# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 125422Orig1s000

# SUMMARY REVIEW

# Deputy Division Director Review of BLA 125422

| | |
|---|---|
| **Date** | October 11, 2012 |
| **From** | Wiley A. Chambers, M.D. |
| **BLA #** | 124422 |
| **Applicant** | Thrombogenics, Inc. |
| **Date of Submission** | April 17, 2012 |
| **PDUFA Goal Date** | October 17, 2012 |
| **Name** | 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) |
| **Recommended:** | 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, a1.25 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 BLA for ocriplasmin (b) (4) (b) (4) BLA 125422.

## 3. Product Quality

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA STN 125422 for JetreaTM (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.

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 intravitreal dose is 125 µg, which corresponds to 0.1 mL of the diluted solution.

**COMPOSITION OF DRUG PRODUCT**

| Ingredient | Concentration (mg/mL) | Function |
|---|---|---|
| Ocriplasmin | 2.5 | Active |
| (b) (4) Mannitol | 3.75 | (b) (4) |
| Citric acid (b) (4) | 1.05 | |
| Sodium hydroxide | (b) (4) | |
| Water for injection | | |

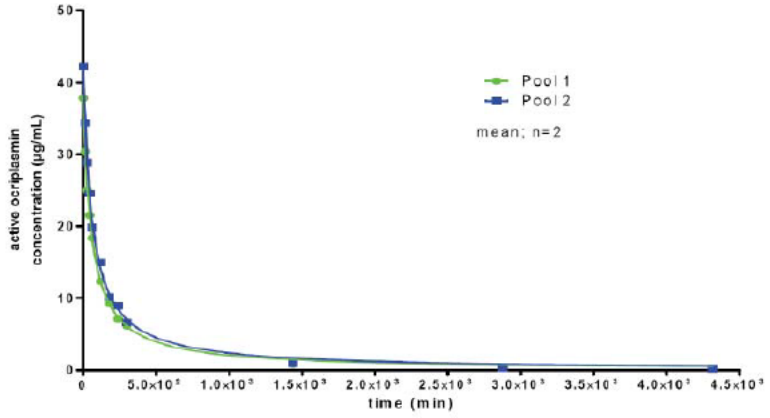
**CONTAINER CLOSURE SYSTEM**

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.

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




There were no outstanding deficiencies, but the review group requested numerous post-marketing commitments (PMC) from the applicant.

# 4. Nonclinical Pharmacology/Toxicology

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 was 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. Iridodenesis (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.

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.

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

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). No drug absorption, distribution and metabolism study has been conducted for ocriplasmin. 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 α2-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.

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

[a]2 subjects below lower limit of detection, other 2 subjects at 0.88 and 0.57 µg/ml
[b]Lower limit of detection

# 6. Sterility Assurance

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 drug product is manufactured by [redacted] Prior to intravitreal administration, ocriplasmin 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 ocriplasmin drug product contains 125µg of ocriplasmin drug product. The proposed ocriplasmin drug product acceptance criteria is [redacted] EU for every 125µg of ocriplasmin administered. If the endotoxin [redacted] EU/mL) from 0.9% w/v sodium chloride is taken into account, in each 100µL dose of ocriplasmin, the endotoxin concentration is [redacted].The endotoxin limit for ocriplasmin drug product is [redacted]. The endotoxin specification of [redacted] /mg is within the limit based on dosage, [redacted] dose.

OC/OMPQ/DGMPA/BMAB has no list of deficiencies to be communicated, but did have a list of drug product PMC's to be communicated to the applicant.

# 7. Clinical/Statistical - Efficacy

| 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 vehicle, randomized 2:1. | 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 vehicle, randomized 3:1. | 320/326 |

## Baseline Demographics for Studies TG-MV-006 and -007

- Ages 18-97, Mean – approx 72 years
- 90% White
- 25-40% Pseudophakic
- 25-30% with Macular Hole
- 30-40% with Epiretinal Membrane
- 5-9% Diabetic Retinopathy
- 80% Expected to need a Vitrectromy

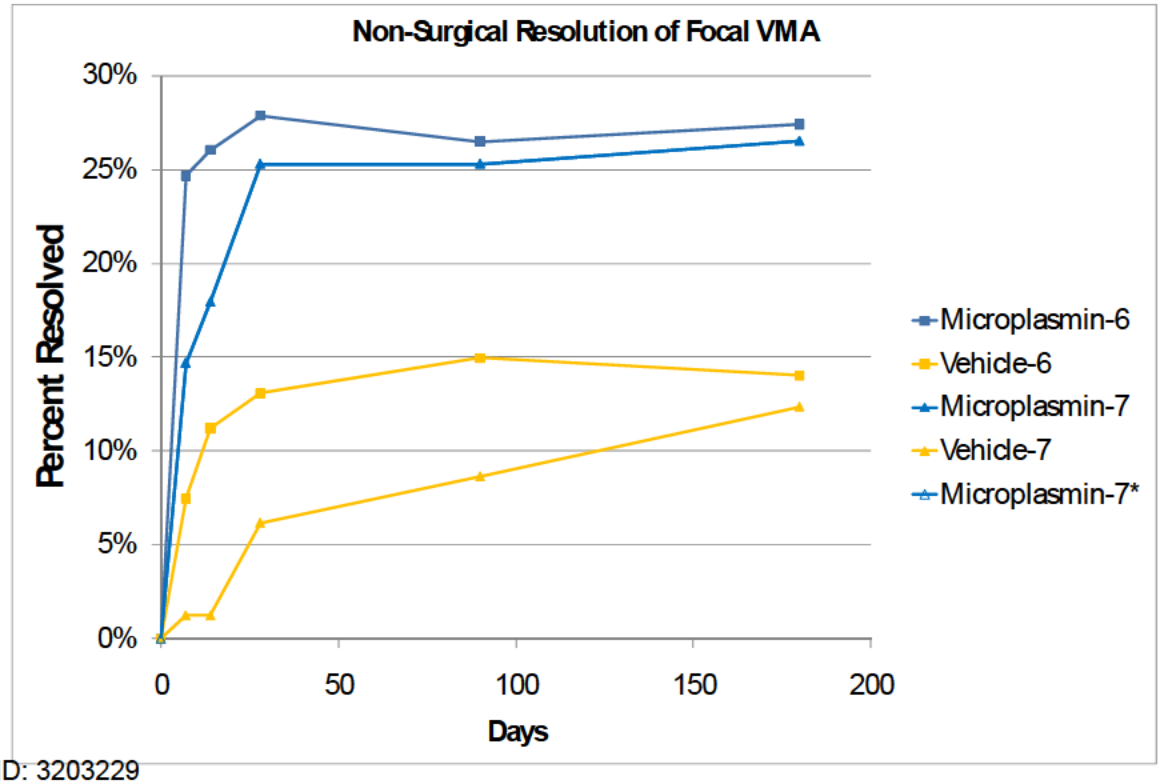
## Analysis of Primary Endpoint(s)

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. Missing data was imputed using the last observation carried forward (LOCF) approach.

**Proportion of Patients with VMA Resolution at Day 28 without Creation of an Anatomical Defect**

| | 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 Confidence Intervals (CI) 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.



## Analysis of Secondary Endpoints(s)

- 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

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 multiple 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 Bonferroni correction for multiplicity, the p-value would need to be less than 0.007 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** | | | | **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.

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).
Ocriplasmin is **not** recommended for the treatment of full thickness macular holes (FTMH) associated with VMA.

# 8. Safety

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 | 01-Aug-2009 | Cardiac arrest |
| Sham injection | TG-MV-002 / 081102 | 82 | male | white | 30-Mar-2007 | 25-Apr-2007 | Intestinal obstruction |
| Ocriplasmin 75µg | TG-MV-003 / 101021 | 75 | male | white | 21-Mar-2008 | 20-Jun-2008 | Myocardial infarction |
| Ocriplasmin 125µg | TG-MV-006 / 603008 | 81 | female | white | 22-Apr-2009 | 04-Jul-2009 | Cerebral hemorrhage |
| Ocriplasmin 125µg | TG-MV-006 / 622012 | 84 | female | white | 08-May-2009 | 29-Aug-2009 | Lung neoplasm malignant |
| Ocriplasmin 125µg | TG-MV-006 / 632008 | 83 | female | white | 22-Jul-2009 | 21-Nov-2009 | Cardiac failure congestive |
| Ocriplasmin 125µg | TG-MV-007 / 721008 | 76 | female | white | 16-Sep-2009 | 11-Dec-2009 | Brain cancer metastatic |
| Ocriplasmin 125µg | TG-MV-007 / 775003 | 88 | female | white | 11-Jun-2009 | 11-Nov-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.

**Patients with Adverse Events Leading to Study Withdrawal**

| 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 | Pivotal Placebo-Controlled Studies | | | | All Studies Combined | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo N=187 | | Ocriplasmin 125µg N=465 | | Control[a] 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 AEs**[b] | | | | | | | | |
| 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[c] | 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[d] | 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%) |

| System Organ Class Preferred Term Category | Pivotal Placebo-Controlled Studies | | | | All Studies Combined | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo N=187 | | Ocriplasmin 125µg N=465 | | Control[a] N=247 | | Ocriplasmin Any Dose N=741 | |
| 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%) |

| System Organ Class Preferred Term Category | Pivotal Placebo-Controlled Studies | | | | All Studies Combined | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo N=187 | | Ocriplasmin 125µg N=465 | | Control[a] N=247 | | Ocriplasmin Any Dose N=741 | |
| 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 | |

[a] Patients allocated to placebo, sham-injection or no treatment.
[b] Includes study eye and non-study eye AEs.
[c] 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.
[d] 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 alternative 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.

**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 |

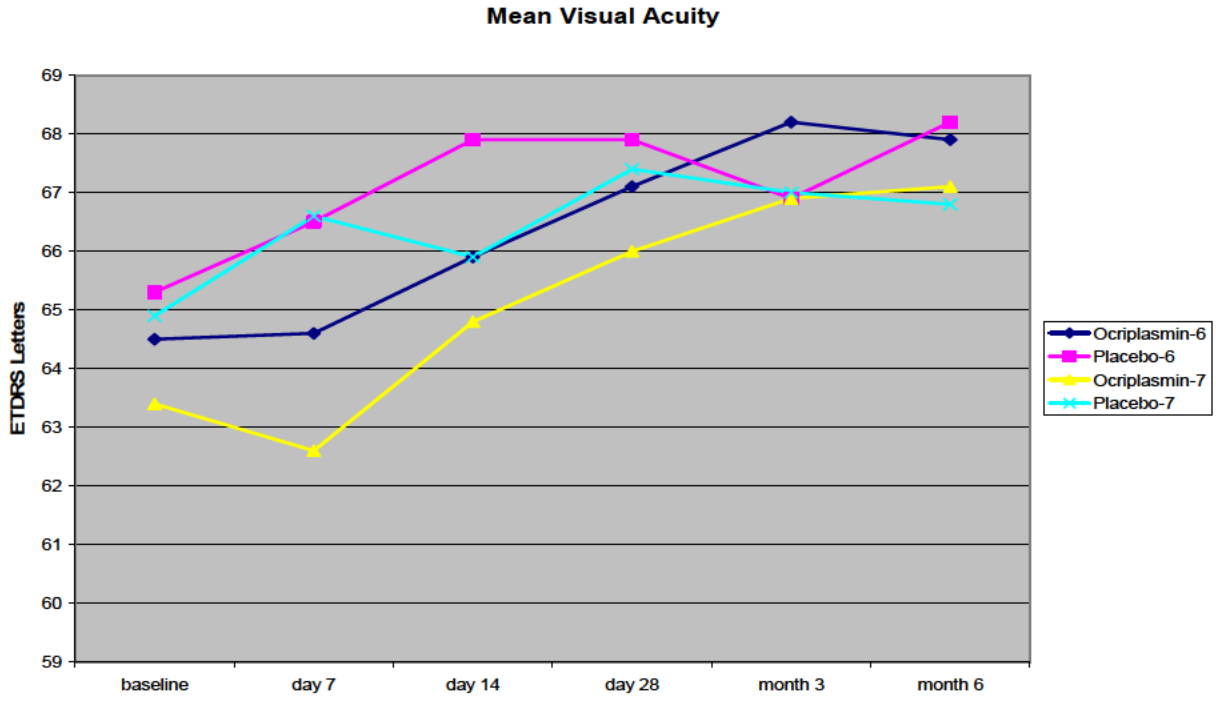
CI=confidence interval
a The (absolute) difference and CIs between treatment groups are based on the percentage of successes.
b p-value is from Fisher's exact test, comparing placebo and ocriplasmin.

**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 |

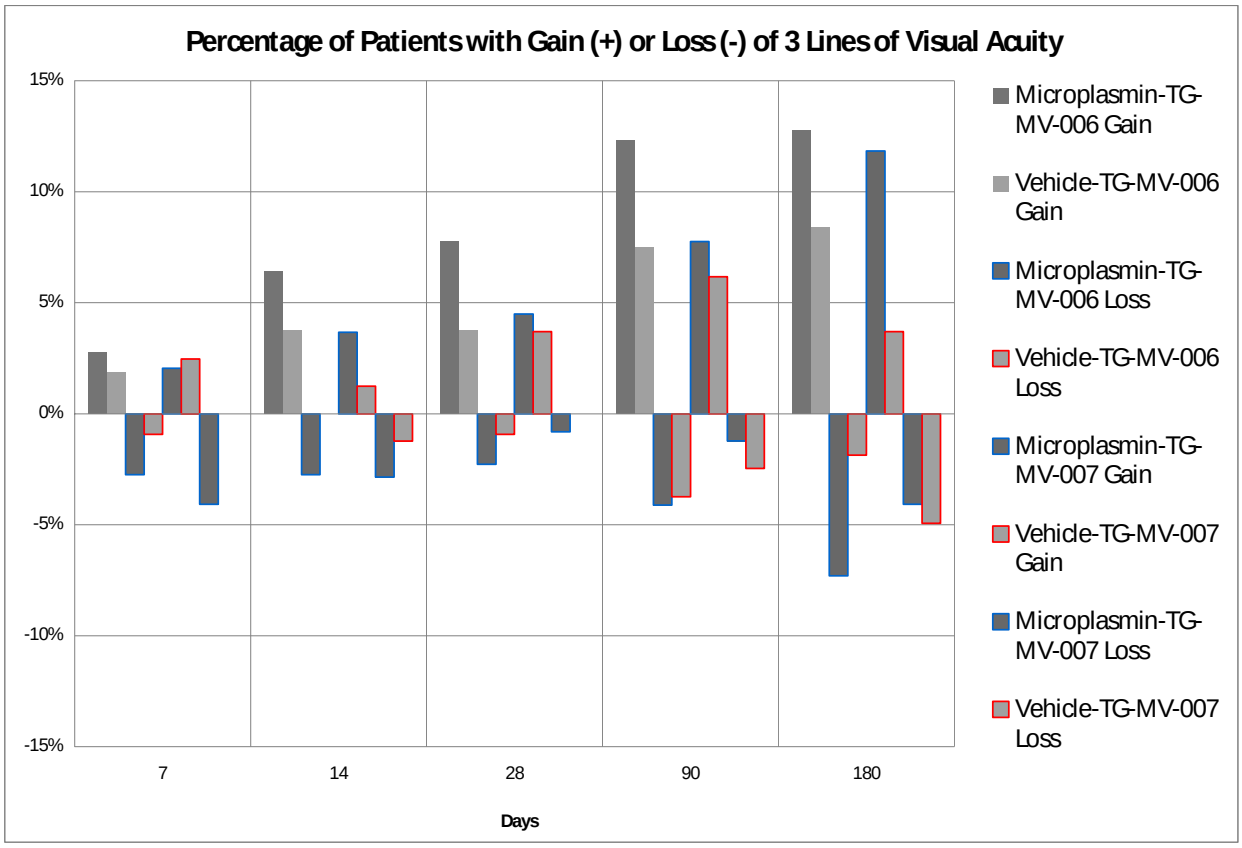
One subject did not have a BCVA measurement at Baseline; therefore, the denominator used in this analysis is 80 for the placebo group.
b The (absolute) difference and CIs between treatment groups are based on the percentage of successes.
c p-value is from Fisher's exact test, comparing placebo and ocriplasmin.

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.




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 little difference between the ocriplasmin group and the placebo group in the mean 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 could 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.

The Medical Officer's 120-Day Safety Update Review provides additional details on all patients with 2 or more Line Loss in BCVA in Phase 3 Studies.

**DYSCHROMATOPSIA 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 125µand 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.

## Safety Summary

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.

# 9. Advisory Committee Meeting

An Advisory Committee meeting was held for ocriplasmin on July 26, 2012.

**Committee Discussion:** The committee unanimously agreed that substantial evidence has been provided to demonstrate that ocriplasmin 125µg is effective for the treatment of vitreomacular adhesions. 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.

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 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. 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.

# 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 for ages (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, but should be available by the end of the 2012.

# 11. Other Relevant Regulatory Issues

**BIOSTATISTICS**

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 recommended the approval of ocriplasmin for the treatment of symptomatic vitreomacular adhesion (VMA). 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 did 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, (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 withdrawal 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. 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. 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.

# 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 an container labeling transmitted to the applicant on 10/11/12.

# 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 an container labeling.

**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).

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 higher in the ocriplasmin treated group compared with the placebo group (7.3% versus 1.9%, respectively). 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 Clinical Phase 4 Commitments. There is adequate information to label the product for its symptomatic vitreomacular adhesion indication and explain the risks in the propose labeling.

**PRODUCT QUALITY**
The Division of Therapeutic Proteins, Office of Biotechnology Products has recommended a number of post-marketing commitments, but none appear critical for the manufacture of this product.

Wiley A. Chambers, MD
Deputy Division Director
Division of Transplant and Ophthalmology Products

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WILEY A CHAMBERS
10/15/2012