

Visual Function Response to Ocriplasmin for the Treatment of Vitreomacular Traction and Macular Hole: The OASIS Study

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PURPOSE. To assess the effect of ocriplasmin on visual function response (VFR) measured using visual acuity (VA) and vision-related quality of life, and to quantify the association between release of vitreomacular adhesion (VMA) at day 28 and VFR.

METHODS. Prespecified analysis of secondary endpoints from a randomized controlled trial. Of 220 participants with symptomatic VMA/vitreomacular traction (VMT), including VMT associated with a macular hole up to 400 μ m, 146 received a single intravitreal injection of 125 μ g ocriplasmin and 74 a sham injection. Based on principal components analysis results, a VFR was defined as either a VA improvement of ≥ 2 lines or an improvement exceeding the minimal clinically important difference (MCID) in the composite or the mental health subscale scores of the Visual Function Questionnaire (VFQ-25). The MCID was estimated using the standard error of measurement approach. The main outcome measure was the VFR at month 6, with further assessments at months 12 and 24.

RESULTS. The MCID was estimated at 3.71 points for the VFQ-25 composite score and 10.71 for the VFQ-25 mental health subscale score. A VFR occurred in 51.0% of ocriplasmin versus 23.3% of sham participants ($P = 0.0001$). The VFR was maintained through months 12 and 24: 53.1% and 50.3% in ocriplasmin versus 21.9% and 20.5% in sham participants, respectively ($P < 0.0001$). Resolution of VMA at day 28 significantly increased the odds of a VFR at each assessment period.

CONCLUSIONS. Treatment with ocriplasmin compared with sham resulted in a significant improvement in VFR. The 6-month treatment effect was sustained at months 12 and 24.

Keywords: macular hole, minimal clinically important difference, ocriplasmin, principal components analysis, patient-reported outcomes, sham, symptomatic vitreomacular adhesion/vitreomacular traction, VFQ-25

Vitreomacular traction (VMT), also referred to as symptomatic vitreomacular adhesion (VMA), is characterized by an incomplete posterior vitreous detachment with persisting VMA that causes distortion of the foveal anatomy. It can be associated with variable loss of visual function.^{1,2} The traction can also progress to cause a full-thickness macular hole. Visual symptoms include metamorphopsia, reduced visual acuity (VA), blurred vision, micropsia, scotoma, and difficulties with daily vision-related tasks.^{1,3,4} Treatment depends largely on the cause, but options include observation, pars plana vitrectomy (PPV), and pharmacologic vitreolysis.⁵⁻⁷ Observation is typically advocated for stable mild VMT that does not justify the risks of surgery, or in the expectation that some cases will resolve spontaneously.^{1,4-6} Vitrectomy is the most common treatment for clinically significant VMT and most cases with macular hole; however, PPV carries the risks of intra- and postoperative complications with modest visual acuity improvements in cases of VMT.^{1,7,8}

Ocriplasmin was approved in the United States in 2012 and Europe in 2013, based on the results of the two MIVI-TRUST

phase 3 clinical trials.⁹ In both regions the indication is VMT, including VMT associated with a macular hole up to 400 μ m in apical diameter. In the United States, these two related indications (VMT and macular hole) are grouped together under the term, "symptomatic."

Subgroup analyses determined that ocriplasmin is most effective for focal VMA ($\leq 1500 \mu$ m), and in the absence of epiretinal membrane (ERM).^{10,11} More recently, the Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole study (OASIS; clinicaltrials.gov identifier: NCT01429441) reported improved efficacy of ocriplasmin using refined case selection that was based on the baseline characteristics predictive of resolution.^{12,13} The OASIS study had longer follow-up than MIVI-TRUST (24 vs. 6 months), higher-resolution optical coherence tomography (OCT), and more visual function tests.¹²

VMT is often discovered in association with decreased VA; however, symptoms, most commonly metamorphopsia, can occur despite good or relatively normal acuity.⁴ Metamorphopsia can be very troublesome for patients, and can markedly



impair reading and face recognition.^{14,15} Metamorphopsia is often overlooked, perhaps due to overreliance on OCT imaging, which often correlates poorly with visual function.^{14,16–19} Likewise, VA can correlate poorly with metamorphopsia and visual dysfunction in patients with VMT and macular hole.^{20–22} Further, quantitative evaluation of metamorphopsia is often difficult, and is not yet part of routine clinical practice.^{14,16,23}

Given the limitations of VA and OCT in patients with VMT, there is a need to find a more patient-centered outcome measure; one that incorporates the complexity of visual dysfunction secondary to VMT, and the impact thereof. With this in mind, we previously studied visual function data obtained during the MIVI-TRUST trials to establish a clinically meaningful definition of visual function response (VFR). Based on a principal components analysis (PCA), a technique to reduce the dimensionality of multivariate data while preserving as much of the relevant information as possible,²⁴ VFR was defined as either a VA improvement of ≥ 2 lines; an improvement in the composite score of the National Eye Institute Visual Function Questionnaire (VFQ-25) exceeding the minimal clinically important difference (MCID), estimated using the standard error of measurement approach; or an improvement in the VFQ-25 driving subscale score exceeding the MCID. Using this established methodology, we showed that ocriplasmin produced a clinically meaningful visual function benefit over placebo.¹⁷

The OASIS study presents the opportunity to repeat our previous analysis in a study group that is more generalizable to current care, as OASIS excluded eyes with ERM and there was a sham rather than placebo-injection control. The OASIS study also has longer follow-up than MIVI-TRUST. We aimed to test the hypothesis that ocriplasmin is more likely to produce a VFR than sham, and that short-term VMA release is associated with longer-term visual function benefit. We tested our hypotheses using a prespecified analysis of visual function data obtained during the OASIS study, looking specifically at VA and the VFQ-25.

METHODS

Participants

We analyzed data from the previously reported OASIS trial.¹² Briefly, OASIS was a phase 3b, randomized, sham-controlled, double-masked, multicenter clinical trial designed to provide longer-term outcomes on the efficacy and safety profile of ocriplasmin, with refined case selection based on the MIVI-TRUST subgroup analyses.^{10,11} OASIS enrolled 220 participants (146 ocriplasmin, 74 sham) across 25 US sites. All participants had a clinical diagnosis of VMT defined as the presence of VMA that was related to decreased visual function. All eyes had either VMT alone, or VMT associated with a full-thickness macular hole. Although ERM was an exclusion criterion, 23.0% of eyes were diagnosed with ERM by the central reading center (CRC) after enrollment, in conflict with the initial assessment by the recruiting clinical investigator. Participants received a single intravitreal injection of 125 μg of ocriplasmin or sham injection, and were assessed over 24 months. The primary efficacy endpoint was the proportion of participants with pharmacologic VMA resolution at day 28. If the underlying condition had not resolved by day 28, or if there was a deterioration before day 28, such as a new macular hole or worsening of best-corrected VA (BCVA), the clinical investigator could advise PPV (data on file).

OASIS was conducted in accordance with the Declaration of Helsinki. Institutional review board approval was obtained at

each site, and participants provided written informed consent before enrollment.

Assessment of Visual Function and VFR Definition

BCVA was measured at each study visit using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart.²⁵ Because metamorphopsia, micropsia, and other symptoms of VMA are not quantifiable on ETDRS charts, another measure was needed to evaluate changes in vision-related function.³ Therefore, in addition to BCVA assessments, participants were examined using a functional assessment of visual ability, the VFQ-25.¹² The VFQ-25 is a validated instrument designed to examine the influence of eye conditions and interventions on a patient's day-to-day functioning and well-being. The 25-item survey measures the patient's subjective assessments of visual function, and has been widely used in ophthalmologic research.^{26,27} In OASIS, the survey was administered at baseline and months 6, 12, and 24. The current VFR analysis was protocol prespecified and explored the change in BCVA and VFQ-25 scores from baseline to months 6, 12, and 24.

Following methods described in our previous analysis, we conducted a responder analysis that classified each participant as having a VFR, or not.¹⁷ First, PCA was used to determine the variables that summarize the VFQ-25 responses best in two dimensions.²⁴ A PCA can reduce a multidimensional response into a restricted set of responses, called Principal Components (PCs), in an objective way while preserving as much of the overall variability in the multidimensional response as possible (see Supplementary Materials for details on PCA and its [dis]advantages). Second, for each of these variables, a threshold for meaningful response reflecting the MCID was required.²⁸ For BCVA, the MCID was defined as a 2-line or larger change, which is believed to be a clinically important change in people with better VA.^{29,30} In the absence of a suitable anchor, a distribution-based metric, the standard error of measurement, was used for the VFQ-25 scores.³¹ These thresholds were determined by the best method available as recommended by the Food and Drug Administration Guidance on Patient-Reported Outcomes.³²

Main Analyses

The primary analysis estimated the effect of treatment (ocriplasmin versus sham) on the VFR measures at month 6 and was performed on all randomized participants, per the intent-to-treat principle. Additional analyses explored the following: (1) the effect of treatment on VFR at months 12 and 24; (2) the association between anatomic response (VMA release versus persisting VMA defined as VMA resolution at day 28 versus no VMA resolution at day 28, respectively) and VFR at the different time points; (3) the effect of treatment in subgroups of participants with VMA release versus persisting VMA (release of VMA did not consider whether or not a macular hole was present); and (4) the effect of treatment on VFR in subgroups defined by whether the participants had a macular hole at baseline or not.

Statistical Methods

Missing data for BCVA were imputed using the last observation carried forward (LOCF). LOCF is an often-used technique in clinical trials to enable the use of all evidence. It does not generate biases in the randomized comparison whenever we can assume that the missingness is random.

VFQ-25 scores were computed on observed individual items as per its scoring algorithm.³³ The effect of treatment on VFR (in the overall study population and in subgroups defined by

TABLE 1. VFR at Month 6, by Treatment Group

Response Variable	Ocriplasmin		Sham		OR	95% CI
	n/N	%	n/N	%		
VFQ-CS	49/145	33.8	9/73	12.3	3.63	1.67–7.90
VFQ-MHS	41/145	28.3	9/73	12.3	2.80	1.28–6.15
BCVA score	42/144	29.2	12/73	16.4	2.09	1.02–4.28
Overall VFR	74/145	51.0	17/73	23.3	3.43	1.82–6.47

VFQ-CS = responder with respect to VFQ-25 composite score difference from baseline to month 6 (increase ≥ 3.7); VFQ-MHS = responder with respect to VFQ-25 mental health subscale score difference from baseline to month 6 (increase ≥ 10.7); BCVA score = responder with respect to BCVA difference from baseline to month 6 (increase ≥ 2 lines); Overall VFR = responder with respect to either VFQ-CS or VFQ-MHS or BCVA score.

anatomic response), and the associations between anatomic response and VFR were estimated through logistic regression models. The latter provided insight into correlations between the anatomic response and the different VFR measures and identified whether participants without anatomic response still obtained a functional benefit. Odds ratios (ORs) reported the measure of association between exposure (active treatment; anatomic response) and outcome (VFR). The proportion of participants with VFR by exposure group was provided as a summary statistic. The likelihood ratio test was used to test whether the ORs differed from 1. All tests were considered significant if $P < 0.05$. All analyses were carried out using SAS version 6.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline Demographics

Demographics and baseline ocular characteristics were comparable between treatment groups. Differences in assessment between investigator and CRC for the presence or absence of VMA, macular hole (including diameter), and ERM led to the enrollment of participants meeting exclusion criteria. Of 145 participants in the ocriplasmin group, 33.0% (48/145) required a vitrectomy by month 24, versus 43.0% (32/73) in the sham group. Overall, 74.0% (108/146) and 68.9% (51/74) of participants randomized to ocriplasmin and sham, respectively, completed the 2 years of follow-up.¹² In the ocriplasmin and sham groups, respectively, mean BCVA scores were 63.5 and 62.4 ETDRS letters, the VFQ-25 composite scores (VFQ-CS) were 78.0 and 80.7 (for scores per VFQ-25 subscale, see Supplementary Table S1).

VFR Definition

According to the PCA, the variables that best summarized the VFQ-25 questionnaire information in two dimensions corresponded to the VFQ-CS and the VFQ-25 mental health subscale score (VFQ-MHS). The BCVA score showed weak correlations with those two variables and was therefore considered to provide complementary information. For the BCVA score, the well-established threshold of an improvement of ≥ 2 VA lines (10 letters) was used to distinguish response from nonresponse. The MCID values obtained were 3.7 points for the VFQ-CS, and 10.7 points for the VFQ-MHS. A PPV was considered a rescue therapy, so participants who required a PPV were classified as a visual function nonresponder. Overall VFR was defined as an improvement exceeding the MCID threshold in any of the three principal traits of visual function identified from the PCA: BCVA, the VFQ-CS, or the VFQ-MHS.

TABLE 2. VFR at Month 6, by Subgroups With and Without Macular Hole at Baseline

Overall VFR Subgroups	Ocriplasmin		Sham		OR	95% CI
	n/N	%	n/N	%		
No macular hole at baseline	61/95	64	13/47	28	4.69	2.18–10.08
Macular hole at baseline	13/50	26	4/26	15	1.93	0.56–6.67

Overall VFR defined by the three VFR measures combined: VFQ-CS or VFQ-MHS or BCVA score. In the subgroup with a macular hole at baseline, the number of participants who achieved a closure at month 6 was 15 and 4 in the ocriplasmin and sham groups, respectively.

Assessment of Treatment Effect

At month 6, 51.0% of ocriplasmin-treated participants had a VFR, in that they improved in at least one of the three visual function scores (VFQ-CS, VFQ-MHS, or BCVA score) versus 23.3% of sham-treated participants (OR 3.43, $P = 0.0001$, χ^2 test) (Table 1).

VFR results assessed at months 12 and 24 were similar to the month 6 analysis (Fig. 1). Treatment with ocriplasmin versus sham showed a significant effect on VFR for the individual visual function scores VFQ-CS, VFQ-MHS, and BCVA, as well as for the composite overall VFR score (Supplementary Table S2.1). Sensitivity analyses, in which participants who underwent vitrectomy were not automatically classified as visual function nonresponders, gave similar results to the primary analysis for the overall VFR (Supplementary Table S2.2).

Association Assessment

Participants who achieved a pharmacological VMA resolution at day 28 showed significantly higher odds of overall VFR at each time point (Fig. 2). Details per individual visual function score over time are provided in Supplementary Table S3.

Subgroup Analyses

In the subgroup of participants with VMA release, no significant differences were observed between ocriplasmin and sham participants for any of the individual VFR scores, or the combined, overall VFR (Fig. 3). In the persisting VMA subgroup, a significantly higher proportion of responders was observed in the ocriplasmin compared with the sham participants for the overall VFR, VFQ-CS, and VFQ-MHS, but not BCVA score (details are provided in Supplementary Table S4).

In the subgroup of participants with no macular hole at baseline, a significant treatment effect on the overall VFR was found at month 6 ($P < 0.0001$), but not for the subgroup with macular hole at baseline ($P = 0.297$). Participants with no macular hole at baseline seem to benefit more from the active treatment. The overall treatment effect (across the total population) mainly comes from the subgroup with no macular hole (larger OR), and less from the subgroup with macular hole at baseline (Table 2).

DISCUSSION

The VFR analysis demonstrated that half of the ocriplasmin-treated participants had a VFR, compared with just under a quarter of those receiving sham (51.0% vs. 23.3%; OR 3.43; $P = 0.0001$). This treatment effect was maintained up to month 24.

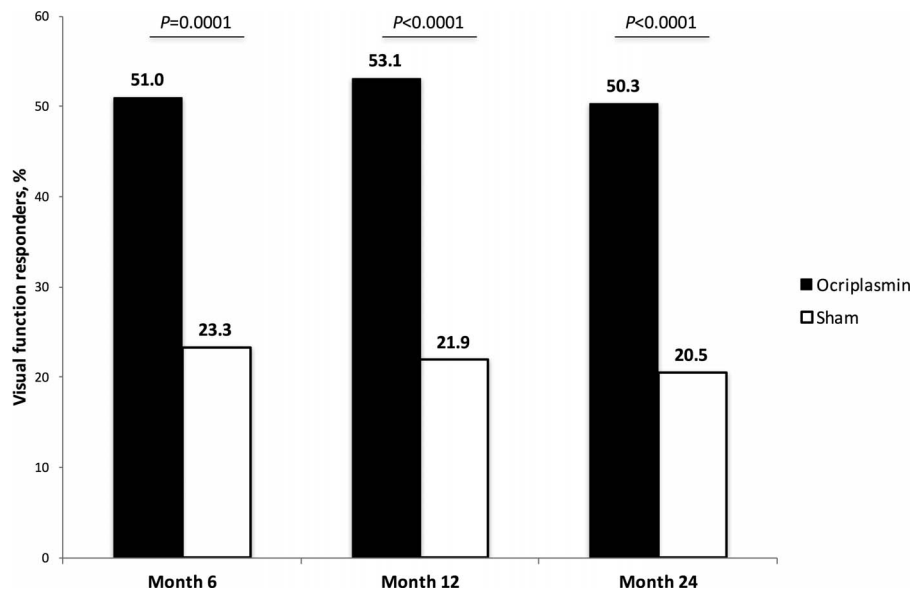


FIGURE 1. VFR at months 6, 12, and 24, by treatment group. Visual function responder, defined as a responder with respect to either VFQ-CS or VFQ-MHS or BCVA score. *N* = 73, sham; *N* = 145, ocriplasmin.

In addition, pharmacological VMA resolution at day 28 was significantly associated with higher VFR, out to 24 months. Finally, the treatment effect at month 6 was significant in the subgroup with no macular hole at baseline but not in the subgroup with macular hole at baseline.

These results are in line with those we obtained using similar methodology on the MIVI-TRUST dataset, although OASIS found a greater magnitude of difference between the ocriplasmin and control groups. For example, there was a 35.5% and 16.5% greater anatomic response compared with the control group, for OASIS and MIVI-TRUST, respectively.^{9,12} This is most likely due to the patient eligibility criteria and the absence of a volume effect from saline placebo injection used in MIVI-TRUST (OASIS used a sham injection). Similarly, a larger difference in VFR response was found in the current OASIS

analysis (27.7% difference favoring ocriplasmin over sham) compared with the MIVI-TRUST study (20.9% difference favoring ocriplasmin over placebo).¹⁷

From the output of the current PCA, the VFQ-25 mental health subscale was retained as the second trait of visual function. This contrasts with our MIVI-TRUST VFR report, whereby the driving subscale of the VFQ-25 was identified as important and complementary information of visual function in symptomatic VMA/VMT patients.¹⁷ This is not totally unexpected, because the OASIS study population differs somewhat from the MIVI-TRUST population in terms of eligible vision (BCVA of 20/32 or worse in study eye), exclusion criteria (e.g., presence of ERM), or the study setting (United States only). In addition, the proportion of participants with a

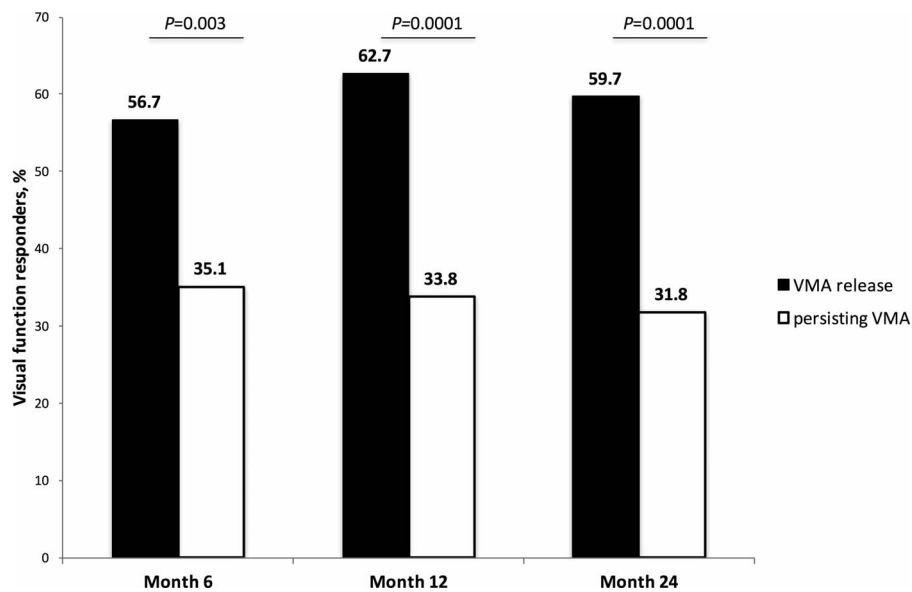


FIGURE 2. Association between VMA resolution at day 28 and VFR over time. VMA release = Participant with VMA resolution at day 28. Persisting VMA = Participant without VMA resolution at day 28. VFR defined as a responder with respect to either VFQ-CS or VFQ-MHS or BCVA score. *N* = 67, VMA release; *N* = 151, persisting VMA.

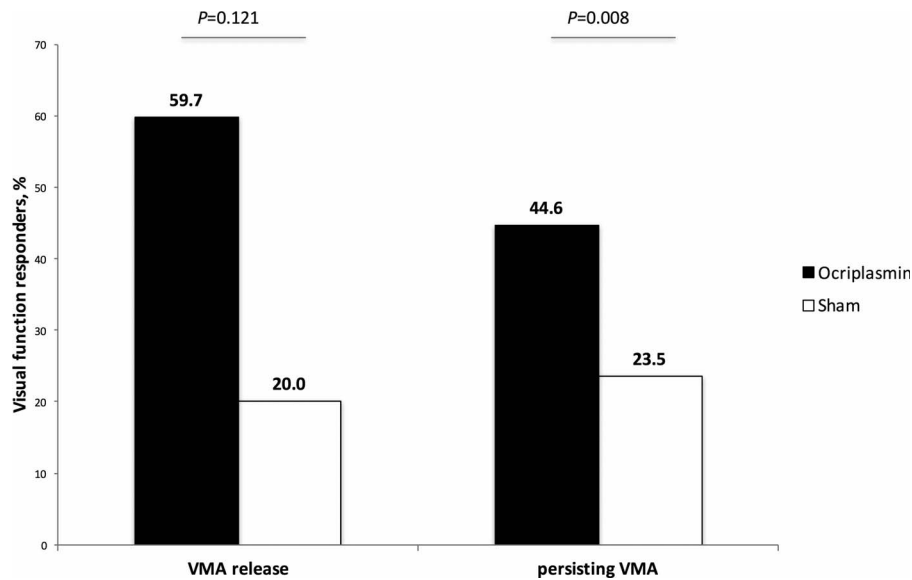


FIGURE 3. Effect of treatment on VFR at month 6, by VMA subgroup. VMA release = Participant with VMA resolution at day 28. Persisting VMA = Participant without VMA resolution at day 28. Visual function responder = Responder with respect to either VFQ-CS or VFQ-MHS or BCVA score. Ocriplasmin: $N = 62$ VMA release, $N = 83$ persisting VMA; Sham: $N = 5$ VMA release, $N = 68$ persisting VMA.

macular hole or with VMA ≤ 1500 μm was higher compared with MIVI-TRUST.^{9,12}

Findings from the current OASIS VFR analysis are consistent with reports that ocriplasmin produced greater BCVA and VFQ-25 improvements than placebo at month 6, and that VMA resolution at day 28 was associated with visual function improvements.^{3,19} Gandorfer et al.¹⁹ reported a higher proportion of eyes with a ≥ 2 -line VA improvement (28.0% vs. 17.1%) and a numerically better improvement in the VFQ-25 composite score (3.4 vs. 0.7 units) comparing ocriplasmin with placebo. With both ocriplasmin and placebo groups combined, the proportion of eyes with a 2-line VA improvement was 2-fold higher in participants with VMA release compared with those with persisting VMA, with similar VFQ-CS findings at month 6.¹⁹ Varma et al.³ likewise observed a significant improvement in the VFQ-CS in ocriplasmin-treated participants with VMA resolution versus those without. Additionally, Varma et al.³ found that ocriplasmin-treated participants with persisting VMA nonetheless gained a benefit, with numerically greater improvement in the VFQ-CS compared with placebo. They hypothesized that partial VMA resolution may explain this benefit.³ Our findings lend support to their hypothesis, as we found that treatment with ocriplasmin resulted in significantly higher VFR than sham despite persisting VMA (44.6% vs. 23.5%; OR 2.61; $P = 0.008$). More recently, case studies reported improved VA and clinical benefits despite only partial release of vitreomacular attachments after ocriplasmin injection.¹⁸ In contrast to others' work, the current analysis uses randomized evidence to assess the effect of treatment on a combined VFR endpoint rather than single functional outcomes such as BCVA or the VFQ-25 composite score.

Treatment may influence the closure of the macular hole, and through this anatomic effect also lead to an improvement of the VFR. In the subgroup with a macular hole at baseline, more participants in the ocriplasmin group compared with the sham group achieved macular hole closure and, therefore, had a higher chance of being a visual function responder. Macular hole closure can thus be considered as a mediator of the treatment effect.

It could be expected that vitrectomy leads to VFR in some participants. This was explored in our sensitivity analysis in which participants who required a vitrectomy were not automatically classified as a failure in terms of their VFR. This sensitivity analysis confirmed higher VFR rates in both treatment groups (Supplementary Table S2.2). However, as the incidence of vitrectomy was higher for sham-treated compared with ocriplasmin-treated participants, the additional increase in VFR was larger in the sham group.

This analysis has several strengths. The randomized, double-masked design of the OASIS trial suggests that the observed differences may be causal and unbiased, the visual and functional outcomes were collected rigorously within a clinical trial, and the total sample size was sufficiently large to detect meaningful clinical differences for most measures. All SD-OCT assessments were determined by a masked CRC. Further, the analysis was protocol prespecified, and used a scientifically accepted method. The MCID for the VFQ-25 scores were established using a data-driven technique and were in line with published evidence.

Limitations of the analysis include the fact that subgroup analyses based on posttreatment variables, such as VMA resolution at day 28 postinjection, are descriptive, as each subgroup represents a selection of participants that may deviate from the randomized population, and may no longer be equally represented across the two arms of the trial. Also, in some subgroups, particularly those with released VMA, there were few sham-injected participants, so results must be interpreted cautiously.

This study focuses on the beneficial effects of ocriplasmin and observes VFR in the OASIS treatment arms as a whole. It does not consider the impact of any safety events on individuals. The decision to use ocriplasmin is based on a benefit-risk consideration, taking also the potential safety risks into account. Adverse events observed in the trial are detailed in the main OASIS report,¹² and summarized in Supplementary Table S5. The three most commonly reported adverse events in the ocriplasmin group (study eye) were vitreous floaters, photopsia, and vision blurred. Retinal breaks (defined as retinal detachment and retinal tear) were more common in the

control arm, most likely due to a higher rate of vitrectomy. Serious adverse events (study eye) were comparable between treatment groups; the most common serious adverse events were macular hole and retinal detachment. Other adverse events are reported in the OASIS study, and other reports in the literature, including outer photoreceptor dysfunction, enlargement of the basal diameter of macular holes, and electrophysiology changes.^{12,34,35} Our study considers adverse events only insofar as they influence the overall VFR.

PCA is a data reduction technique that simplifies complex datasets. It aims to reveal the internal structure of a high-dimensional dataspaces in a way that best explains the variance (or information) in the data. The advantage of our PCA was that the PCs were determined using baseline data, in the form of the VFQ-25 values. As such, the key dimension or internal structure of visual functioning was established independent of treatment. A possible disadvantage of PCA is that its typical outputs (PCs) are rather abstract concepts and difficult to associate with a clinical reality. In the PCA of the OASIS dataset, we could replace the PCs by highly correlated original variables (“response measure”) that are easier to understand from a clinical point of view. The alternative approach would entail an analysis of each of the questionnaire items separately, correctly adjusted for multiple comparisons.

In conclusion, this prespecified analysis suggests that ocriplasmin and VMA release are associated with visual benefit, and that a data-driven, composite patient-reported outcome may provide additional insight into the therapeutic effects of ocriplasmin.

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