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Visual function response to ocriplasmin for the treatment of vitreomacular traction and macular hole

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ABSTRACT.

Purpose: **To assess the effect of an intravitreal ocriplasmin injection on visual function, measured using visual acuity (VA) and vision-related quality of life.**

Methods: ***Post hoc*** **analysis of prespecified secondary end-points in two multicentre, randomized, double-masked, phase 3 clinical trials. A total of 652 participants with symptomatic vitreomacular adhesion were enrolled, of whom 464 received a single intravitreal injection of 125 μg ocriplasmin and 188 received a single intravitreal placebo injection. Based on principal components analysis results, visual function response (VFR) was defined as either a VA improvement of ≥2 lines; or 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. The main outcome measure was VFR at 6 months.**

Results: **A VFR occurred in 55.1% of the ocriplasmin group versus 34.2% of the placebo injection group ($p < 0.0001$). This comprised 23.7% versus 11.2% ($p = 0.0003$) with a ≥ 2-line VA improvement, 35.9% versus 22.7% ($p = 0.0016$) for the VFQ-25 composite score, and 10.2% versus 6.2% ($p = 0.1697$) for the driving subscale.**

Conclusion: **Ocriplasmin produces a clinically meaningful visual function benefit.**

Key words: macular hole – minimal clinically important difference – ocriplasmin – principal components analysis – symptomatic vitreomacular adhesion/vitreomacular traction – VFQ-25

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Introduction

Symptomatic vitreomacular adhesion (sVMA) describes visual dysfunction caused or aggravated by vitreomacular traction (VMT). It results from incomplete posterior vitreous detachment (PVD), where residual vitreous traction leads to structural and functional damage of the macula. It can occur as isolated VMT, but it is also thought to play a pivotal role in the development of macular holes (Gaudric et al. 1999; Chauhan et al. 2000; Tanner et al. 2001). It may also coexist with epiretinal membrane (ERM). More controversially, sVMA may influence the clinical course of diseases such as age-related macular degeneration and diabetic macular oedema (Lee & Koh 2011; Maier et al. 2012; Simpson et al. 2012; Waldstein et al. 2012; Latalska et al. 2013; Kang & Koh 2015). Compared to many other retinal conditions, limited epidemiological data exist for sVMA, but it may affect as many as 15 people per 1000 (Jackson et al. 2013).

The current standard management of VMT is either observation, with the expectation that some cases may resolve spontaneously, or pars plana vitrectomy (PPV). Following the publication of two phase 3 trials (ClinicalTrials.gov identifier: NCT00781859 and NCT00798317), an intravitreal injection of ocriplasmin 125 μg has emerged as an alternative treatment in patients with sVMA/VMT, including when associated with a macular hole (Stalmans et al. 2012). The primary outcome of these trials was non-surgical resolution of VMA at day 28 following a single intravitreal injection of ocriplasmin. A prespecified combined analysis of both trials met its primary end-point with 26.5% of the ocriplasmin-injected participants responding, compared with 10.1% of the placebo-injected participants ($p < 0.001$). In addition, in participants with a macular hole at baseline, non-surgical closure of macular holes at day 28 occurred in 43 (40.6%) of 106 ocriplasmin-treated participants, compared with 5 (10.6%) of 47 placebo-treated participants ($p < 0.001$).

The trial also reported several predetermined secondary end-points, including the percentage of participants gaining at least three lines of best-corrected visual acuity (BCVA) and visual function measured using the National Eye Institute Visual Function Questionnaire (VFQ-25), both of which significantly favoured the ocriplasmin

group (Stalmans et al. 2012). However, it is not certain if a 3-line VA gain was the best threshold, compared with the more commonly used 2-line VA gain, as many participants presented with relatively good VA, making it difficult to gain three lines, and such a high threshold may fail to detect clinically relevant improvements in vision. For example, the median VA at presentation was 67 letters (Snellen equivalent 20/55), so that half of the participants would need to obtain at least 82 letters (20/23) to gain 3 lines (15 letters) (Beck et al. 2003; EMA 2013). Also, many patients with VMT and macular hole may have specific symptoms, such as metamorphopsia, which are not well detected by VA testing.

We hypothesized that there may be a more sensitive and meaningful way of measuring the visual function changes that occur following treatment with ocriplasmin. To test this hypothesis, we aimed first to define a clinically meaningful threshold of visual function response (VFR) and secondly to determine whether ocriplasmin produced a benefit using this threshold. We did this using a *post hoc* analysis of the combined data obtained during the two phase 3 trials, looking specifically at VA and the VFQ-25.

Materials and Methods

Participants

Studies TG-MV-006 and TG-MV-007 (hereafter referred to as 006 and 007) have been described in detail (Stalmans et al. 2012). In brief, both were multicentre, double-masked, placebo-controlled phase 3 efficacy and safety studies, with a total of 652 participants in the combined analysis. Adult participants were eligible if they had sVMA visible on optical coherence tomography (OCT). All eyes had either VMT alone or VMT associated with a macular hole. An ERM was present in 38.7% of eyes. Participants received a single intravitreal injection of 125 μg of ocriplasmin or placebo and were reviewed over 6 months. Investigators could refer participants for PPV at any time if there was a clinical deterioration, at his or her discretion. Institutional Review Board (IRB)/Ethics Committee approval was obtained at each participating site, and all participants provided written informed consent. The studies were conducted in accordance with the Declaration of Helsinki.

Assessment of visual function

These *post hoc* analyses explored the change in VA outcomes and VFQ-25 scores from baseline to month 6. Best-corrected VA was measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart read at 4 m (Early Treatment Diabetic Retinopathy Study research group 1985). The VFQ-25 (2000 version) was self-administered in the participant's native language (Mangione et al. 2001). The VFQ-25 comprises 25 questions that require the patient to assess the levels of difficulty of particular visual symptoms or day-to-day activities. Each question is assigned to one of the following 12 subscales: general health, general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, colour vision and peripheral vision. The subscales scores range from 0 to 100, where 100 indicates the highest possible function or minimal subjective impairment. The VFQ-25 composite score is calculated as the average of the vision-targeted subscale scores, excluding the question on general health (RAND Corporation 2000). The questionnaire has a few optional questions, none of which were used in the trials.

Defining visual function response

We aimed to define a visual function response (VFR) such that participants could be classified as responders or non-responders. There was no reported definition of VFR for sVMA. The available visual outcomes data set included VA and VFQ-25 scores. The VFQ-25 Questionnaire results in a large number of scores, which can make it difficult to interpret. Further, some questions may be closely correlated with others, such that one aspect of visual function has a disproportionate effect on the VFQ-25 composite score. Conversely, other questions that assess another aspect of visual function may fail to influence the composite score. A principal components analysis (PCA) is an accepted means of validating new questionnaires, but it is also a means of validating established questionnaires when applied to new disease states (Dougherty & Bullimore 2010; Abetz et al. 2011). The VFQ-25 has been validated in several eye diseases, but not in sVMA. We therefore performed a PCA to help validate our use of the VFQ-25 and the composite score as a summary measure. A PCA works by grouping together questions whose scores are closely correlated into new variables called principle components (PCs), on the assumption that these are assessing similar aspects of visual function (Jolliffe 2014). The PCs are ordered by the amount of variation they capture such that the first few PCs are the most relevant. In our data set, the first PC was highly correlated with the composite score, which makes it therefore a valid summary measure of most of the information contained in the VFQ-25. The PCA further showed that the questions related to driving, which were mostly captured in the second PC, provided independent information that is complementary to the composite score.

Visual function response (VFR) was therefore defined as an improvement in any one of the three measures: VA, the VFQ-25 composite score and the VFQ-25 driving subscale score, which corresponded to the first three dimensions of visual functioning according to the PCA. For each of these visual function measures, we required a threshold that defined a VFR. Such thresholds should reflect the minimal clinically important difference (MCID). For VA, the MCID was set at 10 letters, corresponding to two lines, as this is a widely used standard and was likely to be more sensitive to change than the three-line gainers used by Stalmans et al. (Early Treatment Diabetic Retinopathy Study research group 1985, Matza et al. 2008; Stalmans et al. 2012). There was, however, no accepted or reported MCID threshold for VFQ-25 scores of participants with sVMA. In other ophthalmological conditions, the MCID is based on a clinical anchor, usually VA, or distribution metrics such as the standard error of measurement (SEM) (Wyrwich et al. 1999; Cella et al. 2002; Naik et al. 2013). Because the VA correlated relatively poorly with the VFQ-25 composite score (Pearson's correlation coefficient = 0.17 for the baseline values and 0.26 for the change between baseline and month 6 values), VA was not used as clinical anchor, and the SEM method was selected to determine the MCID in a prespecified analysis plan.

Any participants undergoing vitrectomy were classified as non-responders. Because ocriplasmin treatment has been shown to prevent PPV in some participants with sVMA, this could potentially favour the ocriplasmin group. A sensitivity analysis was therefore conducted to compare the response rates without systematically classifying those participants who had a PPV as non-responders.

Statistical methods

Analyses were performed on the combined data sets of both trials, including all randomized participants, according to the intent-to-treat principle. Missing data for VA were imputed using the last observation carried forward. The VFQ-25 scores were computed on observed values as per the VFQ-25 scoring algorithm.

The treatment effect on the VFR rates was estimated through logistic regression incorporating study as a fixed effect, and the likelihood ratio test was used to test whether the odds ratio differed from 1 (an odds ratio of 1 corresponds to no difference between the ocriplasmin and placebo group as the same odds of response prevails in both groups). All tests were considered significant if $p < 0.05$. All analyses were carried out using SAS version 6.3 (SAS Inc., Cary, NC, USA).

Results

The ocriplasmin and placebo groups were comparable in baseline demographics; 29 (6.3%) ocriplasmin-treated and 16 (8.5%) placebo-treated participants were discontinued from the studies. A total of 82 (17.7%) ocriplasmin-treated and 50 (26.6%) placebo-treated participants required a PPV by month 6 ($p = 0.02$).

Baseline VA was assessed in all but one participant and in all participants that reached month 6. The VFQ-25 Questionnaire completion rates at baseline and at month 6 were high (99.6% and 92.7% in the ocriplasmin group and 99.5% and 92.6% in the placebo group, respectively). The VFQ-25 mean scores at baseline for each question were comparable between the two treatment groups, but varied considerably between the different VFQ-25 items; in the ocriplasmin group for example, the mean score for the question, 'How much do you worry about your eyesight' was 51.7 compared with a mean score of 92.4 for 'visiting with people' (Table 1).

The first principal component from the PCA using all functional vision questions of the VFQ-25 responses captured 41.1% of the total variability or information in the visual outcomes data set and was highly correlated with the VFQ-25 composite score (Pearson's correlation coefficient of 0.98). The second principal component captured an additional 7.1% of the total variability, but had a high loading (0.58) for one of the VFQ-25 driving items (question 16). The VFQ-25 composite score and the driving subscale score were therefore kept as valid summary measures of patient-reported visual function determined by the VFQ-25 scores. The MCID threshold for defining a responder, based on the SEM method, was 3.6 points for the VFQ-25 composite score and 19.1 points for the VFQ-25 driving subscale score.

Ocriplasmin treatment resulted in a significantly higher proportion of responders for VA defined as an improvement of ≥ 2 lines (23.7% versus 11.2% in the placebo group, OR: 2.51, $p = 0.0003$) and for the VFQ-25 composite score defined as an improvement of ≥ 3.6 points (35.9% versus 22.7% in the placebo group, OR: 1.92, $p = 0.0016$) (Table 2). Ocriplasmin treatment also increased the proportion of participants with an improved driving score, defined as an improvement of ≥ 19.1 points, but this increase was not statistically significant (10.2% versus 6.2% in the placebo group, OR: 1.71, $p = 0.1697$). A total of 55.1% of participants treated with ocriplasmin improved on any of these three visual function scores, versus 34.2% of placebo participants (OR: 2.28, $p < 0.0001$) (Table 2).

The sensitivity analyses, in which participants who underwent PPV between baseline and 6 months after the injection were not automatically classified as visual function non-responders, gave similar results as the primary analysis (Table 2).

Discussion

Based on the PCA results, three scores were used as measures of visual functioning, as each of them represents another dimension of visual functioning: the VA score, and the overall composite score and driving subscale score of the VFQ-25. Ocriplasmin treatment resulted in a better response for all three measures, although the difference did not reach significance for the driving subscale. The proportion of ocriplasmin-treated participants who responded to at least one of these visual function measures was 55.1%, significantly higher than the 34.2% seen in the placebo-injected participants.

We are not aware of any published reports using visual function questionnaires to assess the effect of PPV in patients with VMT. Three studies used the VFQ-25 to assess the effect of PPV for treating idiopathic macular hole. At one year postoperatively, the VFQ-25 composite score improved by 5.6 points in one study and by 12.2 points in another study (Hirneiss et al. 2007; Duan et al. 2015). A further study reported a VFQ-25 composite score improvement by 6.2 points at 4 months postoperatively (Tranos et al. 2004). The anatomical success rates were 96.6%, 97.2% and 86.6%, respectively. All three studies included a range of macular hole stages with results aggregated for stage II to IV macular holes. In the combined phase 3 ocriplasmin studies, participants treated with ocriplasmin showed an overall improvement of 3.4 points in the VFQ-25 composite score at 6 months. When considering ocriplasmin-treated participants with a macular hole at baseline who achieved non-surgical macular hole closure at month 6, the VFQ-25 composite score improved by 9.0 points ($N = 40$, observed cases analysis). Within the limitations of such an indirect comparison across studies, this suggests that ocriplasmin, as a pharmacological alternative to PPV, may result in a similar improvement of visual functioning.

In the absence of a good correlation between VA and the VFQ-25, the SEM was used as a distribution-based measure to estimate the MCID for the VFQ-25 composite score and the driving subscale. The SEM for the composite score was 3.6. Published evidence on MCID thresholds for the VFQ-25 composite score is very limited, with none reported for either macular hole or VMT. The Submacular Surgery Trials Research Group suggested that a 4-point change in the

Table 1. Visual acuity and VFQ-25 scores at baseline and 6 months postinjection in the combined studies TG-MV-006 and TG-MV-007.

	Baseline				6 months					
	Ocriplasmin		Placebo		Ocriplasmin			Placebo		
	n	Mean Score (SD)	*n*	Mean Score (SD)	*n*	Mean Score (SD)	Change from baseline (SD)	*n*	Mean Score (SD)	Change from baseline (SD)
Best-corrected visual acuity (ETDRS score)	464	63.9 (12.4)	187	65.1 (21.5)	464	67.5 (14.2)	3.6 (11.3)	188	67.6 (20.6)	2.5 (20.1)
VFQ-25										
Overall composite score	462	77.1 (15.9)	187	82.0 (12.2)	430	80.5 (16.4)	3.4 (11.9)	174	82.6 (13.7)	0.7 (10.0)
Question 1. Overall health	462	57.7 (24.8)	187	60.4 (22.6)	430	59.1 (24.7)	1.5 (18.2)	174	59.1 (24.1)	−1.0 (18.0)
Question 2. Eyesight using both eyes	462	62.1 (16.7)	187	65.5 (15.3)	430	68.1 (16.2)	6.1 (16.0)	174	67.2 (16.0)	2.1 (15.7)
Question 3. How much do you worry about eyesight	461	51.7 (27.8)	187	52.9 (28.0)	430	57.2 (28.8)	5.3 (26.1)	174	56.8 (29.2)	3.9 (22.9)
Question 4. Pain/discomfort in and around eyes	461	79.6 (21.5)	186	84.5 (20.1)	430	82.4 (20.6)	3.1 (20.1)	174	86.6 (17.3)	1.6 (19.1)
Question 5. Reading ordinary print in newspapers	459	59.9 (27.3)	187	64.8 (25.9)	427	67.7 (26.5)	7.3 (26.5)	173	68.5 (23.8)	3.3 (23.9)
Question 6. Work or hobbies up close	457	63.2 (25.4)	186	68.0 (25.8)	424	69.3 (24.9)	6.0 (25.5)	171	70.9 (24.7)	3.4 (23.2)
Question 7. Finding something on a crowded shelf	459	78.4 (23.1)	187	82.8 (21.4)	427	81.6 (24.0)	3.0 (22.8)	174	85.8 (19.4)	3.0 (20.9)
Question 8. Reading street signs or names of stores	460	68.6 (24.9)	186	71.0 (24.5)	427	74.8 (25.0)	6.3 (24.1)	174	74.1 (25.5)	2.5 (22.6)
Question 9. Going down steps, stairs or curbs in dim light	457	71.3 (26.5)	185	78.0 (24.3)	425	74.4 (24.7)	3.3 (24.1)	172	77.6 (23.9)	−0.7 (20.6)
Question 10. Noticing objects off to the side while walking	460	81.6 (23.6)	187	86.5 (19.4)	429	84.6 (22.3)	3.3 (21.5)	174	86.4 (20.4)	−0.1 (21.7)
Question 11. Seeing how people react to things you say	458	88.1 (18.9)	186	91.5 (18.0)	428	89.2 (18.9)	1.5 (18.4)	172	91.9 (16.0)	−0.1 (17.0)
Question 12. Picking out and matching clothes	456	92.3 (16.0)	186	94.8 (12.6)	427	93.3 (15.7)	1.2 (14.2)	172	95.1 (13.4)	0.9 (13.8)
Question 13. Visiting with people	450	92.4 (16.7)	185	96.1 (11.1)	421	93.4 (15.9)	1.0 (15.2)	172	94.2 (14.6)	−1.8 (12.0)
Question 14. Going out to see movies, plays or sports	408	83.5 (23.2)	178	88.9 (20.1)	375	87.3 (22.1)	2.9 (18.4)	165	88.2 (20.0)	0.0 (22.2)
Question 15c. Difficulty driving during daytime	352	88.4 (25.3)	152	93.3 (16.0)	328	90.0 (24.4)	1.25 (21.8)	143	91.3 (21.4)	−1.1 (16.1)
Question 16. Difficulty driving at night	325	64.3 (29.0)	146	70.2 (23.5)	300	67.8 (28.5)	2.9 (23.0)	133	69.0 (28.6)	−0.4 (22.0)
Question 17. Accomplish less than you would like	461	66.9 (29.4)	187	73.8 (25.8)	430	72.6 (29.6)	5.7 (28.6)	174	74.7 (26.2)	1.6 (24.6)
Question 18. Limited in how long you can work or do other activities	460	73.0 (28.2)	187	79.8 (26.3)	430	77.6 (27.2)	4.3 (26.4)	174	82.3 (25.1)	2.7 (27.6)
Question 19. Eye pain/discomfort keep you from doing what you like	461	85.5 (23.0)	187	87.4 (22.5)	430	85.6 (22.8)	−0.1 (22.6)	174	88.6 (22.1)	0.7 (20.1)
Question 20. I stay home at night	462	89.1 (22.4)	187	96.1 (13.0)	428	89.6 (22.0)	−0.1 (21.6)	174	92.4 (20.0)	−3.6 (16.3)
Question 21. Feel frustrated	462	65.2 (35.3)	186	75.4 (33.0)	427	73.3 (31.8)	8.7 (34.7)	174	76.0 (31.7)	1.9 (31.9)
Question 22. Have much less control over what I do	460	72.3 (32.5)	187	79.1 (29.7)	428	77.9 (29.9)	5.9 (28.6)	174	80.5 (28.2)	2.0 (29.3)
Question 23. Rely too much on what other people tell me	462	84.3 (26.4)	187	91.4 (19.2)	428	86.9 (24.0)	2.6 (25.4)	174	89.8 (22.7)	−1.7 (20.1)
Question 24. Need a lot of help from others	462	85.2 (26.5)	187	90.4 (20.8)	428	87.9 (24.5)	2.7 (22.3)	174	89.8 (20.3)	−0.9 (16.6)
Question 25. Worry about embarrassing self or others	462	87.5 (24.3)	187	92.5 (19.3)	428	90.3 (21.7)	2.8 (22.3)	174	93.7 (18.3)	1.6 (19.3)
Colour vision subscale	456	92.3 (16.0)	173	94.8 (12.6)	427	93.3 (15.7)	1.2 (14.2)	172	95.1 (13.4)	0.9 (13.8)
Dependency subscale	462	86.2 (22.1)	187	92.3 (14.7)	428	88.1 (20.7)	1.7 (18.8)	174	90.7 (185)	−2.1 (13.7)
Distance activities subscale	462	73.6 (21.0)	187	78.9 (17.2)	430	77.7 (20.9)	4.1 (18.2)	174	79.8 (18.8)	0.8 (15.3)
Driving subscale	352	74.8 (25.3)	152	81.6 (17.5)	328	77.7 (25.0)	2.7 (196)	143	79.2 (23.4)	−1.5 (17.8)
General health subscale	462	57.7 (24.8)	187	60.4 (22.6)	430	59.1 (24.7)	1.5 (18.2)	174	59.1 (24.1)	−1.0 (18.0)
General vision subscale	462	62.1 (16.7)	187	65.5 (15.3)	430	68.1 (16.2)	6.1 (16.0)	174	67.2 (16.0)	2.1 (15.7)
Mental health subscale	462	69.2 (23.9)	187	75.0 (21.8)	430	74.5 (23.0)	5.5 (20.0)	174	76.7 (21.3)	2.3 (18.7)
Near activities subscale	462	67.3 (21.4)	187	71.9 (20.3)	430	72.8 (22.0)	5.3 (20.0)	174	75.2 (19.1)	3.3 (17.0)
Ocular pain subscale	461	82.5 (19.9)	187	85.9 (18.7)	430	84.0 (19.3)	1.5 (16.8)	174	87.6 (17.1)	1.1 (16.6)
Peripheral vision subscale	460	81.6 (23.6)	187	86.5 (19.4)	429	84.6 (22.3)	3.3 (21.5)	174	86.4 (19.4)	−0.1 (21.7)
Role difficulties subscale	461	70.0 (26.5)	187	76.8 (24.3)	430	75.1 (26.3)	5.0 (23.9)	174	78.5 (23.6)	2.2 (22.9)
Social functioning subscale	461	89.9 (16.8)	186	93.8 (12.6)	429	91.0 (16.4)	1.3 (15.2)	173	93.0 (13.4)	−0.8 (11.2)

Table 2. Visual function response by treatment group in the combined studies TG-MV-006 and TG-MV-007.

	Primary analysis					Sensitivity analysis*				
	Ocriplasmin		Placebo			Ocriplasmin		Placebo		
Measure	*n*/*N*	%	*n*/*N*	%	OR (95% CIs)	*n*/*N*	%	*n*/*N*	%	OR (95% CIs)
VA	110/464	23.7	21/188	11.2	2.51 (1.52,4.16)‡	130/464	28.0	32/187	17.1	1.91 (1.24, 2.95)‡
VFQ-25 composite score	158/440	35.9	40/176	22.7	1.92 (1.28, 2.88)‡	186/428	43.5	57/173	33.0	1.58 (1.09, 2.29)†
Driving subscale	35/344	10.2	9/146	6.2	1.71 (0.80, 3.65)	41/319	12.9	12/140	8.6	1.54 (0.78, 3.04)
Overall VFR	217/394	55.1	53/155	34.2	2.28 (1.54, 3.37)‡	256/377	67.9	76/148	51.4	1.90 (1.28, 2.81)‡

VA = responder with respect to visual acuity difference from baseline to month 6 (increase ≥2 lines); VFQ-25 composite score = responder with respect to VFQ-25 composite score difference from baseline to month 6 (increase ≥ 3.6); driving subscale = responder with respect to driving subscale score difference from baseline to month 6 (increase ≥ 19.1); overall VFR: a positive response to the VFQ-25 composite score or VA or driving subscale score; OR = odds ratio (ocriplasmin compared to placebo); CIs = confidence intervals.

*In the sensitivity analysis, participants who had a PPV between baseline and month 6 are not automatically classified as visual function non-responders.

†p value < 0.05.

‡p value < 0.01.

composite score would correspond to a minimal clinically meaningful change, based on the combined data of three trials (Submacular Surgery Trials Research Group 2007). Suñer and colleagues found a 4- to 6-point change in the VFQ-25 scores to correspond to a clinically meaningful change, using a 15-letter change in the VA as an anchor among participants with neovascular age-related macular degeneration (Suñer et al. 2009). Our SEM for the driving subscale score is quite large (19.1) and as far as we know has not been determined previously.

The relatively low correlation between the VA and VFQ-25 scores has been seen in studies for other ophthalmology disorders (Hirneiss et al. 2007; Orr et al. 2011; Varma et al. 2012). The absence of such correlation suggests that the improvement in the patient-reported visual functioning, as measured by the VFQ-25 scores, is largely independent of the change in VA, confirming the relevance of our hypothesis and research.

This apparent absence of correlation between VA and VFQ-25 responses may be due to unmeasured symptoms such as metamorphopsia, which is known to affect visual functioning. Metamorphopsia may impact on a patient's subjective visual experience without a commensurate change in VA, and hence, a VFR may be a more sensitive means of detecting visual dysfunction than VA testing. In a study of the effect of PPV for ERM, Okamoto and colleagues found a significant (negative) correlation between the VFQ-25 composite score and the severity of metamorphopsia, but no correlation with VA outcomes, both pre- and postoperative (Okamoto et al. 2009). They further showed that a change in the severity of metamorphopsia was the single explanatory factor relevant to a change in the VFQ-25 composite score in participants with macular hole and ERM, suggesting the VFQ-25 may in part reflect symptoms such as metamorphopsia (Okamoto et al. 2010).

The driving subscale score correlates poorly with the composite score. Similar observations have been made in other studies (Massof & Fletcher 2001; Dougherty & Bullimore 2010; Marella et al. 2010). The absence of a significant difference across treatment groups in the driving subscale scores may be related to the relatively small number of participants included in this analysis. Many of the participants in the 006 and 007 trials have never driven or gave up driving for reasons other than their eyesight, and hence, their data are considered missing.

This analysis has several strengths. The randomized, double-masked design suggests 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. Compared to two recent ocriplasmin publications, this analysis applied a scientifically accepted method, PCA, to condense the available visual function information into one dimension (outcome measure), which captures the full treatment effect (Gandorfer et al. 2015; Varma et al. 2015). Also, this study compared results in the ocriplasmin group to the original control group. Unlike other studies, we used a data-driven technique to establish the MCID for the VFQ-25 composite and driving subscale scores in subjects with VMT (Gandorfer et al. 2015; Varma et al. 2015).

Limitations of this study include the fact that the baseline score for many questions was quite high, resulting in a high mean VFQ-25 composite baseline score, leaving limited room for improvement. Also, the placebo injection may have caused some improvement in the visual function in the control group, as the clinical trial data suggest and as recently observed in the sham injection group of the OASIS trial (ClinicalTrials.gov identifier: NCT01429441) (Dugel PU et al. 2016, Stalmans et al. 2012). This would also reduce the perceived benefit in the ocriplasmin group and may not translate to the usual clinical environment, where ocriplasmin is an alternative to observation or PPV.

In conclusion, treatment with ocriplasmin resulted in a large and clinically meaningful visual function benefit in addition to its anatomical effect on sVMA resolution. Participants treated with ocriplasmin benefitted from an additional visual function improvement of 20% compared with placebo, when considering a clinically meaningful improvement in at least one of three visual function measures. These benefits included a greater proportion of patients with a 2-line VA gain, but importantly there were other functional visual improvements, suggesting that VA alone may not fully capture the benefits of treatment.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. *Meeting presentations:* The material presented in this paper has been partially presented at the British & Eire Association of Vitreoretinal Surgeons 2012 annual meeting, November 2012, Dublin; the 5th World Congress on Controversies in Ophthalmology, March 2014, Lisbon; and the International Society of Pharmacoeconomics and Outcomes Research, June 2014, Montreal. *Financial Support:* This study was funded and supported by ThromboGenics N.V. ThromboGenics conducted the clinical trial that provided the data set for the current analysis. ThromboGenics also participated in the design of the study, interpretation of the data, review and approval of the manuscript. Timothy L. Jackson is a consultant to ThromboGenics N.V. Thomas Verstraeten, Luc Duchateau and Benedicte Lescrauwaet provide consulting services to several biopharmaceutical companies, including ThromboGenics N.V.