

# THE OASIS MP-1 SUBSTUDY

## Characterization of the Effect of Ocriplasmin on Microperimetry Parameters

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**Purpose:** To evaluate the effects of ocriplasmin and symptomatic vitreomacular adhesion resolution on visual fixation and macular sensitivity using microperimetry.

**Methods:** MP-1 parameters were analyzed from 3 OASIS sites after the use of standardized instruments and testing procedures over 24 months.

**Results:** A total of 27 patients (19 ocriplasmin, 8 sham) were evaluated. Mean distance of the preferred fixation locus to the anatomical center was farther in the sham group at baseline and farther in the sham versus ocriplasmin group throughout the study. Retinal sensitivity values were consistently higher in the ocriplasmin versus sham group after Month 3. Fewer patients in the ocriplasmin group had predominantly eccentric fixation at study end compared with the sham group, which also had an increased number of patients with unstable fixation. Patients with vitreomacular adhesion resolution had lower bivariate contour area, fewer relative scotomas, and higher retinal sensitivity parameters at baseline than those with unresolved vitreomacular adhesion.

**Conclusion:** Substudy results suggest that fixation and sensitivity parameters tended to be better in the ocriplasmin group than in the sham group over time. The substudy identified parameters that were distinct between patients with and without vitreomacular adhesion resolution, suggesting that microperimetry warrants further study as a relevant biomarker for visual function.

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Symptomatic vitreomacular adhesion (VMA), also referred to as vitreomacular traction (VMT), can lead to the development of a macular hole and cause visual disturbances that can negatively affect a person's quality of life.<sup>1</sup> The prevalence of isolated VMT/symptomatic VMA has been estimated as approximately 0.35 per 100 patients (excluding epiretinal membrane),<sup>2</sup> and spontaneous resolution of symptomatic VMA has been estimated as approximately 10%.<sup>3</sup>

Successful management of VMA requires an accurate assessment of the underlying pathology. Visual acuity remains the gold standard of visual function examination; however, visual acuity is inadequate to describe the natural history of VMA, in part, because VMA can affect large areas outside the fovea.<sup>4</sup> Visual acuity is measured in an unnatural setting and has a low correlation with visual function; for instance, metamorphopsia and visual field defects affect a person's ability to perform certain functions, such as reading and driving.<sup>5</sup> Therefore, increases in visual acuity do not always lead to improvements in daily vision-

dependent activities.<sup>5</sup> Although other tests are used in addition to visual acuity to evaluate VMA, such as Amsler grid and contrast sensitivity, none of these are able to quantify retinal sensitivity or detect patterns of retinal dysfunction.<sup>6</sup> When VMA causes loss of central vision, functional adaptations may occur in many individuals.<sup>7</sup> In an eye with a central scotoma affecting the fovea, one or more eccentric preferred retinal loci (PRLs) naturally develop to perform the foveal visual tasks.<sup>8</sup> Retinal sensitivity is also an important metric to assess in VMA because areas that have the highest sensitivity and physical proximity to the lost foveal region are likely to assume new retinal functions.<sup>7</sup>

Microperimetry is a technique that can accurately assess both a patient's retinal sensitivity and fixation.<sup>9</sup> Using a microperimeter, a physician can determine the location of a PRL, which may be related to the performance of a specific daily activity.<sup>7</sup> Microperimetry can also map the pattern of a patient's retinal sensitivity and provide information on relative and absolute

scotomas,<sup>10</sup> which can aid in precise clinical evaluation of VMA by correlating both morphologic and functional aspects of the condition. Therefore, PRL may be an appropriate supplemental biomarker for visual function because it provides complementary information. Although microperimetry has been successfully used to characterize disease states such as macular hole,<sup>11</sup> age-related macular degeneration,<sup>12</sup> and Stargardt disease,<sup>13</sup> little is known about the microperimetric characteristics of VMA. Several studies have been published, examining a range of 2 to 16 eyes with VMA, with few microperimetry parameters assessed.<sup>14–16</sup> In the largest of these studies to date ( $n = 16$ ), a significant gain in retinal sensitivity was seen in eyes with anatomical resolution after treatment with intravitreal ocriplasmin injection.<sup>16</sup> Unlike diseases that permanently degenerate the macula, VMA can be successfully treated through surgical or pharmacological intervention,<sup>1</sup> which increases the need for comprehensive assessment through microperimetry both before and after VMA resolution.

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Ocriplasmin, a smaller fragment of the plasmin enzyme, can induce vitreous liquefaction and cleave the vitreoretinal interface by degrading fibronectin and laminin; it was approved as the first nonsurgical treatment for symptomatic VMA (VMT).<sup>17</sup> The Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole (OASIS) study, a 24-month Phase 3b clinical trial, provides long-term results on the efficacy and safety of ocriplasmin versus sham injection.<sup>18</sup> As part of the larger OASIS trial, a microperimetry substudy (MP-1) was performed. The purpose of the substudy was to evaluate the effects of ocriplasmin and to assess whether there is correlation between VMA resolution, microperimetry parameters (such as macular sensitivity and fixation-related assessment), and best-corrected visual acuity. To our knowledge, microperimetry has not previously been used to comprehensively examine VMA in a standardized clinical trial setting. Here we report the results of the MP-1 substudy, which describe the effects of VMA on MP-1 with and without ocriplasmin treatment more than 2 years.

## Methods

### *Overall Trial Design and Ethics*

The OASIS study (TG-MV-014, NCT01429441) was a Phase 3b, randomized, sham-controlled, double-masked, multicenter clinical trial designed to further evaluate the long-term efficacy and safety of ocriplasmin in patients with symptomatic VMA (VMT). Patients were randomized to receive either a single intravitreal injection of ocriplasmin 0.125 mg or sham treatment (full details of the OASIS trial methods and main study results have already been published).<sup>18</sup> Patients were required to provide written informed consent before enrollment in the trial. The final protocol, including amendments and informed consent forms, was submitted to the institutional review board and the approval was obtained. The trial adhered to the provisions of the guidelines of the World Medical Association Declaration of Helsinki. This trial was conducted in compliance with the trial protocol and all federal, local, and/or regional requirements, including with the Health Insurance Portability and Accountability Act (HIPAA).

### *Study Treatment and Plan*

For patients randomized to the active treatment group, ocriplasmin 0.125 mg was injected midvitreous. For patients randomized to the sham group, a syringe identical to ocriplasmin, but without a needle,

was used. The syringe hub was pressed against the conjunctiva to mimic an actual injection procedure but no penetration of the globe occurred. To attempt to isolate the effect of ocriplasmin alone, sham injection was chosen as opposed to a saline injection (which was performed in the MIVI-TRUST trials<sup>17</sup>) in the OASIS trial. As demonstrated in the pivotal Phase 3 trials, saline injection can result in VMA resolution; therefore, a sham injection that mimics an intravitreal injection but does not penetrate the eye is a better comparison for observation and allows for the evaluation of natural disease history. MP-1 involved 12 study visits: a baseline visit, which could be completed up to 2 weeks before injection day (Day 0), and 24 months of postinjection follow-up at Day 7, Day 28, and every 3 months thereafter (Months 3, 6, 9, 12, 15, 18, 21, and 24).

### *Cross-Over*

The study allowed for an optional cross-over treatment for patients who met certain eligibility criteria at Visit 8 (Month 12) or at any time beyond, or at any time during the study after Visit 4 (Day 28) for patients who were scheduled for vitrectomy. Patients eligible for optional cross-over treatment at Visit 8 (Month 12) or any time beyond had continued symptomatic VMA (VMT) in the study eye, which was confirmed on spectral domain optical coherence tomography (OCT) by the investigator. These patients were indicated for additional treatment if the symptomatic VMA (VMT) was persistent, and they met at least one of the following criteria as evidence of disease progression: visual acuity decrease by  $\geq 10$  best-corrected visual acuity letters (BCVA), new or worsening metamorphopsia, and/or new idiopathic macular hole or worsening of existing macular hole no larger than 400  $\mu\text{m}$  in diameter. For patients scheduled for vitrectomy after Visit 4 (Day 28), the cross-over treatment was administered 28 to 42 days before the procedure if patient consent was obtained. Cross-over patients received the opposite treatment to the one they initially received while keeping the double-masked design of the study.

### *MP-1 Substudy*

As part of the larger OASIS study, an MP-1 substudy was initiated involving a subset of the clinical study sites. The purpose of the substudy was to evaluate the effect of symptomatic VMA (VMT) and its resolution on visual fixation and macular sensitivity over time, and the effect of ocriplasmin on the function of the macula. The data were also used to evaluate whether some microperimetry parameters could be potential predictors of VMA resolution.

The MP-1 substudy was conducted at three OASIS study sites where the protocol-specified microperimetric instruments were available. Acceptable instrumentation for MP-1 assessment was the Nidek MP-1 microperimeter with software Version 1.7.0 or higher (Nidek, Inc, Fremont, CA). MP-1 testing was performed by qualified study personnel certified by the masked central reading center at the selected sites. Microperimetry assesses fixation and retinal sensitivity and also characterizes scotoma. The main outcomes of microperimetry are defined in terms of fixation location and stability, number of points within defined decibel (dB) ranges, and retinal sensitivity measured in dB. The obtained data were evaluated by the masked central reading center for MP-1.

Fixation-related data included the following: fixation location, degree of eccentricity (distance of the fixation to the PRL), qualitative fixation stability, and quantitative fixation stability (bivariate contour ellipse area [BCEA; 1SD, 2SD, 3SD] and percent of fixation points within 2° and 4° of center). Retinal sensitivity-related data included quantification of normally functioning and relative and absolute scotomatous points. Scotomas were characterized using three parameters: normal function counts (the number of points  $\geq 12$  dB), relative scotoma counts (the number of points  $> 0$  dB and  $< 12$  dB), and absolute scotoma counts (the number of points equal to 0 dB). The threshold of 12 dB for relative versus absolute scotoma was adapted from a previous publication.<sup>19</sup> When added together, the 3 parameters equal 33 total points. Retinal sensitivity was measured using the following: mean sensitivity and mean defect (relative to normal, as defined by the Nidek instrument normative database) across the macula, and mean sensitivity within the foveal central subfield and surrounding parafoveal and perifoveal rings.

A total of 27 patients were enrolled in the MP-1 substudy (19/146 [13.0%] ocriplasmin, 8/74 [10.8%] sham, after the 2:1 randomization design of the larger OASIS study [N = 220]). Most patients in MP-1 (70.4%) completed the study. By treatment group, 2/19 (10.5%) patients in the ocriplasmin group and 4/8 (50.0%) patients in the sham group discontinued the study without crossing over. One patient in each treatment group crossed over to the opposite treatment arm.

### *Analysis Methods*

The MP-1 subset comprised the group of patients who were enrolled at selected sites in the MP-1 substudy and for whom MP-1 measurements were available before and after injection. Analyses were based on actual treatment received. MP-1 parameters

are also presented in the subgroup of patients who have a pharmacological VMA resolution during the study (without anatomical defect).

Descriptive statistics for continuous variables were calculated by treatment groups and overall. Those included number of patients with available data, mean, SD, median, and minimum and maximum, where appropriate. Categorical data were summarized by treatment groups and overall, where specified, based on counts and percentages.

### Logistic Regression Analysis

To explore whether any of the MP-1 parameters were potential baseline-predictive factors for pharmacological VMA resolution at Day 28 (without anatomical defect), logistic regression models including a factor for treatment and each of the MP-1 parameters were evaluated individually (univariate model). When a parameter was found statistically significant at the Level 0.10, it was included in the multivariate model. The multivariate model included factors for treatment and each of the MP-1 parameters were found to be significant in the univariate model. The factors with a  $P$  value  $<0.05$  in the multivariate model were considered as potential baseline MP-1 predictors. In addition, baseline MP-1 characteristics were summarized by those with and without pharmacological VMA resolution (irrespective of anatomical defect and vitrectomy for patients who were non/previtrectomy during the study). Analysis was performed using SAS software version 9.2 (SAS Institute, Inc, Cary, NC).

The relationship of MP-1 assessments with functional and anatomical ocular measurements was evaluated by calculating 1) linear coefficients of correlation between continuous ocular measurements and continuous MP-1 assessments; 2) mean and mean change from baseline of

continuous ocular measurement by categories of fixation location and fixation stability; 3) mean and mean change from baseline of continuous MP-1 assessments by categories of the categorical ocular measurements; and 4) the number of subjects by categorical MP-1 assessments and those of the categorical ocular measurements.

## Results

### Demographics and Baseline Ocular Characteristics

Demographics for patients in the MP-1 subset by treatment group are shown in Table 1, and baseline ocular characteristics are shown in Table 2. Because of the small sample size in the MP-1 subset, it is difficult to conclude whether the ocular characteristics were equally distributed between treatment arms. However, one critical difference between the treatment groups was the time since VMA diagnosis: patients in the ocriplasmin group had a mean time to diagnosis of 9.90 months, compared with 4.47 months for the sham group. Nine patients in the ocriplasmin group had a time to diagnosis of  $\geq 7$  months, compared with one patient in the sham group.

Baseline microperimetry characteristics for the two treatment arms, the overall MP-1 subset, and the nonstudy eye are presented in Table 3. Regarding fixation parameters, the proportion of patients with qualitative fixation location that was considered predominantly central or poor central was comparable between treatment groups. However, the proportion of patients with predominantly eccentric fixation was higher in the ocriplasmin group (11/19 [57.9%]) compared with the sham group (3/8 [37.5%]). This difference may be attributable to the longer time to VMA diagnosis for the ocriplasmin group. The distance of

Table 1. Patient Demographics of the OASIS Study MP-1 Substudy

Demographics	Sham (N = 8)	Ocriplasmin (N = 19)	Overall MP-1 Substudy (N = 27)	Overall OASIS Trial (N = 220)
Sex, n (%)				
Male	3 (37.5)	5 (26.3)	8 (29.6)	72 (32.7)
Female	5 (62.5)	14 (73.7)	19 (70.4)	148 (67.3)
Race, n (%)				
White	6 (75.0)	16 (84.2)	22 (81.5)	197 (89.5)
Black	2 (25.0)	2 (10.5)	4 (14.8)	18 (8.2)
Other	0	1 (5.3)	1 (3.7)	5 (2.3)
Ethnicity, n (%)				
Non-Hispanic	7 (87.5)	17 (89.5)	24 (88.9)	204 (92.7)
Hispanic	1 (12.5)	2 (10.5)	3 (11.1)	16 (7.3)
Age (y) at baseline				
Mean (SD)	70.1 (11.13)	69.6 (11.69)	69.7 (11.31)	69.1 (10.30)
Median (min, max)	68.5 (52, 87)	68.0 (38, 88)	68.0 (38, 88)	68.0 (38, 94)

Table 2. Baseline Ocular Characteristics of the OASIS Study MP-1 Substudy

Baseline Ocular Characteristics (MP-1 Substudy)	Sham (N = 8)	Ocriplasmín (N = 19)	Overall MP-1 Substudy (N = 27)	Overall OASIS Trial (N = 220)
VMA at baseline, n (%)*				
Present	7 (87.5)	19 (100.0)	26 (96.3)	213 (96.8)
Absent	1 (12.5)	0 (0.0)	1 (3.7)	7 (3.2)
Diameter of VMA at baseline, n (%)*				
≤1,500 μm	6 (75.0)	19 (100.0)	25 (92.6)	192 (87.3)
>1,500 μm	0 (0.0)	0 (0.0)	0 (0.0)	16 (7.3)
Missing	2 (25.0)	0 (0.0)	2 (7.4)	12 (5.5)
FTMH at baseline, n (%)*				
Present	3 (37.5)	3 (15.8)	6 (22.2)	76 (34.5)
Absent	5 (62.5)	16 (84.2)	21 (77.8)	144 (65.5)
Largest of the minimum MH width, n (%)*				
≤250 μm	2 (66.7)	2 (66.7)	4 (66.7)	34 (44.7)
>250–400 μm	0 (0.0)	1 (33.3)	1 (16.7)	28 (36.8)
>400 μm	1 (33.3)	0 (0.0)	1 (16.7)	14 (18.4)
ERM at baseline, n (%)*				
Present	3 (37.5)	3 (15.8)	6 (22.2)	51 (23.2)
Absent	5 (62.5)	16 (84.2)	21 (77.8)	169 (76.8)
Lens status, n (%)				
Phakic	5 (62.5)	14 (73.7)	19 (70.4)	158 (71.8)
Pseudophakic	3 (37.5)	5 (26.3)	8 (29.6)	62 (28.2)
Central retinal thickness (μm)*				
Mean (SD)	220.3 (232.77)	315.2 (235.23)	287.0 (234.19)	231.3 (202.33)
Median	135.5	284.0	268.0	189.0
Subretinal fluid, n (%)*				
No	5 (62.5)	9 (47.4)	14 (51.9)	84 (38.2)
Yes	3 (37.5)	10 (52.6)	13 (48.1)	136 (61.8)
BCVA (ETDRS letter score)				
Mean (SD)	62.1 (13.94)	66.5 (6.65)	65.2 (9.34)	63.2 (9.65)
Snellen	20/63	20/50	20/50	20/63
Median	67.5	67.0	67.0	65.0
Snellen	20/50	20/50	20/50	20/50
Time since VMA diagnosis (mo), n (%)				
Mean (SD)	4.47 (9.426)	9.90 (16.814)	8.29 (15.034)	5.75 (12.275)
Median	0.90	2.77	1.27	1.37
Time since VMA diagnosis (mo), n (%)				
<1	4 (50.0)	5 (26.3)	9 (33.3)	69 (31.4)
1–3	3 (37.5)	5 (26.3)	8 (29.6)	96 (43.6)
4–6	0 (0.0)	0 (0.0)	0 (0.0)	15 (6.8)
7–12	0 (0.0)	4 (21.1)	4 (14.8)	10 (4.5)
13–24	0 (0.0)	4 (21.1)	4 (14.8)	17 (7.7)
>24	1 (12.5)	1 (5.3)	2 (7.4)	13 (5.9)
EZ in the central 1-mm cube, n (%)				
Definitely fully intact	4 (50.0)	8 (42.1)	12 (44.4)	71 (32.3)
Likely site(s) of incomplete EZ, foveal	1 (12.5)	3 (15.8)	4 (14.8)	13 (5.9)
Likely site(s) of incomplete EZ, nonfoveal	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.8)
Definite site(s) of incomplete EZ, foveal	3 (37.5)	7 (36.8)	10 (37.0)	119 (54.1)
Definite site(s) of incomplete EZ, nonfoveal	0	1 (5.3)	1 (3.7)	6 (2.7)
Unable to grade	0 (0.0)	0 (0.0)	0 (0.0)	7 (3.2)

\*Based on SD-OCT.

BCVA, best-corrected visual acuity; ERM, epiretinal membrane; ETDRS, Early Treatment Diabetic Retinopathy Study; EZ, ellipsoid zone; FTMH, full-thickness macular hole; MH, macular hole; SD-OCT, spectral domain optical coherence tomography.

preferred fixation location to anatomical center was greater in the ocriplasmin group compared with the sham group. Also, the BCEA (2SD) was smaller in the ocriplasmin group compared with the sham group. Proportions of both relative and absolute scotomas were comparable between treatment groups. Baseline retinal sensitivity measurements showed that the mean threshold, foveal threshold, mean defect, and inner and

outer ring parameters were all comparable between treatment groups (Table 3).

#### *Pharmacological Vitreomacular Adhesion Resolution*

In the ocriplasmin group of the MP-1 subset, 8/19 (42.1%) patients experienced VMA resolution at

Table 3. Baseline Microperimetry Characteristics of the OASIS Study MP-1 Substudy

Baseline Characteristics (MP-1 Substudy)	Sham (N = 8)	Ocriplasmin (N = 19)	Overall (N = 27)	Nonstudy Eye (N = 23)
Fixation location (qualitative), n (%)				
Predominantly central	3 (37.5)	6 (31.6)	9 (33.3)	9 (39.1)
Poor central	2 (25.0)	2 (10.5)	4 (14.8)	3 (13.0)
Predominantly eccentric	3 (37.5)	11 (57.9)	14 (51.9)	11 (47.8)
BCEA (degrees squared) 2SD				
Mean (SD)	7.730 (7.4012)	5.981 (5.1379)	6.499 (5.8040)	5.473 (5.2046)
Median	5.265	3.490	3.490	3.575
Min, max	1.52, 19.06	0.51, 16.07	0.51, 19.06	0.18, 18.34
Distance of PRL to anatomical center (degrees)				
Mean (SD)	1.19 (0.372)	1.32 (0.506)	1.28 (0.467)	1.30 (0.765)
Median	1.25	1.50	1.50	1.00
Min, max	0.5, 1.5	0.5, 2.0	0.5, 2.0	0.0, 3.0
Fixation stability (qualitative), n (%)				
Stable	5 (62.5)	16 (84.2)	21 (77.8)	19 (82.6)
Relatively unstable	3 (37.5)	3 (15.8)	6 (22.2)	4 (17.4)
Unstable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Normal function (no. of points $\geq 12$ dB)				
Mean (SD)	25.3 (11.08)	27.8 (9.09)	27.1 (9.58)	27.0 (9.48)
Median	29.5	32.0	31.0	31.0
Min, max	0, 33	2, 33	0, 33	0, 33
Relative scotoma (no. of points $>0$ and $<12$ dB)				
Mean (SD)	5.3 (5.55)	3.6 (6.38)	4.1 (6.08)	3.3 (4.14)
Median	3.5	1.0	2.0	2.0
Min, max	0, 15	0, 27	0, 27	0, 14
Absolute scotoma (no. of points = 0 dB)				
Mean (SD)	2.5 (6.28)	1.5 (5.47)	1.8 (5.62)	2.3 (7.40)
Median	0.0	0.0	0.0	0.0
Min, max	0, 18	0, 24	0, 24	0, 32
Mean threshold (whole grid; dB)				
Mean (SD)	13.93 (5.613)	15.75 (4.645)	15.21 (4.914)	15.11 (5.480)
Median	14.75	17.50	17.20	16.50
Min, max	1.9, 20.0	2.0, 20.0	1.9, 20.0	0.2, 20.0
Mean defect (dB)				
Mean (SD)	5.18 (4.964)	3.52 (4.529)	4.01 (4.629)	4.01 (4.385)
Median	4.35	1.50	2.00	2.70
Min, max	0.6, 15.8	0.0, 18.1	0.0, 18.1	0.1, 16.0
Foveal threshold (dB)				
Mean (SD)	13.25 (5.903)	15.12 (4.857)	14.57 (5.145)	15.56 (5.509)
Median	14.30	16.00	15.60	16.80
Min, max	3.4, 20.0	0.8, 20.0	0.8, 20.0	0.7, 20.0
Inner ring (dB)				
Mean (SD)	14.76 (6.021)	16.85 (5.089)	16.23 (5.351)	15.71 (5.569)
Median	16.40	19.10	18.10	17.10
Min, max	0.8, 20.0	0.0, 20.0	0.0, 20.0	0.0, 20.0
Outer ring (dB)				
Mean (SD)	13.85 (5.659)	15.61 (4.554)	15.09 (4.863)	14.58 (5.538)
Median	15.25	17.00	16.80	15.50
Min, max	1.6, 20.0	3.8, 20.0	1.6, 20.0	0.0, 20.0

dB, decibel.

Day 28, the primary endpoint of the OASIS trial, compared with 0/8 (0%) in the sham group. A total of 11/19 (57.9%) patients experienced pharmacological VMA release by the end of the study, compared with 1/8 (12.5%) in the sham group. In the larger OASIS trial, 62/145 (41.7%) patients in the ocriplasmin group experienced VMA resolution by Day 28 and 65/145 (39.8%) experienced pharmacological VMA resolution by Month 24, compared with 5/73 (6.2%) and 11/73 (13.6%) patients in the sham group, respectively. The decrease in the proportion of patients with VMA resolution is due to the endpoint definition used in the study: patients who underwent a vitrectomy after VMA resolution were considered “failures.”

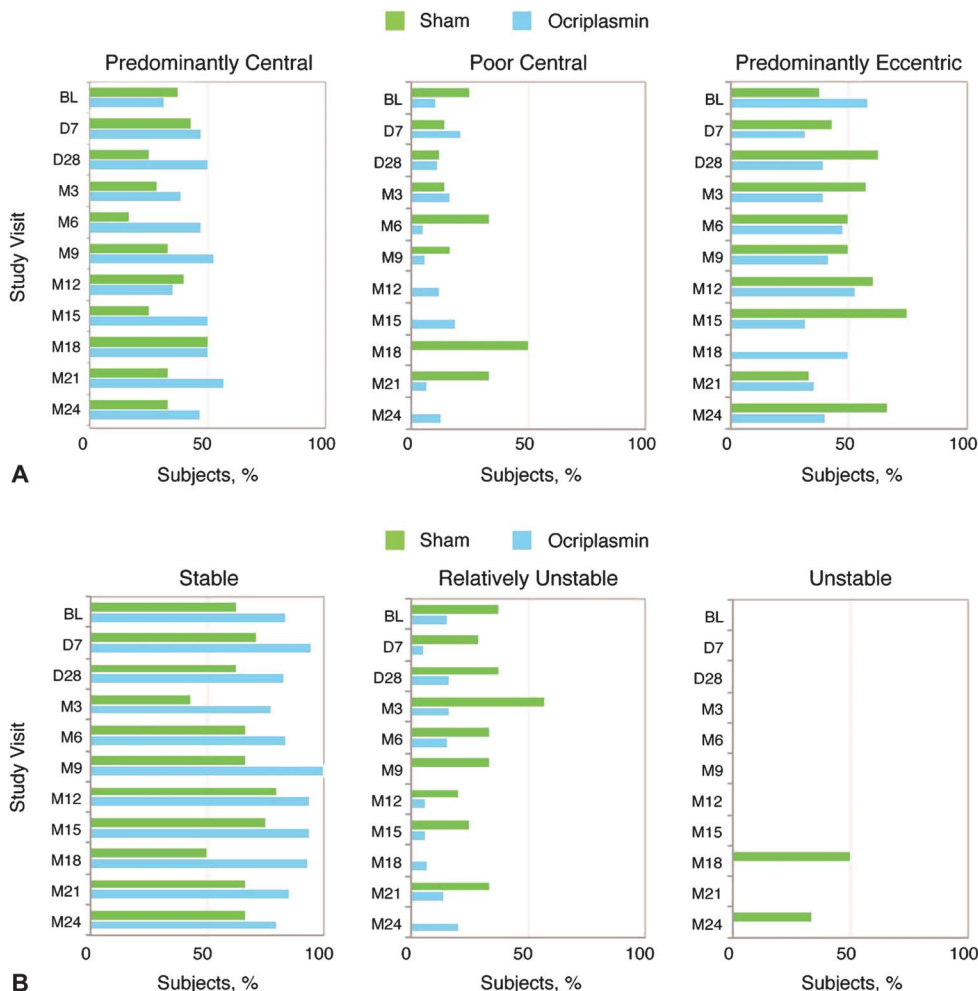
*Fixation Location and Stability*

Fixation location was assessed at each treatment visit in both the ocriplasmin and sham treatment groups. Although the ocriplasmin group showed a higher proportion of patients with predominantly eccentric fixation at baseline compared with the sham

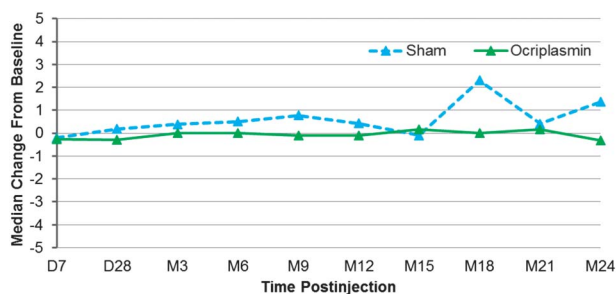
group, there was a tendency for the sham group to fixate more eccentrically over time. At Month 24, there were more sham-treated patients with predominantly eccentric fixation and fewer with predominantly central fixation, compared with the ocriplasmin-treated patients (Figure 1A). In addition, a higher proportion of sham-treated patients showed relatively unstable fixation compared with ocriplasmin-treated patients (Figure 1B).

*Bivariate Contour Ellipse Area*

Fixation stability is typically quantified by calculating the area of an ellipse, which encompasses a given proportion of fixation points, known as the BCEA, where a smaller best-corrected visual acuity correlates with more stable fixation.<sup>20</sup> In ocriplasmin-treated patients, median change from baseline in BCEA increased slightly over the length of the study (Figure 2). By contrast, sham-treated patients showed little change from baseline in BCEA over the course of the study. Furthermore, patients



**Fig. 1.** Fixation location and stability by visit in the ocriplasmin and sham groups in the MP-1 substudy. Patients were evaluated at each study visit for the categorical fixation assessments of fixation location as predominantly central, poor central, or predominantly eccentric (A) or fixation stability as stable, relatively unstable, or unstable (B). Baseline is the last nonmissing value before administration of study treatment. N = 8, sham; N = 19, ocriplasmin. The number of patients assessed at each study visit is given. Sham: BL, n = 8; D7, n = 7; D28, n = 8; M3, n = 7; M6, n = 6; M9, n = 6; M12, n = 5; M15, n = 4; M18, n = 2; M21, n = 3; and M24, n = 3. Ocriplasmin: BL, n = 19; D7, n = 19; D28, n = 18; M3, n = 18; M6, n = 19; M9, n = 17; M12, n = 17; M15, n = 16; M18, n = 14; M21, n = 14; and M24, n = 15. BL, baseline; D, day; M, month.



**Fig. 2.** Bivariate contour ellipse area median change from baseline by visit in the ocriplasmin and sham groups in the MP-1 substudy. Patients were evaluated at each study visit for the continuous fixation assessment of bivariate contour ellipse area. Baseline is the last nonmissing value before administration of study treatment. N = 8, sham; N = 19, ocriplasmin. The number of patients assessed at each study visit is given. Sham: BL, n = 8; D7, n = 7; D28, n = 8; M3, n = 7; M6, n = 6; M9, n = 6; M12, n = 5; M15, n = 4; M18, n = 2; M21, n = 3; and M24, n = 3. Ocriplasmin: BL, n = 19; D7, n = 19; D28, n = 18; M3, n = 17; M6, n = 19; M9, n = 17; M12, n = 17; M15, n = 16; M18, n = 14; M21, n = 14; and M24, n = 15. BL, baseline; D, day; M, month.

who experienced VMA resolution, regardless of treatment, had lower BCEA than those who did not (Table 4).

*Preferred Retinal Locus to Anatomical Center*

Because patients develop eccentric retinal areas in response to lost macular function, the distance of the PRL to the anatomical center (fovea) is an important metric to determine the degree of pathology. In addition, given the normal hill of vision, a more eccentric PRL would be expected to be associated with a lower maximal potential visual acuity. In patients with VMA, those in the ocriplasmin group had a more eccentric PRL at baseline compared with those in the sham treatment group (Figure 3). The distance of the PRL from the anatomical center at baseline was identified as a predictor of VMA resolution, showing shorter distances in patients with VMA resolution compared with those without in both treatment groups (Table 4).

*Scotoma*

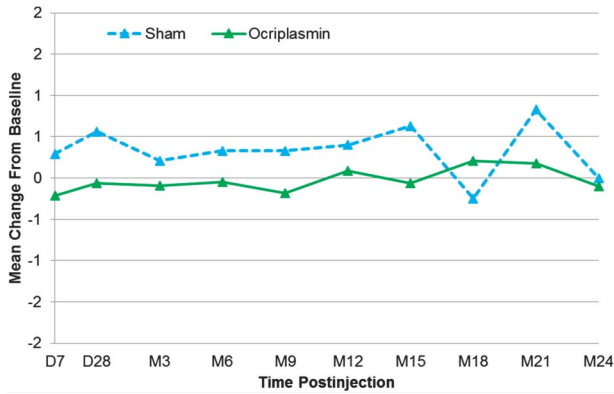
Eccentric viewing patterns in some patients are likely caused by scotomas affecting the fovea. At

Table 4. Microperimetry Parameters at Baseline in Subjects With and Without Vitreomacular Traction Resolution in the MP-1 Substudy

Characteristic	VMA Resolution		No VMA Resolution	
	Sham (N = 1)	Ocriplasmin (N = 12)*	Sham (N = 7)	Ocriplasmin (N = 7)
Distance of preferred fixation locus to anatomical center (degrees)				
Mean (SD)	1.00	1.25 (0.584)	1.21 (0.393)	1.43 (0.345)
Median	1.00	1.25	1.50	1.50
Min, max	1.0, 1.0	0.5, 2.0	0.5, 1.5	1.0, 2.0
BCEA (degrees squared) 2SD				
Mean (SD)	3.320	3.959 (3.4898)	8.360 (7.7591)	9.447 (5.8886)
Median	3.320	2.270	7.210	10.270
Min, max	3.32, 3.32	0.51, 10.28	1.52, 19.06	2.09, 16.07
Relative scotoma at baseline (no. of points >0 and <12 dB)				
Mean (SD)	1.0	1.4 (2.81)	5.9 (5.70)	7.4 (9.00)
Median	1.0	0.5	5.0	5.0
Min, max	1, 1	0, 10	0, 15	0, 27
Mean threshold (whole grid; dB)				
Mean (SD)	16.70	17.88 (2.380)	13.53 (5.940)	12.10 (5.451)
Median	16.70	18.30	13.10	13.30
Min, max	16.7, 16.7	11.9, 20.0	1.9, 20.0	2.0, 17.9
Foveal threshold				
Mean (SD)	15.40	17.15 (3.019)	12.94 (6.306)	11.64 (5.632)
Median	15.40	17.35	13.20	11.70
Min, max	15.4, 15.4	11.3, 20.0	3.4, 20.0	0.8, 18.9
Inner ring				
Mean (SD)	17.90	19.04 (1.943)	14.31 (6.358)	13.09 (6.681)
Median	17.90	19.75	14.90	15.30
Min, max	17.9, 17.9	13.3, 20.0	0.8, 20.0	0.0, 19.1
Outer ring				
Mean (SD)	16.80	17.75 (2.449)	13.43 (5.976)	11.93 (5.125)
Median	16.80	18.35	15.00	13.10
Min, max	16.8, 16.8	11.5, 20.0	1.6, 20.0	3.8, 17.0

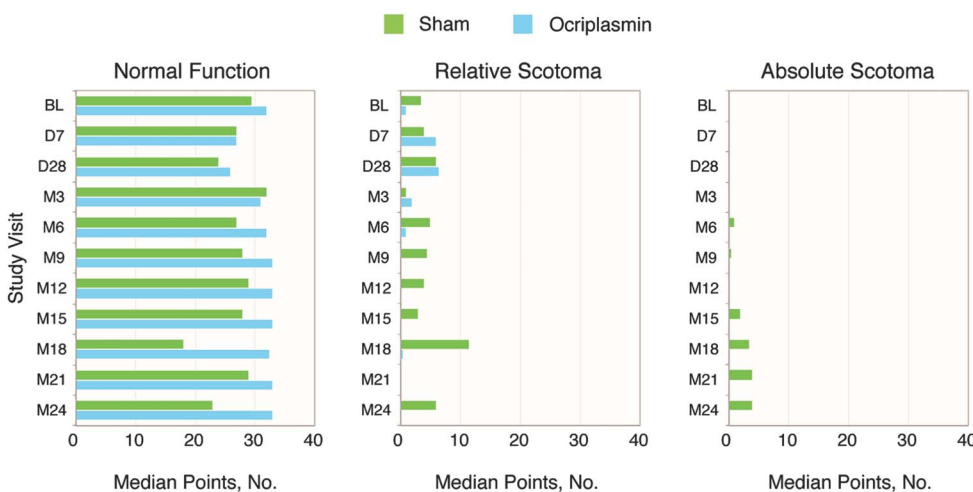
\*One subject in the ocriplasmin group who had a vitrectomy after VMA release is not considered a success at Month 24 for the primary endpoint but is included in the subset of those who experienced VMA resolution during the study for this analysis. dB, decibel.





**Fig. 3.** Distance of preferred retinal locus to anatomical center mean change from baseline by visit in the ocriplasmin and sham groups in the MP-1 substudy. Patients were evaluated at each study visit for the distance of preferred retinal locus to anatomical center. Baseline is the last nonmissing value before administration of study treatment. N = 8, sham; N = 19, ocriplasmin. The number of patients assessed at each study visit is given. Sham: BL, n = 8; D7, n = 7; D28, n = 8; M3, n = 7; M6, n = 6; M9, n = 6; M12, n = 5; M15, n = 4; M18, n = 2; M21, n = 3; and M24, n = 2. Ocriplasmin: BL, n = 19; D7, n = 19; D28, n = 18; M3, n = 17; M6, n = 19; M9, n = 17; M12, n = 17; M15, n = 16; M18, n = 14; M21, n = 14; and M24, n = 15. BL, baseline; D, day; M, month.

baseline, the number of normal function points was comparable between treatment groups (Figure 4). After ocriplasmin treatment, patients experienced an increase in the median number of relative scotomatous points at the Day 7 and Day 28 visits but subsequently recovered to the baseline value by Month 6 and remained lower than baseline for the rest of the study (Figure 4). By contrast, the median number of relative and absolute scotomatous points was higher in the sham group compared with the ocriplasmin group from the Month 6 visit onward (Figure 4). Patients experiencing VMA resolution had fewer relative scotomatous points at baseline than those who did not experience resolution, regardless of treatment group (Table 4).



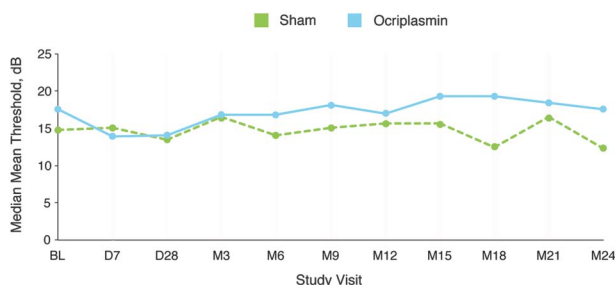
**Fig. 4.** The number of normal and scotomatous points by visit in the ocriplasmin and sham groups in the MP-1 substudy. Patients were evaluated at each study visit for scotomatous points characterized as normal function ( $\geq 12$  dB), relative scotoma ( $>0$  dB and  $<12$  dB), and absolute scotoma (0 dB). Values represent the median number of points. N = 8, sham; N = 19, ocriplasmin. The number of patients assessed at each study visit is given. Sham: BL, n = 8; D7, n = 7; D28, n = 8; M3, n = 7; M6, n = 6; M9, n = 6; M12, n = 5; M15, n = 4; M18, n = 2; M21, n = 3; and M24, n = 3. Ocriplasmin: BL, n = 19; D7, n = 19; D28, n = 18; M3, n = 17; M6, n = 19; M9, n = 17; M12, n = 17; M15, n = 16; M18, n = 14; M21, n = 14; and M24, n = 15. BL, baseline; D, day; M, month.

*Retinal Sensitivity*

Another important metric that can be evaluated by microperimetry is retinal sensitivity. Retinal areas that have the highest sensitivity and physical proximity to the fovea are likely to assume new retinal function in the case of central vision loss; therefore, sensitivity metrics provide insight into the overall condition of the retina. After treatment, the ocriplasmin group showed a decrease in the median of the mean threshold at Day 7 and Day 28 visits but subsequently showed higher sensitivity compared with the sham group (Figure 5). Similar trends were observed with foveal threshold and inner and outer ring assessments, which all showed a decrease in sensitivity in the ocriplasmin group at Day 7 and Day 28, with subsequent recovery to or near baseline by Month 3 (foveal threshold) or Month 9 (inner ring and outer ring), with most values higher than those in the sham group throughout the study (Table 5). Similarly, the mean defect (relative to normal) increased in the ocriplasmin group at Day 7 and Day 28 visits, but returned to near baseline levels by Month 3, showing lower values than the sham group for most of the remaining study visits. Mean threshold, foveal threshold, and inner and outer ring sensitivity assessments at baseline were all higher in patients who experienced VMA resolution compared with those who did not, regardless of treatment group (Table 4).

**Discussion**

The MP-1 substudy of the OASIS clinical trial is the first study that has used microperimetry parameters to evaluate the effect of VMA with and without ocriplasmin treatment as part of a 24-month, prospective,



**Fig. 5.** Median of the mean threshold (whole grid) by visit in the ocriplasmin and sham groups in the MP-1 substudy. Patients were evaluated at each study visit for mean threshold (whole grid). Values represent the median. Baseline is the last nonmissing value before administration of study treatment. N = 8, sham; N = 19, ocriplasmin. The number of patients assessed at each study visit is given. Sham: BL, n = 8; D7, n = 7; D28, n = 8; M3, n = 7; M6, n = 6; M9, n = 6; M12, n = 5; M15, n = 4; M18, n = 2; M21, n = 3; and M24, n = 3. Ocriplasmin: BL, n = 19; D7, n = 19; D28, n = 18; M3, n = 17; M6, n = 19; M9, n = 17; M12, n = 17; M15, n = 16; M18, n = 14; M21, n = 14; and M24, n = 15. BL, baseline; dB, decibel; D, day; M, month.

randomized, sham-controlled clinical trial. The MP-1 substudy was undertaken to evaluate the effect of symptomatic VMA (VMT) and its resolution on visual fixation and macular sensitivity over time as well as the effect of ocriplasmin on the function of the macula.

Visual acuity, which allows one to identify high-contrast letters on an eye chart, can be unrelated to daily life activities<sup>21</sup> and is not a sufficient metric to assess VMA. Visual acuity does not always accurately reflect foveal or macular function because eyes with poor foveal function will often use eccentric fixation. Vitreomacular adhesion can also affect large areas of the macula, not just the foveal center.<sup>4</sup> Patients with VMA commonly report visual disturbances, such as photopsia, micropsia, and metamorphopsia,<sup>1,22</sup> which can significantly affect a patient’s quality of life.<sup>23</sup> A person’s inability to perform routine daily life

activities depends on multiple factors; these include the presence of visual field defects and other anatomical factors in addition to visual acuity.<sup>5</sup> In contrast to visual acuity, which is predominantly a measurement of foveolar vision, microperimetry provides a more global assessment of retinal function outside the fovea.

Despite the limited number of patients in the MP-1 substudy, some interesting observations can be made. At baseline, fewer patients in the ocriplasmin group showed predominantly central and poor central fixation and more showed predominantly eccentric fixation compared with patients in the sham group. This was likely due to the longer time since VMA diagnosis for patients in the ocriplasmin group. However, over time, fewer sham patients showed predominantly central and poor central fixation and more showed predominantly eccentric fixation compared with patients in the ocriplasmin group. In the ocriplasmin group, a greater number of patients experienced increased central fixation over time.

After ocriplasmin treatment, multiple retinal sensitivity parameters showed a transient decrease at Day 7 and Day 28 visits, including mean threshold (whole grid), foveal threshold, and inner and outer ring values. One potential explanation is that these transient decreases were due to transient ellipsoid zone disruption, which is known to occur in some patients after treatment with ocriplasmin.<sup>24</sup> Importantly, these values were subsequently recovered and were higher than the corresponding sham values at most, if not all, of the subsequent study visits. Mean defect showed similar trends, increasing in the first several visits after treatment before returning to below baseline levels at Month 9 and improvement compared with the sham group for most of the remaining study.

**Table 5.** Median Foveal Threshold, Inner Ring, and Outer Ring Values in the Ocriplasmin and Sham Groups in the MP-1 Substudy

Characteristic*	Study Visit										
	BL	D7	D28	M3	M6	M9	M12	M15	M18	M21	M24
<b>Foveal threshold (dB)</b>											
Sham	14.30	10.10	11.80	14.70	12.10	11.10	11.90	11.50	10.85	19.00	13.40
Ocriplasmin	16.00	11.90	13.55	15.70	16.90	16.90	17.00	19.65	19.50	18.80	18.80
<b>Inner ring (dB)</b>											
Sham	16.40	18.10	15.30	18.00	14.70	16.95	15.80	15.65	13.50	9.50	8.40
Ocriplasmin	19.10	15.60	16.00	18.40	17.90	18.80	18.00	19.80	19.25	19.15	18.50
<b>Outer ring (dB)</b>											
Sham	15.25	18.20	15.45	18.20	15.90	16.45	16.10	18.10	13.00	18.90	13.60
Ocriplasmin	17.00	15.30	13.60	15.30	16.10	17.90	16.90	18.75	18.65	17.35	16.20
<b>Mean defect (dB)</b>											
Sham	4.35	3.30	5.55	2.70	5.00	3.95	3.80	2.75	6.50	0.60	5.50
Ocriplasmin	1.50	5.10	5.15	2.50	2.20	1.40	1.90	0.85	0.70	1.10	1.60

\*For sham group, N = 8; for ocriplasmin group, N = 19. BL, baseline; D, day; dB, decibel; M, month.

One of the goals of the MP-1 substudy was to evaluate whether any microperimetry variables would show an association with VMA resolution. After the MIVI-TRUST Phase 3 trials, subgroup analysis showed that patients with baseline ocular characteristics such as absence of epiretinal membrane, VMA diameter of  $\leq 1,500 \mu\text{m}$ , and macular hole  $\leq 400 \mu\text{m}$  were associated with a higher VMA resolution rate.<sup>17,25</sup> Cellular mechanisms have been described that may account for differences in success of VMA resolution. In one study, patients with recalcitrant VMA were treated by surgery and further analyzed.<sup>26</sup> Ultrastructural analysis showed fibrocellular proliferation, including retinal pigment epithelial cells, a typical feature of epiretinal membranes. The presence of these cells may fortify the attachment strength of the VMT to the fovea through increased extracellular matrix deposition.<sup>26</sup> Differences in microperimetry parameters between patients who experienced VMA resolution and those who did not may further define the characteristics of VMA that is more likely to resolve.

Analyses performed on the microperimetry data showed a constellation of microperimetry parameters that were distinct at baseline between patients who experienced VMA resolution and those who did not. Retinal sensitivity is likely a strong indicator of the ability of VMA to resolve because multiple sensitivity parameters were higher at baseline in patients who experienced VMA resolution. Not surprisingly, given that retinal sensitivity and scotomas are interrelated, patients with VMA resolution also had fewer relative scotomas at baseline compared with patients who did not experience resolution, as well as a comparatively lower BCEA at baseline.

Of all the parameters that showed differences based on VMA resolution, the distance of the preferred retinal locus to the anatomical center was identified as a statistically significant predictor of VMA resolution by logistic regression. This result was unexpected given the comparatively small differences at baseline between patients with and without VMA resolution during the study. However, this distance reflects the degree of eccentric fixation, which represents the overall condition of the fovea. The distance of preferred retinal locus to the anatomical center was predominantly lower in ocriplasmin-treated patients, who also had higher rates of VMA resolution compared with sham-treated patients. These results strongly suggest that even small differences can have meaningful effects on VMA resolution outcomes.

Collectively, these factors that show differences between resolution and nonresolution allow for better characterization of VMA. The findings of Chang et al<sup>26</sup> underscore that VMA can have distinct qualities in different patients. These differences may arise in

part from the varying degrees of chronicity of the condition, with a longer time possibly reflecting an increase in epiretinal membrane-like adhesion. Such distinctions would not be detected by conventional visual field examination and may not be clearly evident on spectral domain OCT and thus may only be discernable through microperimetry analysis.

Limitations of the substudy include the small sample size, especially in the sham group, and the fact that 6/27 patients discontinued the study, which precluded the ability to derive statistical significance on parameters that show trends in favor of ocriplasmin. In addition, because of the small sample size, the 12 patients in the ocriplasmin group with VMA resolution may have skewed the results of the ocriplasmin group as a whole. These results suggest that further study involving a larger cohort is warranted and may provide additional support for the use of microperimetry with VMA. Another limitation of this substudy is the lack of available correlation data with OCT-based photoreceptor findings. The central reading center for OCT for the OASIS study only evaluated the ellipsoid zone in the foveal center (central 1 mm), limiting the ability to compare sensitivity values with the status of the photoreceptors in those locations.

Despite these limitations, this is the first study to evaluate microperimetry parameters in patients receiving ocriplasmin as part of a larger trial. Microperimetry is a strong clinical tool to aid in the assessment of VMA and can be used together with electroretinogram recordings and OCT in a multimodal approach to more accurately assess the condition and the likelihood of successful resolution. Ultimately, with VMA as with any macular disease, functional vision rather than visual acuity is the metric by which treatment will be judged a success. Results of the MP-1 substudy provide new information on the effects of VMA on microperimetry parameters over time with and without ocriplasmin treatment, allowing for further insight into the true functional compromise of VMA and benefit of ocriplasmin.

**Key words:** microperimetry, ocriplasmin, visual function, vitreomacular traction.

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