Common Drug Review

Clinical Review Report

January 2014

Drug	ocriplasmin (Jetrea) (125 mcg intravitreal injection)
Indication	For the treatment of symptomatic vitreomacular adhesion
Listing request	As per indication for single-use only (subsequent injections in the same eye will not be covered) and diagnosis should be confirmed through optical coherence tomography
Manufacturer	Alcon Canada Inc.

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ABBREVIATIONS

AE	adverse event
AMD	age-related macular degeneration
BCVA	best-corrected visual acuity
BSE	better-seeing eye
CI	confidence interval
CCB	Canadian Council of the Blind
CNIB	Canadian National Institute for the Blind
CRC	central reader center
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	full analysis set
FTMH	full-thickness macular hole
HRQoL	health-related quality of life
ICUR	incremental cost-utility ratio
LOCF	last observation carried forward
mFAS	modified full analysis set
MH	macular hole
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire-25
OCT	optical coherence tomography
PP	per-protocol (analysis set)
PVD	posterior vitreous detachment
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
sVMA	symptomatic vitreomacular adhesion
VA	visual acuity
VFQ-25	Visual Function Questionnaire-25
VMA	vitreomacular adhesion
VMT	vitreomacular traction
WDAE	withdrawal due to adverse event
WSE	worse-seeing eye

EXECUTIVE SUMMARY

Introduction

Symptomatic vitreomacular adhesion (sVMA) is a rare macular condition caused by an incomplete posterior vitreous detachment of the vitreous from the macula,[1] potentially resulting in irreversible vision loss and blindness if left untreated.[2] Ocriplasmin is a recombinant, truncated form of human plasmin obtained from microplasminogen produced in a *Pichia pastoris* expression system by recombinant DNA technology.[3] The recommended dosage is a single 125 mcg intravitreal injection. Repeated administration of ocriplasmin in the same eye is not recommended. The treatment solution should be diluted by adding 0.2 mL of sodium chloride 9 mg/mL (0.9%). If treatment in the contralateral eye is required, it should not be performed within seven days of the initial injection in order to monitor the post-injection course and the potential for decreased vision in the injected eye.[3]

Indication under review
For the treatment of symptomatic vitreomacular adhesion
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As per indication for single-use only (subsequent injections in the same eye will not be covered) and diagnosis should be confirmed through optical coherence tomography

The objective of this report is to perform a systematic review of the beneficial and harmful effects of ocriplasmin for the treatment of sVMA.

Results and Interpretation

Included Studies

Three multicentre, randomized, parallel group, double-mask, placebo and sham-controlled studies met the inclusion criteria for this systematic review. TG-MV-006[4] (N = 326) and TG-MV-007[5] (N = 326) were identically designed phase III studies which evaluated the safety and efficacy of a single 125 mcg dose injection of ocriplasmin compared with placebo injection for the treatment of sVMA. TG-MV-004[6] (N = 60) was a phase II study which evaluated the safety and preliminary efficacy of ocriplasmin 75 mcg, 125 mcg, 175 mcg single doses and repeated doses of ocriplasmin 125 mcg (up to two additional open-label injections) compared with a sham injection. Given the numerous limitations of TG-MV-004 pertaining to this report, data from this study are not presented or discussed. Thus, the two phase III studies, TG-MV-006 and TG-MV-007, served as the primary demonstration for efficacy and safety in this report. The primary outcome in TG-MV-006 and TG-MV-007 was proportion of patients with VMA resolution, determined by a masked central reader center (CRC) interpreting optical coherence tomography (OCT) at day 28.

Efficacy

In both studies, ocriplasmin revealed statistical superiority over placebo for the achievement of VMA at day 28, 3 months and 6 months. The between-group difference of patients achieving resolution of VMA with ocriplasmin versus placebo was greater in TG-MV-007 at day 28 (19.1%) compared with TG-MV-006 (14.8%). Similar results were seen at 3 months and 6 months. The proportion of patients who achieved resolution of VMA was similar at all follow-up periods for the ocriplasmin groups in both studies. In TG-MV-006, the placebo group had a greater proportion of patients achieving resolution of VMA at day 28, 3 months, and 6 months, compared with TG-MV-007.

Harms

The overall incidence of adverse events (AEs) in both studies was greater when patients were treated with ocriplasmin, with an AE rate approximately twice that observed with placebo. The incidence of serious adverse events (SAEs), withdrawal due to adverse events (WDAEs) and notable harms did not differ significantly between the ocriplasmin and placebo groups in both studies. Occurrences of notable harms such as lens subluxation, cataracts, eye infection, retinal detachment, vitritis, retinal hemorrhage, and vitreous hemorrhage were relatively rare; however, conjunctival hemorrhages were more common.

Conclusions

Two multicentre, randomized, parallel group, double-masked, placebo-controlled studies comparing a single 125 mcg intravitreal injection of ocriplasmin with a placebo injection for the treatment of VMA were reviewed. Overall, treatment with ocriplasmin was superior to placebo for the resolution of VMA and total posterior vitreous detachment (PVD). Although there was a greater overall incidence of AEs for patients treated with ocriplasmin compared with placebo, many events were transient and possibly related to the procedure instead of the drug itself. There is uncertainty regarding the efficacy of ocriplasmin for the treatment of full-thickness macular holes (FTMHs), avoidance of vitrectomy, and improvement in best-corrected visual acuity (BCVA). Moreover, no data were available on whether ocriplasmin prevents VMA-related vision loss or blindness, a key outcome according to patient groups.

SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

Ocriplasmin (Jetrea) is being reviewed for the treatment of sVMA including when it is associated with macular hole (MH). The recommended dose is 0.125 mg (0.1 mL of the diluted solution) administered by intravitreal injection to the affected eye once as a single dose. The cost of ocriplasmin is $3,950 per dose.

Summary of Economic Analysis

The manufacturer conducted a cost-utility analysis (CUA) comparing ocriplasmin to "watchful waiting" (medical management), with the option of surgical vitrectomy in either strategy, using data from two phase III randomized controlled trials in VMA patients (TG-MV-06 and TG-MV-007)—*Manufacturer's Pharmacoeconomic Submission*.[7] The reference-case time horizon was the patient's lifetime (up to 37.5 years), using the Canadian public-payer perspective. The economic submission is based on a six-month (trial duration) decision tree and a long-term Markov model.

In the monthly cycle decision tree, a patient with only vitreomacular traction (VMT), interchangeable with VMA can experience non-surgical VMT resolution at day 28, a vitrectomy for VMT depending on the patient's visual acuity (VA), and non-surgical resolution of MH at 6 months before they enter into the Markov model. Patients with MH can experience non-surgical MH closure at day 28, a vitrectomy, and non-surgical closure at 6 months. At the end of the decision tree, all patients (VMT + MH) are allocated to the following health states and transit into the long-term extrapolation Markov model: resolved; VMT unresolved without MH; VMT unresolved with MH; VMT resolved with MH (no vitrectomy); VMT resolved with MH (one vitrectomy); VMT resolved with MH (two vitrectomies); and death. Within each Markov cycle, patients can transit between disease health states and between VA health states (stay the same, improve, or get worse). Patients continue to experience the following events: VMT resolution only; MH closure only; VMT resolution and MH closure; or, VMT progressing to MH.

Each of the health states is associated with a different distribution of VA categories. For patients achieving resolution of VMT, the VA was assumed to follow the age-matched general Finnish population's long-term VA decline.[8] VA for patients with persistent VMT (all disease states except "resolved") was assumed to decline gradually but at a faster rate than the rate in the general population.[9] Adverse events, including cataract after vitrectomy, retinal tear, retinal detachment, elevated intraocular pressure, and vitreous hemorrhage were also considered in the model based on rates observed from the clinical trials and data on file.

The majority of the transition probabilities in the decision tree (first six months) were taken from the clinical trials, with the exception of the probability of a second vitrectomy for MH and its success rate, which were based on clinical opinion. Transition probabilities in the Markov model were estimated using a regression model based on the trial data, expert opinion, and the literature. Beyond six months, the probability of spontaneous resolution of VMA was assumed to be 0%. Quality of life for each VA category was informed by an United Kingdom quality-of-life study on the general public.[10] In addition, a change in VA in the worse-seeing eye (WSE) was valued at 30% of the same change in the better-seeing eye (BSE). Disutilities for treatment or intervention-associated AEs, metamorphopsia, vitrectomy surgery, and cataract were estimated from the published literature[11-14] and assumptions. Higher mortality rates were assigned to patients whose BSE was VA6.[15] Costs were provided by the manufacturer and based on Canadian sources.[16,17]

Results of Manufacturer's Analysis

The manufacturer reported an incremental cost per quality-adjusted life-year (QALY) for ocriplasmin compared with "watchful waiting" of $40,124 using the Canadian public-payer perspective.

Interpretations and Key Limitations

Generalizability and inclusion of non–health-care payer costs

Resource utilization associated with visual impairment was obtained from a costing study in wet age-related macular degeneration (AMD) patients; however, generalizability to this population was not discussed. Furthermore, the blindness health state included lost productivity and indirect costs, which should not be included in the base case analysis as per CADTH guidelines.[18] By excluding the indirect costs of blindness (VA6), the incremental cost-utility ratio (ICUR) increases to $43,657 per QALY.

Bilateral disease

The submission did not consider the cost of treating bilateral disease; in trial data, bilateral disease occurred in 19.9% of patients. According to the clinical expert, both eyes are likely to be treated in practice. The cost of ocriplasmin, as well as the cost of administration, is increased by 20% in the Common Drug Review (CDR) analysis in order to account for the treatment costs in bilateral disease.

Short duration of clinical trial and assumption of long-term relative efficacy

Given the duration of existing trials (6 months) and use of the outcome of VMA resolution (and not VA), it has not been established that long-term differences in the clinically important outcome of VA (the major factor driving quality of life and disease costs) will occur. If the treatment effect is not durable or if it attenuates, the cost-effectiveness ratio will be greater. In the manufacturer's sensitivity analysis, shortening the time horizon to two years resulted in the incremental QALYs decreasing from 0.069 to 0.024 and the cost per QALY increasing to $147,816, highlighting that a majority of the incremental benefit accrued in the model is well beyond the time frame of current randomized control trials (RCTs).

Uncertainty on VMA status and long-term effects on VA

A major assumption is that the greater VMA resolution achieved with ocriplasmin will ultimately result in improved VA (VA is the major determinant of efficacy in the model). As per the CDR Clinical Report, no statistically significant benefit in BCVA was observed with ocriplasmin. However, based on feedback from a clinical expert, a six-month BCVA for VMA may not be the ideal outcome as patients' VA typically plateaus and does not demonstrate a stepwise progression until they experience MH. The model is limited by poor quality data (due to the use of different patient populations for each health state as well as a small cohort for VMA) to estimate the long-term VA outcomes in patients with unresolved and resolved VMA.

Uncertainty on long-term spontaneous resolution probability

The probability of spontaneous resolution of VMA rate from 6 months to 2 years was set at 0%, but observational data cited by the manufacturer quoted probabilities of 2.2% and 16.5%. Using these values attenuates the relative efficacy of ocriplasmin and leads to a greater ICUR for ocriplasmin.

Results of CDR Analysis

In the CDR new base case where non-health care costs were excluded and costs of ocriplasmin for bilateral disease were included, the ICUR is $55,544 per QALY. In one-way sensitivity analyses exploring long-term efficacy:

- with assumption of no mortality benefit with ocriplasmin: ICUR $65,957 per QALY

- with assumption of the same VA trajectory beyond six months for those with and without VMA resolution: ICUR $94,766 per QALY
- literature cited probabilities of long-term, spontaneous VMA resolution of 2.2% and 16.4%: $63,264 and $124,621 per QALY respectively.

Conclusions

For the treatment of VMT, the manufacturer suggests that ocriplasmin is likely to have a cost per QALY of around $40,000 under assumptions of sustained clinical benefit over a 37.5-year time after one injection. In the CDR reference case, where non-health care costs are excluded and treatment costs of bilateral disease are included, the ICUR increases to $55,544 per QALY. When the uncertainty in long-term relative efficacy is explored in sensitivity analyses using the CDR reference case, the incremental cost per QALY increases from $63,000 to > $100,000.

TABLE 1: SUMMARY OF RESULTS

Outcome	TG-MV-006		TG-MV-007	
	Ocriplasmin (N = 219)	Placebo (N = 107)	Ocriplasmin (N = 245)	Placebo (N = 81)
VMA resolution at day 28				
n (%)	61 (27.9)	14 (13.1)	62 (25.3)	5 (6.2)
Difference (95% CI)	14.8 (6.0 to 23.5)		19.1 (11.6 to 26.7)	
P value	0.003		< 0.001	
VMA resolution at 3 months				
n (%)	58 (26.5)	16 (15.0)	62 (25.3)	7 (8.6)
Difference (95% CI)	11.5 (2.6 to 20.5)		16.7 (8.5 to 24.9)	
P value	0.024		< 0.001	
VMA resolution at 6 months				
n (%)	60 (27.4)	15 (14.0)	65 (26.5)	10 (12.3)
Difference (95% CI)	13.4 (4.5 to 22.2)		14.2 (5.1 to 23.2)	
P value	0.008		0.009	
Withdrawals				
Total, n (%)	19 (8.7)	9 (8.4)	10 (4.1)	7 (8.6)
SAEs				
n (%)	32 (14.5)	13 (12.3)	33 (13.5)	11 (13.6)
WDAEs				
n (%)	2 (0.9)	2 (1.9)	2 (0.8)	0
Notable harms(s) n (%)				
Lens subluxation	0	0	0	0
Cataracts	6 (2.7)	5 (4.7)	6 (2.4)	3 (3.7)
Eye infection	0	1 (0.9)	1 (0.4)	0
Retinal detachment	3 (1.4)	2 (1.9)	1 (0.4)	1 (1.2)
Vitritis	0	0	1 (0.4)	0
Conjunctival hemorrhage	34 (15.5)	14 (13.2)	34 (13.9)	10 (12.3)
Retinal hemorrhage	4 (1.8)	2 (1.9)	4 (1.6)	2 (2.5)
Vitreous hemorrhage	2 (0.9)	2 (1.9)	2 (0.8)	1 (1.2)

CI = confidence interval; SAE = serious adverse event; VMA = vitreomacular adhesion; WDAE = withdrawal due to adverse event.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Symptomatic vitreomacular adhesion (VMA) is a rare macular condition caused by an incomplete posterior vitreous detachment of the vitreous from the macula.[1] Focal traction from the incomplete separation of the posterior vitreous can cause anteroposterior and tangential stretching, distorting the macula,[19] thereby potentially resulting in irreversible visual deterioration and blindness if left untreated.[2] Symptoms of VMA include vision loss and metamorphopsia (distorted vision), decreased VA, central visual field defects, macula distortion, edema, photopsia, and micropsia.[19-22] VMA has also been associated with the development of macular hole (MH), epiretinal membrane, tractional macular edema, and myopic macular retinoschisis.[23] VMA is typically a unilateral condition affecting only one eye, although patients may also present with bilateral VMA.[24]

With no population studies reporting the prevalence or incidence of VMA, the epidemiology of this condition in Canada is uncertain. Based on studies from the US,[25,26] Australia,[27] China[28] and India,[29] the approximate prevalence of VMA is 0.04%.[30] After applying these estimates to the Canadian population,[31] the estimated mean prevalence of VMA would be approximately 16,500 cases with patients older than 40.

1.2 Standards of Therapy

There are no pharmacological treatments available for sVMA, other than ocriplasmin. The current standard of care is “watchful waiting”, a strategy that waits for patients to achieve spontaneous resolution without a clinically significant loss in VA.[32] Surgical vitrectomy, a procedure that dissects the retinal surface from the aspiration of the vitreous, is currently the only procedural treatment option available for VMA. Vitrectomy has a high success rate in VMA patients and has been shown to be effective for releasing VMA and visual improvement.[33] Vitrectomy procedures are, however, invasive and are associated with numerous complications (including cataract formation, retinal detachment or permanent retinal damage or vitritis and/or endophthalmitis). Thus, only patients who have experienced clinically significant visual loss and whose benefits outweigh the risk are recommended for this procedure.[20,34] Furthermore, following vitrectomy, patients typically experience a considerable treatment burden as post-surgery patients are unable to take part in daily activities, and are required to be lying face down for approximately one to two weeks. There is, therefore, a need for a minimally invasive and well-tolerated treatment option that can be provided at an earlier stage of the sVMA disease process).

1.3 Drug

Ocriplasmin is a recombinant truncated form of human plasmin obtained from microplasminogen produced in a *P. pastoris* expression system by recombinant DNA technology.[3] Ocriplasmin has proteolytic activity against protein components of the vitreous, thus dissolving the abnormal adhesion and releasing the associated tractional force on the macula.

In Canada, ocriplasmin is indicated for the treatment of sVMA.[3] The recommended dosage is a single 125 mcg intravitreal injection. Repeated administration of ocriplasmin in the same eye is not recommended. The treatment solution should be diluted by adding 0.2 mL of sodium chloride 9 mg/mL (0.9%). If treatment in the contralateral eye is required, it should not be performed within seven days of the initial injection in order to monitor the post-injection course and the potential for decreased vision in the injected eye.[3]

Based on discussion with the clinical expert involved with the review, ocriplasmin should be prescribed and administered by retinal specialists.

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Listing Criteria Requested By Sponsor
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2. OBJECTIVES AND METHODS

2.1 Objectives

The objective of this report is to perform a systematic review of the beneficial and harmful effects of ocriplasmin 125 mcg for the treatment of sVMA.

2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients (≥ 18 years of age) with sVMA Subpopulation: • Individuals with FTMH at baseline • ≥ 65 and < 65 years of age • Baseline BCVA score
Intervention	Ocriplasmin 125 mcg (in 0.1 mL of diluted solution) administered by intravitreal injection to the affected eye once as a single dose
Comparators	• Placebo or sham injection • Vitrectomy • "Watchful waiting"
Outcomes	**Key efficacy outcomes:** • Prevention of blindness • Resolution of VMA • HRQoL **Other efficacy outcomes:** • Total PVD • Non-surgical closure of FTMH • Proportion of patients receiving vitrectomy (avoidance of vitrectomy) • Change from baseline in BCVA[a] **Harms outcomes:** • AEs, SAEs, WDAEs, • Mortality • Lens subluxation, cataracts, eye infection, retinal detachment, vitritis, conjunctival hemorrhage, retinal hemorrhage, vitreous hemorrhage
Study Design	Published and unpublished double-masked RCTs

AE = adverse event; BCVA = best-corrected visual acuity; FTMH = full-thickness macular hole; HRQoL = health-related quality of life; OCT = optical clearance tomography; PVD = posterior vitreous detachment; RCT = randomized controlled trial; SAE = serious adverse event; sVMA = symptomatic vitreomacular adhesion; VMA = vitreomacular adhesion; WDAE = withdrawal due to adverse event.

[a]Absolute change, percentage of patients with improvement or worsening from baseline of ≥ 15 letters visual acuity, and percentage of patients with severe vision loss (loss of ≥ 30 letters visual acuity).

An information specialist performed the literature search, using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was ocriplasmin (Jetrea).

No methodological filters were applied to limit retrieval to study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2: LITERATURE SEARCH STRATEGY for the detailed search strategy.

The initial search was completed on July 10, 2013. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on November 20, 2013. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH "Grey Matters" checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and by contacting appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

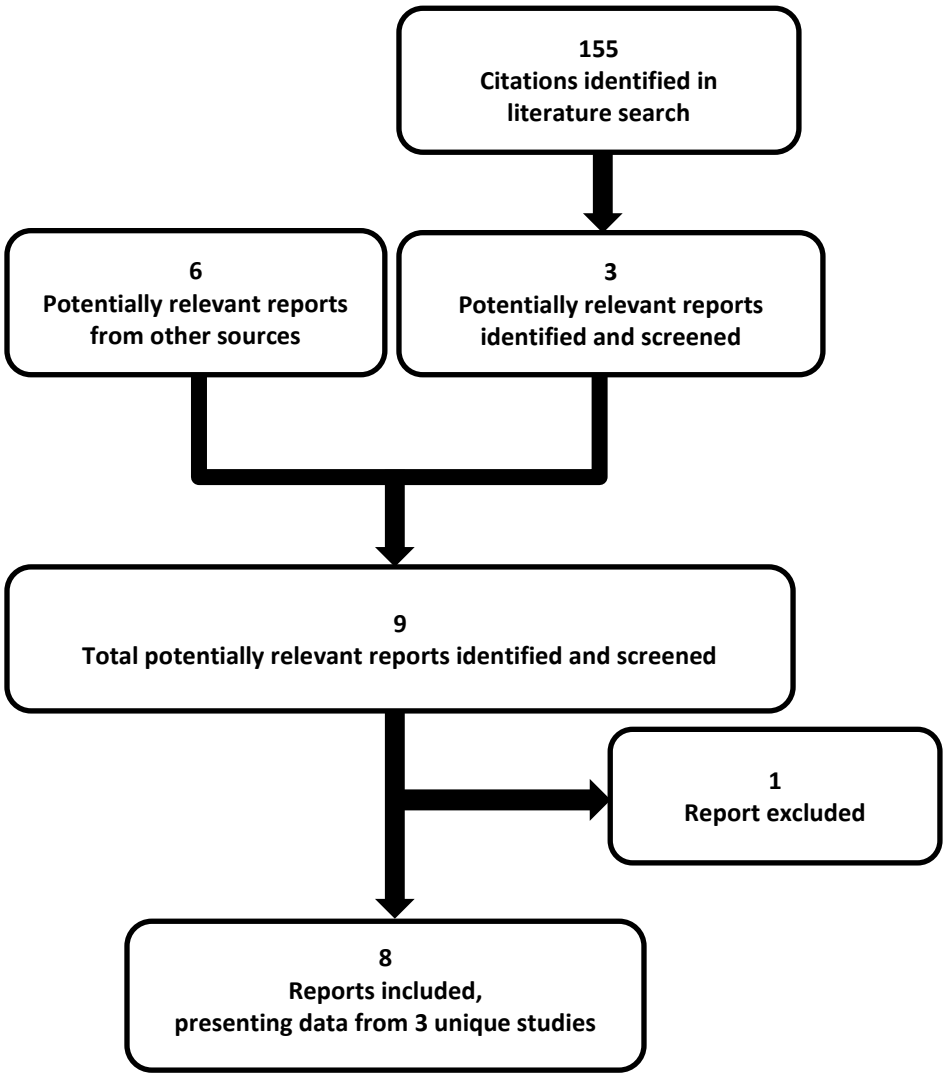
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. The reviewers independently made the final selection of studies to be included in the review; any differences were resolved through discussion. The included studies are presented in Table 3 and described in Section 3.2. A list of excluded studies is presented in Appendix 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings from the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 3.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



QUOROM = Quality of Reporting of Meta-analyses.

TABLE 3: DETAILS OF INCLUDED STUDIES

		TG-MV-004	TG-MV-006	TG-MV-007
DESIGNS AND POPULATIONS	**Study design**	Double-mask RCT	Double-mask RCT	Double-mask RCT
	Locations	Belgium and Germany	US	US and European Union
	Randomized (N)	60	326	326
	Inclusion criteria	• Adults (≥ 18 years of age) • Symptomatic focal VMA (including VMT with and without FTMH) • BCVA ≤ 20/40 in study eye, ≥ 20/400 in non-study eye	• Adults (≥ 18 years of age) • Symptomatic focal VMA • BCVA ≤ 20/25 in study eye, ≥ 20/800 in non-study eye	• Adults (≥ 18 years of age) • Symptomatic focal VMA • BCVA ≤ 20/25 in study eye, ≥ 20/800 in non-study eye
	Exclusion criteria	• Previous intravitreal injections in past 3 months in study eye • Intraocular surgery or laser photocoagulation in past 3 months in study eye • Rhegmatogenous retinal detachment in either eye	• Previous intravitreal injections in past 3 months in study eye • Intraocular surgery or laser photocoagulation in past 3 months in study eye • Rhegmatogenous retinal detachment in either eye • Proliferative diabetic retinopathy • Neovascular age-related macular degeneration • Retinal vascular occlusion, • Aphakia • High myopia (> –8 diopters) • Uncontrolled glaucoma • Macular hole > 400 mcm in diameter • Vitreous opacification • Lenticular/zonular instability	• Previous intravitreal injections in past 3 months in study eye • Intraocular surgery or laser photocoagulation in past 3 months in study eye • Rhegmatogenous retinal detachment in either eye • Proliferative diabetic retinopathy • Neovascular age-related macular degeneration • Retinal vascular occlusion, • Aphakia • High myopia (> –8 diopters) • Uncontrolled glaucoma • Macular hole > 400 mcm in diameter • Vitreous opacification • Lenticular/zonular instability
DRUGS	**Intervention**	Ocriplasmin, single dose 75 mcg, 125 mcg, 175 mcg, or repeat dose of 125 mcg, intravitreal injection	Ocriplasmin, single dose 125 mcg	Ocriplasmin, single dose 125 mcg
	Comparator(s)	Sham injection	Placebo (0.1 mL vehicle) intravitreal injection	Placebo (0.1 mL vehicle) intravitreal injection

		TG-MV-004	TG-MV-006	TG-MV-007
DURATION	**Phase**			
	Run-in	NA	NA	NA
	Double-blind	6 months	6 months	6 months
	Follow-up	NA	~ 2 years (TG-MV-012)	~ 2 years (TG-MV-012)
OUTCOMES	**Primary end point**	Total PVD at day 14	Resolution of VMA at day 28, 3 months, and 6 months	Resolution of VMA at day 28, 3 months, and 6 months
	Other end points	• Resolution of VMA at day 28, 3 months, and 6 months • Non-surgical closure of FTMH at day 28 and 6 months • Avoidance of vitrectomy at day 28 and 6 months • Change in baseline BCVA at day 28	• Total PVD at day 28 • Non-surgical closure of FTMH at day 28 and 6 months • Avoidance of vitrectomy at day 28 and 6 months • Change in baseline BCVA at day 28 and 6 months • Change in baseline QoL (VFQ-25) at 6 months	• Total PVD at day 28 • Non-surgical closure of FTMH at day 28 and 6 months • Avoidance of vitrectomy at day 28 and 6 months • Change in baseline BCVA at day 28 and 6 months • Change in baseline QoL (VFQ-25) at 6 months
NOTES	**Publications**	Stalmans et al. (2010)[35]	Stalmans et al. (2012)[19]	Stalmans et al. (2012)[19]

BCVA = best-corrected visual acuity; FTMH = full-thickness macular hole; NA = not applicable; RCT = randomized controlled trial; PVD = posterior vitreous detachment; QoL = quality of life; VMA = vitreomacular adhesion; VMT = vitreomacular traction.
Note: Five additional reports were included: Clinical Study Reports,[4-6] United States Food and Drug Administration Medical and Statistical Reports,[36,37] Common Drug Review Submission Binder.[38]

3.2 Included Studies

3.2.1 Description of Studies

Three multicentre, randomized, parallel group, double-mask, placebo and sham controlled studies met the inclusion criteria for this systematic review. TG-MV-006 (N = 326) and TG-MV-007 (N = 326) are identically designed phase III studies which evaluated the safety and efficacy of a single 125 mcg dose injection of ocriplasmin compared with placebo injection for the treatment of sVMA (focal VMA leading to symptoms).

TG-MV-004 (N = 60) is a phase II study, which evaluated the safety and preliminary efficacy of ocriplasmin 75 mcg, 125 mcg, and 175 mcg single doses and repeated doses of ocriplasmin 125 mcg (up to two additional open-label injections) compared with a sham injection. Although TG-MV-004 met the inclusion criteria for this report, the study comprised a small sample size that was likely not sufficiently powered to detect differences in resolution of VMA, as it was a secondary end point and was analyzed in an exploratory manner. Furthermore, the primary analyses were pre-specified to pool data from the 125 mcg single-dose group with the treatment group, which received more than one dose of ocriplasmin 125 mcg; ocriplasmin is indicated for a single dose only. Given these important limitations of TG-MV-004, data from this study are not presented. Thus, the two pivotal phase III studies, TG-MV-006 and TG-MV-007, are the focus of this report.

Patients in both TG-MV-006 and TG-MV-007 were followed for 6 months. The allocation ratio was 2:1 (ocriplasmin:placebo) in TG-MV-006 and 3:1 in TG-MV-007. In both studies, patients in the treatment group received a single 0.1 mL intravitreal injection containing the study drug and 0.75 mL normal saline, while patients in the placebo group received only the intravitreal injection of the normal saline solution. The studies consisted of seven visits: baseline, injection day, post-injection day 7, post-injection day 14, post-injection day 28 (primary outcome assessment), post-injection month 3, and post-injection month 6.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

The main inclusion criteria in TG-MV-006 and TG-MV-007 were patients 18 years of age or older with a presence of sVMA (i.e., central vitreal adhesion within 6 mm optical coherence tomography [OCT] field surrounded by elevation of the posterior vitreous cortex) related to decreased visual function as per the opinion of the investigator. Patients must have had a BCVA of 20/25 or worse in the study eye, and BCVA of 20/800 in the non-study eye. Both eyes were examined; the eye with the worst BCVA was selected as the study eye if both eyes met the inclusion criteria.

A patient was excluded from the studies if he or she had had previous treatment with intravitreal injections in the past three months in the study eye, rhegmatogenous retinal detachment in either eye, proliferative diabetic retinopathy, neovascular age-related macular degeneration (AMD), retinal vascular occlusion, aphakia, high myopia (greater than –8 diopters), uncontrolled glaucoma, MH > 400 mcm in diameter, vitreous opacification, or lenticular/zonular instability.

b) Baseline Characteristics

Baseline characteristics were generally well balanced across treatment groups in both studies (Table 4). Patients had a mean age of approximately 71 years and most (~65%) were female. The majority of patients were Caucasian (~92%), had VMA with a diameter of 1,500 mcm or smaller (~70%), and had an expected need for vitrectomy (~83%). Approximately 24% of patients had a baseline diagnosis of full-thickness macular hole (FTMH) and approximately 76% of patients had a baseline diagnosis of vitreomacular traction (VMT), including diabetic retinopathy. None of the patients, with the exception of one in the ocriplasmin group in TG-MV-006, had total posterior vitreous detachment (PVD) at baseline. The mean baseline BCVA letter scores ranged from 63.4 to 65.3 in both studies.

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS — TG-MV-006 AND TG-MV-007

Characteristics	TG-MV-006		TG-MV-007	
	Ocriplasmin (N = 219)	Placebo (N = 107)	Ocriplasmin (N = 245)	Placebo (N = 81)
Age, years (SD)	71.5 (10.25)	71.1 (10.04)	72.6 (7.56)	70.2 (10.85)
Female, n (%)	148 (67.6)	59 (55.1)	166 (67.8)	56 (69.1)
Unilateral versus bilateral VMA at baseline, n (%)				
Unilateral VMA	174 (79.5)	81 (75.7)	196 (80.0)	70 (86.4)
Bilateral VMA	45 (20.6)	26 (24.3)	48 (19.6)	11 (13.6)
Race, n (%)				
White	195 (89.0)	97 (90.7)	233 (95.1)	77 (95.1)
Black	13 (5.9)	4 (3.7)	10 (4.1)	2 (2.5)
Asian	6 (2.7)	2 (1.9)	2 (0.8)	2 (2.5)
Other	5 (2.3)	4 (3.7)	0	0
Baseline diagnosis, n (%)				
FTMH	57 (26.0)	32 (29.9)	49 (20.0)	15 (18.5)
VMT (including DR)	162 (74.0)	75 (70.0)	196 (80.0)	66 (81.5)
Type (diameter) of focal VMA, n/N (%)				
> 1500 mcm	47/207 (22.7)	19/99 (19.2)	55/223 (23.6)	22/77 (28.6)
≤ 1500 mcm	145/207 (70.0)	74/99 (74.7)	169/233 (72.5)	49/77 (63.6)
Could not determine	15/207 (7.2)	6/99 (6.1)	9/233 (3.9)	6/77 (7.8)
Expected need for vitrectomy, n (%)				
Yes	174 (79.5)	85 (79.4)	222 (90.6)	67 (82.7)
No	44 (20.1)	22 (20.6)	23 (9.4)	14 (17.3)
Missing	1 (0.5)	0	0	0
Total PVD at baseline, n (%)				
Yes	1 (0.5)	0	0	0
No	218 (99.5)	107 (100.0)	245 (100.0)	81 (100.0)
BCVA letter score at baseline				
Mean (SD)	64.5 (10.86)	65.3 (9.83)	63.4 (13.69)	64.9 (11.58)
Median	67.0	67.0	67.0	66.5

BCVA = best-corrected visual acuity; DR = diabetic retinopathy; FTMH = full-thickness macular hole; PVD = posterior vitreous detachment; SD = standard deviation; VMA = vitreomacular adhesion; VMT = vitreomacular traction.

3.2.3 Outcomes

The primary outcome in TG-MV-006 and TG-MV-007 was the proportion of patients with VMA resolution, determined by masked central reader center (CRC) by OCT at day 28. OCT measurements were made by a certified assessor of patients after dilating the pupil. Patients who experienced anatomical defects such as retinal holes or retinal detachments, resulting in vision loss, were considered treatment failures for the primary outcome. Success on the primary end point was defined as per the CRC OCT interpretation document, which was finalized prior to unmasking (Table 5). VMA was defined by categories 1, 2, and 4.

TABLE 5: VITREOMACULAR ADHESION STATUS CATEGORIES

Category	Description
0	No visible vitreous separation
1	Vitreous attached from fovea to optic nerve; separated elsewhere
2	Vitreous attached at fovea and optic nerve and separated between; may be separated outside
3	Vitreous attached only at optic nerve or at optic nerve and elsewhere, but attached at fovea
4	Vitreous attached only at fovea
5	Vitreous visible with complete separation and no attachment
6	Vitreous separation visible somewhere but unable to determine state of separation
7	Unable to determine state of separation

The CRC defined the following categories of progression as being consistent with "resolution of focal VMA" for the primary end point (Table 6).

TABLE 6: RESOLUTION OF VITREOMACULAR ADHESION PROGRESSION STATUS CATEGORIES

Category Change from Baseline to Day 28	
1 to 0	2 to 5
1 to 3	4 to 0
1 to 5	4 to 3
2 to 0	4 to 5
2 to 3	

Secondary outcomes of interest included the proportion of patients with total PVD at day 28, as determined by masked investigator assessment of B-scan ultrasound; non-surgical closure of FTMH at day 28 and 6 months, evaluated during the masked CRC review of the OCTs; the proportion of patients who received vitrectomy at day 28 and 6 months; and change in baseline BCVA at day 28 and 6 months, measured as the proportion of patients achieving greater than 15 letters (3 lines) improvement or worsening in BCVA from baseline, without the need for vitrectomy. Severe vision loss (a loss of > 30 letters in BCVA) from baseline was also an outcome of interest.

VA was measured using Prevision Vision's backlit Early Treatment Diabetic Retinopathy Study (ETDRS) charts that were set four metres away from the patient. A 12 mm vertex distance was set by a phoropter to obtain manifest refraction measurements. A patients was retested at 1 metre (following instructions provided for 1-metre testing) if he or she was unable to read 20 or more letters on the ETDRS chart at 4 metres.

Health-related quality of life (HRQoL) was measured using the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25). Specifically, the general health subscale and the composite score were the primary indicators of HRQoL. Changes from baseline in the general health subscale and composite scores were measured at six months.

Adverse events (AEs) were considered as events with an onset on or after the time of study drug injection. Serious adverse events (SAEs) were defined as an AE that either resulted in death, was immediately life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or as a congenital anomaly or birth defect. Other safety outcomes of interest included lens subluxation, cataracts, eye infection, retinal detachment, vitritis, conjunctival hemorrhage, retinal hemorrhage, and vitreous hemorrhage

3.2.4 Statistical Analysis

a) Efficacy Criteria

The sample size for TG-MV-006 and TG-MV-007 was calculated assuming an event rate of 27.5% in the 125 mcg dose group and 10% in the placebo group. A total of 320 participants were expected to be sufficient to achieve 90% power with a two-sided significance level of 5%. The calculation was applied for a randomization ratio of 3:1, which was used in TG-MV-007. The original randomization ratio was also 3:1 in TG-MV-006, but was changed to 2:1 before the commencement of the study as per a recommendation by the United States Food and Drug Administration.[36]

The analysis for the primary end point (resolution of VMA) and key secondary end points (total PVD detachment, non-surgical closure of FTMH) was performed using the full analysis set (FAS) population, using the last observation carried forward (LOCF) approach for missing observations. The proportion of patients who had resolution of VMA was compared by treatment group using Fisher's exact test. In TG-MV-006, the primary end point analyses were adjusted for the randomization ratios as 3:1 or 2:1 using conditional logistic regression (with randomization ratio as the factor for stratification) and Cochran-Mantel-Haenszel tests. The per-protocol (PP) population was used for supportive efficacy analyses.

Secondary analyses were calculated using the FAS with observed case approach, with missing data for any reason excluded. Other than the secondary end point for the proportion of patients with total PVD, no adjustments for multiple comparisons/end points were made for the secondary end points. The proportions of patients who had total PVD, who had non-surgical closure of FTMHs, who received vitrectomy, and categorical changes (improvement or worsening of ≥ 15 and ≥ 30 letters) in BCVA score, were compared by treatment group using Fisher's exact test. Mean changes in BCVA letter scores were calculated using the Wilcoxon rank-sum test, comparing change from baseline between-treatment groups. Patients with total PVD at baseline were included as failures. Patients who achieved total PVD at two consecutive visits did not require an additional B-scan ultrasound at subsequent visits; thus, patients who had missing data at day 28 were considered successes if they had total PVD at day 7 and day 14.

Two subgroup analyses for resolution of VMA at day 28 were established a priori and performed for patients with and without FTMH determined by the CRC at baseline, and by baseline VA category. A post-hoc subgroup analysis for resolution of VMA at day 28 by age group (patients ≥ 65 years of age and < 65 years of age) was performed. A sensitivity analysis using a multiple imputation method for missing data for the resolution of VMA and the proportion of patients with total PVD was performed. Based on the conditional probabilities of success or failure using observed probabilities within the study, missing data were imputed with results using 100 iterations.

c) Analysis Populations

In TG-MV-006 and TG-MV-007, the following data sets were defined:

Full Analysis Set

All patients randomized to receive study medication (ocriplasmin and placebo). The full analysis set (FAS) was the primary population for all analyses.

Modified Full Analysis Set (FAS in patients with VMA)

FAS in patients with VMA included all patients who received treatment with the investigational drug and who were judged by the investigator as having sVMA at screening, which was confirmed by masked CRC OCT evaluation at baseline. The modified FAS (mFAS) excluded patients with either no or undetermined focal VMA status at baseline. Patients without VMA at baseline, by definition, had no possibility of being a success on the primary end point of VMA resolution. This population was of secondary importance and was utilized to determine the most accurate point estimate of event rates in both the active and placebo groups.

Per-protocol set

A subset of the FAS population that excluded patients with a protocol deviation that was of sufficient concern to warrant exclusion.

Safety data set

Patients in the FAS population who were randomized and received treatment. Patients were counted in the group in which they were actually treated.

3.3 Patient Disposition

Patient disposition is summarized in Table 7. A total of 326 patients in TG-MV-006 and 326 patients in TG-MV-007 were randomized. Overall, the number of premature discontinuations in both studies was low. In TG-MV-006, discontinuation was similar between both groups with rates of 8.7% and 8.4% for the ocriplasmin and placebo groups respectively. In TG-MV-007, discontinuation was lower among the ocriplasmin group (4.1%) compared with the placebo group (8.6%). Reasons for discontinuation were generally similar in all treatment arms, with the exception of three deaths in TG-MV-006 and one death in TG-MV-007.

TABLE 7: PATIENT DISPOSITION

	TG-MV-006		TG-MV-007	
	Ocriplasmin (N = 219)	Placebo (N = 107)	Ocriplasmin (N = 245)	Placebo (N = 81)
Screened, N	326		326	
Randomized, N (%)	219 (100.0)	107 (100.0)	245 (100.0)	81 (100.0)
Discontinued, N (%)	19 (8.7)	9 (8.4)	10 (4.1)	7 (8.6)
Adverse event	2 (0.9)	2 (1.9)	2 (0.8)	0
Investigator decision	0	0	0	1 (1.2)
Withdrew consent	8 (3.7)	4 (3.7)	5 (2.0)	4 (4.9)
Lost to follow-up	6 (2.7)	3 (2.8)	2 (0.8)	2 (2.5)
Death	3 (1.4)	0	1 (0.4)	0
FAS, N	219)	107	245	81
mFAS[a], N (%)	207 (94.5)	99 (92.5)	233 (95.1)	77 (95.1)
PP, N (%)	189 (86.3)	94 (87.9)	214 (87.3)	71 (87.7)
Safety, N	220	106	245	81

FAS = full analysis set; mFAS = modified full analysis set; PP = per-protocol set.
[a]Modified full analysis set included patients with focal VMA at baseline confirmed by optical coherence tomography.

3.4 Exposure to Study Treatments

In both studies, on day 0, all patients in the Safety Sets received a single intravitreal injection, administered using either a 30G or 27G-size needle, of ocriplasmin 125 mcg or matching placebo of equal volume.

3.5 Critical Appraisal

3.5.1 Internal Validity

a) Selection, Allocation, and Disposition of Patients

- Both studies were randomized and double-masked.
- The studies employed appropriate methods of allocation concealment. Patients were randomized centrally through a telephone-based, interactive voice response system (IVRS) to either ocriplasmin or placebo. Study personnel called IVRS on the day of the study and were informed which vial number to use for the patient's injection. Vials containing placebo were identical in appearance, having the same components and concentrations without the ocriplasmin.
- Baseline characteristics of both the ocriplasmin and placebo groups were generally similar in both studies. In study TG-MV-006, there was a greater proportion of individuals with FTMH and a smaller proportion of patients with VMT with an expected need for vitrectomy.
- One patient was inadvertently treated with ocriplasmin after being randomized to receive placebo; this was unlikely to have influenced the efficacy results.
- In both studies, the proportion of patients who discontinued was generally low and similar in all treatment groups with the exception of the ocriplasmin group in TG-MV-007, which, for an unknown reason, had fewer withdrawals (approximately half the proportion of the other treatment groups).

b) Intervention and Comparator

- A placebo injection instead of sham injection was used as the comparator treatment in both studies. Based on discussion with the clinical expert involved in the review, insertion of a needle and administration of saline may affect the natural history of VMA, including precipitating vitreous detachment. Moreover, placebo injection (versus sham injection where no needle is inserted into the eye) may increase the likelihood of causing SAEs, such as serious ocular infections and retinal detachment. However, these concerns are somewhat mitigated by the much larger (and statistically significant) rate of VMA resolution at day 28 in favour of ocriplasmin versus placebo in both studies, and the very low rate of eye infection and retinal detachment in the placebo group in both studies.
- Although subgroup analyses for the primary end point among patients with and without FTMH at baseline and by baseline VA category were established a priori, analyses of two other subgroups of interest (≥ 65 years of age and < 65 years of age) were performed post hoc. It was unlikely that there was sufficient statistical power to detect differences in the primary end point among these subgroups and randomization would have been broken.
- Other than the secondary end point of total PVD at 28 days, the authors did not adjust for the multiplicity of additional secondary end points. The authors stated that the additional secondary end points were of a supportive nature only and were interpreted as such.
- The use of LOCF in the context of the differential withdrawal rates could have biased the FAS results of the primary end point among the ocriplasmin group in TG-MV-007. However, this concern is mitigated to an extent by the fact that the multiple imputation sensitivity analysis (Table 18) and per protocol set (PPS) results (Table 15) were consistent with the FAS.

3.5.2 External Validity

a) Patient Characteristics

- The FAS included a small proportion of patients who did not have VMA as determined by masked CRC OCT evaluation at baseline. Therefore, the FAS comprised patients who, by definition, had no possibility of achieving the primary end point of VMA resolution. The mFAS was considered to be a secondary efficacy population, as it did not contain enough patients, thereby lacking statistical power according to the sample size calculation.
- With only one extension study (TG-MV-012) with a small sample size (N = 24) assessing patients approximately 2.5 years after initial intravitreal injection (Appendix 6: SUMMARY OF FOLLOW-UP STUDY TG-MV-012), there is limited long-term efficacy and safety data for ocriplasmin.
- With no head-to-head trials comparing ocriplasmin with “watchful waiting” or vitrectomy alone, ocriplasmin could not be compared with other current treatments used in Canada for VMA.
- The generalizability of the findings is somewhat limited by specific inclusion and exclusion criteria. For example, participants were excluded — in part — based on specific baseline BCVA scores; hence, the study populations were not wholly inclusive of all patients with VMA. However, this limitation is somewhat mitigated given the broad criteria of including patients with BCVA scores of ≤ 20/25 in the study eye and ≥ 20/800 in the non-study eye.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 2).

3.6.1 Prevention of Blindness

Prevention of blindness was not evaluated in TG-MV-006 and TG-MV-007.

3.6.2 Resolution of Vitreomacular Adhesion

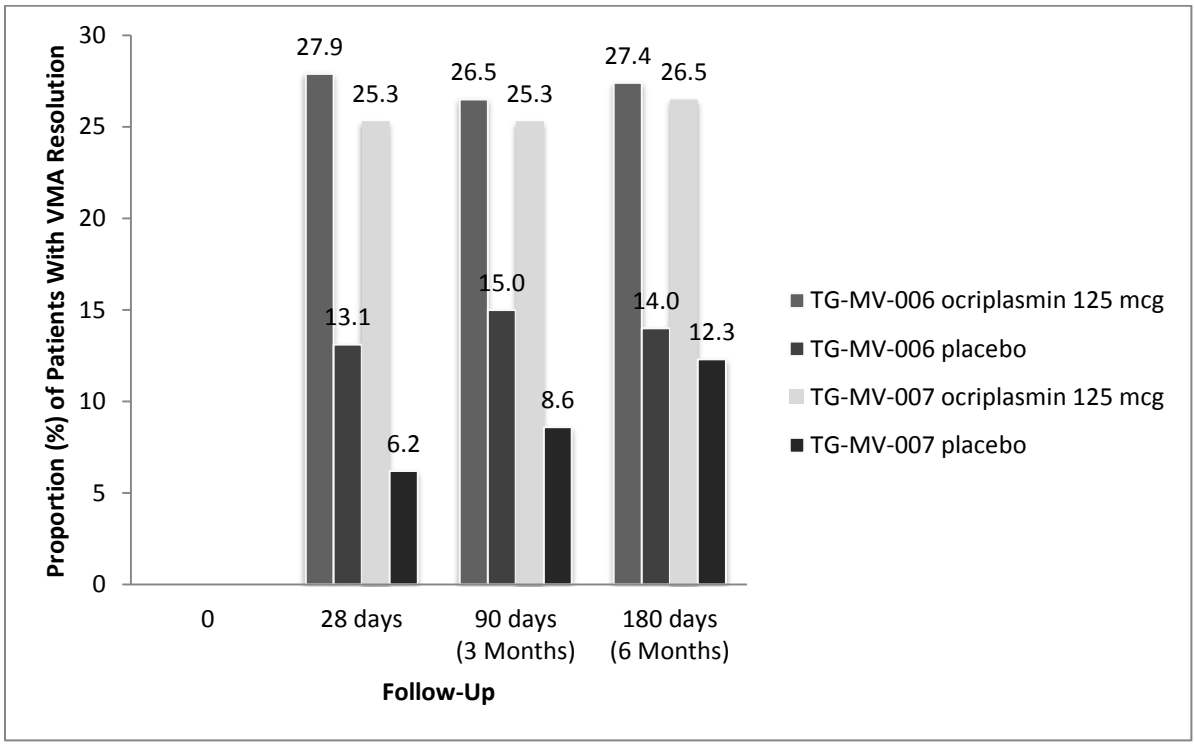
Results for resolution of VMA are summarized in Table 8 for the FAS population. In both studies, ocriplasmin revealed statistical superiority over placebo for the achievement of VMA at day 28, 3 months, and 6 months. At day 28, the percentage of patients achieving VMA resolution were 27.9% and 25.3% in the ocriplasmin groups, and 13.1% and 6.2% in the placebo groups for TG-MV-006 and TG-MV-007 respectively. The between-group difference of patients achieving resolution of VMA with ocriplasmin versus placebo was greater in TG-MV-007 (19.1%) compared with TG-MV-006 (14.8%). Similar results were seen at 3 months and 6 months. The proportion of patients who achieved resolution of VMA was similar at all follow-up periods for the ocriplasmin groups in both studies (Figure 2). In TG-MV-006, the placebo group had a greater proportion of patients achieving resolution of VMA at day 28, 3 months, and 6 months compared with TG-MV-007. Results for resolution of VMA were consistent among all analysis populations (FAS, mFAS, and PP) (Table 15).

TABLE 8: RESOLUTION OF VMA — FULL ANALYSIS SET

Outcome[a]	TG-MV-006		TG-MV-007	
	Ocriplasmin (N = 219)	Placebo (N = 107)	Ocriplasmin (N = 245)	Placebo (N = 81)
VMA resolution at day 28				
n (%)	61 (27.9)	14 (13.1)	62 (25.3)	5 (6.2)
Difference (95% CI)[b]	14.8 (6.0, 23.5)		19.1 (11.6, 26.7)	
P value	0.003		< 0.001	
VMA resolution at 3 months				
n (%)	58 (26.5)	16 (15.0)	62 (25.3)	7 (8.6)
Difference (95% CI)[b]	11.5 (2.6, 20.5)		16.7 (8.5, 24.9)	
P value	0.024		< 0.001	
VMA resolution at 6 months				
n (%)	60 (27.4)	15 (14.0)	65 (26.5)	10 (12.3)
Difference (95% CI)[b]	13.4 (4.5, 22.2)		14.2 (5.1, 23.2)	
P value	0.008		0.009	

CI = confidence interval; VMA = vitreomacular adhesion.
[a]Outcomes identified as important to the review (see section 2.2.1 for review protocol).
[b]Analyses were performed on last observation carried forward (LOCF) data set. Between-group differences are based on the percentage of successes.

FIGURE 2: PROPORTION OF PATIENTS WITH RESOLUTION OF VMA, BY LENGTH OF FOLLOW-UP



VMA = vitreomacular adhesion.
Source: Figure adapted from data in Clinical study report TG-MV-006[4] and clinical study report TG-MV-007.[5]

Results from the sensitivity analysis using a multiple imputation method for missing data were consistent with between-group differences of 13.5% (95% confidence interval [CI], 4.3 % to 22.7%) and 19.2% (95% CI, 10.5 % to 27.8%) at day 28 for TG-MV-006 and TG-MV-007 respectively (Table 18).

Subgroup analyses for resolution of VMA, performed for patients with and without FTMH at baseline, by baseline VA category (ETDRS score > 60, > 65 and > 70 letters) and by age group (≥ 65 years of age and < 65 years of age), are summarized in Table 9 and Table 10. Among patients with FTMH, the between-group difference of patients achieving resolution of VMA with ocriplasmin versus placebo at day 28 was 33.1% (95% CI, 8.5% to 57.7%) in TG-MV-007. The between-group difference of patients achieving resolution of VMA among patients with FTMH was not statistically significant in TG-MV-006. Among patients without FTMH, the between-group difference of patients achieving resolution of VMA with ocriplasmin versus placebo at day 28 was 14.3% (95% CI, 5.9 % to 22.8%) in TG-MV-006 and 15.3% (95% CI, 8.5% to 22.2%) in TG-MV-007.

Among patients with a baseline VA of > 60 letters, ocriplasmin was statistically superior to placebo with a between-group difference of 20.8% (95% CI, 5.0% to 36.7%) in TG-MV-006 and 23.9% (95% CI, 8.7% to 39.1%) in TG-MV-007. For patients with a baseline VA of > 65 letters, ocriplasmin was statistically superior to placebo with a between-group difference of 17.7% (95% CI, 4.0% to 31.3%) in TG-MV-006 and 27.3% (95% CI, 15.9% to 38.7%) in TG-MV-007. In TG-MV-006, the between-group difference of patients with a baseline VA of > 70 letters was 16.3% (95% CI, 3.5% to 29.1%). In TG-MV-007, the results for patients with a baseline VA of > 70 letters favoured the ocriplasmin group, although the results were not statistically significant.

Among patients ≥ 65 years of age, ocriplasmin was statistically superior to placebo with a between-group difference of 13.1% (95% CI, 4.7% to 21.4%) in TG-MV-006 and 18.8% (95% CI, 11.1% to 26.5%) in TG-MV-007. The results for patients < 65 years of age favoured the ocriplasmin groups, although the results were not statistically significant.

TABLE 9: VITREOMACULAR ADHESION RESOLUTION AT DAY 28 FOR TG-MV-006 AND TG-MV-007 — SUBGROUP ANALYSES, FULL ANALYSIS SET

VMA Resolution at Day 28	TG-MV-006		TG-MV-007	
	Ocriplasmin (N = 219)	Placebo (N = 107)	Ocriplasmin (N = 245)	Placebo (N = 81)
FTMH Status at Baseline				
FTMH present				
n/N (%)	27/57 (47.4)	9/32 (28.1)	26/49 (53.1)	3/15 (20.0)
Difference (95% CI)	19.2 (–1.0 to 39.5)		33.1 (8.5 to 57.7)	
P value[a]	0.115		0.037	
FTMH absent				
n/N (%)	34/162 (21.0)	5/75 (6.7)	36/196 (18.4)	2/66 (3.0)
Difference (95% CI)	14.3 (5.9 to 22.8)		15.3 (8.5 to 22.2)	
P value[a]	0.005		0.001	
Age in Years at Baseline				
≥ 65 years				
n/N (%)	35/171 (20.5)	6/81 (7.4)	50/213 (23.5)	3/64 (4.7)
Difference (95% CI)	13.1 (4.7 to 21.4)		18.8 (11.1 to 26.5)	
P value[a]	0.010		< 0.001	
< 65 years				
n/N (%)	26/48 (54.2)	8/26 (30.8)	12/32 (37.5)	2/17 (11.8)
Difference (95% CI)	23.4 (0.7 to 46.1)		25.7 (3.0 to 48.4)	
P value[a]	0.086		0.096	

CI = confidence interval; FTMH = full-thickness macular hole; VMA = vitreomacular adhesion.

[a] *P* value is from Fisher's exact test, comparing placebo and ocriplasmin. Between-group differences are based on the percentage of successes. Non-surgical improvement is defined as values observed at month 6 among patients who did not receive vitrectomy.

TABLE 10: VITREOMACULAR ADHESION RESOLUTION AT DAY 28 BY BASELINE BCVA SUBGROUP — FULL ANALYSIS SET

	TG-MV-006		TG-MV-007	
	Ocriplasmin (N = 219)	Placebo (N = 107)	Ocriplasmin (N = 245)	Placebo (N = 81)
Subgroup				
Overall				
n/N (%)	61/219 (27.9)	14/107 (13.1)	62/245 (25.3)	5/81 (6.2)
Difference (95% CI)	14.8 (6.0 to 23.5)		19.1 (11.6 to 26.7)	
P value[a]	0.003		< 0.001	
≤ 60 letters				
n/N (%)	26/74 (35.1)	5/35 (14.3)	28/86 (32.6)	2/23 (8.7)
Difference (95% CI)	20.8 (5.0 to 36.7)		23.9 (8.7 to 39.1)	
P value[a]	0.025		0.033	
> 60 letters				
n/N (%)	35/145 (24.1)	9/72 (12.5)	34/159 (21.4)	3/57 (5.3)
Difference (95% CI)	11.6 (1.3 to 22.0)		16.1 (7.5 to 24.7)	
P value[a]	0.050		0.004	
≤ 65 letters				
n/N (%)	35/104 (33.7)	8/50 (16.0)	36/110 (32.7)	2/37 (5.4)
Difference (95% CI)	17.7 (4.0 to 31.3)		27.3 (15.9 to 38.7)	
P value[a]	0.023		< 0.001	
> 65 letters				
n/N (%)	26/115 (22.6)	6/57 (10.5)	26/135 (19.3)	3/43 (7.0)
Difference (95% CI)	12.1 (1.0 to 23.1)		12.3 (2.2 to 22.4)	
P value[a]	0.063		0.061	
≤ 70 letters				
n/N (%)	41/137 (29.9)	11/70 (15.7)	45/162 (27.8)	3/53 (5.7)
Difference (95% CI)	14.2 (2.7 to 25.7)		22.1 (12.8 to 31.4)	
P value[a]	0.028		< 0.001	
> 70 letters				
n/N (%)	20/82 (24.4)	3/37 (8.1)	17/83 (20.5)	2/27 (7.4)
Difference (95% CI)	16.3 (3.5 to 29.1)		13.1 (−0.1 to 26.2)	
P value[a]	0.045		0.150	

BCVA = best-corrected visual acuity; CI = confidence interval.
[a]*P* value is from Fisher's exact test, comparing placebo and ocriplasmin. Between-group differences are based on the percentage of successes.

3.6.3 Health-related quality of life

Results for HRQoL are summarized in Table 11. Statistically significant results were observed only in TG-MV-007 for the VFQ-25 composite score. At six months, the ocriplasmin group had a greater mean (standard deviation [SD]) change from baseline in composite score (3.3 [11.97]) compared with the placebo group (–0.1 [10.29]), (*P* = 0.013).

TABLE 11: CHANGE IN HEALTH-RELATED QUALITY OF LIFE AT SIX MONTHS — FULL ANALYSIS SET

Outcome	TG-MV-006		TG-MV-007	
	Ocriplasmin (N = 218)	Placebo (N = 107)	Ocriplasmin (N = 245)	Placebo (N = 81)
General health subscale score[a]				
Mean (SD) score at baseline	64.6 (22.83)	66.4 (22.02)	51.5 (24.95)	52.5 (20.90)
Mean (SD) score at 6 months	64.6 (22.92)	65.9 (22.72)	54.3 (25.27)	50.0 (22.88)
Mean change from baseline (SD)	0.8 (19.33)	0.0 (18.21)	2.2 (17.19)	–2.4 (17.64)
P value[c]	0.555		0.056	
Composite score[b]				
Mean (SD) score at baseline	78.8 (15.02)	83.0 (11.56)	75.6 (16.54)	80.6 (12.85)
Mean (SD) score at 6 months	82.3 (15.88)	84.3 (11.93)	80.3 (15.49	78.9 (16.65)
Mean change from baseline (SD)	3.5 (11.74)	1.2 (9.86)	3.3 (11.97)	–0.1 (10.29)
P value[c]	0.094		0.013	

SD = standard deviation.
[a]Based on the average of the individual item scores within the subscale. Items that were left blank (missing) were excluded from the calculation so any patient with at least one response within the subscale was included in the summary of the subscale score. Responses were converted to a number on a 0 to 100 scale (0 = worst possible score, 100 = best possible score).
[b]The composite score was calculated as the average of the 11 vision-targeted subscale scores, excluding the general health-rating question.
[c]*P* value is based on the Wilcoxon rank-sum test, comparing change from baseline between placebo and ocriplasmin.

3.6.4 Total posterior vitreous detachment

Results for patients who achieved total PVD at day 28 are summarized in Table 12. Patients in the ocriplasmin groups revealed greater achievement of total PVD at day 28 in both studies, with a between-group difference of 9.9% (95% CI, 3.1% to 16.7%) in TG-MV-006 and 10.6% (95% CI, 6.8% to 14.5%) in TG-MV-007.

3.6.5 Non-surgical closure of full-thickness macular holes

Results for patients who achieved non-surgical closure of FTMHs are summarized in Table 12. At day 28, the ocriplasmin groups were statistically superior to placebo for the achievement of non-surgical closure of FTMH, with a between-group difference of 31.4% (95% CI, 14.1% to 48.6%) in TG-MV-006 and 30.1% (95% CI, 11.6% to 48.6%) in TG-MV-007. At six months, similar results were seen, though statistical significance was only reached in TG-MV-006, with a between-group difference of 30.0% (95% CI, 11.9% to 48.0%).

3.6.6 Proportion of patients receiving vitrectomy

Results for patients who received vitrectomy are summarized In Table 12. In both studies, the proportion of patients receiving vitrectomy was greater in the placebo groups compared with the ocriplasmin group at day 28 and 6 months, though differences were not statistically significant.

TABLE 12: OTHER EFFICACY OUTCOMES — FULL ANALYSIS SET

Outcome	TG-MV-006		TG-MV-007	
	Ocriplasmin (N = 219)	Placebo (N = 107)	Ocriplasmin (N = 245)	Placebo (N = 81)
Total posterior PVD at day 28 [a]				
n (%)	36 (16.4)	7 (6.5)	26 (10.6)	0
Difference (95% CI)	9.9 (3.1 to 16.7)		10.6 (6.8 to 14.5)	
P value [b]	0.014		< 0.001	
Non-surgical closure of FTMH at day 28 [a]				
n/N (%)	25/57 (43.9)	4/32 (12.5)	18/49 (36.7)	1/15 (6.7)
Difference (95% CI)	31.4 (14.1 to 48.6)		30.1 (11.6 to 48.5)	
P value [b]	0.002		0.028	
Non-surgical closure of FTMH at 6 months [a]				
n/N (%)	26/57 (45.6)	5/32 (15.6)	17/49 (34.7)	3/15 (20.0)
Difference (95% CI)	30.0 (11.9 to 48.0)		14.7 (–9.5 to 38.9)	
P value [b]	0.005		0.354	
Proportion of patients receiving vitrectomy in study eye at day 28 [a]				
n (%)	1 (0.9)	3 (1.4)	0	1 (1.2)
Difference (95% CI)	0.4 (–2.0 to 2.8)		–1.2 (–3.6 to 1.2)	
P value	> 0.999		0.248	
Proportion of patients receiving vitrectomy in study eye at 6 months [a]				
n (%)	45 (20.5)	31 (29.0)	37 (15.1)	19 (23.5)
Difference (95% CI)	–8.4 (–18.5 to 1.7)		–8.4 (–18.6 to 1.9)	
P value [b]	0.096		0.091	

CI = confidence interval; FTMH = full-thickness macular hole; PVD = posterior vitreous detachment.
[a]Analyses were performed on the last observation carried forward (LOCF) data set.
[b]*P* value is based on the Wilcoxon rank-sum test, comparing change from baseline between-treatment groups.

3.6.7 Change from baseline in best-corrected visual acuity

Results for categorical changes (≥ 15 and ≥ 30 letters) in BCVA from baseline and mean BCVA letter scores from baseline are summarized in Table 13. The proportion of patients who had an improvement of 15 letters or more at 6 months was greater in the ocriplasmin group compared with placebo in TG-MV-007, with a between-group difference of 8.1% (95% CI, 2.3% to 13.9%). The between-group difference for patients achieving an improvement of 15 letters or more in BCVA at 6 months was not statistically significant in TG-MV-006. In both studies, no statistically significant differences were observed for improvement or worsening of 15 letters or more at day 28, worsening of 15 letters or more at 6 months, improvement of 30 letters or more, and worsening of 30 letters or more at day 28 and 6 months. Change in mean BCVA ETDRS letters scores at day 28 and 6 months were not statically significant.

TABLE 13: CHANGES IN VISUAL ACUITY — FULL ANALYSIS SET

	TG-MV-006		TG-MV-007	
	Ocriplasmin (N = 219)	Placebo (N = 107)	Ocriplasmin (N = 245)	Placebo (N = 81)
Improvement in BCVA (≥ 15 letters) from baseline at day 28 [a]				
n (%)	17 (7.8)	4 (3.7)	11 (4.5)	3 (3.8)
Difference (95% CI)	4.0 (–1.0 to 9.1)		0.7 (–4.2 to 5.6)	
P value	0.230		> 0.999	
Improvement in BCVA (≥ 15 letters) from baseline at 6 months [a]				
n (%)	28 (12.8)	9 (8.4)	29 (11.8)	3 (3.8)
Difference (95% CI)	4.4 (–2.5 to 11.2)		8.1 (2.3 to 13.9)	
P value	0.270		0.049	
Worsening in BCVA (≥ 15 letters) from baseline at day 28 [a]				
n (%)	5 (2.3)	1 (0.9)	2 (0.8)	0
Difference (95% CI)	1.3 (–1.3 to 4.0)		0.8 (–0.3 to 1.9)	
P value	0.668		> 0.999	
Worsening in BCVA (≥ 15 letters) from baseline at 6 months [a]				
n (%)	16 (7.3)	2 (1.9)	10 (4.1)	4 (5.0)
Difference (95% CI)	5.4 (1.1 to 9.7)		-0.9 (–6.3 to 4.5)	
P value	0.067		0.753	
Worsening in BCVA (≥ 30 letters) from baseline at day 28 [a]				
n (%)	3 (1.4)	0	0	0
Difference (95% CI)	1.4 (–0.2 to 2.9)		0.0 (0.0 to 0.0)	
P value	0.554		-	
Worsening in BCVA (≥ 30 letters) from baseline at 6 months [a]				
n (%)	3 (1.4)	1 (0.9)	3 (1.2)	1 (1.3)
Difference (95% CI)	0.4 (–2.0 to 2.8)		–0.0 (–2.8 to 2.8)	
P value	> 0.999		> 0.999	
Change in BCVA Letter Scores from baseline at day 28 [a]				
Mean (SD)	2.6 (10.58)	2.6 (6.50)	2.6 (6.64)	2.8 (6.13)
P value [b]	0.788		0.699	
Median	3.0	2.0	2.0	2.0
Change in BCVA Letter Scores from baseline at 6 months [a]				
Mean (SD)	3.5 (12.30)	2.8 (9.89)	3.6 (10.35)	2.1 (9.49)
P value [b]	0.315		0.380	
Median	3.0	2.0	3.0	2.0

BCVA = best-corrected visual acuity; CI = confidence interval.
[a] Analyses were performed on last observation carried forward (LOCF) data set.
[b] *P* value is based on the Wilcoxon rank-sum test, comparing change from baseline between-treatment groups.

3.7 Harms

Only those harms identified in the review protocol are reported below (2.2.1, Protocol). *See* Appendix 4: DETAILED OUTCOME DATA *for detailed harms data.*

3.7.1 Adverse Events

In both studies, the overall incidence of AEs was greater among the ocriplasmin groups compared with placebo. A total of 42.3% and 38.0% of patients in the ocriplasmin groups experienced at least one treatment-emergent AE compared with 19.8% and 23.5% of patients receiving placebo in TG-MV-006 and TG-MV-007 respectively. The most common AEs included vitreous floaters, photopsia, vision loss, and eye pain (Table 14).

3.7.2 Serious Adverse Events

The incidence of SAEs was similar between ocriplasmin and placebo in TG-MV-006 (14.5% versus 12.3% respectively) and in TG-MV-007 (13.5 % versus 13.6% respectively). In general, the incidence of individual SAEs was low. The most common SAEs were macular hole, maculopathy, retinal detachment, vitreous adhesion, and reduction in visual acuity (Table 14).

3.7.3 Withdrawals Due to Adverse Events

Table 14 summarizes withdrawals due to adverse events (WDAEs). Overall incidence of WDAEs was low and similar between the ocriplasmin and placebo groups (0.9% versus 1.9% in TG-MV-006 respectively). In TG-MV-007, the proportion of patients experiencing WDAEs was 0.8% in the ocriplasmin group, with no WDAEs occurring in the placebo group.

3.7.4 Mortality

There were three deaths (1.4%) in the ocriplasmin group in TG-MV-006 and one death (0.4%) in the ocriplasmin groups in TG-MV-007. There were no deaths in the placebo groups. According to the investigators, the deaths were not considered related to the study drug according to the investigators (Table 14).

3.7.5 Notable Harms

In discussion with the clinical expert involved in the review, the CDR reviewers identified a priori several AEs of interest: lens subluxation, cataracts, eye infection, retinal detachment, vitritis, conjunctival hemorrhage, retinal hemorrhage, and vitreous hemorrhage. There were no events of lens subluxation reported in either study. The incidence of AEs was generally low and similar between the ocriplasmin and placebo groups in TG-MV-006 and TG-MV-007 respectively: cataracts (2.7% versus 4.7% and 2.4% versus 3.7%); retinal detachment (1.4% versus 1.9% and 0.4% versus 1.2%); retinal hemorrhage (1.8% versus 1.9% and 1.6% versus 2.5%); and vitreous hemorrhage (0.9% versus 1.9% and 0.8% versus 1.2%). Conjunctival hemorrhage (15.5% versus 13.2% and 13.9% versus 12.3%) was also similar between ocriplasmin and placebo in TG-MV-006 and TG-MV-007 respectively. There was one eye infection (0.9%) in the placebo group of TG-MV-006, one eye infection (0.4%) in the ocriplasmin group of TG-MV-007, and one event of vitritis (0.4%) in the ocriplasmin group of TG-MV-007.

TABLE 14: SUMMARY OF HARMS

Harms[a]	TG-MV-006		TG-MV-007	
	Ocriplasmin (N = 220)	Placebo (N = 106)	Ocriplasmin (N = 245)	Placebo (N = 81)
AEs				
Patients with > 0 AEs, n (%)	93 (42.3)	21 (19.8)	93 (38.0)	19 (23.5)
Most common AEs[b]				
Vitreous floaters	33 (15.0)	5 (4.7)	31 (12.7)	4 (4.9)
Photopsia	27 (12.3)	2 (1.9)	15 (6.1)	1 (1.2)
Vision loss	15 (6.8)	0	5 (2.0)	1 (1.2)
Eye pain	8 (3.6)	0	13 (5.3)	3 (3.7)
SAEs				
Patients with > 0 SAEs, n (%)	32 (14.5)	13 (12.3)	33 (13.5)	11 (13.6)
Most common SAEs				
Macular hole	15 (6.8)	11 (10.4)	15 (6.1)	6 (7.4)
Maculopathy	3 (1.4)	0	5 (2.0)	1 (1.2)
Retinal detachment	2 (0.9)	2 (1.9)	1 (0.4)	1 (1.2)
Vitreous adhesions	2 (0.9)	0	3 (1.2)	2 (2.5)
Visual acuity reduced	1 (0.5)	0	1 (0.4)	0
WDAEs				
WDAEs, n (%)	2 (0.9)	2 (1.9)	2 (0.8)	0
Deaths				
Number of deaths, n (%)	3 (1.4)	0	1 (0.4)	0
Notable harms				
Lens subluxation	0	0	0	0
Cataracts	6 (2.7)	5 (4.7)	6 (2.4)	3 (3.7)
Eye infection	0	1 (0.9)	1 (0.4)	0
Retinal detachment	3 (1.4)	2 (1.9)	1 (0.4)	1 (1.2)
Vitritis	0	0	1 (0.4)	0
Conjunctival hemorrhage	34 (15.5)	14 (13.2)	34 (13.9)	10 (12.3)
Retinal hemorrhage	4 (1.8)	2 (1.9)	4 (1.6)	2 (2.5)
Vitreous hemorrhage	2 (0.9)	2 (1.9)	2 (0.8)	1 (1.2)

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a]Outcomes identified as important to the review (see Table 2 for review protocol).
[b]Frequency ≥ 2%.

4. DISCUSSION

4.1 Summary of Available Evidence

Three published, manufacturer-sponsored double-masked RCTs were included in this systematic review: TG-MV-004,[6,35] TG-MV-006,[4,19] and TG-MV-007.[5,19] Given the limitations of study TG-MV-004, only data from TG-MV-006 and TG-MV-007 were presented; they served as the primary evidence for the efficacy and safety of ocriplasmin as compared with placebo for sVMA in this report (See 3.2Included Studies). Patients in both TG-MV-006 (N = 326) and TG-MV-007 (N = 326) received either a single intravitreal injection of ocriplasmin 125 mcg or a placebo injection. No trials comparing ocriplasmin to "watchful waiting" or vitrectomy alone were found in the scientific literature.

Both studies had appropriate randomization and allocation concealment strategies, with similar treatment groups at baseline. Overall, withdrawal rates were generally low (≤ 9%) and similar across treatment groups, except in the ocriplasmin group in TG-MV-007, where the proportion was approximately half that of the other treatment groups. Most discontinuations were due to patients withdrawing consent or being lost to follow-up.

Although a placebo injection was chosen as the comparator in both studies, a sham injection would have provided a better comparison in regard to the natural history of the disease process; there is a possibility that the placebo injection may have induced a treatment response as manipulation of the vitreous by intravitreal injection can cause a PVD.[39,40] Furthermore, the use of a placebo may increase the risk of eye infection in the recipient eye.

4.2 Interpretation of Results

4.2.1 Efficacy

Ocriplasmin is the first pharmacological treatment option for VMA. Other treatment options for VMA include "watchful waiting" and vitrectomy, although no head-to-head trials comparing ocriplasmin with these other options have been performed.

The non-invasive technique of OCT is typically used for measuring VMA as it is capable of displaying spatial relationships between the posterior vitreous and the inner retina.[41] The clinical expert involved in the review stated that OCT is the only definitive measure of vitreal attachment, and felt that both instruments used in TG-MV-006 and TG-MV-007 (Stratus OCT and spectral domain OCT) were appropriate for assessing VMA.

The primary efficacy outcome in TG-MV-006 and TG-MV-007 was the proportion of patients with non-surgical resolution of VMA. In both studies, ocriplasmin was statistically superior to placebo after 28 days of treatment, as well as at 3 months and 6 months. The rates of VMA resolution in those treated with ocriplasmin were similar in both studies, although the rate among placebo-treated patients in TG-MV-006 was approximately twice that observed in TG-MV-007. Although unclear, a potential reason for differences between the placebo groups in the two studies could be the somewhat higher proportion of patients with VMA diameter ≤ 1500 mcm at baseline in TG-MV-006. As a result, the between-group difference of ocriplasmin versus placebo for the resolution of VMA was slightly greater in TG-MV-007 at day 28, and at 3 months and 6 months. Results suggest that ocriplasmin was consistently statistically superior to placebo at day 28, 3 months, and 6 months for resolution of VMA, yet < 30% of patients responded to the ocriplasmin. Hence, approximately 70% of patients treated with ocriplasmin did not achieve VMA resolution. Whether a certain subgroup of responders exists is

unclear. VMA resolution was statistically significantly in favour of ocriplasmin over placebo at day 28 among patients with FTMH at baseline in TG-MV-007, but not in TG-MV-006. Ocriplasmin was statistically superior to placebo for resolving VMA in older patients (≥ 65 years) at day 28, but not in younger patients (< 65 years). However, subgroup results from both studies should be interpreted with caution for the following reasons: they were based on a statistical significance level of 0.05 without adjusting for multiplicity; analysis for resolution of VMA at day 28 by age group was performed post-hoc (not pre-specified in the statistical plan); and no tests for interaction were conducted in the subgroup analyses.

According to the clinical expert involved in the review, the time point of 28 days post-injection is sufficient, as the biological effect of the drug would be expected to be visible by that time. The results of the primary analysis were consistent with the mFAS and PP populations. In addition, a sensitivity analysis confirmed that the LOCF approach to adjusting for missing observations did not affect the results of the primary end point (Table 18).

Baseline BCVA is typically an important cofactor to consider in studies of treatments for ocular conditions (e.g., AMD). Measurement of BCVA using ETDRS charts has been shown to be reliable for identifying changes in VA of 2 lines (10 letters) or more.[42] A loss or gain of 3 lines (15 letters) is considered a clinically relevant degree of change that is commonly used in clinical trials.[43] However, according to the clinical expert involved in the review, the measurement of BCVA for VMA may not be clinically relevant, as patients' VA typically plateaus and does not demonstrate a stepwise progression. It is only until patients experience MH where VA starts to worsen to a clinically meaningful extent. Subgroup analyses results for VMA resolution for different baseline BCVA categories in both trials did not reveal any significant differences among patients with better VA compared with those with poorer VA at baseline (Table 19).

Posterior vitreous detachment, as determined by masked CRC using B-scan ultrasounds, was a secondary end point in the two studies. B-scan ultrasounds were performed by a certified echographer. Ocriplasmin was statistically superior to placebo in achieving total PVD at day 28 in both studies. The ocriplasmin and placebo event rates were greater in TG-MV-006 when compared with TG-MV-007. It was not clear why there were differences in event rates between studies. Formal statistical testing for total PVD at day 28 was evaluated only if statistical significance ($P < 0.05$) was achieved in the analysis of the primary efficacy end point for at least two of the three predefined study populations. The remaining secondary end points were not adjusted for multiplicity and were considered supportive or exploratory. Without a pre-specified statistical plan to determine the statistical significance of these end points, results for non-surgical closure of FTMH, patients receiving vitrectomy, improvement or worsening of BCVA, and changes in BCVA letter scores from baseline were inconclusive at day 28 and 6 months.

Outcomes reported by patient groups as important and having an impact on quality of life were vision loss and avoidance of vitrectomy (Appendix 1: PATIENT INPUT SUMMARY). The prevention of blindness was a key efficacy outcome for the systematic review, but was not evaluated in the RCTs. BCVA was assessed, but as mentioned previously, this does not represent an ideal marker of patients' sight in VMA until MH occurs. In both studies, the results for BCVA — improvement in BCVA (≥ 15 letters) or worsening in BCVA (≥ 15 and ≥ 30 letters) at day 28 and 6 months — were not statistically significant. The proportion of patients receiving vitrectomy after 6 months was non-statistically smaller with ocriplasmin versus placebo in both studies. The actual effect of ocriplasmin in avoiding vitrectomy is therefore uncertain, because the between-group differences in the proportion of patients receiving

vitrectomy was not statistically significant. There is potential patient selection bias given that the decision to perform vitrectomy was at the discretion of patients and investigators.
HRQoL was measured by both the general health subscale and the composite score of the VFQ-25. Ocriplasmin demonstrated an improvement in HRQoL at 6 months versus placebo, but the difference was only statistically significant in TG-MV-007; however, the change from baseline was smaller than the threshold typically considered as clinically meaningful in the assessment of the worse-seeing eye (WSE) (Appendix V).[44] HRQoL was considered a secondary end point in both pivotal studies; thus, results should be interpreted with caution, as this outcome was likely not powered accordingly.

MH, a defect in retinal tissue located at the centre of the macula, is a condition that may be caused by VMA.[21] It is believed that the formation of MH is a result of perifoveal vitreous separation creating tractional forces to the fovea.[21] The clinical expert felt that patients presenting with stage I MHs or stage II MHs are an important subgroup for the treatment of VMA. Non-surgical closure of FTMH was achieved in a statistically significantly larger percentage of patients receiving ocriplasmin versus placebo after 28 days in both studies; however, the significant difference between groups did not persist until 6 months in TG-MV-007. Similar inconsistency was observed in subgroup analyses; as mentioned previously, ocriplasmin was statistically superior to placebo for VMA resolution at day 28 among patients with FTMH at baseline in TG-MV-007, but not in TG-MV-006. Ocriplasmin was statistically superior to placebo at day 28 for VMA resolution among those without FTMH at baseline in both studies.

Long-term efficacy results for ocriplasmin were limited, with only one extension study (TG-MV-012)[45] assessing 24 patients approximately two years after the completion of TG-MV-006 and TG-MV-007 (Appendix 6: SUMMARY OF FOLLOW-UP STUDY TG-MV-012). Overall, efficacy results were similar to what was observed in the same group of patients at the end of the double-masked studies. After excluding post-vitrectomy data, only one additional patient in TG-MV-012 (from the ocriplasmin group) had complete resolution of VMA.

4.2.2 Harms

The overall incidence of AEs in both studies was greater when patients were treated with ocriplasmin, with an AE rate approximately twice that observed with placebo. Although AEs were consistent with known ocular AEs associated with intraocular injections,[3] the higher incidence of AEs among patients treated with ocriplasmin suggests a drug-related effect, although is not conclusive as neither study was designed to determine causation with respect to AEs. Ocriplasmin appeared to affect the retina, as events of vitreous floaters and photopsia occurred far more frequently in the ocriplasmin groups. However, the clinical expert involved in the review confirmed that both vitreous floaters and photopsia are common AEs seen during the treatment of VMA, and that photopsia in particular may occur with acute vitreous separation. Thus, the higher proportion of AEs in the ocriplasmin groups is likely a reflection of the natural treatment process for VMA. The overall incidence of SAEs, WDAEs, and notable harms did not clearly differ between the ocriplasmin and placebo groups in both studies. Occurrences of notable AEs were relatively rare, with the exception of conjunctival hemorrhage, which is common with intravitreal injections.[3]

According to the clinical expert involved in the review, the threshold for performing vitrectomies for different ophthalmologic conditions has increased in recent years due to its potential harms and post-operative AEs. There appears to be an increased incidence of AEs when performing vitrectomies on younger patients, in part due to increased adherence of the vitreous to the retina. Also, if vitreous scaffolding is left behind, further retinal problems could develop. The clinical expert also stated that

adults with diabetic macular edema appear to have more favourable outcomes post-vitrectomy due to the preoperative vitreal separation. Treatment of VMA with ocriplasmin might pose a smaller risk of AEs including cataract formation, retinal detachment, permanent retinal damage, vitritis, or endophthalmitis compared with vitrectomy; however, this is speculative until head-to-head or formal indirect comparisons between ocriplasmin and vitrectomy are done.

The long-term safety profile from TG-MV-012[45] was generally similar to that observed in the same group of patients at the end of TG-MV-006 and TG-MV-007 (Appendix 6: SUMMARY OF FOLLOW-UP STUDY TG-MV-012). A total of six of the nine patients in the ocriplasmin group and one of the five patients in the placebo group experienced at least one newly reported ocular AE in the study eye at the TG-MV-012 follow-up visit or an ongoing AE at the end of the TG-MV-006 and TG-MV-007 studies. There were no deaths, new SAEs, or unexpected AEs at the end of TG-MV-012.

5. CONCLUSIONS

Two multi-centre, randomized, parallel group, double-masked, placebo-controlled studies comparing a single 125 mcg intravitreal injection of ocriplasmin with a placebo injection for the treatment of VMA were reviewed. Overall, treatment with ocriplasmin was superior to placebo for the resolution of VMA and total PVD. Although there was a greater overall incidence of AEs for patients treated with ocriplasmin compared with placebo, many events were transient and were possibly related to the procedure instead of the drug itself. There is uncertainty regarding the efficacy of ocriplasmin for the treatment of FTMHs, avoidance of vitrectomy, and improvement in BCVA. Moreover, no data were available on whether ocriplasmin prevents VMA-related vision loss or blindness, which are key outcomes according to patient groups.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH staff based on the input provided by patient groups. It has not been systematically reviewed.

Brief Description of Patient Group(s) Supplying Input

The Canadian Council of the Blind (CCB) is a registered charity whose officers and directors are all blind or vision impaired, giving them a unique sensitivity to the needs of the community with vision loss. The objectives of the CCB are: to promote the well-being of individuals who are blind or vision impaired through education, profitable employment, social association, creating closer relationships between blind and sighted friends; to maintain a nationwide organization of people who are blind and vision impaired throughout Canada; and to promote measures for the conservation of sight and the prevention of blindness. The CCB declares sponsorship from Novartis for "White Cane Week" activities and for an educational forum. It declares no conflict in the preparation of their submission.

The Canadian National Institute for the Blind (CNIB) is a registered charity providing community-based support to ensure that blind and partially sighted Canadians have the confidence, skills, and opportunities to fully participate in life. To do this, the CNIB provides programs and services that: help overcome the challenges of sight loss, increase independence, advocate for equal access and an inclusive society; and strive to reduce vision loss by promoting research and training into effective prevention, diagnosis, treatment, and rehabilitation of eye disease. Six per cent of the 10,000 new clients CNIB sees each year have diabetic retinopathy, while over 40% have some form of AMD, both of which may be associated with VMA. In 2012, CNIB provided vision rehabilitation services to 253 new clients with macular holes, presumably people whose vision was not improved by available treatments. In the same year, a further 614 new clients came to CNIB as a result of retinal detachments. It is not known how many of these were the result of surgery. It is estimated that 1.2% to 6.6% of people undergoing vitrectomy experience retinal detachment, with 15% experiencing retinal tears. The CNIB declared occasional, relatively small, unrestricted educational grants from Alcon, Novartis, and Pfizer, but declared no conflict in the preparation of its submission.

Condition and Current Therapy-Related Information

Information in the submissions was gathered through printed sources, online research, personal experience and knowledge, and one-to-one conversations with people who have been treated for VMA.

VMA can lead to macular holes and serious vision loss. The effect of loss of sight on quality of life has been explored in a number of large epidemiological studies. Vision loss can result in a loss of independence, employment and income, the inability to drive, hardship on family, social isolation, depression, and falls or other injuries. Adults with vision loss have twice the risk of a serious fall, triple the risk of depression, and four times the risk of hip fracture compared with an age-matched sighted cohort. Almost half of adults with vision loss have gross annual incomes of $20,000 or less, and only 35% of those of working age are employed.

A United States study estimated the incidence of macular holes at 7.8 people per 100,000 per year, which if applied to the Canadian population yields an estimated 2,700 people with macular holes per year.

The current therapy for VMA is surgical vitrectomy. This treatment is expensive for the health care system, but can be effective if all post-operative care guidelines are followed and there are no complications. However, guidelines include the patient lying face down for at least 7 days, 24-hours a day. Patients must have a live-in caregiver for the full amount of this time, have or procure access to a specialty mattress, and take time off of work or other activities, all of which have financial impacts. Wait times for the surgery can be extensive, and it is generally only offered in major centres, requiring the patients and their caregivers to travel both for the surgery itself and for pre- and post-operative appointments, which may be onerous and expensive if the distance is considerable. As patients with VMA are often elderly, they may have comorbid conditions, which can complicate the surgery or make lying face down impossible. Patients who are unable to remain face down for the full amount of time can experience permanent vision loss.

Caregivers who live with a patient often need to take time off from work, thereby incurring a loss of income. Before surgery, patients may have blurry vision and require assistance with daily routines while they wait. After surgery, patients require full-time care for at least one week, as they are unable to move; many loved ones may have neither the physical ability nor the knowledge to provide the care needed, nor the financial ability to cover the cost of hiring assistance. Should the recovery go poorly and result in vision loss, caregivers may be required to assist the patient on a permanent basis, which may have huge social and economic impacts for the whole family.

Related Information About the Drug Being Reviewed

No patients in either submission reported direct experience with ocriplasmin. As ocriplasmin is a single injection rather than a surgical procedure, patients can expect less waiting time before treatment (reducing reliance on caregivers) and a lower risk of injury caused by blurry vision. Other potential benefits include less hospitalization, fewer doctor visits, less anesthesia (of significant concern for older people), fewer side effects, less need for travel and associated economic burdens, shorter recovery times, easier recuperation, less fear of surgery, greater quality of life, and a faster return to work or other activities.

Additionally, patients receiving ocriplasmin would not have to lie face down for a week post-treatment, resulting in reduced reliance on caregivers, less difficulty with post-treatment management particularly for patients with comorbid conditions, and reduced likelihood of vision loss due to an inability to comply with difficult post-operative instructions. This reduced risk of vision loss would result in fewer patients requiring rehabilitation related to vision loss, greater quality of life due to improved vision, fewer falls and fractures, less depression, more independence, and a greater ability to be active.

While no patients reported first-hand experience with ocriplasmin, patients must currently tolerate the side effects, risks of AEs, and inconveniences associated with surgery, and would therefore be likely to tolerate similar or reduced risks and side effects in new treatments, particularly if they are short-lived.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 10, 2013
Alerts:	Weekly search updates until November 20, 2013
Study Types:	No search filters were applied
Limits:	No date or language limits were used. Conference abstracts were excluded.

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	*ocriplasmin/ or *microplasmin/
2	(jetrea* or ocriplasmin* or microplasmin* or 7V6HE3DM5A*).ti,ab.
3	1 or 2
4	3 use oemezd
5	conference abstract.pt.
6	4 not 5
7	(ocriplasmin* or Jetrea* or microplasmin* or 7V6HE3DM5A*).ti,ot,ab,sh,rn,hw,nm.
8	1048016-09-6.rn,nm.
9	7 or 8
10	9 use pmez
11	6 or 10
12	remove duplicates from 11

Grey Literature

Dates for Search:	July 2013
Keywords:	Jetrea; ocriplasmin; vitreomacular adhesion
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Benz et al. 2010[46]	Inappropriate population

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 15: VITREOMACULAR ADHESION RESOLUTION AT DAY 28 FOR TG-MV-006 AND TG-MV-007 — MODIFIED FULL ANALYSIS AND PER-PROTOCOL SETS

VMA Resolution at Day 28	TG-MV-006		TG-MV-007	
	Ocriplasmin (N = 219)	Placebo (N = 107)	Ocriplasmin (N = 245)	Placebo (N = 81)
Modified Full Analysis Set[a]				
n/N (%)	61/207 (29.5)	14/99 (14.1)	62/233 (26.6)	5/77 (6.5)
Difference (95% CI)	15.3 (6.1 to 24.6)		20.1 (12.2 to 28.0)	
P value	0.004		< 0.001	
Per-Protocol Set[a]				
n/N (%)	58/189 (30.7)	14/94 (14.9)	56/214 (26.2)	4/71 (5.6)
Difference (95% CI)	15.8 (6.0 to 25.5)		20.5 (12.6 to 28.5)	
P value	0.004		< 0.001	

CI = confidence interval; VMA = vitreomacular adhesion.
[a]Analyses were performed on the last observation carried forward (LOCF) data set. The between-group differences are based on the percentage of successes.

TABLE 16: OTHER EFFICACY OUTCOMES — MODIFIED FULL ANALYSIS SET

Outcome	TG-MV-006		TG-MV-007	
	Ocriplasmin (N = 207)	Placebo (N = 99)	Ocriplasmin (N = 233)	Placebo (N = 77)
Total PVD at day 28[a]				
n (%)	30 (14.5)	6 (6.1)	24 (10.3)	0
Difference (95% CI)	8.4 (1.7 to 15.1)		10.3 (6.4 to 14.2)	
P value	0.037		0.001	
Non-surgical closure of FTMH at day 28 [a]				
n/N (%)	24/53 (45.3)	4/28 (14.3)	18/44 (40.9)	1/14 (7.1)
Difference (95% CI)	31.0 (12.4 to 49.6)		33.8 (13.9 to 53.6)	
P value	0.007		0.023	
Non-surgical closure of FTMH at 6 months [a]				
n/N (%)	25/53 (47.2)	5/28 (17.9)	17/44 (38.6)	2/14 (14.3)
Difference (95% CI)	29.3 (9.8 to 48.9)		24.4 (1.0 to 47.7)	
P value	0.015		0.113	
Proportion of patients receiving vitrectomy in study eye at day 28 [a]				
n (%)	1 (0.5)	1 (1.0)	NA	
Difference (95% CI)	–0.5 (–2.7 to 1.7)			
P value	0.543			
Proportion of patients receiving vitrectomy in study eye at 6 months [a]				
n (%)	41 (19.8)	28 (28.3)	35 (15.0)	18 (23.4)
Difference (95% CI)	–8.5 (–18.9 to 1.9)		–8.4 (–18.9 to 2.2)	
P value	0.109		0.115	
Change in BCVA Letter Scores from baseline at day 28 [a]				
Mean (SD)	3.0 (9.41)	2.6 (6.69)	2.6 (6.70)	2.5 (5.92)
P value[b]	0.742		0.985	
Median	3.0	2.0	2.0	2.0
Change in BCVA Letter Scores from baseline at 6 months [a]				
Mean (SD)	3.9 (11.16)	3.5 (8.10)	3.8 (10.35)	1.9 (9.61)
P value[b]	0.422		0.269	
Median	3.0	3.0	3.0	2.0

BCVA = best-corrected visual acuity; CI = confidence interval; PVD = posterior vitreous detachment; SD = standard deviation.
[a]Analyses were performed on the last observation carried forward (LOCF) data set. Between-group differences are based on the percentage of successes.
[b]*P* value is based on the Wilcoxon rank-sum test, comparing change from baseline between-treatment groups.

TABLE 17: OTHER EFFICACY OUTCOMES — PER-PROTOCOL SET

Outcome	TG-MV-006		TG-MV-007	
	Ocriplasmin (N = 189)	Placebo (N = 94)	Ocriplasmin (N = 214)	Placebo (N = 71)
Total PVD at day 28 [a]				
n (%)	28 (14.8)	6 (6.4)	24 (11.2)	0
Difference (95% CI)	8.4 (1.4 to 15.5)		11.2 (7.0 to 15.4)	
P value[b]	0.051		< 0.001	
Non–surgical closure of FTMH at day 28 [a]				
n/N (%)	24/46 (52.2)	4/28 (15.4)	18/36 (50.0)	1/12 (8.3)
Difference (95% CI)	36.8 (16.8 to 56.8)		41.7 (19.1 to 64.3)	
P value[b]	0.002		0.016	
Non–surgical closure of FTMH at 6 months [a]				
n/N (%)	25/46(54.3)	5/26 (19.2)	17/36 (47.2)	2/12 (16.7)
Difference (95% CI)	35.1 (14.2 to 56.0)		30.6 (3.9 to 57.2)	
P value[b]	0.006		0.091	
Proportion of patients receiving vitrectomy in study eye at day 28 [a]				
n (%)	0	0	NA	
Difference (95% CI)	0			
P value	NA			
Proportion of patients receiving vitrectomy in study eye at 6 months [a]				
n (%)	34 (18.0)	26 (27.7)	29 (13.6)	17 (23.9)
Difference (95% CI)	–9.7 (–20.2 to 0.9)		–10.4 (–21.3 to 0.5)	
P value[b]	0.066		0.061	
Change in BCVA letter scores from baseline at day 28 [a]				
Mean (SD)	3.3 (8.73)	2.7 (6.80)	2.7 (6.70)	2.5 (5.93)
P value[c]	0.852		0.984	
Median	3.0	2.0	2.0	2.0
Change in BCVA letter scores from baseline at 6 months [a]				
Mean (SD)	3.9 (11.44)	3.5 (8.21)	3.8 (10.19)	1.8 (9.94)
P value[c]	0.412		0.260	
Median	3.0	3.0	4.0	2.5

BCVA = best-corrected visual acuity; CI = confidence interval; FTMH = full-thickness macular hole; PVD = posterior vitreous detachment; SD = standard deviation.

[a]Analyses were performed on last observation carried forward (LOCF) data set. The between-group differences are based on the percentage of successes.

[b]*P* value is based on Fisher's exact test comparing placebo with ocriplasmin.

[c]*P* value is based on the Wilcoxon rank-sum test, comparing change from baseline between-treatment groups.

TABLE 18: VITREOMACULAR ADHESION RESOLUTION AND POSTERIOR VITREOUS DETACHMENT AT DAY 28 FOR TG-MV-006 AND TG-MV-007 — SENSITIVITY ANALYSIS

Outcome[a]	TG-MV-006		TG-MV-007	
	Ocriplasmin (N = 219)	Placebo (N = 107)	Ocriplasmin (N = 245)	Placebo (N = 81)
VMA resolution at day 28				
Difference (95% CI)	13.5 (4.3 to 22.7)		19.2 (10.5 to 27.8)	
P value	0.004		< 0.001	
Total posterior PVD at day 28				
Difference (95% CI)	12.2 (4.2 to 20.1)		8.8 (2.1 to 15.4)	
P value	0.003		0.010	

CI = confidence interval; PVD = posterior vitreous detachment; VMA = vitreomacular adhesion.
[a]Sensitivity analysis using multiple imputation method for missing data. Between-group differences are based on the percentage of successes.

TABLE 19: NON-SURGICAL IMPROVEMENT OF AT LEAST THREE LINES FROM BASELINE IN BCVA AT 6 MONTHS BY BASELINE BCVA SUBGROUP — FULL ANALYSIS SET

	TG-MV-006		TG-MV-007	
	Ocriplasmin (N = 219)	Placebo (N = 107)	Ocriplasmin (N = 245)	Placebo (N = 81)
Subgroup				
Overall				
n/N (%)	23/219 (10.5)	7/107 (6.5)	29/245 (11.8)	3/81 (3.8)
Difference (95% CI)	4.0 (–2.2 to 10.2)		8.1 (2.3 to 13.9)	
P value[a]	0.310		0.049	
≤ 60 letters				
n/N (%)	17/43 (39.5)	4/22 (18.2)	23/86 (26.7)	1/23 (4.3)
Difference (95% CI)	21.4 (–0.4 to 43.1)		22.4 (9.9 to 34.9)	
P value[a]	0.099		0.023	
> 60 letters				
n/N (%)	6/131 (4.6)	3/54 (5.6)	6/159 (3.8)	2/57 (3.5)
Difference (95% CI)	–1.0 (–8.1 to 6.1)		0.3 (–5.4 to 5.9)	
P value[a]	0.722		> 0.999	
≤ 75 letters				
n/N (%)	23/145 (15.9)	7/59 (11.9)	28/201 (13.9)	3/69 (4.3)
Difference (95% CI)	4.0 (–6.2 to 14.2)		9.6 (2.8 to 16.4)	
P value[a]	0.521		0.030	
> 75 letters				
n/N (%)	0/29 (0)	0/17 (0)	1/44 (2.3)	0/11 (0)
Difference (95% CI)	0.0 (0.0 to 0.00)		2.3 (–2.1 to 6.7)	
P value[a]	NA		> 0.999	

BCVA = best-corrected visual acuity; CI = confidence interval; NA = not applicable.
[a]*P* value is from Fisher's exact test, comparing placebo and ocriplasmin. The between-group differences are based on the percentage of successes. Non-surgical improvement is defined as values observed at month six among patients who did not receive vitrectomy.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Issues considered in this section are provided as supporting information. The information has not been systematically reviewed.

Objective

To review the validity of efficacy measures used in the Jetrea clinical studies.

Findings

Optical Coherence Tomography (OCT)

OCT is a fast, non-invasive technique that may be used to create cross-sectional maps of the retinal structures and to quantify retinal thickness in patients with macular edema.[47] OCT directs a laser-generated, infrared light beam onto the retina and records the light reflected from interfaces between materials with different refractive indices, and from materials that scatter light. The latest generation machines (OCT3) are able to differentiate three reflecting layers thought to be the vitreous/retina, inner/outer photoreceptor segments, and the retinal pigment epithelium/choriocapillaris interfaces. Ultra–high-resolution machines can differentiate a fourth layer. During the OCT scan, a series of intersecting, radial cross-sections of the retina are measured. Resolution depends on the software as well as the hardware used, and is better around the central axis than the lateral areas.[47,48]

Repeatability and reproducibility of measurements depend on a number of factors including retinal pathology, retinal region, region size, OCT model, equipment settings, manual or automated analysis, and operator experience.[47] To assess the reproducibility of OCT in vitreoretinal disorders, DeCroos et al. examined vitreoretinal interface findings in patients who had VMA with or without MH being treated with ocriplasmin.[41] The relationship among optic nerve, fovea, and retinal VMA was acquired using standardized OCT scans. The scans were able to reproducibly identify various pathologic features (VMA, FTMH) and the presence of epiretinal membrane, and also enable the categorization of vitreous morphologies (vitreous adhesion width). In addition, the team-based grading approach, using primary readers and a main senior reader to resolve any discrepancies, further enhanced the reproducibility and effectiveness of diagnosing and identifying resolution of VMA and MH upon administration of ocriplasmin. The percentage agreements in this analysis were 97%, 92%, 95%, and 82% for VMA, vitreous adhesion width, FTMH, and epiretinal membrane respectively. Hence, the combination of the standardized OCT scans and a team-based grading approach was effective in reproducibly being able to diagnose and identify vitreous pathologies and morphologies.[41]

Measuring Visual Acuity

The Snellen eye chart is a commonly employed, well-recognized test of VA in clinical practice.[49,50] The chart presents a series of letters of decreasing size, with an increasing number of letters on subsequent lines. One or two mistakes per line are allowed and the smallest line that can be read corresponds to the VA. The resultant measure of VA is expressed as a Snellen fraction, in which the numerator indicates the distance at which the chart was read, and the denominator the distance at which a person may discern letters of a particular size. A larger denominator indicates worsening vision. For example a person with 20/100 vision can read letters at 20 feet that a person with 20/20 vision could read at 100 feet. Snellen acuity may also be expressed in metric units. As 20 feet is roughly equivalent to 6 metres, 20/20 vision may be expressed 6/6, and 20/100 as 6/30. Snellen fractions may be expressed as decimal acuity where 20/20 is expressed as 1.00 and 20/100 as 0.2. Further, the logarithm of the reciprocal Snellen fraction may be calculated to produce a linear scoring system suitable for statistical analysis; Snellen fractions of 20/20 and 20/100 would correspond to log scores of 0.0 and 0.7 respectively.

A number of limitations of the Snellen charts, especially for clinical research, have been identified.[49,50] Specifically, the use of letters with different difficulty scores (A and L are more easily discernable than B, E, and F) and an unequal number of letters on each line allowing (i.e., one or two errors per line allows different percentage errors depending on the line read).[50] In addition, the change in letter size between chart lines is not uniform, thus moving from line 20/25 to 20/20 represents a 20% improvement, compared with a 16% improvement when moving from line 20/30 to 20/25. Finally, differences in background luminance between charts due to ageing or different manufacturers, and dusty or ageing projector equipment reduce contrast and can result in unreliable measures of VA.[50]

In response to the above limitations, alternative charts have been developed that are more appropriate in research.[49,50] The Early Treatment Diabetic Retinopathy Study (ETDRS) charts are based on a design by Bailey and Lovie, and are commonly used in clinical research.[49,51-54] ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between letters and rows, for a total of 14 lines (70 letters). Charts are used in a standard light box with a background illumination of approximately 150 cd/m^2. Standard chart testing distance is 4 metres; however, shorter distances may be used when vision is severely impaired.[49,55] Letters range from 58.18 mm to 2.92 mm in height, corresponding to Snellen VA fractions of 20/200 to 20/10 respectively. Further letter sizes increase geometrically and equivalently in every line by a factor of 1.2589 (or 0.1 log unit) moving up the chart. Scoring for EDTRS charts is designed to produce a logarithmic score (logMAR) allowing for statistical analysis, in which individual letters score 0.02 log units. Holladay and Prager published the following formula to convert VA scores derived from a Bailey-Lovie-style chart read at 2 metres into a Snellen denominator, where X is the number of correctly read letters (see below).[56] Thus, reading all 70 letters on a Bailey-Lovie chart corresponds to a Snellen VA of 20/10.

$$\text{Snellen Acuity} = 20 \times 10^{[(55-X)/50]}$$

ETDRS charts may reliably identify changes in VA of 2 lines (10 letters) or more, but not changes of 1 line (5 letters) or less.[42] The reliability of ETDRS charts depends on the baseline VA. For eyes with acuity better than 20/100, a change in VA of ≥ 5 letters has > 90% probability of being a real change, while for eyes with acuity worse than 20/100, a change of ≥ 10 letters is required for the same reliability.[57] A loss or gain of 3 lines (15 letters) is considered a moderate degree of change and is commonly used as an outcome in clinical trials.[43] The United States Food and Drug Administration recommends a mean change of 15 letters or more on an ETDRS chart, or a statistically significant difference in the proportion of patients with ≥ 15 letter change in VA, as clinically relevant outcome measures in trials of interventions for macular edema.[58]

Relationship of visual acuity to visual function and vision-related quality of life

Measures of high-contrast visual distance acuity, using ETDRS charts, are commonly used to assess treatment outcomes in clinical studies. A loss of ≥ 3 lines (≥ 15 letters) on an ETDRS chart corresponds to a doubling of the visual angle and is considered moderate vision loss, while a loss of ≥ 6 lines (≥ 30 letters) corresponds to a quadrupling of the visual angle and is considered severe vision loss. However, VA is only one component contributing to overall visual function, the ability to perform everyday visual tasks (e.g., reading, recognizing faces, driving, and using the telephone). Overall visual function also depends upon variables such as contrast sensitivity, near vision, colour vision, and sensitivity to glare.[59] The various components of visual function will affect the performance of different vision-related tasks by varying degrees. For example, the use of distance acuity to measure the success of treatments for AMD is not optimal given that distance vision is usually two ETDRS lines better than reading vision,[43]

and difficulty with reading is a common complaint among persons with eye disease.[60] Rather, contrast sensitivity is a more important contributor to reading performance.[43,61]
Visual function and the resultant ability to perform everyday visual tasks have important implications for quality of life. Quality of life is very much a person-specific measure, which ultimately depends upon the value an individual places upon the ability to perform specific tasks. Quality-of-life instruments that do not include domains/tasks that are important to individuals will lack sensitivity to changes in their quality of life. Further the impact of vision loss on quality of life may vary greatly depending upon the vision status of the better-seeing eye. For these reasons, there are limitations in the use of quality of life instruments to compare treatment effectiveness.[59]

National Eye Institute Visual Function Questionnaire (NEI-VFQ)
The NEI-VFQwas developed as a means to measure vision-targeted quality of life. The original 51-item questionnaire was developed based on focus groups comprised of persons with a number of common eye conditions (e.g., age-related cataracts, AMD, and diabetic retinopathy), and thus may be used to assess quality of life for a broad range of eye conditions.[60] The original 51-item questionnaire comprises 12 subscales related to general vision, ocular pain, near vision, distance vision, social functioning, mental health, role functioning, dependency, driving, peripheral vision, colour vision, and expectations for future vision. In addition, the questionnaire includes one general health subscale.[62]

A shorter version of the original instrument, the VFQ-25, was subsequently developed, which retained the multidimensional nature of the original and is more practical and efficient to administer.[63] With the exception of the expectations for future vision, all the constructs listed above were retained in the shortened version, with a reduced number of items within each. Thus, the VFQ-25 includes 25 items relevant to 11 vision-related constructs, in addition to a single-item general health component. Responses for each item are converted to a 0 to 100 scale, with 0 representing the worst visual functioning and 100 the best visual functioning. Items within each construct, or subscale, are averaged to create 12 subscale scores; averaging the subscale scores produces the overall composite score. Different scoring approaches for the VFQ-25 have been proposed.[64] Rasch modelling is used to obtain measurements from categorical data. When comparing standard scoring to Rasch analysis and an algorithm to approximate Rasch scores, all methods were highly correlated.[64] However, standard scoring is subject to floor and ceiling effects whereby the ability of the least visually able is overestimated and the ability of the most visually able is underestimated.[64]

Determination of what constitutes a clinically meaningful change in the NEI-VFQ appears to be linked to its correlation with VA. A 3-line (15 letter) change in VA has been used as the outcome of interest in clinical trials, and corresponding changes in the NEI-VFQ are suggested as clinically meaningful end points. Specifically, for the study eye, which is typically the WSE, a 15-letter change in VA corresponds to a 4-point change in overall VFQ-25 score.[44] For the better-seeing eye (BSE), the clinically relevant difference for VFQ-25 scores based on a 3-line change is 7 to 8 for overall score. Other studies have shown similar estimated, clinically relevant differences.[65] The instrument showed weaker correlation or was not responsive to changes in the VA of the WSE.[66,67] This may have implications when evaluating patients with unilateral disease.

Both versions of the NEI-VFQ were reported to be valid and reliable measures of health-related quality of life among patients with a wide range of eye conditions.[62,63,67] All but two subscale scores (general health and ocular pain) have been shown to be responsive to changes in VA in the BSE.[66,67] However, more recent studies have indicated that the NEI-VFQ measures visual functioning, not quality of life.[68] Assessments of the psychometric validity of the NEI-VFQ-25 using Rasch scoring and principal

component analysis have identified issues with multi-dimensionality (measurement of more than one construct) and poor performance of the subscales.[68,69] The NEI-VFQ-25 subscales were found to have too few items and were unable to discriminate among the population under measurement, and thus were not valid.[68,69] Re-engineering the NEI-VFQ into two constructs (visual functioning and socio-emotional factors) and removing misfit items (e.g., pain around eyes, general health, and driving in difficult conditions) improved the psychometric validity of the scale in individuals with low vision.[68,69] Considering this recent evidence of multi-dimensionality, the validity of the single composite score of the NEI-VFQ may be questioned.

Summary

The validity of VA, reproducibility of OCT, NEI-VFQ-25, and the relationship between VA, visual function, and quality of life were reviewed.

OCT is a non-invasive technique used to create cross-sectional maps of the retinal structures and to quantify retinal thickness in patients with macular edema.[47] Intra- and inter-device reproducibility of measurements depend on several factors, including the OCT device and software and the retinal pathology (a more reliable measurement in healthy than diseased eyes).[47] Using standardized OCT scans and a team-based grading approach, vitreous pathologies and morphologies are reproducibly and effectively identified in patients receiving ocriplasmin.[41]

VA, measured using the ETDRS charts, is a suitable outcome measure for statistical analysis in clinical trials. Visual function depends on several components including VA, contrast sensitivity, near vision, colour vision and sensitivity to glare.[59] The various components of visual function affect performance of different vision-related tasks by varying degrees, and have important implications for quality of life.

The NEI-VFQ-25 is an outcome measure with 11 vision-related constructs and one single-item general health component that is subject to ceiling and floor effects.[64] In more recent studies, the NEI-VFQ-25 has been shown to measure visual functioning better than it measures quality of life[68] because of issues related to multi-dimensionality and poor subscale performance.[68,69] Hence, the NEI-VFQ single composite score may not be as valid in measuring HRQoL.

APPENDIX 6: SUMMARY OF FOLLOW-UP STUDY TG-MV-012

Issues considered in this section are provided as supporting information. The information has not been systematically reviewed.

Objective

To provide a brief summary of the TG-MV-012 study that assessed visual function in a subset of patients with VMA who had previously been treated with either placebo or ocriplasmin in either of the TG-MV-006 or TG-MV-007 phase III studies. This was an extension study that was not included in the systematic review.

Findings

Study Characteristics

TG-MV-012 was a follow-up study that examined visual function in a subset of patients who had previously participated in either the TG-MV-006 or TG-MV-007 phase III trials. Patients remained allocated to their respective treatment groups from TG-MV-006 and TG-MV-007; however, there was no new administration of ocriplasmin or placebo during TG-MV-012. Twenty-four patients who had been treated with either ocriplasmin 125 mcg (n = 19) or placebo (n = 5) were enrolled in the extension study that consisted of one subsequent study visit (mean [SD] of approximately 726 days [67.31 days, ocriplasmin group] and 746 days [62.62 days, placebo group] from the end of the original phase III studies). Of these, six patients in the ocriplasmin group and two patients in the placebo group underwent vitrectomy in the study eye. Two patients in the ocriplasmin group underwent vitrectomy during TG-MV-006 and TG-MV-007, while the other four patients in the ocriplasmin group and two patients in the placebo group underwent vitrectomy between TG-MV-006/TG-MV-007 and TG-MV-012. The primary outcome of interest was resolution of VMA, while the secondary outcomes included closure of FTMH and improvement in BCVA.

Patient characteristics were similar between sample groups, although the ocriplasmin group (n = 19) contained almost four times as many patients compared with the placebo group (n = 5). The majority of patients were white females with mean ages between 75.2 years and 72.8 years. The median duration of this follow-up study was approximately 2.5 years. Other baseline characteristics and patient characteristics are shown in Table 20 and Table 21. Included in Table 21 are baseline characteristics associated with the outcomes of interest.

TABLE 20: PATIENT CHARACTERISTICS — SAFETY SET

Characteristic	Treatment Group		
	Ocriplasmin (N = 19)	Placebo (N = 5)	Total (N = 24)
Mean (SD) age in years at TG-MV-012 visit	72.8 (9.25)	75.2 (7.85)	73.3 (8.87)
Gender, n (%)			
Female	14 (73.7)	2 (40.0)	16 (66.7)
Male	5 (26.3)	3 (60.0)	8 (33.3)
Race, n (%)			
White	18 (94.7)	5 (100.0)	23 (95.8)
Black	0	1 (5.3)	1 (4.2)
Diagnosis in the study eye at baseline in TG-MV-006/007[a], n (%)			
VMA	17 (89.5)	5 (100.0)	22 (91.7)
FTMH	4 (21.1)	0	4 (16.7)
ERM	13 (68.4)	5 (100.0)	18 (75.0)

ERM = epiretinal membrane; FTMH = full-thickness macular hole; SD = standard deviation; VMA = vitreomacular adhesion.
[a]Patients may be included in multiple baseline diagnosis categories, as appropriate. All other diagnoses are based on the re-read baseline Cirrus OCT assessments from the Optic Nerve Research Center.

TABLE 21: PATIENTS CHARACTERISTICS AT END OF TG-MV-006/TG-MV-007 AND AT TGMV-012 VISIT — SAFETY SET

Characteristic	Treatment Group		
	Ocriplasmin (N=19)	Placebo (N=5)	Total (N=24)
EOS for TG-MV-006 and TG-MV-007			
Ocular conditions in the study eye[a], n (%)			
VMA	[redacted]	[redacted]	[redacted]
FTMH	[redacted]	[redacted]	[redacted]
ERM	[redacted]	[redacted]	[redacted]
BCVA (letters)			
Mean (SD)	[redacted]	[redacted]	[redacted]
TG-MV-012 visit			
Ocular conditions in the study eye*, n (%)			
VMA	[redacted]	[redacted]	[redacted]
FTMH	[redacted]	[redacted]	[redacted]
ERM	[redacted]	[redacted]	[redacted]
BCVA (letters)			
Mean (SD)	[redacted]	[redacted]	[redacted]

BCVA = best-corrected visual acuity; EOS = end of study; ERM = epiretinal membrane; FTMH = full-thickness macular hole; SD = standard deviation; VMA = vitreomacular adhesion.
[a]OCT parametres are based on Cirrus scans as evaluated by the masked Optic Nerve Research Center.

Results

Vitreomacular Adhesion: Post-Vitrectomy Data Excluded

In addition to six of the 15 patients in the ocriplasmin group shifting from having VMA in the study eye at baseline to not having VMA in the study at the end of the original phase III trials, one other patient shifted from having to not having VMA in the study eye at the follow-up study visit (TG-MV-012). Two patients in the placebo group shifted from having VMA in the study eye at baseline to not having VMA at the end of the original trials; however, no additional patients in the placebo group shifted to not having VMA in the follow-up trial visit. One patient in the ocriplasmin group shifted from not having VMA at baseline to having VMA at the follow-up trial visit. The Optic Nerve Research Center used the terms "VMA," "vitreomacular traction" (VMT) and "VMA with tenting" synonymously; hence, the patient was actually diagnosed with VMA without tenting at baseline and then with VMA with tenting at the follow-up trial visit. Details regarding VMA changes are presented in Table 22.

TABLE 22: TG-MV-012 SUMMARY OF SHIFTS IN VMA IN THE STUDY EYE — SAFETY SET

Finding[a]	Treatment Group		
	Ocriplasmin n/N (%)[b]	Placebo n/N (%)[b]	Total n/N (%)[b]
Shift from baseline[c] to TG-MV-006 and TG-MV-007 EOS			
Yes to No	[redacted]	[redacted]	[redacted]
No to Yes	[redacted]	[redacted]	[redacted]
Shift from TG-MV-006 and TG-MV-007 EOS to TG-MV-012 visit			
Yes to No	[redacted]	[redacted]	[redacted]
No to Yes	[redacted]	[redacted]	[redacted]
Shift from baseline[c] to TG-MV-012 visit			
Yes to No	[redacted]	[redacted]	[redacted]
No to Yes	[redacted]	[redacted]	[redacted]

EOS = end of study; FTMH = full-thickness macular hole.
[a]Cirrus scans; post-vitrectomy data excluded.
[b]Percentages are based on the number of patients with the matched result from the beginning of the comparison interval.
[c]Baseline was the baseline OCT as taken for TG-MV-006/TG-MV-007 and analyzed by the Optic Nerve Research Center.

Full-Thickness Macular Hole: Post-Vitrectomy Data Excluded

Two patients in the ocriplasmin group shifted from having FTMH in the study eye to FTMH resolution between baseline and the end of the original phase III studies. However, two patients (one each from the ocriplasmin and placebo groups) also developed FTMH in their study eye during this same time period. No additional changes in FTMH in the study eye were observed in either treatment group between the end of the original phase III studies and the follow-up visit of TG-MV-012. Details of FTMH changes are presented in Table 23.

TABLE 23: TG-MV-012 SUMMARY OF SHIFTS IN FTMH IN THE STUDY EYE, CIRRUS SCANS, POST-VITRECTOMY DATA EXCLUDED — SAFETY SET

Finding	Treatment Group		
	Ocriplasmin n/N (%)[a]	Placebo n/N (%)[a]	Total n/N (%)[a]
Shift from baseline[b] to TG-MV-006/007 EOS			
Yes to No	[redacted]	[redacted]	[redacted]
No to Yes	[redacted]	[redacted]	[redacted]
Shift from TG-MV-006/007 EOS to TG-MV-012 visit			
Yes to No	[redacted]	[redacted]	[redacted]
No to Yes	[redacted]	[redacted]	[redacted]
Shift from baseline[b] to TG-MV-012 visit			
Yes to No	[redacted]	[redacted]	[redacted]
No to Yes	[redacted]	[redacted]	[redacted]

EOS = end of study; FTMH = full-thickness macular hole.
[a]Percentages are based on the number of patients with the matched result from the beginning of the comparison interval.
[b]Baseline was the baseline OCT as taken for TG-MV-006/TG-MV-007 and analyzed by the Optic Nerve Research Center.

Best-Corrected Visual Acuity

Categorical Improvement in best-corrected visual acuity (BCVA) Irrespective of Vitrectomy: Four patients in the ocriplasmin group and one patient on the placebo group had a greater than two-line improvement in BCVA from baseline to the end of the original phase III studies. In addition, two of these four patients in the ocriplasmin group had a greater than three-line improvement in BCVA in the same time period. In the time period from the end of the original phase III studies to the follow-up study visit, two additional patients in the ocriplasmin group obtained a greater than two-line improvement in BCVA. No patients in the placebo group obtained a two-line or greater improvement in BCVA in this time period and no patients in the ocriplasmin group had a greater than three-line improvement in BCVA. Details of the categorical improvement in BCVA in the study eye, irrespective of vitrectomy, are presented in Table 24.

TABLE 24: CATEGORICAL IMPROVEMENT IN BCVA IN THE STUDY EYE, IRRESPECTIVE OF VITRECTOMY — SAFETY SET

Finding	Treatment Group		
	Ocriplasmin (n = 19) n (%)	Placebo (n = 5) n (%)	Total (n = 24) n (%)
From baseline[a] to TG-MV-006/007 EOS			
≥ 2-line improvement in BCVA	[redacted]	[redacted]	[redacted]
≥ 3-line improvement in BCVA	[redacted]	[redacted]	[redacted]
From TG-MV-006/007 EOS to TG-MV-012 study visit			
≥ 2-line improvement in BCVA	[redacted]	[redacted]	[redacted]
≥ 3-line improvement in BCVA	[redacted]	[redacted]	[redacted]
From baseline[a] to TG-MV-012 study visit			
≥ 2-line improvement in BCVA	[redacted]	[redacted]	[redacted]
≥ 3-line improvement in BCVA	[redacted]	[redacted]	[redacted]

BCVA = best-corrected visual acuity; EOS = end of study.
[a]Baseline was defined as the last non-missing value before administration of study drug during the original TG-MV-006/TG-MV-007 studies.

Categorical Improvement in BCVA: Post-Vitrectomy Data Excluded: The denominators of both treatment groups changed to reflect the exclusion of patients who had undergone vitrectomy. Four patients in the ocriplasmin group and one patient in the placebo group had a two-line improvement in BCVA in their study eye from baseline to the end of the original phase III studies, with two of these patients in the ocriplasmin group having a three-line or greater improvement in BCVA. One patient had a two-line improvement in BCVA in their study eye during the time from the end of the original phase III studies to the follow-up visit. Details of the categorical improvement in best-corrected visual acuity in the study eye, excluding post-vitrectomy data, are presented in Table 25.

TABLE 25: CATEGORICAL IMPROVEMENT IN BCVA IN THE STUDY EYE, POST-VITRECTOMY DATA EXCLUDED — SAFETY SET

Finding	Treatment Group		
	Ocriplasmin n/N (%)	Placebo n/N (%)	Total n/N (%)
From baseline[a] to TG-MV-006/007 EOS[b]			
2-line improvement in BCVA	[redacted]	[redacted]	[redacted]
≥ 3-line improvement in BCVA	[redacted]	[redacted]	[redacted]
From TG-MV-006/007 EOS to TG-MV-012 study visit[c]			
2-line improvement in BCVA	[redacted]	[redacted]	[redacted]
≥ 3-line improvement in BCVA	[redacted]	[redacted]	[redacted]
From baseline[a] to TG-MV-012 study visit			
2-line improvement in BCVA	[redacted]	[redacted]	[redacted]
≥ 3-line improvement in BCVA	[redacted]	[redacted]	[redacted]

BCVA = best-corrected visual acuity; EOS = end of study.
[a]Baseline was defined as the last non-missing value prior to administration of study drug during the original TG-MV-006/007 study.
[b]Two patients were excluded from the analysis of change from baseline to TG-MV-006/007 EOS because they underwent vitrectomy during TG-MV-006/TG-MV-007. Thus, in this analysis, the denominator for the ocriplasmin group was 17.
[c]For the analysis of change from baseline to the TG-MV-012 study visit, 8 patients (2, placebo; 6 ocriplasmin) were excluded because they underwent vitrectomy prior to the TG-MV-012 study visit. Thus, in this analysis, the denominators were 3 for the placebo group and 13 for the ocriplasmin group.

Mean Changes in Visual Acuity (BCVA Letter Scores): A mean change of 2.8 letters (SD of 8.46) in the ocriplasmin group and 2.4 letters (SD of 4.72) in the placebo group was observed when examining the time period between baseline and the end of the original phase III studies. A nominal mean change of 0.7 (SD of 7.70) in the ocriplasmin group and a worsening in BCVA of –5.2 (mean change; SD 3.03) in the placebo group was observed when examining the time period from the end of the original phase III studies to the follow-up visit of TG-MV-012. Details of the mean changes in VA according to BCVA letter scores are presented in Table 26.

TABLE 26: TG-MV-012 SUMMARY OF VISUAL ACUITY (ETDRS LETTER SCORE) AND CHANGE FROM BASELINE BY STUDY VISIT IN THE STUDY EYE — SAFETY SET

Finding	Treatment Group		
	Ocriplasmin (n = 19)	Placebo (n = 5)	Total (n = 24)
Baseline of study TG-MV-006 and TG-MV-007			
Mean (SD)	[redacted]	[redacted]	[redacted]
TG-MV-006/007 EOS			
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to TG-MV-006 and TG-MV-007 EOS			
Mean (SD)	[redacted]	[redacted]	[redacted]
Study TG-MV-012 study visit			
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to TG-MV-012 study visit			
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from TG-MV-006 and TG-MV-007 EOS to TG-MV-012 study visit			
Mean (SD)	[redacted]	[redacted]	[redacted]

EOS = end of study; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation.

Adverse Events: More patients in the ocriplasmin group experienced AEs than those patients in the placebo group; however, the small sample numbers in both treatment groups precludes any definitive conclusions regarding these AEs. The most common AE was cataract formation. All AEs were considered mild to moderate in severity and were assessed either as not related or remotely related to the study drug. Details of the AEs and SAEs are presented in Table 27.

TABLE 27: SUMMARY OF OCULAR ADVERSE EVENTS ONGOING AT THE TG-MV-012 VISIT — SAFETY SET

	Ocriplasmin (N = 19) n (%)	Placebo (N = 5) n (%)
Patients with ≥ 1 AE	6 (31.6)	1 (20.0)
Blepharitis	1 (5.3)	0
Cataract	3 (15.8)	0
Macular fibrosis	1 (5.3)	0
Retinal edema	0	1 (20.0)
Visual acuity reduced	1 (5.3)	0
Patients with SAEs		
Macular hole	0	1 (20.0)

AE = adverse event; SAE = serious adverse event.

Summary

Similar results were obtained in both treatment groups at the end of the original phase III studies (TG-MV-006 and TG-MV-007) and in the follow-up study (TG-MV-012). With post-vitrectomy results excluded, patients in the ocriplasmin group were found to have better VMA resolution and two-line improvements in BCVA in their study eyes compared with those in the placebo group. A nominal improvement was observed in VA (using the ETDRS letter scores) in the ocriplasmin group, while patients in the placebo group experienced a worsening of their VA during this time period. No changes in FTMH were observed in either treatment group. AEs were mild to moderate in severity and were assessed as either not related or remotely related to the study drug. However, definitive conclusions and the significance of the treatments of the AEs cannot be ascertained due to the small sample size in the follow-up study.

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