups. The most common ocular-specific (> 2%) AEs for the Sham treatment group in decreasing frequency included: nAMD (n = 2; 3.6%), Vitreous Floaters (n = 4; 7.3%), Dry Eye (n = 2; 3.6%), Punctate Keratitis (n = 2; 3.6%), and Cystoid Macular Edema (n = 2; 3.6%). The most common ocular-specific (> 2%) AEs for the PBM treatment group included: nAMD (n = 7; 7.5%), Allergic Conjunctivitis (n=2; 2.2%), Blepharitis (n=2; 2.2%), Conjunctival Hemorrhage (n=2; 2.2%), Eye Pain (n=2; 2.2%), Foreign Body Sensation in Eyes (n=2; 2.2%), Increased Lacrimation (n=2; 2.2%), Lamellar Macular Hole (n=2; 2.2%), Photopsia (n=2; 2.2%) and Vitreous Detachment (n=2; 2.2%) The AE of dry eye was observed in both Sham treatment eyes (3.6%) of one subject and considered probably related to the device.

Three subjects had ocular-specific AEs that were considered related to the study procedure. These AEs included punctate keratitis (Sham; n = 2, 3.6%), visual perseveration (after image) (Sham; n

= 1, 1.8%), and application site warmth (PBM; n = 1, 1.1%). No ocular-specific AEs led to study discontinuation.

A total of 204 non-ocular AEs were reported from 57 subjects (57.0%). A total of 4 (4.0%) non-ocular AEs led to study discontinuation including 3 (3.0%) which led to death. Twenty non-ocular SAEs (all unrelated) were reported in 14 subjects. One subject (1.5%) in the PBM treatment group experienced mild headache that was possibly related to the study device. No non-ocular SAE were considered related to the treatment.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

The labeling is sufficient and satisfies the requirements of 21 CFR 801.109 for prescription devices.

The labeling describes how the prescribing user is to use the device, including preparation steps for device and patient and the beam alignment procedure. It also describes the treatment procedure, which is uniform for all patients. It describes all components of the user interface, including all prompts to select and initiate the treatment.

The labeling provides a description of the intended patient population that may be treated with the device and includes a summary of the clinical study performed to support the device's safety and effectiveness in this population, including a summary of the demographics of the study cohort.

The labeling includes contraindications, warnings, and precautions to ensure safe use of the device in the intended patient population.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of light based device for dry age-related macular degeneration and the measures necessary to mitigate these risks.

Risks to Health	Mitigation Method
Ineffective treatment leading to worsening of condition	Clinical performance data Non-clinical performance testing Labeling
Therapeutic effect not sustained leading to delay of treatment and worsening of vision or progression of disease	Clinical performance data Non-clinical performance testing Labeling

Failure of software or system components leading to ineffective treatment or ocular adverse events	Clinical performance data Non-clinical performance testing Software verification, validation, and hazard analysis Labeling
Ocular light hazard	Clinical performance data Non-clinical performance testing
Equipment malfunction leading to user or patient injury (e.g., shock, burn, interference)	Electromagnetic compatibility (EMC) testing Electrical safety testing Labeling
Adverse tissue reaction	Biocompatibility evaluation

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the light based device for dry age-related macular degeneration is subject to the following special controls:

(1) Clinical performance data must demonstrate that the device or representative test device performs as intended under anticipated conditions of use. Data must include:

(i) Adverse events, including all ocular and periorbital events;
(ii) Assessment of ocular and retinal tissue damage;
(iii) Assessment of best corrected visual acuity; and
(iv) Assessment of progression to neovascular age-related macular degeneration and to geographic atrophy.

(2) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. Testing must include:

(i) Optical radiation safety evaluation (including a description of the optical path and light sources); and
(ii) Testing to demonstrate that the device maintains optical output specifications within all intended environmental operating conditions.

(3) Software verification, validation, and hazard analysis must be performed. Documentation must include characterizations of the technical specifications of the software including a description of interactions between software and hardware and the controlling and monitoring of treatment related hardware.

(4) Performance testing must demonstrate the electromagnetic compatibility (EMC) and electrical safety of the device in the intended use environment.

(5) Patient-contacting components of the device must be demonstrated to be biocompatible.

(6) Labeling must include:

(i) Device treatment procedure and parameters for each treatment session supported by clinical performance data;
(ii) The frequency and length of treatment regimen supported by clinical performance data; and
(iii) A summary of the clinical performance data obtained with the device or representative test device.

BENEFIT/RISK DETERMINATION

The probable risks of the device are based on data collected in the LIGHTSITE III study as described above. The treatment arm in the LIGHTSITE III study observed a higher rate of progression to neovascular AMD (nAMD) than the sham arm. Uncertainty remains regarding whether the higher rate in progression to nAMD in the treatment arm was caused by an imbalance in baseline risk factors between the two study arms, random variability in rates of progression, an effect of the treatment, or a combination of these factors. The large majority of eyes that converted to nAMD in the study had a contralateral eye with nAMD; therefore, the precautions state that the eye care practitioner should consider the benefit/risk profile in this subpopulation and closely monitor patients whose fellow eye has nAMD.

The probable benefits of the device are also based on data collected in the LIGHTSITE III study as described above. In terms of the primary effectiveness endpoint (difference between study arms in terms of mean BCVA change from baseline), the device demonstrated a statistically significant improvement which is of marginal clinical significance. Sources of uncertainty include uncertainty due to the relatively small difference in mean BCVA change from baseline between the two arms. However, early-to-intermediate dry AMD patients that have vision loss due to AMD typically have a small amount of best corrected visual acuity (BCVA) loss; therefore, it would be difficult for any treatment to show a large vision benefit at this relatively early stage of disease. Other sources of uncertainty stem from uncertainty regarding the mechanism of action (ie. based on the available study data there is some uncertainty regarding whether the mechanism of vision improvement is due to a retinal effect, due to some other mechanism, or due to an effect on other ocular structures). The effect of treatment with the device past 2 years and the duration of treatment effect is also unknown at this time.

Therefore, although there is some uncertainty concerning the benefit and risks of the treatment, given that there is no existing, approved treatment to improve BCVA in patients with vision loss who have early-to-intermediate AMD, this treatment option can provide a probable benefit that outweighs the probable risks.

PATIENT PERSPECTIVES

This submission included analyses on patient reported outcome measures of visual function for this device.

BENEFIT/RISK CONCLUSION

In conclusion, given the available information above, for the following indication statement:

The Valeda Light Delivery System is intended to provide improved visual acuity in patients with best-corrected visual acuity of 20/32 through 20/70 and who have dry age-related macular degeneration (AMD) characterized by:

- *The presence of at least 3 medium drusen (> 63 µm and ≤ 125 µm in diameter), or large drusen (> 125 µm in diameter), or non-central geographic atrophy, AND*
- *The absence of neovascular maculopathy or center-involving geographic atrophy.*

After about two years, the Valeda Light Delivery System treatment provides improved mean visual acuity of approximately one line of visual acuity (ETDRS) compared to those not receiving the treatment.

The probable benefits outweigh the probable risks for the Valeda Light Delivery System. The device provides benefits, and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The De Novo request for the Valeda Light Delivery System is granted and the device is classified under the following:

Product Code: SDE
Device Type: Light based device for dry age-related macular degeneration
Class: II
Regulation: 21 CFR 886.5520