Longitudinal Assessment of Ellipsoid Zone Integrity, Subretinal Hyperreflective Material, and Subretinal Pigment Epithelium Disease in Neovascular Age-Related Macular Degeneration

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Purpose: To assess longitudinally the effect of anti–vascular endothelial growth factor (VEGF) treatment on ellipsoid zone (EZ) integrity, subretinal hyperreflective material (SHRM), and the sub—retinal pigment epithelium (sub-RPE) compartment in eyes with neovascular age-related macular degeneration (nAMD).

Design: Post hoc analysis of the OSPREY clinical trial, a prospective, double-masked, phase 2 study comparing brolucizumab 6 mg with aflibercept 2 mg over 56 weeks.

Participants: Participants with treatment-naïve nAMD at the initiation of the trial were included in the analysis.

Methods: Eyes were evaluated with spectral-domain OCT at 4-week intervals in the OSPREY trial (n = 81). Spectral-domain OCT scans collected from each visit were segmented automatically using a proprietary, machine learning—enabled higher-order feature-extraction platform for retinal layer, SHRM, and sub-RPE boundary lines, which were evaluated and corrected as needed by masked trained graders. The current analysis focused only on patients evaluated with the Cirrus (Zeiss) platform (n = 28).

Main Outcome Measures: Outcome measures included change from baseline in EZ-RPE (i.e., photoreceptor outer segment) volume, EZ-RPE central subfield thickness (CST), total EZ attenuation, SHRM volume, SHRM CST, and total sub-RPE volume. The correlation between each of these measures and best-corrected visual acuity (BCVA) at each visit was evaluated.

Results: EZ-RPE volume and EZ-RPE CST showed significant increases, and total EZ attenuation, SHRM volume, SHRM CST, and total sub-RPE volume showed significant decreases from baseline at each visit from weeks 4 through 56 (P < 0.05 at each visit). Ellipsoid zone integrity measures and SHRM volume correlated significantly with BCVA at most visits (P < 0.05). No significant correlation was found between total sub-RPE volume and BCVA.

Conclusions: EZ integrity, SHRM, and sub-RPE disease features in eyes with nAMD showed improvement as early as week 4 of anti-VEGF treatment. EZ integrity measures and SHRM volume were predictors of visual acuity over the first year of treatment. Ophthalmology Retina 2021;5:1204-1213 © 2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
consisting of multilayer segmentation and feature extraction (e.g., fluid object and subretinal material). Detailed and quantitative characterization of specific imaging features over the course of therapy with higher-order OCT analysis techniques may help to facilitate personalized and targeted clinical care using such techniques and to inform clinicians better regarding biomarkers that may predict functional outcomes.

Although primary indicators of treatment response are reductions in retinal fluid, other important retinal features include the integrity of the outer retinal layers, subretinal material, and disease burden of the sub-RPE compartment. Quantitative and automated measures of outer retinal integrity via measures of the EZ on OCT are potentially of significant value, because EZ integrity has been a consistent biomarker of visual acuity. Assessment of subretinal material also may be valuable because the presence of SHRM on OCT is associated with poorer preservation of the EZ and decreased visual acuity. In addition, new and emerging therapeutics may have a differential impact on subretinal fibrosis and subretinal material. Thus, being able to measure alterations in this feature would be critical to understanding drug effect better. In contrast with outer retinal integrity and subretinal disease, within the sub-RPE compartment has not been associated consistently with visual acuity. However, PED has been associated with neovascular reactivations, suggesting that the sub-RPE compartment is an important disease component to monitor. In addition, the sub-RPE compartment often is more resistant to therapeutic intervention. The ability to quantify this compartment reliably could provide significant new insights to emerging therapeutics and their impact on the sub-RPE area, such as drusen resolution and PED response. Previous studies have demonstrated that quantification of these features is possible with a variety of higher-order approaches.

However, panmacular quantitative assessment of these disease features and their correlation with visual acuity in nAMD over the course of anti-VEGF treatment have not been characterized adequately. Therefore, the present analysis used a proprietary higher-order OCT analysis technique to assess longitudinally OCT imaging features (EZ integrity, SHRM, and the sub-RPE compartment) in nAMD over the course of anti-VEGF treatment. This exploratory post hoc analysis made use of data from the OSPREY study, in which the efficacy of brolucizumab and aflibercept were evaluated over 56 weeks in treatment-naïve patients with nAMD.

Methods

OSPREY Study Design

The OSPREY trial (ClinicalTrials.gov identifier, NCT01796964) has been described previously. Briefly, treatment-naïve participants 50 years of age or older with active choroidal neovascularization secondary to age-related macular degeneration (AMD) were recruited at 41 investigational centers across the United States. The study eye had to have best-corrected visual acuity (BCVA) of between 73 and 23 letters inclusive and to show leakage on fluorescein angiography as well as subretinal fluid, intraretinal fluid, and sub-RPE fluid on spectral-domain OCT. Ninety participants were randomized 1:1 to receive intravitreal injections of either brolucizumab (6 mg/50 µl) or aflibercept (2 mg/50 µl). Both groups received loading doses at baseline (week 0), week 4, and week 8 and then were treated every 8 weeks (injections at weeks 16, 24, and 32) with assessment up to week 40. After the 8-week dosing cycle, the brolucizumab group was extended to a 12-week dosing cycle (injection at week 44), whereas the aflibercept group continued with the 8-week dosing cycle (injections at weeks 40 and 48), with assessment up to week 56. Unscheduled treatments were allowed at the investigator’s discretion. Efficacy assessments were conducted at each study visit, which occurred every 4 weeks. Investigational centers obtained spectral-domain OCT scans according to a standardized study protocol and conducted BCVA assessments according to the Early Treatment Diabetic Retinopathy Study visual acuity protocol. The OSPREY trial was performed at 41 investigational centers where each site obtained institutional review board approval and complied with the ethical standards defined by the Declaration of Helsinki and Good Clinical Practice. All participants provided written informed consent before participating in the study.

Higher-Order OCT Analysis

The spectral-domain OCT scans conducted for the OSPREY study were transferred to the Cleveland Clinic for post hoc exploratory analyses. Eighty-one participants (41 brolucizumab patients and 40 aflibercept patients) of the 89 who received treatment were analyzed initially, including those eyes imaged with the Cirrus (Carl Zeiss Meditec, Dublin, CA) or the Spectralis (Heidelberg Engineering, Heidelberg, Germany) system. The imaging protocol for the Spectralis system in the OSPREY study included a more sparsely sampled macular cube (49 lines) compared with more densely sampled Cirrus scans (128 lines). Given the novel nature of this analysis and potential for interpolation errors in the less densely sampled Spectralis scans, only participants (n = 28) who had spectral-domain OCT scans obtained with the Cirrus spectral-domain OCT system were included in this initial report. Four eyes with scans obtained with the Cirrus system were excluded because of lack of spectral-domain OCT scan availability (n = 3) or poor-quality spectral-domain OCT scans at baseline (n = 1), limiting the ability to segment fluid, SHRM, or layer boundaries. As noted, the macular cube scans were obtained using a 512 × 128 macular cube covering a 6 × 6-mm area of the macula centered on the foveal center point. Spectral-domain OCT macular cube scans from each study visit were imported into the automated machine learning augmented segmentation and feature extraction platform (Cleveland Clinic, Cleveland, OH). The software platform used a combination of image processing and filters, machine learning augmentation, and logic to extract each feature of interest. This process was performed simultaneously for each feature (i.e., fluid, retinal layers, and SHRM enclosure boundaries). A higher-order classifier then was used to determine the type of fluid (e.g., subretinal or intraretinal). After identification of each individual feature or line of interest, the outputs were transformed into segmentation masks. The masks then were assembled into a fusion editable overlay that was used within the user interface. Each feature could be edited for any segmentation errors as needed within the bounds of the logic in place for anatomic feasibility (e.g., the internal limiting membrane could not go below the RPE). Subretinal hyperreflective material was defined as a hyperreflective signal above the RPE and below the visualized boundary of the outer retina that was not consistent with the hyporeflective signal of subretinal fluid. Two masked and trained expert readers consecutively checked the automatic segmentations and manually corrected segmentation errors of specific lines and features of interest. All readers received the same training for the spectral-domain OCT analysis, and the same trained readers...
reviewed and corrected the segmentations for all time points for any given participant to minimize inter–time-point and interreader variability. The reading environment was standardized for location, computer configuration, monitor settings, and lighting configuration. The interreader intraclass correlation coefficient across the metrics assessed for this analysis ranged from 0.85 to 0.99. After the initial read, a senior analyst reviewed each scan to confirm consistency and accuracy of segmentation. This same process of automatic segmentation followed by as-needed manual correction was used to segment the features of interest shown in the example B-scans of the present study. Using the segmentation boundaries, several measures were exported for evaluation, including EZ-to-RPE (EZ-RPE) volume, SHRM volume, and total sub-RPE volume across the entire macular cube; the percentage of the macular cube showing total EZ attenuation (i.e., 0-μm EZ-RPE thickness), EZ-RPE central subfield thickness (CST), and SHRM CST. For the present analysis, EZ integrity was described based on the EZ-RPE compartment (i.e., a surrogate for photoreceptor outer segment length), and it was expressed through the multiple specific EZ metrics, including the panmacular assessments (i.e., EZ-RPE volume and percentage total EZ attenuation) and central assessment (i.e., EZ-RPE CST). EZ-RPE metrics measured the retinal tissue from the EZ to the RPE band (or the top of the SHRM boundary if present) and excluded intraretinal and subretinal fluid. Total sub-RPE volume was defined as the total volume between the RPE and Bruch’s membrane across the macular cube. EZ-RPE CST and SHRM CST were calculated based on the mean thickness of each parameter on each A-scan within the 1-mm diameter area centered on the fovea. The EZ-RPE CST reflected the mean thickness of each EZ-RPE point thickness within the central 1-mm area. The SHRM CST was calculated in a similar manner, as the mean height of any EZ-RPE point thickness within the central 1-mm area. The SHRM CST re

### Statistical Analysis

Analyses were conducted with the treatment groups combined. Change from baseline was evaluated using t tests. Statistical analyses were conducted for hypothesis generation and were not adjusted for multiple comparisons. P values were considered significant at P < 0.05. Mean BCVA analyses have been described previously. Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

### Results

#### Patient Characteristics

Participant characteristics at baseline are shown in Table 1. Overall, the mean age was 77 years. Forty-three percent of participants showed predominantly classic lesions, 32% showed minimally classic lesions, and 25% showed occult lesions. Most participants showed presence of subretinal fluid, intraretinal fluid, and hyperreflective material at baseline. Mean BCVA was 58 letters at baseline and 65 letters at week 56 (Table 1).

#### Outer Retinal Integrity and Quantitative Features

**Ellipsoid Zone-to-Retinal Pigment Epithelium Volume.** Baseline mean EZ-RPE volume was 0.78 mm³ (standard deviation [SD], 0.30 mm³). EZ-RPE volume showed a significant increase from baseline beginning at week 4 (P < 0.001), which was maintained through week 56 (P < 0.001 at each visit), suggesting improvement in EZ integrity after anti-VEGF treatment (Fig 1A). Mean increase from baseline ranged from 0.13 to 0.23 mm³ over weeks 4 through 56. The mean time to the maximum EZ-RPE volume was 35.9 weeks (SD, 15.3 weeks), which was longer than the mean time to the maximum BCVA (26.0 weeks [SD, 18.1 weeks]). When expressed as a percentage change from baseline, the mean percentage change ranged from 28.0% to 44.5%.

**Ellipsoid Zone-to-Retinal Pigment Epithelium Central Subfield Thickness.** Baseline mean EZ-RPE CST was 2.81 μm (SD, 6.41 μm). EZ-RPE CST showed a significant increase from baseline at each visit from weeks 4 through 56 (P < 0.05 at each visit; Fig 1B), indicating improvements in EZ integrity within the central subfield. Mean increase from baseline ranged from 2.72 to 12.15 μm over weeks 4 through 56. The mean time to the maximum EZ-RPE CST was 38.7 weeks (SD, 15.9 weeks).

**Percentage Total Ellipsoid Zone Attenuation.** At baseline, the mean percentage of the macular cube demonstrating total EZ attenuation (0-μm EZ-RPE thickness) was 35.43% (SD, 20.79%). The percentage of EZ total attenuation showed a significant decrease from baseline at each visit (P < 0.001), suggesting some recovery of the EZ in areas that had shown 0-μm thickness. The mean change from baseline in the percentage of total EZ attenuation ranged from −13.37% to −21.87% across weeks 4 through 56. The mean time to the minimum total EZ attenuation was 38.9 weeks (SD, 14.8 weeks).

**Correlation between Ellipsoid Zone Integrity and Best-Corrected Visual Acuity.** A significant positive correlation was found between EZ-RPE volume and BCVA at each visit from weeks 4 through 56 (P < 0.05) and between EZ-RPE CST and BCVA at each visit from weeks 8 through 56 (P < 0.05; Fig 2). The significant correlations ranged from weak to moderate (0.40 ≤ r ≤ 0.62) for EZ-RPE volume and typically were moderate for EZ-RPE CST (0.54 ≤ r ≤ 0.66, except at week 24 [r = 0.43]). A significant negative correlation was found between percentage of total EZ attenuation and BCVA at most visits from weeks 4 through 56 (P < 0.05, excluding weeks 12, 16, and 40; Fig 2). These correlations generally were weaker
(0.38 ≤ r ≤ 0.55) at corresponding weeks than those for EZ-RPE volume or EZ-RPE CST. The correlation with BCVA was not significant at baseline for any of the 3 EZ integrity metrics.

Change in BCVA from baseline to week 56 showed a significant and weak correlation with change in EZ-RPE CST from baseline to week 56 (r = 0.39; P = 0.04) and change in percentage of total EZ attenuation (r = 0.46; P = 0.02), indicating that greater improvement in EZ integrity was weakly associated with greater increase in BCVA. Change in BCVA from baseline to week 56 was not significantly correlated with change in EZ-RPE volume from baseline to week 56 (r = −0.20; P = 0.32). Change in BCVA from baseline to week 56 also was correlated significantly with early change in percentage of total EZ attenuation, quantified as change from baseline to week 4 (r = 0.49; P = 0.009). Change in BCVA from baseline to week 56 was not correlated significantly with early change in EZ-RPE volume (r = −0.28; P = 0.16) or early change in EZ-RPE CST (r = 0.07; P = 0.74).

**Subretinal Material**

**Subretinal Hyperreflective Material Volume.** Baseline mean SHRM volume was 0.37 mm³ (SD, 0.32 mm³). Subretinal hyperreflective material volume showed a significant decrease from baseline at each visit (P < 0.001; Fig 3A). Mean change from baseline in SHRM volume ranged from −0.25 to −0.32 mm³ across weeks 4 through 56. The mean time to the minimum...
SHRM volume was 25.6 weeks (SD, 16.5 weeks), which was similar to the mean time to the maximum BCVA (26.0 weeks [SD, 18.1 weeks]). The mean percentage change ranged from −70.0% to −87.3% over weeks 4 through 56.

**Subretinal Hyperreflective Material Central Subfield Thickness.** Baseline mean SHRM CST was 57.39 μm (SD, 49.55 μm). A significant decrease was found from baseline in SHRM CST at each visit (P < 0.001; Fig 3B). Mean change from baseline in SHRM CST ranged from −33.48 to −46.93 μm from weeks 4 through 56. The mean time to the minimum SHRM CST was 15.9 weeks (SD, 14.9 weeks), which was shorter than the mean time to maximum BCVA (26.0 weeks [SD, 18.1 weeks]).

**Correlation between Subretinal Hyperreflective Material Metrics and Best-Corrected Visual Acuity.** The correlations between each of the SHRM metrics and BCVA for each study visit are shown in Figure 2. A significant negative correlation was found between SHRM volume and BCVA at baseline and most subsequent study visits (P < 0.05, excluding weeks 20, 24, 40, and 56). Also a significant negative correlation was found between SHRM CST and BCVA at baseline and weeks 4, 8, 28, and 32 (P < 0.05). The significant correlations were weak to moderate for both SHRM volume (0.40 ≤ r ≤ 0.62) and SHRM CST (0.38 ≤ r ≤ 0.59).

Change in BCVA from baseline to week 56 showed a significant weak negative correlation with change in SHRM volume from baseline to week 56 (r = 0.44; P = 0.02) and from baseline to week 4 (r = 0.41; P = 0.04), suggesting that greater decrease in SHRM volume was associated with greater increase in BCVA. Change in BCVA from baseline to week 56 was not correlated significantly with change in SHRM CST from baseline to week 56 (r = 0.32; P = 0.10) or from baseline to week 4 (r = 0.36; P = 0.07).

**Sub–Retinal Pigment Epithelium Compartment**

Baseline mean total sub-RPE volume was 0.80 mm³ (SD, 0.65 mm³). Total sub-RPE volume showed a significant decrease from baseline at each visit (P < 0.05 at each visit; Fig 4A). Mean change from baseline ranged from −0.14 to −0.20 mm³ over weeks 4 through 56, whereas mean percentage change from baseline ranged from −10.1% to −15.5%. The mean time to the minimum sub-RPE volume was 29.6 weeks (SD, 18.3 weeks), which was somewhat longer than the mean time to maximum BCVA (26.0 weeks [SD, 18.1 weeks]).

The correlation between total sub-RPE volume and BCVA was not significant at any visit (Fig 2). The correlation between change in BCVA from baseline to week 56 was not correlated significantly with change in total sub-RPE volume from baseline to week 56 (r = 0.23; P = 0.24) or from baseline to week 4 (r = 0.17; P = 0.40).

**Discussion**

The present post hoc exploratory analysis of the OSPREY study examined longitudinal changes in spectral-domain OCT imaging features of patients with treatment-naïve nAMD from the initiation of anti-VEGF therapy through 56 weeks of treatment. Using higher-order OCT analysis, we observed that anti-VEGF treatment improved EZ integrity, reduced SHRM, and reduced disease within the sub-RPE compartment. Correlations between anatomic features and visual acuity were observed for EZ-RPE as well as SHRM metrics, but not for sub-RPE volume.

Improvement in EZ integrity compared with baseline was evident as early as week 4 of treatment and throughout the 56-week treatment period (Fig 1). These findings are consistent with the finding of improvement in EZ integrity as early as month 3 of treatment. Analysis of the percentage of the macular cube with total EZ attenuation indicated improvement in EZ integrity, even in macular areas that had shown EZ-RPE thickness of 0 μm. Findings that EZ integrity improves with treatment suggest that some of the disruptions are the result of misplacement or attenuation of outer retinal structures as opposed to permanent damage. Although not in nAMD, a similar analysis was completed in the VISTA study in patients...

**Figure 2.** Heatmap showing correlations with best-corrected visual acuity (BCVA). Pearson correlation coefficients between OCT outcome measures and BCVA (Early Treatment Diabetic Retinopathy Study letters) at each study visit. Red indicates a positive correlation, and blue indicates a negative correlation. Lighter tints correspond to weaker correlations. *P ≤ 0.05. **P ≤ 0.01. ***P ≤ 0.001. CST = central subfield thickness; EZ = ellipsoid zone; RPE = retinal pigment epithelium; SHRM = subretinal hyperreflective material.
with diabetic macular edema. Using higher-order OCT, this analysis quantitatively demonstrated improvement in EZ integrity with anti-VEGF treatment (afibcept). Previous studies showed an association between EZ integrity and visual acuity in patients with nAMD before treatment or at the end of treatment. Although the present study did not find an association at baseline, the present study demonstrated a consistent correlation with visual acuity at
each visit beginning at week 4 or 8 of treatment for EZ-RPE volume and EZ-RPE CST, respectively, and at most visits beginning at week 4 for percentage total EZ attenuation (Fig 2). The finding of a correlation after initiation of treatment is likely because of a high incidence of complete EZ attenuation in the foveal area before the onset of treatment. In addition, increase in EZ-RPE CST and decrease in percentage of total EZ attenuation over the course of treatment were associated with increase in visual acuity, which is consistent with previous findings of EZ features in the central subfield.28 The present study also found that early decrease (from baseline to week 4) in percentage total EZ attenuation was associated with increase in visual acuity over the course of treatment (from baseline to week 56), suggesting that this early biomarker is a potential predictor of future outcomes. Reliable measurement of the outer retinal layers has been the major limiting factor in using the outer retina as an imaging biomarker.17 However, higher-order OCT analysis techniques, including machine learning augmentation and advanced image analysis methods, enable efficient evaluation of the outer retinal layers.9–12

In addition to improvements in EZ integrity, analyses of OCT imaging features showed reduction from baseline in SHRM with anti-VEGF treatment, which was observed throughout the 56-week treatment period (Fig 3). Subretinal hyperreflective material is thought to consist of fibrovascular tissue and other material such as blood, fluid, and lipids in the subretinal space.17,29 In the present study, SHRM volume decreased by an average of 72.2% from baseline to week 4, consistent with the hypothesis that SHRM largely comprises fluid, which can resolve readily with anti-VEGF therapy.9 The observed reduction in SHRM volume and SHRM CST in the present analysis is consistent with the previous finding that the proportion of patients who show SHRM decreases with anti-VEGF therapy.9 Subretinal hyperreflective material has been shown to be correlated negatively with visual acuity.6,29 The proximity of SHRM to the photoreceptors and the barrier created by the SHRM between the photoreceptors and the RPE have been hypothesized to play roles in the association between SHRM and poor visual acuity.6,29

In the present study, SHRM volume was found to correlate negatively with visual acuity at baseline and most subsequent study visits (Fig 2). The correlations between SHRM volume across the entire macular cube with visual acuity were found more consistently than the correlations between SHRM CST and visual acuity. Decrease in SHRM volume was also correlated with increase in BCVA, which is consistent with previous findings in the central subfield.28 Interestingly, the present study found that early decrease in SHRM volume (from

Figure 4. Change in total sub–retinal pigment epithelium (RPE) volume. A, Bar graph showing mean change from baseline in total sub-RPE volume. B, Representative B-scans (top row) and en face sub-RPE thickness maps (bottom row) for 1 participant from the OSPREY study showing reduction in sub-RPE volume with treatment.

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baseline to week 4) was a predictor of increase in BCVA over the duration of treatment (from baseline to week 56).

Reduction in total sub-RPE volume compared with baseline also was evident throughout the 56-week treatment period (Fig 4). Total sub-RPE volume in the present study referred to the entire disease burden in the sub-RPE compartment, including fluid, fibrovascular material, and drusen.\textsuperscript{17} The reduction in total sub-RPE volume observed is consistent with previous studies that showed that anti-VEGF therapy reduces the proportion of patients with PED and that sub-RPE volume is reduced after 1 month of therapy.\textsuperscript{17,18,31} In contrast, the sub-RPE area has been found to increase from months 1 to 2 after the initiation of treatment in a subgroup of patients with nAMD showing eventual recurrence of neovascular activity.\textsuperscript{29,30} Pigment epithelium detachment volume also has been found to increase at clinical visits preceding those at which anti-VEGF injection was administered in patients with vascularized PEDs receiving treatment as needed, suggesting that volumetric changes in PED may be a useful predictor of disease progression and retreatment needs.\textsuperscript{23,24} These findings highlight the value of monitoring for changes in sub-RPE area and volume. No correlation between total sub-RPE volume and visual acuity was observed in the present study at baseline or during treatment. The lack of correlation is consistent with other studies that have shown no association between PED volume and visual acuity before treatment.\textsuperscript{25,30} In addition, no association was found between change in total sub-RPE volume and change in BCVA.

Limitations of the present analysis include the small sample size and the exploratory post hoc nature of the analysis. Additional limitations relate to the measurements of the outer retina. The measurement approach to EZ integrative assessment of the EZ-RPE compartment with the entire disease burden in the sub-RPE area and volume. No correlation between total sub-RPE volume and visual acuity was observed in the present study at baseline or during treatment. The lack of correlation is consistent with other studies that have shown no association between PED volume and visual acuity before treatment.\textsuperscript{25,30} In addition, no association was found between change in total sub-RPE volume and change in BCVA.

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Data collection: Jehovah, Reese, Le, Lunasco, Hu
No animal subjects were included in this study.

HUMAN SUBJECTS: Human subjects were included in this study. The study institutional review board approved at all participating investigational sites for the OSPREY study. All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were included in this study.

Author Contributions:
Conception and design: Ehlers
Data collection: Jehovah, Zahid, Reese, Le, Lunasco, Hu

Obtained funding: Ehlers


Abbreviations and Acronyms:

BCVA = best corrected visual acuity; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; EZ = ellipsoid zone; nAMD = neovascular age-related macular degeneration; PED = pigment epithelium detachment; RPE = retinal pigment epithelium; SD = standard deviation; SHRM = subretinal hyperreflective material; VEGF = vascular endothelial growth factor.

Keywords: Ellipsoid zone, subretinal hyperreflective material, sub—retinal pigment epithelium, neovascular age-related macular degeneration, OCT.

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