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RESEARCH**

APPLICATION NUMBER:

125422Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review BLA 125422

Date	October 11, 2012
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
BLA #	124422
Applicant	Thrombogenics, Inc.
Date of Submission	April 17, 2012
PDUFA Goal Date	October 17, 2012
Proprietary Name / Established (USAN) names	Jetrea (ocriplasmin) Intravitreal Injection, 2.5 mg/mL
Dosage forms / Strength	2.5 mg/mL solution for intravitreal injection
Indication(s)	Treatment of vitreomacular adhesion (VMA)
Recommendation:	Recommended for Approval

1. Introduction

Ocriplasmin (also referred to as microplasmin) is a recombinant truncated form of human plasmin produced in a *Pichia pastoris* expression system by recombinant DNA technology with a molecular weight of 27.2kDA.

The drug product is a sterile, clear and colorless solution with no preservatives in a single use glass vial containing 0.5 mg of ocriplasmin in 0.2 mL. After dilution with 0.2 mL of 0.9% (w/v) sodium chloride solution, a 1.25 mg/mL solution is available for intravitreal injection. The intended dose is 0.1 mL of the diluted ocriplasmin.

Ocriplasmin was developed for the treatment of vitreomacular adhesion (VMA). The goal of therapy for VMA is to relieve tractional effects on the macula with subsequent functional improvement. Ocriplasmin is a serine protease shown to cleave both physiological substrates (such as fibronectin, fibrinogen, collagen, laminin, gelatin, ocriplasmin etc) as well as synthetic peptide substrates (such as S-2403 and S-2444). Following intravitreal administration, the proteolytic activity of ocriplasmin is purported to help in dissolution of the vitreal matrix proteins at the vitreoretinal interface focal points thereby resolving or reducing the complications associated with VMA.

2. Background

The original IND 100370 was submitted on 10/11/2006.

The design of the Phase 3 studies was discussed with the FDA at an End of Phase 2 meeting in September 2008 and subsequent discussions through January 2009. The following recommendations from the Agency on the study design of the Phase 3 protocol were implemented:

- placebo intravitreal injection of vehicle was chosen over a sham injection
- a 6-month follow-up period in the phase 3 trials was implemented to allow ocriplasmin to exert its effect, to assess whether the resultant effect is sustained for a suitable period without reversals and to observe any complications of a single ocriplasmin injection.
- a change in the allocation ratio in TG-MV-006 (from a 3:1 to a 2:1 ratio) was implemented. The change was requested by the FDA and took place when 55 patients were already randomized.

A pre-BLA CMC discussion was held on the NIH Campus on 9/30/2011. Representatives from Thrombogenics, Biotechnology Manufacturing Assessment Branch, Division of Therapeutic Proteins, and Division of Transplant and Ophthalmology Products were in attendance.

The BLA for ocriplasmin (b) (4)

BLA 125422.

3. Product Quality

From the Division of Therapeutic Proteins Product Quality Review finalized 9/20/2012:

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA STN 125422 for Jetrea™ (Ocriplasmin) manufactured by Thrombogenics, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Jetrea (ocriplasmin) is well controlled, and leads to a product that is pure and potent. It is recommended that this product be approved for human use (under conditions specified in the package insert).

The final drug product is a sterile, clear and colorless solution containing 0.5mg ocriplasmin in 0.2mL solution (at 2.5 mg/mL concentration, pH 3.1) in 2 mL single use (b) (4) glass vials, stored frozen at -20 (b) (4) C. Prior to use, the vial is thawed and diluted with 0.9% (w/v) sodium chloride solution at 1:1 ratio. The recommended dose for the current indication is 125 µg, which corresponds to 0.1 mL of the diluted solution and is administered by intravitreal injection.

COMPOSITION OF DRUG PRODUCT

Table 1: Composition of Ocriplasmin Drug Product

Ingredient	Unit Formula (mg/0.200mL)	Concentration (mg/mL)	Function	Quality Standard
Drug Substance				
Ocriplasmin	0.500	2.50	Active ingredient	Manufacturer specifications (3.2.S.4.1)
Excipients				
(b)(4) Mannitol	0.750	3.75	(b)(4)	USP/Ph. Eur.
Citric acid (b)(4)	0.210	1.05		USP/Ph. Eur.
Sodium hydroxide ^a	(b)(4)	(b)(4)		NF/Ph. Eur.
Water for injection				USP/Ph. Eur.

^a For pH adjustment to pH 3.1 ± 0.1 if necessary
^b Quantum satis

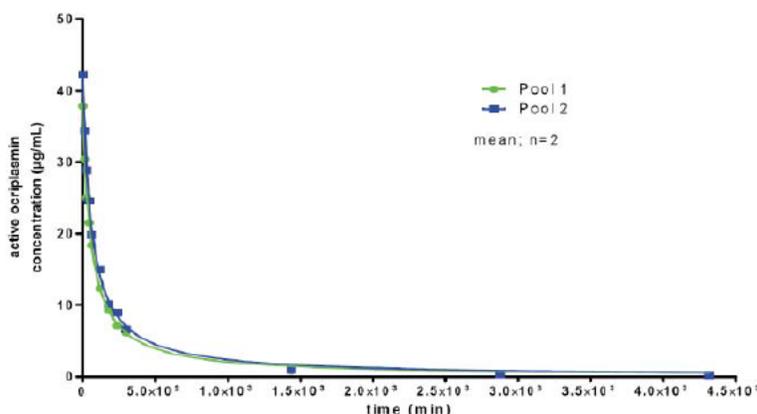
CONTAINER CLOSURE SYSTEM

Ocriplasmin drug product (DP) is stored as a single dose vial. The container closure system (CCS) consists of (b)(4) USP/Ph. Eur. (b)(4) glass vials (b)(4) (b)(4) rubber (USP/Ph. Eur. (b)(4) stopper. The stoppers are capped with an aluminum crimp seal equipped with a (b)(4) flip-off cap.

IMMUNOGENICITY

Immunogenicity for this product has not been evaluated. This product is injected directly into the eye and will be indicated for a one time dose in the eye. Below is a summary of a study Thromobogenics performed to assess the enzymatic activity of ocriplasmin in human vitreous fluid. This data shows that ocriplasmin is generally cleared within 4 hours of dosing. See table below.

Figure 6: Inactivation of Ocriplasmin in Pooled Human Vitreous Fluid (3mL) Following the Addition of 125 µg Ocriplasmin and Incubation at +37°C



RELEASE AND STABILITY SPECIFICATIONS

Table 1: Release and Stability Specifications for Ocriplasmin Drug Product

Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
General Properties				
Appearance	visual inspection (Ph.Eur. 2.2.2 and Ph.Eur. 2.2.1 - ATP957)	turbidity, coloration and particulate matter	clear, colourless solution practically free from visible particulate matter	colour less than or equivalent to Ph.Eur. B ₉ reference solution, clarity less than or equivalent to Ph.Eur. reference suspension I, sample solution is practically free from visible particulate matter
pH	potentiometric (USP<791> and Ph.Eur. 2.2.3 - ATP164)	pH	pH 2.8 to pH 3.4	pH 2.8 to pH 3.4
Osmolality	freezing point depression (USP<785> and Ph.Eur. 2.2.35 - ATP841)	osmolality	report result	(b) (4)
Sub-visible Particles (particles/container) ^a	light obscuration test (ATP838)	particle count	(b) (4)	(b) (4)
Sub-visible Particles (particles/mL) ^b	membrane microscopy test (SOPQA-OCRIPLAS-MIN-MP-001)	particle count	(b) (4)	(b) (4)

Table 1: Release and Stability Specifications for Ocriplasmin Drug Product (Continued)

Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
Identity				
Size and Epitope	Western Blot (PIC09-053)	immunological specificity for ocriplasmin	comparable to reference standard profile	(b) (4)
Isoelectric Point	IEF (ATP953)	pH at isoelectric point	comparable to reference standard profile	
Purity and Impurities				
Molecular Size Variants (Reduced and Non-reduced Conditions)	reduced SDS-PAGE (AM0710) non-reduced SDS-PAGE (AM0710)	(b) (4)		

Table 1: Release and Stability Specifications for Ocriplasmin Drug Product (Continued)

Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
Hydrophobic Molecular Variants	RP-HPLC (AM0704)	(b) (4)		
Molecular Charge Variants	CEX-HPLC (pH 5.5) ^c (AM0702)			
	Low pH CEX-HPLC (pH 4.0) ^e (SOPQA-MICROPLAS M-R-001)			

Table 1: Release and Stability Specifications for Ocriplasmin Drug Product (Continued)

Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
Molecular Size Variants	SE-HPLC (pH 7.4) ^f (AM0698)			(b) (4)
Molecular Size Variants	low pH SE-HPLC (pH 3.1) ^g (SOPQA-MICROPLAS M-R-002)			(b) (4)
Quantity				
Protein Concentration	UV 280nm (ATP655)	quantity		(b) (4)
Potency				
Potency	enzymatic activity ^h (AM0634)	proteolytic activity		(b) (4)
Enzyme Kinetic Properties ⁱ	enzyme activity (SOPQA-MicroplasmKm-A-001)	K _m		(b) (4)
		k _{cat}		(b) (4)
Other Quality Characteristics				
Uniformity of Dosage Units	quantity (USP<905> and Ph.Eur. 2.9.40 - ATP954)	quantity		(b) (4)

Table 1: Release and Stability Specifications for Ocriplasmin Drug Product (Continued)

Test	Analysis (Method Reference Number)	Test Parameter	Current Acceptance Criteria	Proposed Acceptance Criteria
Endotoxin	turbidity of LAL reagent (USP<85> and Ph.Eur. 2.6.14 - M103-R70-2.2)	endotoxin quantity		(b) (4)
Sterility	membrane filtration (USP<71> and Ph.Eur. 2.6.1 - M103-R70-2.1)	sterility	absence of growth	absence of growth
Container closure integrity	Blue dye ingress test (ATP 900)	Blue dye ingress	N/A ^d	No ingress

^a Method used historically for batch release and stability testing. Superseded by membrane microscopy sub-visible particles method

^b Replaces the light obscuration sub-visible particles method

^c Method used historically for batch release and stability testing. Superseded by low pH CEX-HPLC (pH 4.0) method. Method will continue to be used for ongoing stability studies in accordance to 3.2.P.8.1. For ongoing stability studies the current acceptance criteria will be used

^d N/A = not applicable as method has been superseded or only recently introduced

^e Replaces the CEX-HPLC (pH 5.5) method for batch release and stability testing

^f Method used historically for batch release and stability testing. Superseded by low pH SE-HPLC (pH 3.1) method. Method will continue to be used for ongoing stability studies in accordance to 3.2.P.8.1. For ongoing stability studies the current acceptance criteria will be used

^g Replaces the SE-HPLC (pH 7.4) method for batch release and stability testing

^h Method used historically for batch release and stability testing. Superseded by enzyme kinetic properties km/k_{cat} method. Method will continue to be used for ongoing stability studies in accordance to 3.2.P.8.1. For ongoing stability studies the acceptance criterion will be between $37\mu M/min/mg$ and $59\mu M/min/mg$

ⁱ Replaces the potency method AM0634 for batch release and stability testing

The Division of Therapeutic Proteins, Office of Biotechnology Products has no list of deficiencies to be communicated, but they do have a list of PMC's to be communicated to the applicant. See Section 13 Recommendations/Risk Benefit Assessment this review.

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review finalized 10/2/2012:

Ocriplasmin can be approved from the nonclinical perspective at a dosing regimen of a single intravitreal dose of 125 µg (i.e., 0.125 mg).

The intravitreal toxicity of ocriplasmin has been evaluated in rabbits, monkeys and minipigs. Findings after a single intravitreal injection included narrowing of the retinal vessels with associated retinal atrophy in rabbits only, lens subluxation in all 3 species, and changes in intraocular pressure (IOP), inflammation, and electroretinography (ERG) changes in rabbits and monkeys. One monkey developed a hyphema and retinal atrophy, however, a relationship to ocriplasmin treatment is uncertain.

A second intravitreal administration of ocriplasmin (28 days apart) in monkeys was associated with an increase incidence of lens subluxation, sustained increases in IOP, and a series of adverse microscopic findings in the eye. The lens subluxation was associated with degeneration/disruption of the hyaloideocapsular ligament observed microscopically, accompanied by loss of the ciliary zonular fibers. Iridodonesis (quivering of the iris) was noted in most animals with lens subluxation, as expected due to lack of support from the lens. Therefore, the lens subluxation is considered a consequence of the proteolytic activity of ocriplasmin. In monkeys and minipigs, vitreous gel breakdown was reported. This finding was an expected pharmacological action of the drug.

The exposure margins (0.1-1.5-fold) for the findings of inflammation, ERG changes and lens subluxation observed in rabbits and monkeys after a single intravitreal dose are low. A more favorable exposure margin (3.7-fold) was observed for the microscopic retinal changes observed in the monkey. However, except for lens subluxation, the nonclinical findings were reversible after administration of a single intravitreal dose.

Safety Pharmacology studies in dogs showed a significant decrease in blood pressure, a slight increase in QT/QTc intervals and P-wave amplitude, and a slight decrease in tidal volume. Except for P-wave amplitude, all findings showed a trend toward recovery. The exposure margin at the no-observed-effect level (NOEL) of 1.5 mg/kg is >130-fold the estimated systemic concentration of 46 ng/mL in humans after a single intravitreal dose, indicating low concern for similar effects to be observed in humans. In addition, no effects were observed in electrocardiographic (ECG) parameters in a 14-day repeated-dose toxicology study in dogs at intravenous (IV) doses up to 10 mg/kg every other day.

The systemic toxicity of ocriplasmin was evaluated in rats and dogs after IV administration. The adverse findings observed were related to the thrombolytic action of the drug. The NOEL levels were 10 mg/kg every other day in rats and 2 mg/kg every other day in dogs. These doses are 220- and 675-fold the estimated systemic concentration of 46 ng/mL in humans after an intravitreal clinical dose of 125 µg.

Therefore, the nonclinical data provides support to conclude that systemic toxicity of ocriplasmin is unlikely following a single 125 µg intravitreal injection in humans. Additional support for the systemic safety of ocriplasmin at the proposed human dose is provided by the following observations:

- If ocriplasmin was completely systemically absorbed after intravitreal injection, the amount (46 ng/mL) would be miniscule compared to the amount of plasminogen in the human blood (200 µg/mL).
- If systemic bioavailability of the intraocular dose is 100% (i.e., 4.6 nmol), there would be sufficient α 2-antiplasmin present in the blood to neutralize all ocriplasmin, based on the normal plasma concentration of the serine protease inhibitor α 2-antiplasmin (1 nmol/mL of plasma).

Genetic toxicology studies have not been conducted with ocriplasmin. These are not generally required for biologic products.

Animal carcinogenicity studies have not been conducted with ocriplasmin. Carcinogenicity studies with microplasmin were not considered necessary as the applicant was not seeking a clinical indication entailing chronic use.

Animal reproduction studies have not been conducted with ocriplasmin. Reproductive and developmental toxicity studies were not conducted because the weight of evidence supports that significant systemic exposure is not expected in humans following a single intravitreal injection of 125 µg ocriplasmin.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 9/26/2012:

The intravitreal (IVT) pharmacokinetic (PK) profile of ocriplasmin was determined in a clinical Phase 2 Study TG-MV-010 after IVT administration by measuring ocriplasmin activity levels in the vitreous humor in patients with eye disease for which a primary vitrectomy was indicated (n=38). In addition, the systemic PK profile of ocriplasmin was determined in a clinical Study TG-M-001 after intravenous (IV) administration in healthy volunteers (n=62) by measuring ocriplasmin antigen levels, as ocriplasmin was originally developed as a thrombolytic agent for intravascular use (terminated for commercial reasons). To support approval for this indication, the sponsor conducted two Phase 3 Studies TG-MV-006 and TG-MV-007 in patients with symptomatic VMA.

No drug absorption, distribution and metabolism study has been conducted for ocriplasmin. Ocriplasmin is a biologic product, and ocriplasmin is inactivated via auto proteolysis and its interactions with protease inhibitor α 2-antiplasmin or α -macroglobulin. Concentrations of active ocriplasmin in pooled human vitreous fluid were evaluated in an *in vitro* study following the addition of 125µg ocriplasmin and incubation at +37°C. Approximately 16% of the initial actual concentrations were left after 5 hours incubation. Less than 0.6% of the initial actual concentrations were left after 3 days incubation. Ocriplasmin was inactivated quickly in this *in vitro* study, which is similar to the inactivation observed in patients' eyes in Study TG-MV-010. The result suggests that ocriplasmin is inactivated via α 2-antiplasmin, and the systemic absorption of ocriplasmin following a single dose of IVT injection is expected to be minimal.

In Study TG-M-001, there was no evidence of a dose-related trend of elevated titers of anti-ocriplasmin antibodies and none of the elevated titers of anti-ocriplasmin antibodies was associated with clinical findings following a single IV dose of ocriplasmin to healthy volunteers.

Recommended package insert language from the Clinical Pharmacology review finalized 9/26/2012:

The intravitreal pharmacokinetics of ocriplasmin were determined in a clinical study in patients scheduled for vitrectomy where 0.125 mg ocriplasmin (corresponding to an average concentration of 29 µg ocriplasmin per mL vitreous volume [approximately 4.3 mL/eye]) was administered as a single intravitreal dose at different time points prior to vitrectomy. (b) (4)

At 24 hours post-injection the levels in the vitreous were below 3% of the theoretical concentration reached immediately after injection.

Because of the small dose administered (0.125 mg), detectable levels of ocriplasmin in systemic circulation are not expected after intravitreal injection.

Table 2: Mean Ocriplasmin Activity Levels in Vitreous Samples after Intravitreal Injection of 0.125 mg JETREA

Time post-injection (subjects) Mean ± SD Ocriplasmin levels (µg/mL)	5-30min (n=8)	31-60min (n=8)	2-4hours (n=8)	24hr ± 2hr (n=4)	7 days ± 1day (n=4)
	12 ±7.6	8.1 ±5.2	2.6 ±1.6	0.5 ±0.3 ^a	<0.27 ^b

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6. Sterility Assurance

From the original drug substance OC/OMPQ/DGMPA/BMAB Review dated 10/2/2012:

Drug substance is manufactured by Fujifilm Diosynth Biotechnologies UK Limited.

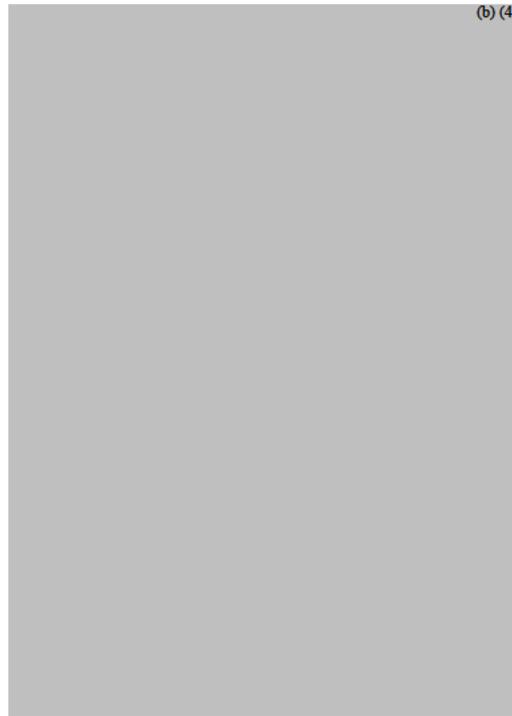
The drug substance part of this application is recommended for approval from microbiology product quality perspective.

Ocriplasmin is produced in *Pichia pastoris* (b) (4)

(b) (4)

The ocriplasmin drug substance manufacturing process (b) (4) comprises (b) (4) steps described in Figure 1 duplicated from the submission.

Figure 1: Manufacturing Process of Ocriplasmin DS



OC/OMPQ/DGMPA/BMAB has no list of deficiencies to be communicated, but they do have a list of 6 drug substance PMC's to be communicated to the applicant. See Section 13 Recommendations/Risk Benefit Assessment this review.

From the original drug product OC/OMPQ/DGMPA/BMAB Review dated 10/2/2012:

Ocriclasmin drug product is manufactured by (b) (4)

(b) (4)
Prior to intravitreal administration, ocriclasmin drug product is diluted using an equal volume of a 0.9% w/v sodium chloride solution.

The treatment dose for the DP is 100µL. A 100µL volume of the 1:1 diluted ocriclasmin drug product contains 125µg of ocriclasmin drug product. The proposed ocriclasmin drug product acceptance criteria is (b) (4) for every 125µg of ocriclasmin administered. If the endotoxin ((b) (4) from 0.9% w/v sodium chloride is taken into account, in each 100µL dose of ocriclasmin, the endotoxin concentration is (b) (4). The endotoxin limit for

ocriplasmin drug product is (b) (4) which is (b) (4) The endotoxin specification of < (b) (4) within the limit based on dosage, (b) (4)

OC/OMPQ/DGMPA/BMAB has no list of deficiencies to be communicated, but they do have a list of 2 drug product PMC's to be communicated to the applicant. See Section 13 Recommendations/Risk Benefit Assessment this review.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review finalized 9/26/2012:

Study ID	Design / Control / Indication	Route and Regimen	Total Enrolment (Planned / Actual)
UNCONTROLLED STUDIES			
TG-MV-001	Phase 2 multicenter, open-label, non-controlled 6-month trial with ascending dose / exposure time in 6 sequential cohorts in patients with VMT maculopathy	Single intravitreal injection of ocriplasmin Dose / time before vitrectomy: 25µg/1h; 25µg/24h; 25µg/7d; 50µg/24h; 75µg/24h or 125µg/24h	60/61
TG-MV-010	Phase 2 single center, ascending-exposure time 6-week pharmacokinetic trial prior to pars plana vitrectomy	Single intravitreal injection of ocriplasmin Dose / time before vitrectomy: 125µg/5-30min; 125µg/31-60min; 125µg/2-4h; 125µg/24h; 125µg/7d; no ocriplasmin treatment	36/38
CONTROLLED STUDIES			
TG-MV-002	Phase 2 multicenter, randomized, sham-injection controlled, double-masked, ascending-dose, dose-range-finding 12-month study in patients with diabetic macular edema	Single intravitreal injection of ocriplasmin (25µg, 75µg or 125µg) or sham injection	60/51
TG-MV-003	Phase 2 multicenter, randomized, placebo-controlled, double-masked, parallel-group, dose-ranging 6-month study in patients undergoing vitrectomy for non-proliferative vitreoretinal disease	Single intravitreal injection of ocriplasmin (25µg, 75µg or 125µg) or placebo	120/125
TG-MV-004	Phase 2 multicenter, randomized, sham-injection controlled, double-masked, ascending-dose, dose-range-finding 6-month trial in patients with VMT	Single intravitreal injection of ocriplasmin (75µg, 125µg or 175µg) or sham injection per cohort ^b	60/61
TG-MV-006	Phase 3 multicenter, randomized, placebo-controlled, double-masked 6-month study in patients with symptomatic VMA (i.e. focal VMA leading to symptoms)	Single intravitreal injection of ocriplasmin 125µg or placebo	320/326
TG-MV-007	Phase 3 multicenter, randomized, placebo-controlled, double-masked 6-month study in patients with symptomatic VMA (i.e. focal VMA leading to symptoms)	Single intravitreal injection of ocriplasmin 125µg or placebo	320/326

The safety and efficacy of ocriplasmin for the treatment of VMA was evaluated in two phase 3 trials (TG-MV-006 and TG-MV-007). Both trials were multicenter, randomized, placebo-controlled, double-masked, 6 month studies that investigated the safety and efficacy of a single intravitreal injection of ocriplasmin 125µg in patients with symptomatic VMA. The two trials were identical in design (except for allocation ratio of 2:1 in TG-MV-006 and 3:1 in TG-MV-007) and conduct (except for geography: TG-MV-006 conducted in the United States and TG-MV-007 conducted in the European Union and the US).

Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the proportion of patients with non-surgical resolution of focal VMA at Day 28 post-injection as determined by masked CRC OCT evaluation. Any patients who had creation of an anatomical defect (i.e. retinal break, retinal detachment) that resulted in loss of vision or that required additional intervention were not counted as successes for the primary endpoint. The Full Analysis Set was the primary population for all analyses of baseline/demographic and efficacy data. Missing data was imputed using the last observation carried forward (LOCF) approach. The treatment groups were compared using Fisher's exact test. The two-sided 95% CIs for the difference between the 2 groups were also calculated. For the integrated analysis of the two studies, differences between treatments were evaluated using Cochran-Mantel-Haenszel test, stratified by study.

Proportion of Patients with VMA Resolution in the Study Eye at Day 28 without Creation of an Anatomical Defect (TG-MV-006, TG-MV-007 and Integrated Studies: Full Analysis Set, Modified Full Analysis Set and Per-Protocol Set)

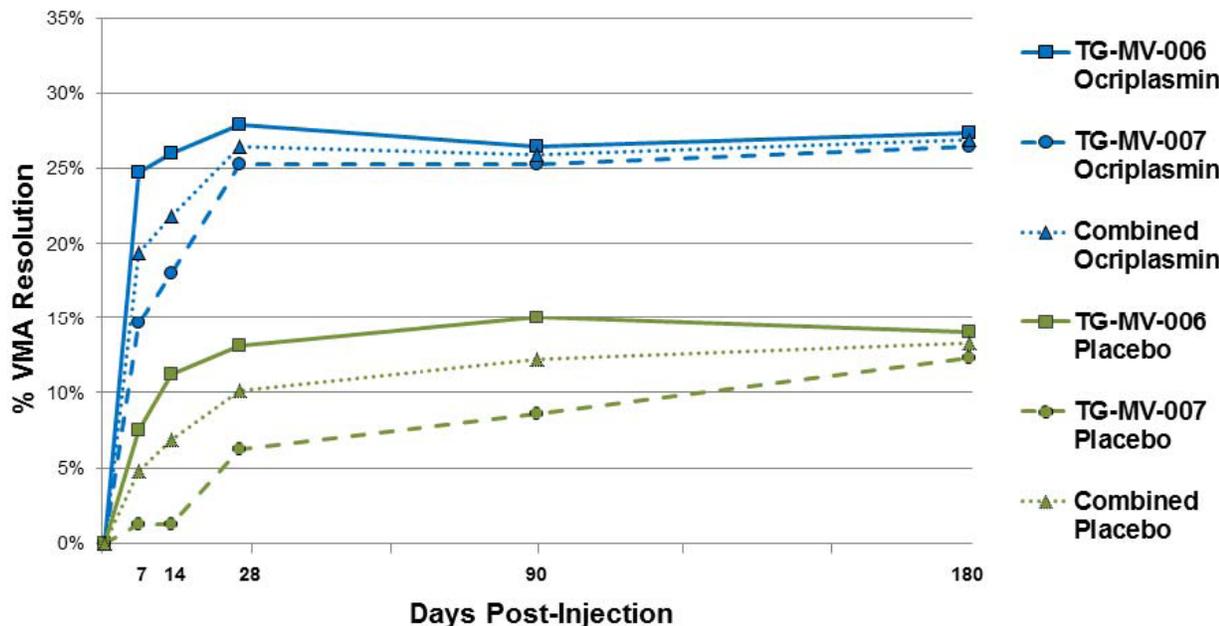
	TG-MV-006				TG-MV-007			
	PL	Ocriplasmin	Difference (95% CI) ^a	p-value ^b	PL	Ocriplasmin	Difference (95% CI) ^a	p-value ^b
Full Analysis Set								
N	107	219			81	245		
n (%)	14 (13.1)	61 (27.9)	14.8(6.0,23.5)	0.003	5 (6.2)	62 (25.3)	19.1 (11.6,26.7)	<0.001
Modified Full Analysis Set								
N	99	207			77	233		
n (%)	14 (14.1)	61 (29.5)	15.3 (6.1,24.6)	0.004	5 (6.5)	62 (26.6)	20.1 (12.2,28.0)	<0.001
Per-Protocol Set								
N	94	189			71	214		
n (%)	14 (14.9)	58 (30.7)	15.8 (6.0,25.5)	0.004	4 (5.6)	56 (26.2)	20.5 (12.6,28.5)	<0.001

^a The (absolute) difference and CIs between treatment groups are based on the proportion of successes.

^b For individual studies, p-value is from Fisher's exact test, comparing placebo and ocriplasmin. For pooled studies, p-value is from Cochran-Mantel-Haenszel test comparing placebo and ocriplasmin, stratified by study.

Ocriplasmin is statistically superior to placebo in both of the phase 3 trials for all of the analysis sets.

Proportion of Patients with VMA Resolution in the Study Eyes: Full Analysis Set)



Due to protocol violations there were 4 patients (1 placebo, 3 ocriplasmin) in the FAS group and 2 patients (1 placebo, 1 ocriplasmin) in the modified FAS groups who underwent vitrectomy prior to day 28. By the end of the study 28.3% (28/99) placebo patients and 19.8% (41/207) ocriplasmin patients underwent vitrectomy.

Proportion of Patients with VMA Resolution in the Study Eye without Creation of an Anatomical Defect by Study Visit (Integrated Studies: Full Analysis Set)

Time Point	Treatment Group		Difference (95% CI) ^a	p-value ^b
	Placebo (N=188) n (%)	Ocriplasmin (N=464) n (%)		
Day 7	9 (4.8)	90 (19.4)	14.6 (9.9, 19.3)	<0.001
Day 14	13 (6.9)	101 (21.8)	14.9 (9.6, 20.1)	<0.001
Day 28	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)	<0.001
Month 3	23 (12.2)	120 (25.9)	13.6 (7.5, 19.8)	<0.001
Month 6	25 (13.3)	125 (26.9)	13.6 (7.3, 20.0)	<0.001

Reference: [Table 2.1.1.18, Module 5.3.5.3](#)

CI=confidence interval; VMA=vitreomacular adhesion

^a The (absolute) difference and CIs between treatment groups are based on the proportion of successes.

^b P-value is from Cochran-Mantel-Haenszel test comparing placebo and ocriplasmin, stratified by study.

The proportion of patients who achieved VMA resolution without creation of an anatomical defect was greater in the ocriplasmin group compared with the placebo group at each post-injection visit through Month 6.

Analysis of Secondary Endpoints(s)

Secondary Efficacy Endpoint

- Proportion of subjects with total PVD at Day 28, as determined by masked Investigator assessment of B-scan ultrasound

Proportion of Patients with Total PVD in the Study Eye at Day 28 (FAS with LOCF and PP)

TG-MV-006				
	Ocriplasmin	Placebo	p-value	Difference (95% CI)
FAS	36/219 (16.4%)	7/107 (6.5%)	0.014	9.9% (3.1%, 16.7%)
PP	28/189 (14.8%)	6/94 (6.4%)	0.051	8.4% (1.4%, 15.5%)
TG-MV-007				
	Ocriplasmin	Placebo	p-value	Difference (95% CI)
FAS	26/245 (10.6%)	0/81 (0.0%)	<0.001	10.6% (6.8%, 14.5%)
PP	24/214 (11.2%)	0/71 (0.0%)	<0.001	11.2% (7.0%, 15.4%)

p-value based on Fisher's exact test

The formal statistical testing of the key secondary efficacy endpoint (total PVD) was to be evaluated only if statistical significance ($p < 0.05$) was achieved in the analysis of the primary efficacy endpoint for 2 of the 3 predefined study populations (i.e. Full Analysis Set and Modified Full Analysis Set). Both trials demonstrate efficacy for total PVD in accordance with the predefined statistical analysis plan.

Analyses of the remaining secondary endpoints were considered supportive or exploratory. No prespecified statistical plan was in place to determine statistical significance of these endpoints. The results of those endpoints were described with nominal 95% CIs and nominal p-values without any statistical significance statements.

There were a least six predefined exploratory endpoints (note: BCVA was tested at ≥ 2 and ≥ 3 lines) proposed in the phase 3 studies. In addition to the predefined exploratory endpoints, the applicant also evaluated FTMH closure at two timepoints. Based on a conservative Bonferroni correction for multiplicity, the p-value would need to be approximately 0.007 to 0.008 to be statistically significant. None of the exploratory endpoints demonstrate replicated efficacy in the two phase 3 trials.

Efficacy Results for FTMH Endpoint (TG-MV-006 and TG-MV-007)

TG-MV-006				TG-MV-007			
Placebo n/N (%)	Ocriplasmin n/N (%)	Difference (95% CI) ^a	p-value ^b	Placebo n/N (%)	Ocriplasmin n/N (%)	Difference (95% CI) ^a	p-value ^b
Proportion of Patients with FTMH at Baseline who achieved Non-Surgical FTMH Closure at Day 28							
4/32 (12.5%)	25/57 (43.9%)	31.4 (14.1, 48.6)	0.002	1/15 (6.7%)	18/49 (36.7%)	30.1 (11.6, 48.5)	0.028
Proportion of Patients with FTMH at Baseline who achieved Non-Surgical FTMH Closure at Month 6							
5/32 (15.6%)	26/57 (45.6%)	30.0 (11.9, 48.0)	0.005	3/15 (20.0%)	17/49 (34.7%)	14.7 (-9.5, 38.9)	0.354

^a The (absolute) difference and CIs between treatment groups are based on the proportion of patients with FTMHC.

^b For individual studies, p-value is from Fisher's exact test, comparing placebo and ocriplasmin. For pooled studies, p-value is from Cochran-Mantel-Haenszel test comparing placebo and ocriplasmin, stratified by study.

FTMH was an exploratory endpoint in both of the phase 3 trials. Efficacy for this endpoint was not demonstrated.

Summary Efficacy Statement

The clinical trials submitted in support of this BLA demonstrate that a single injection of ocriplasmin 125µg is superior to vehicle for the primary efficacy endpoint of treatment of symptomatic vitreomacular adhesions (VMA).

Ocriplasmin is **not** recommended for the treatment of full thickness macular holes (FTMH) associated with VMA because the difference between groups was not statistically significant in both trials after an adjustment for multiplicity.

8. Safety

From the original Medical Officer Review finalized 9/26/2012:

The safety results from the seven completed clinical trials evaluating intravitreal injection of ocriplasmin were pooled for analyses of AEs and other safety assessments performed during the studies.

Safety results from the seven completed studies were grouped into two major pooling blocks. The first pooling block included only controlled studies without pre-planned vitrectomy. This grouping includes the following studies: TG-MV-002, TG-MV-004, TG-MV-006 and TG-MV-007. The second pooling block included all seven completed controlled and uncontrolled studies, including studies with pre-planned vitrectomy (defined as studies in which investigational drug treatment was to occur at protocol-specified times before a pre-planned vitrectomy).

DEATHS

Treatment	Study / Patient Number	Age (y)	Gender	Race	Injection Date	Date of Death	AE Resulting in Death (MedDRA Preferred Term)
Sham injection	TG-MV-002 / 011301	74	male	white	10-Dec-2008	(b) (4)	Cardiac arrest
Sham injection	TG-MV-002 / 081102	82	male	white	30-Mar-2007		Intestinal obstruction
Ocriplasmin 75µg	TG-MV-003 / 101021	75	male	white	21-Mar-2008		Myocardial infarction
Ocriplasmin 125µg	TG-MV-006 / 603008	81	female	white	22-Apr-2009		Cerebral hemorrhage
Ocriplasmin 125µg	TG-MV-006 / 622012	84	female	white	08-May-2009		Lung neoplasm malignant
Ocriplasmin 125µg	TG-MV-006 / 632008	83	female	white	22-Jul-2009		Cardiac failure congestive
Ocriplasmin 125µg	TG-MV-007 / 721008	76	female	white	16-Sep-2009		Brain cancer metastatic
Ocriplasmin 125µg	TG-MV-007 / 775003	88	female	white	11-Jun-2009		Lung neoplasm malignant

For the placebo-controlled studies (TG-MV-006 and TG-MV-007), the death rate for placebo was 0/187 (0.0%); and the death rate for ocriplasmin (125µg) was 5/465 (1.1%).

Overall, for all the studies combined, 8 deaths occurred during the clinical development program: 6/741 (0.8%) ocriplasmin-treated patients and 2/247 (0.8%) placebo or sham controlled patients.

NONFATAL SERIOUS ADVERSE EVENTS

	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo N=187		Ocriplasmin 125µg N=465		Control ^a N=247		Ocriplasmin Any Dose N=741	
Preferred Term	n	%	n	%	n	%	n	%
Number of ocular SAEs	20	(10.7%)	37	(8.0%)	22	(8.9%)	59	(8.0%)
Study eye	20	(10.7%)	36	(7.7%)	22	(8.9%)	57	(7.7%)
Non-study eye	0		2	(0.4%)	0		3	(0.4%)
Study eye SAEs by Preferred Term								
Macular hole	16	(8.6%)	24	(5.2%)	16	(6.5%)	35	(4.7%)
Vitreous adhesions	1	(0.5%)	5	(1.1%)	2	(0.8%)	5	(0.7%)
Visual acuity reduced	1	(0.5%)	3	(0.6%)	1	(0.4%)	3	(0.4%)
Retinal detachment	3	(1.6%)	2	(0.4%)	3	(1.2%)	4	(0.5%)
Eye inflammation	0		1	(0.2%)	0		1	(0.1%)
Hyphema	0		1	(0.2%)	1	(0.4%)	1	(0.1%)
Posterior capsule opacification	0		1	(0.2%)	0		2	(0.3%)
Vitreous hemorrhage	0		1	(0.2%)	1	(0.4%)	1	(0.1%)
Macular edema	1	(0.5%)	0		1	(0.4%)	1	(0.1%)
Cataract	0		0		0		3	(0.4%)

Optic disc vascular disorder	0		0		0		1	(0.1%)
Retinal artery occlusion	0		0		0		1	(0.1%)
Retinal vein occlusion	0		0		0		1	(0.1%)
Intraocular pressure increased	0		0		0		1	(0.1%)
Anterior chamber inflammation	0		0		0		1	(0.1%)
Choroidal detachment	0		0		0		1	(0.1%)
Macular degeneration	0		0		0		1	(0.1%)
Retinal tear	0		0		0		1	(0.1%)
Cataract traumatic	0		0		0		1	(0.1%)
Choroidal hemorrhage	0		0		1	(0.4%)	0	

^a Patients allocated to placebo, sham injection or no treatment.

There are no significant differences in the rate of serious non-fatal adverse events between ocriplasmin and placebo.

DROPOUTS AND/OR DISCONTINUATIONS

	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo N=187		Ocriplasmin 125µg N=465		Control ^a N=247		Ocriplasmin Any Dose N=741	
	n	(%)	n	(%)	n	(%)	n	(%)
Safety set	187	(100.0%)	465	(100.0%)	247	(100.0%)	741	(100.0%)
Completed study	171	(91.4%)	436	(93.8%)	228	(92.3%)	701	(94.6%)
Discontinued from study	16	(8.6%)	29	(6.2%)	19	(7.7%)	40	(5.4%)
Reasons for discontinuation								
Adverse event	2	(1.1%)	4 ^b	(0.9%)	2	(0.8%)	7 ^c	(0.9%)
Investigator decision	1	(0.5%)	0		1	(0.4%)	0	
Withdrew consent	8	(4.3%)	13	(2.8%)	9	(3.6%)	17	(2.3%)
Lost to follow-up	5	(2.7%)	8	(1.7%)	5	(2.0%)	10	(1.3%)
Death ^d	0		4	(0.9%)	2	(0.8%)	5	(0.7%)
Other	0		0		0		1	(0.1%)

^a Patients allocated to placebo, sham injection, or no treatment

^b Patient 721008 discontinued the study due to an AE (metastatic brain cancer, unrelated to ocriplasmin) and subsequently died due to this condition more than 30 days after study discontinuation and is therefore counted in this table in the "Adverse event" row rather than the "Death" row.

^c In the clinical database and in [Tables 1.1.2](#) and [1.1.3](#), the reason for discontinuation was reported as "Other" for

Patient 001304 and as "Investigator decision" for Patient 002406. After reviewing these cases, the Sponsor concluded that "Adverse event" was a more appropriate reason for discontinuation for these patients. Therefore, each patient is counted in the "Adverse event" row rather than the "Investigator decision" and "Other" rows.

^dDeaths were due to non-ocular AEs and were considered unrelated to study drug.

Patients with Adverse Events Leading to Study Withdrawal (Safety Set)

Treatment	Study / Patient Number	Age (y)	Gender	Race	Injection Date	Last Study Visit Attended by Patient	AE Leading to Withdrawal
Placebo	TG-MV-006/601002	64	male	white	06JAN2009	Month 3	spondylolisthesis
Placebo	TG-MV-006/638003	64	female	black	15JUN2009	Month 3	cataract subcapsular
Ocriplasmin 25µg ^a	TG-MV-001/001304	61	male	unknown ^b	21NOV2005	Day 90	recurrent retinal detachment
Ocriplasmin 50µg ^c	TG-MV-001/002406	82	male	unknown ^b	09MAR2006	Day 3	pancreatic carcinoma
Ocriplasmin 75µg	TG-MV-003/108014	69	female	white	25MAR2008	Day 90	macular edema
							retinal depigmentation
							vitreous inflammation
Ocriplasmin 125µg	TG-MV-006/603007	62	female	white	14APR2009	Month 3	breast cancer
Ocriplasmin 125µg	TG-MV-006/627008	65	female	white	26AUG2009	Month 3	pancreatic carcinoma
Ocriplasmin 125µg	TG-MV-007/721008	76	female	white	16SEP2009	Day 7	brain cancer metastatic
Ocriplasmin 125µg	TG-MV-007/774004	65	female	white	05NOV2009	Month 3	breast cancer

a In the clinical database, the reason for withdrawal is reported as "Other".

b Race was not recorded in [TG-MV-001](#)

c In the clinical database, the reason for withdrawal was reported as "Investigator decision".

In review of the cases of adverse events that led to study withdrawal, the majority were due to existing systemic medical conditions. There are no significant differences in the rate of study withdrawal due to adverse events between ocriplasmin and placebo.

COMMON ADVERSE EVENTS

System Organ Class Preferred Term Category	Phase 3 Placebo-Controlled Studies				All Studies Combined			
	Placebo N=187		Ocriplasmin 125µg N=465		Control ¹⁾ N=247		Ocriplasmin Any Dose N=741	
Number of adverse events	n	%	n	%	n	%	n	%
Any event	129	(69.0%)	356	(76.6%)	180	(72.9%)	593	(80.0%)
Any non-ocular event	53	(28.3%)	140	(30.1%)	82	(33.2%)	255	(34.4%)
Any ocular event	106	(56.7%)	324	(69.7%)	149	(60.3%)	538	(72.6%)
Study eye event	99	(52.9%)	317	(68.2%)	141	(57.1%)	529	(71.4%)
Non-study eye event	22	(11.8%)	61	(13.1%)	29	(11.7%)	101	(13.6%)
Eye disorders								
Any event	101	(54.0%)	321	(69.0%)	142	(57.5%)	518	(69.9%)
Study eye event	95	(50.8%)	314	(67.5%)	135	(54.7%)	510	(68.8%)
Non-study eye event	20	(10.7%)	57	(12.3%)	26	(10.5%)	90	(12.1%)
Ocular AEs²⁾								
Vitreous floaters	16	(8.6%)	82	(17.6%)	20	(8.1%)	123	(16.6%)
Conjunctival hemorrhage	24	(12.8%)	68	(14.6%)	49	(19.8%)	129	(17.4%)
Eye pain	11	(5.9%)	62	(13.3%)	19	(7.7%)	91	(12.3%)
Photopsia	5	(2.7%)	56	(12.0%)	7	(2.8%)	67	(9.0%)
Vision blurred	8	(4.3%)	41	(8.8%)	9	(3.6%)	50	(6.7%)
Macular hole	19	(10.2%)	36	(7.7%)	20	(8.1%)	56	(7.6%)
Visual acuity reduced	9	(4.8%)	30	(6.5%)	9	(3.6%)	42	(5.7%)
Visual impairment ³⁾	3	(1.6%)	26	(5.6%)	3	(1.2%)	28	(3.8%)
Retinal edema	2	(1.1%)	25	(5.4%)	2	(0.8%)	32	(4.3%)
Macular edema	3	(1.6%)	19	(4.1%)	10	(4.0%)	45	(6.1%)
Intraocular pressure increased	10	(5.3%)	18	(3.9%)	17	(6.9%)	65	(8.8%)
Anterior chamber cell	5	(2.7%)	17	(3.7%)	12	(4.9%)	57	(7.7%)
Photophobia ⁴⁾	0		17	(3.7%)	0		25	(3.4%)
Vitreous detachment	3	(1.6%)	13	(2.8%)	3	(1.2%)	14	(1.9%)
Ocular discomfort	2	(1.1%)	13	(2.8%)	4	(1.6%)	17	(2.3%)
Iritis	1	(0.5%)	13	(2.8%)	1	(0.4%)	13	(1.8%)
Cataract	8	(4.3%)	12	(2.6%)	12	(4.9%)	39	(5.3%)
Dry eye	2	(1.1%)	11	(2.4%)	3	(1.2%)	14	(1.9%)
Metamorphopsia	1	(0.5%)	11	(2.4%)	1	(0.4%)	15	(2.0%)
Conjunctival hyperemia	4	(2.1%)	10	(2.2%)	6	(2.4%)	25	(3.4%)
Vitreous adhesions	2	(1.1%)	10	(2.2%)	3	(1.2%)	13	(1.8%)
Retinal degeneration	1	(0.5%)	10	(2.2%)	1	(0.4%)	13	(1.8%)
Eye irritation	6	(3.2%)	9	(1.9%)	9	(3.6%)	19	(2.6%)
Maculopathy	4	(2.1%)	9	(1.9%)	9	(3.6%)	25	(3.4%)
Eye pruritus	3	(1.6%)	9	(1.9%)	3	(1.2%)	25	(3.4%)
Foreign body sensation in eyes	3	(1.6%)	9	(1.9%)	6	(2.4%)	16	(2.2%)
Punctate keratitis	2	(1.1%)	9	(1.9%)	2	(0.8%)	10	(1.3%)
Conjunctival edema	5	(2.7%)	8	(1.7%)	6	(2.4%)	13	(1.8%)

Retinal hemorrhage	4 (2.1%)	8 (1.7%)	11 (4.5%)	29 (3.9%)
Blepharitis	2 (1.1%)	8 (1.7%)	3 (1.2%)	13 (1.8%)
Conjunctival bleb	2 (1.1%)	8 (1.7%)	2 (0.8%)	9 (1.2%)
Retinal pigment epitheliopathy	0	8 (1.7%)	4 (1.6%)	25 (3.4%)
Lacrimation increased	2 (1.1%)	7 (1.5%)	4 (1.6%)	14 (1.9%)
Eyelid edema	1 (0.5%)	7 (1.5%)	8 (3.2%)	22 (3.0%)
Retinal tear	5 (2.7%)	6 (1.3%)	7 (2.8%)	25 (3.4%)
Conjunctivitis	2 (1.1%)	6 (1.3%)	3 (1.2%)	8 (1.1%)
Anterior chamber flare	2 (1.1%)	6 (1.3%)	8 (3.2%)	32 (4.3%)
Macular degeneration	2 (1.1%)	6 (1.3%)	2 (0.8%)	13 (1.8%)
Cataract nuclear	4 (2.1%)	5 (1.1%)	12 (4.9%)	29 (3.9%)
Ocular hyperemia	1 (0.5%)	5 (1.1%)	1 (0.4%)	15 (2.0%)
Scotoma	0	5 (1.1%)	0	5 (0.7%)
Miosis	0	5 (1.1%)	0	5 (0.7%)
Corneal abrasion	0	5 (1.1%)	1 (0.4%)	7 (0.9%)
Vitreous hemorrhage	3 (1.6%)	4 (0.9%)	6 (2.4%)	15 (2.0%)
Posterior capsule opacification	3 (1.6%)	4 (0.9%)	5 (2.0%)	10 (1.3%)
Retinal detachment	3 (1.6%)	4 (0.9%)	4 (1.6%)	11 (1.5%)
Macular cyst	2 (1.1%)	4 (0.9%)	2 (0.8%)	4 (0.5%)
Cataract cortical	3 (1.6%)	3 (0.6%)	5 (2.0%)	5 (0.7%)
Corneal disorder	3 (1.6%)	3 (0.6%)	3 (1.2%)	7 (0.9%)
Corneal erosion	2 (1.1%)	3 (0.6%)	3 (1.2%)	6 (0.8%)
Eyelid ptosis	2 (1.1%)	1 (0.2%)	3 (1.2%)	2 (0.3%)
Vitreous opacities	2 (1.1%)	1 (0.2%)	3 (1.2%)	2 (0.3%)
Vitritis	0	2 (0.4%)	2 (0.8%)	13 (1.8%)
Cataract subcapsular	0	0	2 (0.8%)	8 (1.1%)
Corneal edema	0	0	3 (1.2%)	5 (0.7%)
Non-Ocular AEs				
Bronchitis	3 (1.6%)	13 (2.8%)	5 (2.0%)	16 (2.2%)
Headache	4 (2.1%)	12 (2.6%)	11 (4.5%)	32 (4.3%)
Nausea	1 (0.5%)	12 (2.6%)	3 (1.2%)	22 (3.0%)
Nasopharyngitis	5 (2.7%)	9 (1.9%)	9 (3.6%)	21 (2.8%)
Upper respiratory tract infection	2 (1.1%)	7 (1.5%)	3 (1.2%)	10 (1.3%)
Urinary tract infection	2 (1.1%)	7 (1.5%)	4 (1.6%)	7 (0.9%)
Dyspnea	1 (0.5%)	7 (1.5%)	1 (0.4%)	9 (1.2%)
Back pain	1 (0.5%)	6 (1.3%)	1 (0.4%)	8 (1.1%)
Influenza	2 (1.1%)	5 (1.1%)	3 (1.2%)	14 (1.9%)
Arthralgia	2 (1.1%)	3 (0.6%)	2 (0.8%)	3 (0.4%)
Oropharyngeal pain	2 (1.1%)	3 (0.6%)	2 (0.8%)	4 (0.5%)
Sinusitis	3 (1.6%)	2 (0.4%)	4 (1.6%)	7 (0.9%)
Constipation	2 (1.1%)	2 (0.4%)	3 (1.2%)	3 (0.4%)

Toothache	2 (1.1%)	2 (0.4%)	2 (0.8%)	2 (0.3%)
Vomiting	2 (1.1%)	2 (0.4%)	2 (0.8%)	5 (0.7%)
Insomnia	2 (1.1%)	2 (0.4%)	4 (1.6%)	4 (0.5%)
Pneumonia	2 (1.1%)	1 (0.2%)	3 (1.2%)	2 (0.3%)
Pyrexia	2 (1.1%)	1 (0.2%)	2 (0.8%)	1 (0.1%)
Anemia	2 (1.1%)	1 (0.2%)	2 (0.8%)	1 (0.1%)
Muscle strain	2 (1.1%)	0	2 (0.8%)	0
Gout	2 (1.1%)	0	2 (0.8%)	0

- 1 Patients allocated to placebo, sham-injection or no treatment.
- 2 Includes study eye and non-study eye AEs.
- 3 The verbatim term entopic phenomena (as can occur in setting of PVD) was conservatively coded to the preferred term (PT) visual impairment instead of floaters/photopsia in the appendix tables and in-text tables.
- 4 Two reports of photosensitivity (Patient 602-001 and Patient 602-005, Study TG-MV-006) that occurred in the study eye were coded to the preferred term Photosensitivity reaction. These events may represent 2 additional reports of photophobia.

Adverse events in the above table are listed in order of frequency seen in the ocriplasmin groups with those events highlighted that occur at a rate of ≥ 2 times the rate of the placebo group. While several adverse events seen are consistent with the known adverse events associated with intraocular injections, many occur at a much higher rate in the ocriplasmin group which may suggest a drug related effect in addition to the background rate. These events include eye pain, ocular discomfort, and iritis.

In addition there are several adverse events which occur at a much higher rate in ocriplasmin treated patients which raise concerns about the drugs potential effect on the retina. Photopsia, blurred vision, visual impairment, retinal edema, macular edema, metamorphopsia and retinal degeneration occur at a rate of 2-4 times more in the ocriplasmin group versus placebo. Photopsia is known to occur during release of traction and may be the result of a higher incidence of adhesions in the drug group.

VISUAL ACUITY

Categorical Change from Baseline in Best Corrected Visual Acuity at Day 28 and Month 6 (Full Analysis Set)-Study 006

Time Point	Placebo (N=107)	Ocriplasmin (N=219)	Difference (95% CI) ^a	p-value ^b
	n (%)	n (%)		
At Least 1 Line Improvement				
Day 28	37 (34.6)	79 (36.1)	1.5 (-9.5, 12.5)	0.807
Month 6	38 (35.5)	99 (45.2)	9.7 (-1.5, 20.9)	0.120
At Least 2 Lines Improvement				
Day 28	9 (8.4)	42 (19.2)	10.8 (3.4, 18.2)	0.014
Month 6	18 (16.8)	66 (30.1)	13.3 (4.0, 22.7)	0.010

At Least 3 Lines Improvement				
Day 28	4 (3.7)	17 (7.8)	4.0 (-1.0, 9.1)	0.230
Month 6	9 (8.4)	28 (12.8)	4.4 (-2.5, 11.2)	0.270
At Least 3 Lines Worsening				
Day 28	1 (0.9)	5 (2.3)	1.3 (-1.3, 4.0)	0.668
Month 6	2 (1.9)	16 (7.3)	5.4 (1.1, 9.7)	0.067
At Least 6 Lines Worsening				
Day 28	0	3 (1.4)	1.4 (-0.2, 2.9)	0.554
Month 6	1 (0.9)	3 (1.4)	0.4 (-2.0, 2.8)	>0.999

CI=confidence interval

a The (absolute) difference and CIs between treatment groups are based on the percentage of successes.

b p-value is from Fisher's exact test, comparing placebo and ocriplasmin.

**Categorical Change from Baseline in Best Corrected Visual Acuity at Day 28
 and Month 6 (Full Analysis Set)-Study 007**

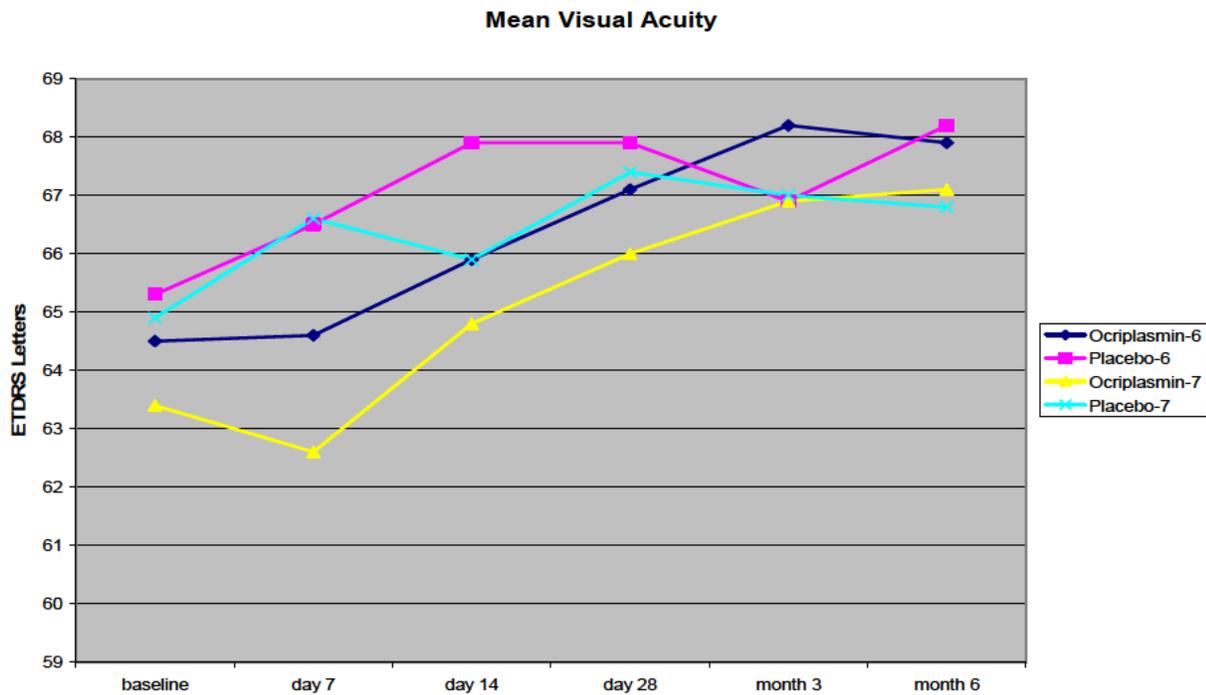
Time Point	Placebo (N=81) ^a	Ocriplasmin (N=245)	Difference (95% CI) ^b		p-value ^c
	n (%)	n (%)			
At Least 1 Line Improvement					
Day 28	32 (40.0)	82 (33.5)	-6.5 (-18.8, 5.7)		0.345
Month 6	34 (42.5)	106 (43.3)	0.8 (-11.7, 13.2)		>0.999
At Least 2 Lines Improvement					
Day 28	7 (8.8)	37 (15.1)	6.4 (-1.3, 14.0)		0.188
Month 6	14 (17.5)	64 (26.1)	8.6 (-1.4, 18.6)		0.133
At Least 3 Lines Improvement					
Day 28	3 (3.8)	11 (4.5)	0.7 (-4.2, 5.6)		>0.999
Month 6	3 (3.8)	29 (11.8)	8.1 (2.3, 13.9)		0.049
At Least 3 Lines Worsening					
Day 28	0	2 (0.8)	0.8 (-0.3, 1.9)		>0.999
Month 6	4 (5.0)	10 (4.1)	-0.9 (-6.3, 4.5)		0.753
At Least 6 Lines Worsening					
Day 28	0	0	0.0 (0.0, 0.0)		----
Month 6	1 (1.3)	3 (1.2)	-0.0 (-2.8, 2.8)		>0.999

One subject did not have a BCVA measurement at Baseline; therefore, the denominator used in this analysis is 80 for the placebo group.

b The (absolute) difference and CIs between treatment groups are based on the percentage of successes.

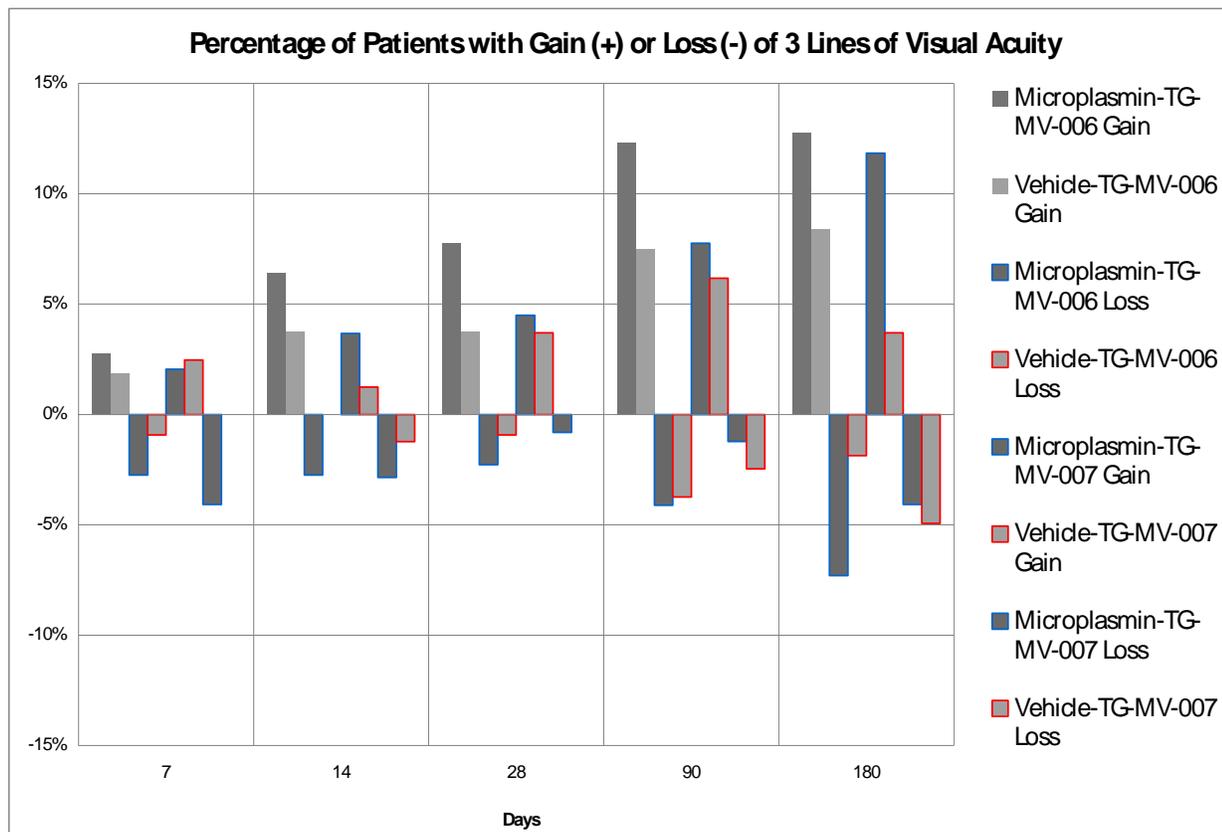
c p-value is from Fisher's exact test, comparing placebo and ocriplasmin.

The number of patients with at least 3 lines increase in visual acuity was numerically higher in the ocriplasmin group compared to placebo in both of the phase 3 trials. Although the improvement in visual acuity at Month 6 seems to favor the ocriplasmin treated group, more patients in the ocriplasmin treated group had ≥ 2 -line or 3-line **worsening** in visual acuity compared with the placebo group in study TG-MV-006. The proportion of patients with a ≥ 3 lines (15 letters) worsening in the visual acuity was much higher in the ocriplasmin treated group compared with the placebo group (7.3% versus 1.9%, respectively).



Compared to placebo treated patients, more ocriplasmin treated patients had worsening of BCVA as well as improvement of BCVA at Month 6; consequently, there was no difference between the ocriplasmin group and the placebo group in the change from baseline of BCVA at Month 6. The mean change from baseline in BCVA at Month 6 were similar for both the ocriplasmin and placebo groups in study TG-MV-006 (ocriplasmin vs. placebo: 3.5 vs. 2.8 letters) and study TG-MV-007 (ocriplasmin vs. placebo: 3.6 vs. 2.1 letters).

A review of subjects that loss ≥ 3 lines of vision at any point during the clinical trial was done since this may indicate a safety concern potentially related to the effect of ocriplasmin on the retina. Subjects who underwent vitrectomy during the study were not included since surgery would account for the decrease in vision. There were approximately 5.8% (27/465) ocriplasmin subjects and 2.1% (4/187) placebo subjects who experience ≥ 3 lines of vision loss.



An analysis of the reason for vision decrease as it relates to the OCT findings was requested and conducted by the sponsor. Based on this data, it appears that the overwhelming majority of vision decreases was due to progression in VMT or MH progression in both the ocriplasmin and placebo groups. Twenty three of twenty seven (23/27) ocriplasmin subjects and 3/4 placebo subjects had a progression in VMT/MH on OCT which could account for the decrease in visual acuity.

See also the Medical Officer’s 120-Day Safety Update Review finalized 9/26/2012, page 13, for additional detail on ≥ 2 -Line Loss in BCVA in Phase 3 Studies.

DYSCHRMATOPSIA AND LENS SUBLUXATION

Dyschromatopsia was reported in 16 of 820 patients (2.0%). The majority of cases were reported from 2 uncontrolled open-label clinical studies (TGMV-008 and TG-MV-010) that were conducted in the same (single) center where the intravitreal injections were administered by the same investigator. Eight of the 16 patients with dyschromatopsia were also found to have ERG changes. In 13 of the 16 cases, the dyschromatopsia resolved. Of the remaining 3 patients, 1 patient died after completion of the study, 1 patient was lost to follow-up and 1 patient is being followed for resolution.

Lens instability was observed during vitrectomy in 1 patient 323 days after the patient was treated with ocriplasmin. Lens subluxation was observed during vitrectomy in a 4-month old premature infant. He received a single intravitreal injection of ocriplasmin 175µg in the left eye approximately 1

hour before vitrectomy for retinopathy of prematurity. The same infant received ocriplasmin 175µg in the fellow eye 1 week later with no reported lens subluxation.

IOP MEASUREMENT

The mean IOP at Baseline and the mean change from Baseline at each visit were similar for the ocriplasmin 125µg and placebo groups. No patient in either the ocriplasmin or placebo group had an IOP > 30mmHg at any study visit.

RETINAL BREAKS

	Pivotal Placebo-Controlled Studies						All Studies Combined					
	Placebo N=187			Ocriplasmin 125µg N=465			Control ^a N=247			Ocriplasmin Any Dose N=741		
Preferred Term	n	%	E	n	%	E	n	%	E	n	%	E
Any event	8	(4.3%)	11	9	(1.9%)	10	11	(4.5%)	15	33	(4.5%)	40
Retinal tear	5	(2.7%)	6	6 ^b	(1.3%)	6	7	(2.8%)	8	25 ^b	(3.4%)	25
Retinal detachment	3	(1.6%)	5	4	(0.9%)	4	4	(1.6%)	7	11	(1.5%)	15

^a Patients allocated to placebo, sham injection or no treatment.

^b The convention used in the setting of retinal detachment was to report the overriding retinal detachment as an AE and not report the associated retinal tear separately. In 1 ocriplasmin patient in the pivotal placebo-controlled studies and in 3 ocriplasmin patients in all studies combined (including the patient from the pivotal placebo-controlled studies), the associated retinal tear was also reported as an AE along with the AE of retinal detachment. Therefore, the percent of patients in the ocriplasmin group with retinal tear without detachment is 1.1% and 3.0% in the pivotal placebo-controlled studies and in all studies combined, respectively.

The majority of retinal breaks occurred during or after vitrectomy: 2 (0.4%) retinal detachments in the ocriplasmin group and 1 (0.5%) retinal tear in the placebo group occurred prior to any vitrectomy. Note that the incidence of iatrogenic retinal breaks with vitrectomy has been reported to be approximately 15% (1.2-6.6% retinal detachment rate).

CATARACT

	Pivotal Placebo-Controlled Studies						All Studies Combined					
	Placebo N=187			Ocriplasmin 125µg N=465			Control ^a N=247			Ocriplasmin Any Dose N=741		
Preferred Term	n	%	E	n	%	E	n	%	E	n	%	E
Any event	17	(9.1%)	19	26	(5.6%)	28	29	(11.7%)	40	77	(10.4%)	102
Cataract	8	(4.3%)	8	11	(2.4%)	11	12	(4.9%)	12	34	(4.6%)	36
Cataract nuclear	3	(1.6%)	3	5	(1.1%)	5	11	(4.5%)	15	29	(3.9%)	35
Cataract subcapsular	1	(0.5%)	1	4	(0.9%)	5	2	(0.8%)	2	8	(1.1%)	14
Posterior capsule opacification	3	(1.6%)	3	4	(0.9%)	4	5	(2.0%)	5	10	(1.3%)	10
Cataract cortical	3	(1.6%)	4	3	(0.6%)	3	5	(2.0%)	6	5	(0.7%)	5
Lenticular opacities	0		0	0		0	0		0	2	(0.3%)	2

^a Patients allocated to placebo, sham injection or no treatment.

Subjects treated with ocriplasmin do not have an increased risk of developing cataracts compared to placebo.

Safety Summary Statement

There was no statistically significant difference in the rate of common adverse events or serious adverse events in the study eye between the ocriplasmin treated patients and placebo overall.

It was noted that in one of the phase 3 trials that the proportion of patients with a ≥ 3 lines (15 letters) worsening in the visual acuity was much higher in the ocriplasmin treated group compared with the placebo group (7.3% versus 1.9%, respectively). The number of patients with at ≥ 3 lines increase in visual acuity was numerically higher in the ocriplasmin group compared to placebo in both of the phase 3 trials, therefore there was no difference between the ocriplasmin group and the placebo group in the change from baseline of BCVA at Month 6.

An analysis of the reason for vision decrease findings was requested and conducted by the Thrombogenics. Based on this data submitted to the Division, it appears that the overwhelming majority of vision decreases were due to progression in VMT or MH progression in both the ocriplasmin and placebo groups. Twenty three (23/27) ocriplasmin subjects and 3/4 placebo subjects had a progression in VMT/MH on OCT which could account for the decrease in visual acuity.

9. Advisory Committee Meeting

An Advisory Committee meeting was held for ocriplasmin on July 26, 2012. Michael X. Repka, M.D., Professor of Ophthalmology and Pediatrics at the Wilmer Ophthalmological Institute, chaired the meeting. A synopsis of the outcome of this meeting follows.

1) **VOTE:** Has substantial evidence been provided to demonstrate that ocriplasmin 125 μ g is effective for the treatment of vitreomacular adhesions?

YES: 10 NO: 0 ABSTAIN: 0

Committee Discussion: The committee unanimously agreed that substantial evidence has been provided to demonstrate that ocriplasmin 125 μ g is effective for the treatment of vitreomacular adhesions. However, some of the committee members noted concerns with the secondary efficacy endpoints. In addition, some committee members noted they would like to see a more robust effect size.

2) **VOTE:** Has substantial evidence been provided to demonstrate that ocriplasmin 125 μ g is effective for the treatment of macular holes associated with vitreomacular adhesions?

YES: 7 NO: 3 ABSTAIN: 0

Committee Discussion: The majority of the committee agreed that substantial evidence has been provided to demonstrate that ocriplasmin 125 μ g is effective for the treatment of macular holes associated with vitreomacular adhesions. The committee members who voted "Yes" noted that the data was favorable. Those who voted "No" were concerned that the sample size of the secondary endpoint presented by the Sponsor was not sufficient to make a determination.

3) **VOTE:** Has substantial evidence been provided to demonstrate that ocriplasmin 125µg is effective for the treatment of all macular holes regardless of the presence of adhesions?

YES: 1 NO: 8 ABSTAIN: 1

***Committee Discussion:** The majority of the committee agreed that substantial evidence has not been provided to demonstrate that ocriplasmin 125µg is effective for the treatment of all macular holes regardless of the presence of adhesions. The committee noted that there was no data presented by the Sponsor regarding this proposed indication.*

4) **VOTE:** Are additional studies needed prior to approval to evaluate the safety of ocriplasmin's effect on the retina?

YES: 3 NO: 6 ABSTAIN: 1

***Committee Discussion:** The majority of the committee agreed that additional studies are not needed prior to approval to evaluate the safety of ocriplasmin's effect on the retina.*

a) **DISCUSSION:** If so, what studies?

***Committee Discussion:** The majority agreed that no additional studies are needed prior to approval. In summary, the panel felt that the additional studies of the drug prior to approval for safety were not necessary, that there was some discomfort with the current outcomes and additional review of those outcomes, particularly the OCT data, may be of benefit.*

5) **VOTE:** Do the benefits of administering ocriplasmin for the treatment of vitreomacular adhesions outweigh the potential risks?

YES: 10 NO: 0 ABSTAIN: 0

***Committee Discussion:** The committee unanimously agreed that the benefits of administering ocriplasmin for the treatment of vitreomacular adhesions outweigh the potential risks. However, some committee members noted the concern that ocriplasmin will benefit a proportion, not the majority, of the population.*

6) **DISCUSSION:** If this product is approved, are there any suggestions concerning labeling for this product?

***Committee Discussion:** In summary, the committee suggested the following information to be included in the labeling of ocriplasmin:*

- *State "for single use in one eye only"*
- *Include the term "symptomatic" in the indication*
- *Patient information should accompany the labeling*

10. Pediatrics

Safety and effectiveness in pediatric patients have not been established. Jetrea (ocriplasmin) Intravitreal Injection 2.5 mg/mL went to the Pediatric Review Committee (PeRC) on 10/3/12. Pediatric studies are being deferred [REDACTED] (b) (4) because the product is ready for approval in adults; an ongoing pediatric phase 2 study TG-MV-009 entitled “The MIC (Microplasmin In Children) Trial: A randomized, placebo-controlled, double-masked, clinical trial of intravitreal microplasmin in infants and children scheduled for vitrectomy” will not be finished in time for the assessment for the indication in pediatric patients.

The clinical study report will be available for submission later in 2012.

11. Other Relevant Regulatory Issues

BIOSTATISTICS

Per the original Biostatistics review finalized 9/21/2012:

Based on non-clinical and several Phase I and II study results, the Applicant conducted two Phase 3 pivotal studies (TG-MV-006 and TG-MV-007) to assess the efficacy and safety of 125µg intravitreal ocriplasmin in subjects with symptomatic VMA (i.e. focal VMA leading to symptoms). Both studies were multicenter, randomized, placebo-controlled, double-masked, 6-month studies that investigated the safety and efficacy of a single intravitreal injection of ocriplasmin 125µg in patients with symptomatic VMA (i.e. focal VMA leading to symptoms).

In both studies TG-MV-006 and TG-MV-007, ocriplasmin 125 µg showed statistical superiority over placebo in achieving the primary efficacy endpoint, resolution of focal VMA at post-injection Day 28, as determined by masked CRC evaluation of OCT scans. In the Full Analysis Set, in study TG-MV-006, more patients treated with ocriplasmin had resolution of VMA at Day 28, compared with placebo: 27.9% versus 13.1%, respectively, with absolute difference between treatment groups of 14.8% (95% CI: 6.0% – 23.5%, $P=0.003$); and in study TG-MV-007, 25.3% versus 6.2% with absolute difference of 19.1% (95% CI: 11.6% – 26.7%, $P<0.001$).

Based on the results of both studies, the statistical reviewer recommends the approval of ocriplasmin for the treatment of symptomatic vitreomacular adhesion (VMA).

The Applicant seeks labeling claim of treatment of VMA including macular hole. The addition “including macular hole” in the labeling claim was based on the results of the secondary endpoint “full thickness macular hole closure (FTMHC)”. The statistical review does not recommend this addition in the labeling because the current Phase 3 studies do not have adequate statistical evidence to support this additional claim.

DMEPA

Thrombogenics submitted the proprietary name, [REDACTED] (b) (4) on 7/15/2010 under IND 100370. This name was found conditionally acceptable by DMEPA on 1/12/2011.

On 6/24/2011, Thrombogenics requested to withdraw the proprietary name, (b) (4), and the name was withdrawn on 6/27/2011. No reason was provided for withdrawing the name. On 2/2/2012, the proposed proprietary name, Jetrea, was submitted to the IND. On 4/17/2012, Thrombogenics submitted BLA 125422, which was given priority review status. The request for proprietary name review under the BLA was submitted on 4/26/2012.

The proposed proprietary name, Jetrea, was found acceptable from both a promotional and safety perspective, and Thrombogenics was informed in a letter dated 7/25/2012. As of the date of this review, DMEPA provided formal labeling comments for the package insert and carton and container labeling in a review dated 10/2/2012; they participated in the review team labeling meetings held 10/2/2012 and 10/3/2012.

FINANCIAL DISCLOSURE

Thrombogenics has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for ocriplasmin. There were three investigators who participated in the phase 3 safety and efficacy trials that disclosed financial ties to the sponsor/applicant.

Investigators with Financial Interests or Arrangements

Details of (b) (6) disclosable financial arrangements

Study	Site N°	LPI-LPO	Financial Disclosure Form	Enrolment by site
(b) (6)	(b) (6)	(b) (6)	disclosable info	(b) (6) patients
			disclosable info	patients
			disclosable info	patients

Details of (b) (6) disclosable financial arrangements

Study	Site N°	LPI-LPO	Financial Disclosure Form	Enrolment by site
(b) (6)	(b) (6)	(b) (6)	disclosable info	(b) (6) patients
			disclosable info	(b) (6) patients
			disclosable info	(b) (6) patients

Details of (b) (6) disclosable financial arrangements

Study	Site N°	LPI-LPO	Financial Disclosure Form	Enrolment by site
(b) (6)	(b) (6)	(b) (6)	disclosable info	(b) (6) patients
			disclosable info	(b) (6) patients

A review of these arrangements do not raise question about the integrity of the clinical data.

OSI

An Office of Scientific Investigations (OSI) audit was requested; OSI completed their review on 10/1/2012. Per the DSI review:

Four domestic clinical investigators were selected for inspection, mainly due to enrollment of large numbers of study subjects, high number of INDs, and previous inspectional history. There was no site specific safety or efficacy concern.

Based on these four inspections, the data appear reliable and can be used in support of this application.

DRISK

In a review finalized 10/4/2012, Division of Risk Management (DRISK) agrees that labeling and routine pharmacovigilance measures are appropriate for ocriplasmin.

Name of CI	Protocol # /Site # and # of Subjects enrolled:	Inspection Date	Classification
Matthew Benz, M.D. Vitreoretinal Consultants 6560 Fannin Street, Ste 750 Houston, TX 77030	TG-MV-006 Site 601 n=20 subjects	June 25 to June 28, 2012	Pending (Preliminary Classification NAI)
Carl Baker, M.D. Paducah Retinal Center 1900 Broadway Street, Ste. 2 Paducah, KY 42001, USA	TG-MV-007 Site 764 n=16 subjects	July 16 to July 18, 2012	Pending (Preliminary Classification NAI)
J. Michael Jumper, M.D. West Coast Retina Group, Inc 185 Berry Street Suite 130 San Francisco, CA 94107, USA	TG-MV-007 Site 719 n=14 subjects	June 25 to July 9, 2012	Pending (Preliminary Classification NAI)
Michael Tolentino, M.D. Center for Retina and Macular Disease 250 Avenue K SW, Suite 200 Winter Haven, FL 33880	TG-MV-006 Site 622 n=18 subjects	July 9 to July 25, 2012	Pending (Preliminary Classification VAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

Regarding the preliminary VAI classification for Dr. Tolentino:

- The review of source document files revealed that two subjects (Subject 014 and 015) had experienced adverse events (nausea and vomiting) during the fluorescein angiography procedures that were not reported on the case report forms.
- One subject (Subject 005) had out of window study visits for visits 3 (by 1 day), 4 (by 3 days) & 5 (by 4 days).
- There were discrepancies in data initially recorded on source documents that were later changed to reflect data submitted in the electronic case report forms (eCRF) for 5 subjects (Subjects 004, 005, 006, 008, 015). The changes were not reviewed/approved by the principal clinical investigator and were made without properly documenting the reasons for such changes.

12. Labeling

BLA 125422 for Jetrea (ocriplasmin) Intravitreal Injection 2.5 mg/mL, is recommended for approval for the treatment of vitreomacular adhesion (VMA) with the revised package insert and carton and container labeling found in this CDTL review and transmitted to the applicant on 10/11/12 (see Appendix).

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

BLA 125422 for Jetrea (ocriplasmin) Intravitreal Injection 2.5 mg/mL, is recommended for approval for the treatment of vitreomacular adhesion (VMA) with the revised package insert and carton and container labeling found in this CDTL review (see Appendix).

RISK BENEFIT ASSESSMENT:

The clinical trials submitted in support of this BLA (study TG-MV-006 and TG-MV-007) demonstrate that a single injection of ocriplasmin 125µg is superior to vehicle for the primary efficacy endpoint of treatment of symptomatic vitreomacular adhesions (VMA).

The efficacy of this product was based on an anatomical endpoint of complete VMA resolution as documented by optical coherence topography (OCT). The clinical benefit of this anatomical finding has been documented in the literature (see Medical Officer's review finalized 9/26/12).

Ocriplasmin is **not** recommended for the treatment of full thickness macular holes (FTMH) associated with VMA. The percentage of macular hole closures in both of the phase 3 trials was numerically greater in the ocriplasmin treated patients compared to placebo; however, this difference was **not** statistically significant. FTMH was one of several endpoints evaluated by Thrombogenics that were considered supportive or exploratory with no prespecified statistical plan in place to determine statistical significance.

There was no statistically significant difference in the rate of common adverse events or serious adverse events in the study eye between the ocriplasmin treated patients and placebo overall.

It was noted that in one of the phase 3 trials that the proportion of patients with a ≥ 3 lines (15 letters) worsening in the visual acuity was much higher in the ocriplasmin treated group compared with the placebo group (7.3% versus 1.9%, respectively). The number of patients with at ≥ 3 lines increase in visual acuity was numerically higher in the ocriplasmin group compared to placebo in both of the phase 3 trials, therefore there was no difference between the ocriplasmin group and the placebo group in the change from baseline of BCVA at Month 6.

An analysis of the reason for vision decrease findings was requested and conducted by the Thrombogenics. Based on this data submitted to the Division, it appears that the overwhelming majority of vision decreases were due to progression in VMT or MH progression in both the

ocriplasmin and placebo groups. Twenty three (23/27) ocriplasmin subjects and 3/4 placebo subjects had a progression in VMT/MH on OCT which could account for the decrease in visual acuity.

Clinical, Biostatistics, Pharmacology/Toxicology, Clinical Pharmacology, and Division of Therapeutic Proteins have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

CLINICAL

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments. There is adequate information to label the product for its symptomatic vitreomacular adhesion indication and explain the risks in the proposed labeling.

PRODUCT QUALITY

The Division of Therapeutic Proteins, Office of Biotechnology Products has generated the following draft list of 25 PMC's regarding product quality, and drug substance / drug product microbiology:

We remind you of your postmarketing commitments:

1. To perform a feasibility study to adjust the drug product final fill volume or concentration to reduce the likelihood that more than one patient could be dosed from the same single use vial due to excess reconstituted drug product remaining in the vial after the initial dosing.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

2. Revise the acceptance criteria for the drug substance and drug product release and stability specifications for low pH CEX-HPLC, RP-HPLC, and low pH SEC-HPLC to include "No new peaks above the limit of quantitation" and for non-reduced SDS-PAGE "No new bands greater than the limit of quantitation."

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Interim Report Submission: 12/12
Final Report Submission: 04/13

3. Establish an upper limit for the acceptance criterion for (b) (4) potency assay or provide data to justify why this is not necessary.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 12/12

4. Evaluate and revise, as needed, the acceptance criteria for all the drug substance and release specifications based on data from at least thirty lots.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 12/15

5. Evaluate and revise, as needed, the acceptance criteria for all the drug product and release specifications based on data from at least thirty lots.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 12/17

6. Revise the system suitability criteria for RP-HPLC drug substance and drug product release and stability method to ensure adequate column performance.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

7. Revise the system suitability criteria for the SDS-PAGE the drug substance and drug product release and stability methods to establish an acceptance criterion for the (b) (4) (b) (4)

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

8. Establish the limit of quantitation for the RP-HPLC and SDS-PAGE methods.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

9. Provide data to support alternative sampling methodology for sub-visible particles testing using USP <789> monograph.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 10/12

10. Develop release and stability method(s) to detect all types of aggregates observed in your drug product. (b) (4)

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 08/13

11. Provide the results of the study conducted to evaluate the discrepancy in copy number results between the (b) (4) assay and the (b) (4) assay.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

12. Determine the approximate percentage (b) (4) by 2D SDS-PAGE or a similarly sensitive and discriminating assay.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 06/13

13. Submit a reference (standard) material qualification protocol for new primary and secondary reference materials which contains characterization testing and more stringent acceptance criteria for release assays performed as part of the qualification of the new reference materials.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

14. Conduct an extractable study for the (b) (4) rubber stoppers used for the drug product container closure (b) (4). This information should be used in the risk assessment conducted for drug product final container closure system leachable study.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 12/12

15. Conduct a quantitative (ppb and ppm) leachables study and risk assessment of leachates into the drug product in the final container closure system at the end shelf-life.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 12/13

16. Evaluate drug substance for the presence of (b) (4). Provide a risk assessment of the potential impact these (b) (4) impurities may have on the quality, safety and efficacy of ocriplasmin and propose an appropriate control strategy.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

17. Conduct a drug product stability study demonstrating that drug product stored at -70°C for 120 days followed by storage at -20°C up to the expiry (18 months) does not adversely impact product quality.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 12/13

18. Validate the (b) (4) with sufficient controls for use with the LAL endotoxin assay using 3 lots of Ocriplasmin Drug substance /Drug product samples.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

19. Validate yeast and mold recovery in TSA and demonstrate the comparability to the traditional compendial method or requalify the method suitability using SDA plates for mold & yeast incubated at 30-35°C for ≤ 5 days as per USP<61> with 3 lots of in process samples.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

20. Submit new limits for bioburden (action limit (b) (4) and endotoxin (action limit (b) (4) alert limit (b) (4)) in (b) (4). We request that you submit the new limits as a CBE-0.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

21. Qualify bioburden and endotoxin methods for (b) (4) and (b) (4) and establish bioburden and endotoxin specifications based on an assessment of risk to ocriplasmin product quality. We request that you submit the outcome of the risk assessment and the bioburden and endotoxin specifications as a CBE-0.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

22. Investigate the use of (b) (4) for endotoxin measurements of in-process samples (b) (4) and revise the endotoxin methods accordingly. We request that you submit any changes to the in-process endotoxin methods CBE-0.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

23. Validate the efficacy of the (b) (4) and submit a protocol with pre-established acceptance criteria. We request that

you submit the protocol as a CBE-0. Fulfillment of acceptance criteria at the [REDACTED] (b) (4) [REDACTED] should be filed in subsequent Annual Reports.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

24. Evaluate the effects of freezing on endotoxin recovery from ocriplasmin drug substance. These studies will include [REDACTED] (b) (4) [REDACTED] as appropriate. We request that you submit any changes to the in-process endotoxin methods as a CBE-0.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

25. Qualify the bioburden method for [REDACTED] (b) (4) [REDACTED] and submit a report. We request that you submit the report as a CBE-0.

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

APPENDIX

BLA 125422 for Jetrea (ocriplasmin) Intravitreal Injection 2.5 mg/mL, is recommended for approval for the treatment of vitreomacular adhesion (VMA) with the revised package insert and carton and container labeling found in this CDTL review and transmitted to the applicant on 10/11/12.

15 Pages of Draft
Labeling have been
Withheld in Full as b4
(CCI/TS) immediately
following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
10/15/2012

WILEY A CHAMBERS
10/15/2012