

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125422Orig1s000

MEDICAL REVIEW(S)

Division Director Review #2

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products
Subject	Division Director Review #2
BLA Number	BLA 125422
Related INDs	IND 100,370
Review type	Priority
Applicant Name	ThromboGenics, Inc.
Date of Submission	April 16, 2012
Date of Receipt	April 17, 2012
PDUFA Goal Date	October 17, 2012
Proprietary Name / Established (USAN) Name	JETREA ocriplasmin
Formulation Dose How supplied	(Ophthalmic) intravitreal injection 0.125 mg (125 µg) in 0.1 mL (diluted solution) One single-use 2-mL glass vial containing 0.5 mg ocriplasmin in 0.2 mL solution (2.5 mg/mL) To be diluted with 0.2 mL sodium chloride 0.9% before use (final concentration 0.5 mg/0.4mL)
Proposed Indication(s)	Treatment of symptomatic vitreomacular adhesion
Action for NME	<i>Approval</i>

Purpose:

The purpose of this review is to respond to the Therapeutic Biological Establishment Evaluation Request (TB-EER) dated October 17, 2012.

Background:

This application was received April 17, 2012, given a priority review, and the PDUFA goal date is October 17, 2012.

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form:

On October 17, 2012, the TB-EER for ocriplasmin was entered into DARRTS and made an overall recommendation of:

“There are no pending or ongoing compliance actions that prevent approval of this BLA.”

Also within the document was a recommendation regarding one of the testing facilities responsible for the DS release testing for endotoxin:

Firm Name:

Address:

DUNS:

FEI:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The inspection of this facility took place [REDACTED] (b) (4) and at the end of the inspection, the Office of Compliance (see review dated October 17, 2012 by Mahesh Ramanadham, attached to this review) made the following recommendation:

“In summary, DGMPA finds this site acceptable for the purposes of this BLA based on the acceptance of the PMC.”

OC therefore requested that the following PMC be included in the action letter:

[REDACTED] (b) (4)

Review:

This PMC is requesting that the applicant submit a supplement [REDACTED] (b) (4)

Comment:

The problem with this PMC is that it presupposes an activity which may or may not happen, given that it is a future activity.

This request is also inappropriate, because the requirement to report any change to an approved application, [REDACTED] (b) (4) is regulated under 21 CFR 601.12 Changes to an approved application. According to 601.12 (a)(2,) an applicant must assess the effects of the change and demonstrate the lack of adverse effect on the identity, quality, purity, or potency of the product as they may relate to safety or effectiveness of the product. In this specific case [REDACTED] (b) (4) the requirement to report the change [REDACTED] (b) (4) may be covered under 21 CFR 601.12 (c) Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change. Per regulation, the supplement would be labeled “Supplement – Changes Being Effected in 30 Days” or if applicable under 601.12(c)(5), the supplement would be labeled “Supplement – Changes Being Effected.”

Furthermore, applicants are also expected to comply with 21 CFR 601.12(c)(3) (4) and (6).

The use of a PMC to request an action that is already required under the Code of Federal Regulation is against CDER policy and should not be done.

Recommendation:

Given that the PMC above is asking the applicant to commit to take an action that is already required under the Code of Federal Regulations and is against CDER policy, it therefore should not be requested.

In addition, BLAs include in the approval letter the following statement, which serves as a reminder to the applicant of their reporting obligations under the Code of Federal Regulations.

Any changes in the manufacturing, testing, packaging, or labeling of Jetrea, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

Therefore, the PMC above will not be included in the approval letter.

Attachment: TB-EER dated October 17, 2012 for Jetrea BLA 125422

5 Page(s) has been Withheld in Full immediately following
this page as duplicate copy of TB-EER 10.17.12

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

/s/

RENATA ALBRECHT
10/17/2012

EDWARD M COX
10/17/2012

Division Director Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products ¹
Subject	Division Director Review #1
BLA Number	BLA 125422
Related INDs	IND 100,370
Review type	Priority
Applicant Name	ThromboGenics, Inc.
Date of Submission	April 16, 2012
Date of Receipt	April 17, 2012
PDUFA Goal Date	October 17, 2012
Proprietary Name / Established (USAN) Name	JETREA ocriplasmin
Formulation Dose How supplied	(Ophthalmic) intravitreal injection 0.125 mg (125 µg) in 0.1 mL (diluted solution) One single-use 2-mL glass vial containing 0.5 mg ocriplasmin in 0.2 mL solution (2.5 mg/mL) To be diluted with 0.2 mL sodium chloride 0.9% before use (final concentration 0.5 mg/0.4mL)
Proposed Indication(s)	Treatment of symptomatic vitreomacular adhesion
Action for NME	<i>Approval</i>

¹ The Office of Antimicrobial Products was reorganized effective May 2011; specifically the Division of Special Pathogen and Transplant Products (DSPTP) and Division of Anti-Infective and Ophthalmology Products (DAIOP) were reorganized into the Division of Transplant and Ophthalmology Products (DTOP) and the Division of Anti-Infective Products (DAIP).

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Jennifer Harris, Bill Boyd 9/26/2012, 10/11/2012
120-day Safety Update Review	Jennifer Harris, Bill Boyd 9/26/2012
CDTL Review	Bill Boyd 10/15/2012, 10/17/2012
Deputy Director Review	Wiley Chambers 10/15/2012, 10/17/2012
Statistical Review	Yunfan Deng, Yan Wang 9/21/2012
Pharmacology/Toxicology Review	Maria Rivera, Lori Kotch 10/2/2012
TL Review	Lori Kotch 10/2/2012
Associate Director, P/T	Abigail Jacobs 9/28/2012
Clinical Pharmacology Review	Yoriko Harigaya, Philip Colangelo 9/26/2012
Product Quality Reviews OPS/OBP/DTP	Ramesh Potla, Richard Ledwidge, Leslie Rivera Rosado, Maria Teresa Gutierrez-Lugo, Nikolay Spiridonov, Frederick Mills, Jee Chung, Mary Kathy Lee 9/20/2012
Team Leader review	Mary Kathy Lee, Susan Kirshner 10/15/2012
Quality Microbiology Reviews OC/OMPQ/DGMPA/BMAB	Drug Substance: Reyes Candau-Chacon, Patricia Hughes 10/2/2012 Drug Product: Lakshmi Rani Narasimhan, Patricia Hughes 10/2/2012
PMR/PMC Developmental Template Reviews	Ramesh Potla, Mary K Lee 10/12/2012 (DTP) Lakshmi Rani Narasimhan, Patricia Hughes 10/15/2012 Reyes Candau-Chacon, Patricia Hughes 10/15/2012
OC/Facilities Inspection/TB-EER	Mahesh Ramanadhan 10/17/2012
OSI/DGCPC	Kassa Ayalew, Susan Leibenhaut, Susan Thompson 10/01/2012
OSE/DMEPA Proprietary Name Letter	Jung Lee, Jamie Wilkins Parker, Kellie Taylor, Carol Holquist 7/25/2012 Carol Holquist 7/25/2012
OBP/DTP Label and Labeling Review	Kimberly Rains, Ramesh Potla, Mary (Kathy) Lee 9/26/2012
OSE/OMEARM/DMEPA Label, Labeling and Packaging Review	Jung Lee, Jamie Wilkins Parker, Carol Holquist 10/2/2012
OPDP/DPP (formerly DDMAC)	Christine Corser 10/11/2012
Pediatric Review Committee	Pediatric studies deferred at PeRC 10/3/2012
Advisors and Consultants Staff	Yvette Waples Quick Notes 7/26/2012

OND=Office of New Drugs, CDTL=Cross-Discipline Team Leader

OC/OMPQ/DGMPA/BMAB=Office of Compliance, Office of Manufacturing Product Quality, Division of Good Manufacturing Practice Assessment, Biotech Manufacturing Assessment Branch; formerly

OC/DMPQ/MAPCB/BMT = Office of Compliance/Division of Manufacturing and Product Quality/Manufacturing and Pre Approval Chemistry Branch/ Biologics Microbiology Team

OPS/OBP/DTP = Office of Pharmaceutical Sciences/Office of Biologics Products/Division of Therapeutic Proteins
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI))

OSE= Office of Surveillance and Epidemiology

OMEARM=Office of Medication Error Prevention and Risk Management

DMEPA=Division of Medication Error Prevention and Analysis

OPDP/DPDP=Office of Prescription Drug Promotion/Division of Professional Drug Promotion; formerly,

DDMAC=Division of Drug Marketing, Advertising and Communication

PMHT=Pediatric and Maternal Health Staff

TB-EER Therapeutic Biological Establishment Evaluation Request

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1. Summary and Recommendations

JETREA (ocriplasmin) Intravitreal Injection, 2.5 mg/mL is recommended for approval for the treatment of symptomatic vitreomacular adhesion (VMA). To support the approval of JETREA, ThromboGenics, Inc. submitted results of two randomized, placebo-controlled, double-masked, multicenter Phase 3 trials, Study TG-MV-006 (006) and Study TG-MV-007 (007) conducted in the US and Europe that established the efficacy and safety of ocriplasmin for this indication.

The proposed treatment regimen is a single 125 µg (0.125 mg) dose, delivered as a 0.1 mL diluted solution by intravitreal injection under sterile conditions. The drug product is supplied as a preservative-free solution in a single use glass vial containing 0.5 mg of ocriplasmin in 0.2 mL liquid (2.5 mg/mL). Prior to intravitreal administration, the product is thawed and diluted using 0.2 mL of a 0.9% w/v sodium chloride solution, to a final concentration of 0.5 mg/0.4 mL. Therefore, the treatment dose is 0.1 mL of diluted solution which contains 0.125 mg (125 µg) ocriplasmin.

The normal young eye has gel-like fluid in the middle of the eye (vitreous) attached to the retina, including the portion of the retina called the macula. Because the macula is located near the center of the retina, it is responsible for central vision. As the eye ages, the vitreous liquefies and shrinks, causing it to pull away from the retina. If portions of the vitreous remain attached to the macula, they may cause the vitreous to “tug on the macula.” The tugging can lead to distorted vision, light flashes and vision loss. The attachment between the vitreous and the macula is called a vitreomacular adhesion (VMA). Ocriplasmin is an enzyme that breaks down proteins in the eye responsible for VMA. The breakdown of these proteins allows a better separation between the vitreous and macula and can reduce the chances that tugging will occur. The alternative treatment for this condition is a surgical procedure called a vitrectomy. In these Phase 3 trials, patients were evaluated for the resolution of VMA at Day 28 based on optical coherency tomography (OCT) by a Central Reading Center; this was the primary endpoint). The single intravitreal ocriplasmin dose was established to be superior to vehicle intravitreal injection in both trials, as shown below:

FAS population	Ocristasmin	Placebo	P value
TG-MV-006	61/219 (27.9%)	14/107 (13.1%)	0.003
TG-MV-007	62/245 (25.3%)	5/81 (6.2%)	<0.001
Overall	123/464 (26.5%)	19/188 (10.1%)	<0.001

Overall, the efficacy in the two trials was 26.5% for ocristasmin and 10.1% for vehicle, with a treatment effect of 16.4% (95% CI=10.5%, 22.3%). The application was presented and discussed at the Dermatologic and Ophthalmic Drugs Advisory Committee meeting on July 26, 2012. The committee voted unanimously that the product showed efficacy and the benefits outweighed the risks for the treatment of symptomatic VMA. Some committee members described the treatment effect as modest, and noted that while patients with VMA resolution had an increase in BCVA, there were others who lost two or more lines (10 or more letters) of visual acuity in the ocristasmin arms, and asked FDA to examine the adverse reactions. The

Division asked the applicant to provide details on all these patients and the information was reviewed in detail by the clinical reviewers, and led to the conclusion that the majority of patients whose visual acuity declined was due to progression of VMA and macular hole.

The clinical and statistical reviewers also concluded the product is effective and the benefits outweigh the risks. The specific efficacy results and important warnings, precautions and adverse reactions are included in the product labeling. Furthermore, based on one pediatric patient with subluxation after receiving a higher-than-recommended dose and data on subluxation in three animal species (rabbits, minipigs and monkeys) after a single ocriplasmin injection and findings that a second intravitreal dose of ocriplasmin was associated with subluxation in all exposed monkeys, the labeling will include a warning about the risk of subluxation.

The applicant originally requested a broader indication of “treatment of symptomatic vitreomacular adhesion including macular hole;” however, based on the clinical and statistical reviews, it was determined that the data were insufficient to support treatment of macular hole.

Ocriplasmin is a biologic product; it is the truncated form of human plasmin with retained protease activity and is produced using recombinant DNA technology from the yeast *Pichia pastoris*. The established pharmacologic class is designated as “proteolytic enzyme,” and the product has proteolytic activity against protein components of the vitreous body and the vitreoretinal interface (e.g. laminin, fibronectin, fibrinogen, gelatin and collagen). Ocriplasmin is intended to dissolve the protein matrix responsible for the vitreomacular adhesion (VMA).

The product quality and microbiology sterility reviewers concluded that the product is pure and potent and can be approved, although there are over twenty post-marketing commitments that ThromboGenics has agreed to address (Section 13.3). The clinical, statistical, pharmacology/toxicology, clinical pharmacology reviewers all recommend approval of the application. Inspections of clinical sites have been completed and the data are considered reliable. Manufacturing facility inspections were completed and the TB-EER issued (b) (4) (b) (4) with an overall recommendation of, “There are no pending or ongoing compliance actions that prevent approval of this BLA.” However, the TB-EER document also summarizes inspection of the drug substances endotoxin testing facility and “finds this site acceptable for the purposes of this BLA based on the acceptance of the PMC.” Reporting a change in a manufacturing or testing facility is required under the Code of Federal Regulations and including it as a PMC in the approval letter is against CDER policy. (See Division Director Review #2 dated October 17, 2012 for details.) Labeling has been reviewed by all disciplines and consulting groups, differences in labeling recommendations were discussed during the labeling meetings on October 2 and 3, 2012 and subsequently. The established name “ocriplasmin” was recommended and agreed to, the proprietary name “JETREA” was approved by DMEPA. The application is recommended for approval.

1.1 Deficiencies

None

1.2 Post-Marketing Studies:

- a. Post Marketing Requirements (PMR)

The medical officer notes that the sponsor is currently conducting an efficacy trial in patients ≤ 16 as an adjunct to conventional vitrectomy. The action letter will specify that results of this study should be submitted to the application as a PMR under PREA.

b. Post Marketing Commitments (PMC)

See complete list of Product Quality and Microbiology Sterility PMCs in Section 13.3 of this document.

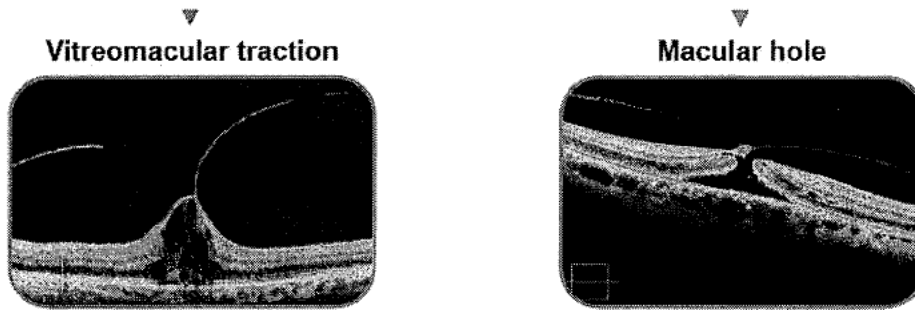
1.3 Other Issues

The product quality reviewers initially recommended a PMR for the applicant to perform a feasibility study to adjust the drug product final fill volume or concentration to reduce the likelihood that a patient could be overdosed, or that more than one patient could be dosed from the same single vial due to excess reconstituted drug product remaining in the vial after the initial dosing. However, such a request does not meet the three conditions listed in Section 505(o)(3)(A) of the FD&C Act under which a PMR can be required; therefore, this request has been changed to a PMC and the applicant agreed to it (see Section 13.3).

The advisory committee members voted that ocriplasmin is effective and the benefit outweighed the risk and further premarketing studies were not needed before approval. However, several committee members commented on the modest treatment effect, and requested the FDA further examine the safety within the existing studies and post-marketing, mainly the higher rates of worsening in best corrected visual acuity (BCVA). The applicant submitted further detailed information on all patients who had ≥ 2 lines of worsening in BCVA which were reviewed by the clinical reviewers who determined that the majority of patients had worsening of BCVA due to progression of the underlying condition of VMA and macular hole (MH). These findings are discussed in details in the clinical reviews. The reviewers discussed whether a post-marketing safety study should be requested; however, given the demonstrated benefit, the association of the visual changes with progression of disease, the risks associated with vitrectomy (the only other available treatment currently available), the product labeling that presents information on visual adverse reactions, and current ongoing Phase 3 studies with ocriplasmin that will provide additional efficacy and safety information, a PMR will not be requested.

2. Background

Ocriplasmin is a new biologic product developed by ThromboGenics, Inc. for the treatment of symptomatic vitreomacular adhesion (VMA). As discussed in greater detail in Appendix A of this document, in the normal aging eye, the vitreous body undergoes liquefaction resulting in liquid pockets within the vitreous gel. This predisposes the gel to collapse with separation of the posterior vitreous cortex from the retinal surface. Incomplete separation may lead to traction on the macula, resulting in retinal distortion and macular edema, with resultant vision loss, metamorphopsia, micropsia, and photopsia. The diagnosis of VMA (as well as macular hole) can be made by optical coherence tomography (OCT), as shown in the images below..



From applicant's DODAC briefing material (page 6)

The only currently available treatment options are to wait for spontaneous detachment which is rare, or to perform a vitrectomy and release the adhesion by surgery. Surgical vitrectomy can generally correct the anatomic defect, however, the procedure is not without significant morbidity and complications, which include retinal detachment and retinal tear. In addition, although many patients who undergo vitrectomy for VMA may show improvement in BCVA, others have no change or even decrease in visual acuity. Ocriplasmin was developed to provide a non-surgical treatment of symptomatic VMA, as shown in the results of the trials submitted in this application.

(b) (4)

2.1 Priority Review

The application was granted a priority review, because VMA is a serious, sight-threatening disease and JETREA is the first non-surgical treatment for this condition and has the potential to offer a significant improvement to available therapies.

2.2 Meetings with Applicant during Development

IND 100,370 was submitted on October 12, 2006. The end-of-Phase 2 meeting was held September 24, 2008, during which the non-clinical and clinical developmental program was discussed. A pre-BLA meeting was held on September 21, 2012 during which nonclinical, clinical, statistical and administrative questions were discussed.

(b) (4)

(b) (4)

ThromboGenics was then given a new BLA number for the product, and BLA 125422 was submitted on April 16, 2012 and received April 17, 2012, for the same proposed indication, but with a new proposed trade name of JETREA.

3. CMC/Product Quality Microbiology

For complete details on manufacture of drug substance (DS) and drug product (DP), see the review by the Division of Therapeutic Proteins (DTP) reviewers, Ramesh Potla, Richard Ledwidge, Leslie Rivera Rosado, Maria Teresa Gutierrez-Lugo, Nikolay Spiridonov, Frederick Mills, Jee Chung, Mary Kathy Lee; and Quality Microbiology Sterility reviews by Reyes Candau-Chacon (DS), Lakshmi Rani Narasimhan (DP) and Patricia Hughes.

The individual reviews summarize that the bulk drug substance (DS) is manufactured at Fujifilm Diosynth Biotechnologies UK Ltd. and the drug product (DP) is manufactured at (b) (4). The reviews provide information on the manufacturing process and process controls, including (b) (4) in-process controls, process validation, hold times, container closure validation, freezing and shipping validation, manufacturing process development, release specifications for bioburden and endotoxin, stability, (b) (4), container closure integrity, and freeze/thaw. The reviews include the text of multiple information requests sent to the applicant as well as the applicant's responses. The reviewers conclude that the responses provided are satisfactory or that further information can be provided in response to post-marketing commitments. There are no outstanding deficiencies identified by the product quality and microbiology sterility reviewers. The reviewers recommend approval and consider 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, under conditions specified in the package insert.

Comments:

The Product Quality and Microbiology Sterility reviewers recommend approval of the application; they have a series of PMC requests to which the applicant has agreed. All labeling recommendations have been addressed. Language regarding licensure of the product for inclusion in the Approval letter for this biologic product is included in Section 13.1. A summary of information from individual reviews is provided below.

3.1 Drug Substance

As summarized in the product quality review, "ocriplasmin is a 27,237 Dalton recombinant protein with trypsin-like serine protease activity that selectively cleaves the peptide bonds at the carboxyl termini of arginine or lysine residues in target proteins and peptides. Ocriplasmin acts on dissolving protein matrix components at focal adhesion points of vitreoretinal interface thereby reducing and/or resolving vitreomacular adhesion including macular hole.

BLA 125422 JETREA (ocriplasmin) Intravitreal Injection, 2.5 mg/mL
Indication: treatment of symptomatic vitreomacular adhesions

Ocriplasmin (previously known as microplasmin) is produced as an inactive precursor microplasminogen (zymogen) using a yeast *Pichia pastoris* production system. (b) (4)

Ocriplasmin's primary structure is comprised of 249 amino acid residues that constitute two polypeptide chains. The first peptide is 19-aa long where as the second peptide contains 230-aa. The second peptide has 4 intrachain disulfide bonds (C46:C62, C138:C205, C168:C184 and C195:C223). Both polypeptide chains are linked together by 2 disulfide bridges (C6:C124 and C16:C24). (b) (4)

Structure of Plasminogen, Miniplasminogen and Microplasminogen and Formation of Ocriplasmin

From applicant non-clinical overview, (page 6 of 43)



3.2 Drug Product

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 liquid, which is diluted with 0.2 mL NaCl 0.9% for a final concentration of 0.5 mg/0.4 mL. The treatment dose is 0.1 mL of diluted solution which contains 0.125 mg (125 µg) ocriplasmin.

Ocriplasmin drug product is manufactured (b) (4)

(b) (4)

Ocriplasmin drug product is filled in (b) (4) USP/Ph. Eur. glass vials with a 0.2mL fill volume. The vials are closed with (b) (4) rubber stoppers. The stoppers are capped with an aluminium crimp seal equipped with a (b) (4) flip-off cap. The composition of ocriplasmin drug product is presented in the following table:

Composition of Ocriplasmin Drug Product

Ingredient	Unit Formula (mg/0.200mL)	Concentration (mg/mL)	Function
Drug Substance			
Ocriplasmin	0.500	2.50	Active ingredient
Excipients			
(b) (4) Mannitol	0.750	3.75	cryoprotectant
Citric acid (b) (4)	0.210	1.05	formulation buffer
Sodium hydroxide ^a	(b) (4)		pH adjustment
Water for injection	(b) (4)		diluent

(b) (4)

Ocriplasmin drug product manufacturing process started from (b) (4)

(b) (4)

(b) (4)

Stability studies for ocriplasmin drug substance and ocriplasmin drug product batches demonstrated that ocriplasmin has good stability when buffered at pH 3.1 and stored frozen.

(b) (4)

An

expiry of 18 months for the DP is proposed.

Container Closure System

Ocriplasmin drug product is stored frozen and the container closure system comprises (b) (4) USP / Ph. Eur. (b) (4) glass vial with a USP / Ph. Eur. (b) (4) rubber stopper. The stoppers are capped with an aluminium crimp seal equipped with a (b) (4) flip-off cap. The glass vials are manufactured by (b) (4). The rubber stoppers are (b) (4) manufactured by (b) (4). (b) (4) The vials are placed in an upright position in a secondary cardboard container for protection from physical damage and light.

Product Information:

- Active Ingredient: Ocriplasmin
- Indication of Use: Treatment of symptomatic vitreomacular adhesion
- Route of Administration: Intravitreal injection
- Dosage Form: Injection Solution
- Strength: 0.5 mg/0.2 mL, concentration 2.5 mg/mL
- Dose and Frequency: Dilute with 0.2 mL of sterile sodium chloride (0.9% w/v) solution for injection into the vial. Administer 0.125 mg (0.1 mL of the diluted solution) by intravitreal injection to the affected eye once as a single dose
- How Supplied: 0.5 mg ocriplasmin in 0.2 mL citric-buffered solution (2.5 mg/mL) in a 2 mL single-use glass vial with a latex rubber stopper. Each vial contains 0.5 mg

ocriplasmin (active) and 0.21 mg citric acid, 0.75 mg mannitol, sodium hydroxide (for pH adjustment) and water for injection. The pH of the solution is 3.1.

- Storage: Store frozen at or below -20°C (-4°F) until ready to use
- Distribution: Controlled distribution by specialty pharmacy network directly to the treating physician clinics and hospitals. In the US, drop shipment deliveries on a 24 hour schedule will be provided.

Specifications/Endotoxin: Ocriplasmin should be sterile with endotoxin limit of (b) (4)

Environmental Assessment: The applicant is granted categorical exclusion for marketing under 21 CFR 25.31(c).

4. Nonclinical Pharmacology/Toxicology

For detailed information, see Pharmacology/Toxicology reviews by Dr. Maria and Dr. Kotch.

Established pharmacologic class is designated as *proteolytic enzyme*. This issue was discussed among the pharmacology/toxicology, product quality, clinical and other reviewers during the October 2, 2012 labeling meeting, and consulted with Paul Brown, Associate Director for Pharmacology/Toxicology. Agreement on the designation was reached.

Pharmacology

The reviewers note that ocriplasmin is a recombinant human protein that has proteolytic activity against protein components of the vitreous body and the vitreoretinal interface (e.g. laminin, fibronectin, fibrinogen, gelatin and collagen), thereby dissolving the protein matrix responsible for the abnormal vitreomacular adhesion (VMA). The activity is similar to intact plasmin: In testing, ocriplasmin was more effective on collagen type IV compared to plasmin, whereas plasmin was more effective on fibrinogen, gelatin, laminin and fibronectin.

Intravitreal administration of ocriplasmin was demonstrated to induce vitreous liquefaction and posterior vitreous detachment (PVD) in various animal models and human donor eyes.

Toxicology - Intravitreal Studies

The intravitreal toxicity of ocriplasmin was 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 (lens displacement due to damage of ciliary zonular fibers) in all 3 species, and changes in intraocular pressure (IOP), inflammation, and electroretinography (ERG) changes in rabbits and monkeys. Pathological changes related to intraocular hemorrhage were also observed in rabbits and monkeys; however it is uncertain whether this effect is a result of the injection procedure itself or a pharmacologic effect of ocriplasmin. The exposure margins for the findings of inflammation, ERG changes and lens subluxation observed in rabbits and monkeys after a single intravitreal dose were modest (0.1-fold to 1.5-fold). A larger exposure margin (3.7-fold) was observed for the microscopic retinal changes observed in the monkey. With the exception of lens subluxation, the nonclinical findings tended to resolve over time after administration of a single intravitreal dose.

A second intravitreal administration of ocriplasmin (28-days apart) in monkeys at doses of 75 µg/eye (41 µg/mL vitreous) or 125 µg/eye (68 µg/mL vitreous) was associated with lens subluxation in all ocriplasmin treated eyes, sustained increases in IOP and associated glaucoma in two animals with severe lens subluxation, and multiple adverse microscopic findings in the eye including vitreous liquefaction, degeneration/disruption of the hyaloideocapsular ligament (with loss of ciliary zonular fibers), lens degeneration, mononuclear cell infiltration of the vitreous, and vacuolation of the retinal inner nuclear cell layer. These doses were 1.4-fold and 2.3-fold the intended clinical concentration of 29 µg/mL vitreous, respectively.

Intravenous testing

Following intravenous dosing, 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. 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 (review page 15).

The reviewers further note that there are no novel excipients in the formulation. Genetic toxicity studies were not done and are not required for biologic products. Carcinogenicity studies are not required given the recommended single dose for the eye of the patient. Reproductive and developmental studies are not needed given lack of systemic absorption.

Comment:

The application is recommended for approval from a pharmacology/toxicology standpoint. The labeling revisions regarding the ocular findings on repeat doses of ocriplasmin in monkeys have been included in Sections (b) (4) and 13.2 of labeling, given the potential risk associated with repeat injection and the importance of communicating this information to health care providers. The information has also been included in Highlights, consistent with the applicant's proposed labeling.

5. Clinical Pharmacology/Biopharmaceutics

For complete information, see clinical pharmacology review by Drs. Harigaya and Colangelo.

The intravitreal (IVT) pharmacokinetic (PK) profile of ocriplasmin was determined in a Phase 2 Study, TG-MV-010, after IVT administration by measuring ocriplasmin activity levels in the vitreous humor in patients who received a single dose of 125µg ocriplasmin administered at different times before vitrectomy. The maximum IVT ocriplasmin level observed at 5-30 min was approximately 22 µg/mL, most patients (n=16) had IVT ocriplasmin activity levels above LLOQ (<272.37ng/mL) between 0.5 and 4 hours post-dose, some had levels detected at 24 hours and none have levels at Day 7 post-dose.

Ocriplasmin levels in vitreous samples from Study TG-MV-010 and from pig vitreous are reported in the following table.

TABLE 1
a below
b concentration
extracellular

Ocriplasmin enters the endogenous protein catabolism pathway through which it is rapidly inactivated via its interactions with protease inhibitor α 2-antiplasmin or α 2 macroglobulin. “The normal plasma concentration of the serine protease inhibitor α 2-antiplasmin is 1000 nM or 1 nmol/mL of plasma. The intended dose of 125 μ g for intravitreal administration of ocriplasmin is equivalent to 4.6 nmol of active substance. An average individual, 80 kg body mass with a normal blood volume of 72 mL/kg, has approximately 3600 mL plasma. Taken together, there is thus sufficient α 2-antiplasmin present in as small a volume as 4.6 mL plasma to neutralize all ocriplasmin even if the systemic bioavailability of the intraocular dosage is 100%.”

Comment:

The reviewer recommends approval from the clinical pharmacology perspective; labeling revisions have been made and no phase 4 studies are requested.

6. Clinical Microbiology/Immunology

Per Dr. Hariyaga, in Study TG-M-001, there was no evidence of a dose-related trend of elevated titers of anti-ocriplasmin plasma 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.

Comment:

Given the product is intended for single administration, and there is language cautioning about the risk of ocular damage (subluxation) with more than one dose based on a monkey study, and systemic exposure is not expected with the 0.125 mg dose, the likelihood that patients there will receive repeated dosing and develop antibodies with this product are low. The product quality reviewers did recommend that an immunology study should be performed if multiple doses will be administered; however, as noted a safety margin based on non-clinical data for multiple dosing has not been established.

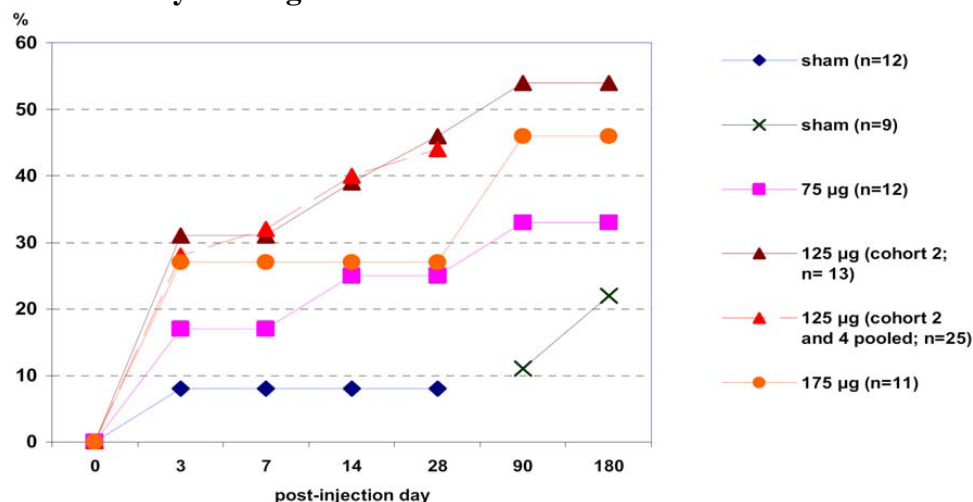
7. Clinical/Statistical-Efficacy

For complete details, see clinical reviews by Drs .Harris, Boyd and Chambers and statistical reviews by Drs. Deng and Wang.

Dr. Harris notes that the clinical development program involved 10 studies, including 8 Phase 2 studies (TG-MV-001, TG-MV-002, TG-MV-003, TG-MV-004, TG-MV-005, TG-MV-008, TG-MV-009 and TGMV-010) and 2 Phase 3 studies (TG-MV-006 and TG-MV-007). These included studies that were ongoing as of the cut-off date for the submission (TG-MV-005, TG-MV-008, TG-MV-009), an uncontrolled safety study (TG-MV-001) and a pharmacokinetic study (TG-MV-010).

In brief, Studies TG-MV-002, TG-MV-003, TG-MV-004 were Phase 2 dose ranging studies that compared sham or vehicle injection to several doses of ocriplasmin: 25 µg, 75 µg, 125 µg and 175 µg. Dr. Hariyaga includes the following summary and table from Study TG-MV-004 in her review: The vitreomacular traction (VMT) resolution rates in placebo, 75 µg and 125 µg ocriplasmin treatment groups at Day 180 were increased dose proportionally up to 125 µg (22%, 33% and 54%, respectively). No clear difference in VMT resolution rate was observed between the 125 µg group (54% VMT resolution) and the 175 µg group (46% VMT resolution) at Day 180.

Figure 4: Proportion of subjects with resolution of VMT (TG-MV-004) based on assessment by investigator



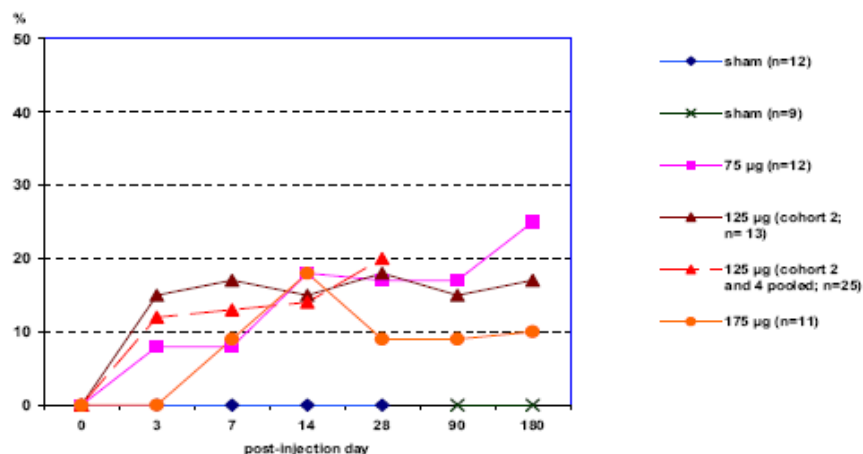
Comment: The approximately 50% response rate in this Phase 2 study in this study is higher than was subsequently seen in the Phase 3 studies. The assessment of VMT was done by the investigator, the assessment of posterior vitreous detachment (PVD) was done by a masked central reading center; the study report from the applicant includes the following information.

Primary efficacy variable is the Proportion of subjects with total PVD (i.e., vitreous detachment to the equator) as determined by masked CRC evaluation of B-scan ultrasound imaging at the first day 14 post-injection visit.

Table 5 Proportion of subjects with total PVD at post-injection day 14 (CRC assessment)

Sham	Microplasmin 75 µg	Microplasmin 125 µg ¹	Microplasmin 125 µg pooled ²	Microplasmin 175 µg
n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
0/11 (0.0)	2/11 (18.2)	2/13 (15.4)	3/22 (13.6)	2/11 (18.2)

Figure 1 Proportion of subjects with total PVD though post-injection day 180 (CRC assessment)



In the follow-up period between post-injection days 28 and 180, 1 subject of the 75 µg microplasmin group, 1 subject of the 125 µg microplasmin group, 3 subjects of the 175 µg microplasmin group and 3 sham subjects had a vitrectomy (Table 14.2.1.2.13a and 14.2.1.2.13b).

12.5.4 Best Corrected Visual Acuity 15 and 30 letter decrease

BCVA was measured at all study visits to evaluate both the efficacy and safety of the study drug treatment. The percentage of subjects experiencing a 15 or 30 letter decrease in BCVA during the study is tabulated and analyzed in Tables 14.3.5.17 and 14.3.5.18, respectively. In total 7 subjects experienced a decrease in BCVA compared to baseline of more than 15 letters at any time point; 1 sham subject, 2 subjects in the 75 µg microplasmin treatment group, 2 subjects in the 175 µg microplasmin treatment group and 2 subjects in the 125 µg microplasmin repeat injection treatment group. In 2 subjects, the decrease occurred at day 3 after the injection and was resolved at day 7. In the other 5 subjects, the decrease occurred at day 90 and/ or day 180. Of the 7 subjects that had a 15-letter decrease in BCVA, 1 subject had a decrease in BCVA of more than 30 letter on post-injection days 90 and 180 (subject 12104, 75 µg microplasmin). This decrease in BCVA coincided with a retinal vein occlusion in this subject, reported as an SAE on post-injection day 97.

7.1 Phase 3 clinical trials

Two Phase 3 trials were conducted, both vehicle-controlled, masked trials: Study TG-MV-006 was conducted in the United States; Study TG-MV-007 was done in Europe and United States. Male or female subjects aged ≥18 years with symptomatic vitreomacular adhesion (VMA) documented by optical coherence tomography (OCT) and best corrected visual acuity (BCVA) of 20/25 or worse in the study eye were enrolled. Patients with proliferative retinopathy, full

thickness macular hole (FTMH) diameter >400 µm, high myopia, prior retinal detachment, or a history of macular laser or vitrectomy in the study eye were excluded.

Primary Efficacy Endpoint

The primary efficacy endpoint was nonsurgical resolution of VMA at Day 28, as determined by masked Central Reading Center (CRC) OCT evaluation. Any subjects who had a creation of an anatomical defect (i.e. retinal hole, retinal detachment) that resulted in loss of vision or that required additional intervention were not counted as successes for this primary endpoint. Following discussion during the end-of Phase 2 meeting, it was agreed that this endpoint was clinically meaningful and an appropriate primary endpoint for demonstration of efficacy. In addition, reviewers conducted a literature search and found that the spontaneous resolution of VMA was low. Persistent VMA was generally associated with decrease in visual symptoms as well as photopsia, metamorphopsia, or micropsia. With spontaneous or surgical resolution of the VMA, there was generally stabilization or improvement in visual acuity, although some patients have worsening in vision (Appendix A)

Secondary Efficacy Endpoints

- Proportion of subjects with total PVD at day 28, as determined by masked investigator assessment of B-scan ultrasound.
- Proportion of subjects not requiring vitrectomy
- Proportion of macular holes that close without vitrectomy as determined by CRC
- Achievement of ≥ 2 and ≥ 3 lines improvement in Best Corrected Visual Acuity (BCVA) without need for vitrectomy
- Improvement in BCVA
- Improvement in VFQ-25

Safety Endpoints

The safety endpoints included information on post-injection complications and included adverse reactions such as ocular events, worsening VA, worsening macular edema, vitreous hemorrhage, retinal tear or detachments, increase in ocular inflammation, or IOP increases.

Study Schedule

There were 7 pre-specified visits: Baseline, Injection Day (Day 0), Post-Injection Day 7, Post-Injection Day 14, Post-Injection Day 28, Post-Injection Month 3 and Post-Injection Month 6. Baseline and Injection Day visits were combined at the Investigator's discretion.

7.2 Efficacy Results

Study TG-MV-006 enrolled a total of 326 patients from 42 study sites in the U.S: 217 randomized to receive ocriplasmin, and 107 randomized to receive placebo (2:1).

Study TG-MV-007 enrolled a total of 326 patients from 48 study sites in the EU (n=179) and U.S (n=147): 245 randomized to receive ocriplasmin, and 81 randomized to receive placebo (3:1). A total of 652 patients were randomized (ocriplasmin 464, placebo 188) were randomized.

Ocriplasmin was superior to vehicle control in both studies in VMA resolution at Day 28 and this difference continued to be statistically significant through Month 6 in each study

BLA 125422 JETREA (ocriplasmin) Intravitreal Injection, 2.5 mg/mL
Indication: treatment of symptomatic vitreomacular adhesions

($p \leq 0.024$), as shown in the Table 9 and 10 (below) from Dr. Deng's review and Figure 5 from the Applicant's Advisory Committee (AC) briefing material, page 11.

Table 9: Primary Efficacy Endpoint – Proportion of Patients Who Had Resolution of Focal VMA in the Study Eye at Day 28 (LOCF)

	TG-MV-006				TG-MV-007				Combined Analysis			
	PL	Ocri	Difference (95% CI)	p-value	PL	Ocri	Difference (95% CI)	p-value	PL	Ocri	Difference (95% CI)	p-value
Full Analysis Set												
N	107	219			81	245			188	464		
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	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)	<0.001
Modified Full Analysis Set												
N	99	207			77	233			176	440		
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	19 (10.8)	123 (28.0)	17.2 (10.9, 23.4)	<0.001
Per-Protocol Set												
N	94	189			71	214			165	403		
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	18 (10.9)	114 (28.3)	17.4 (10.9, 23.9)	<0.001

Source: Table 10 of the Applicant's Advisory Committee (AC) Meeting Briefing Package

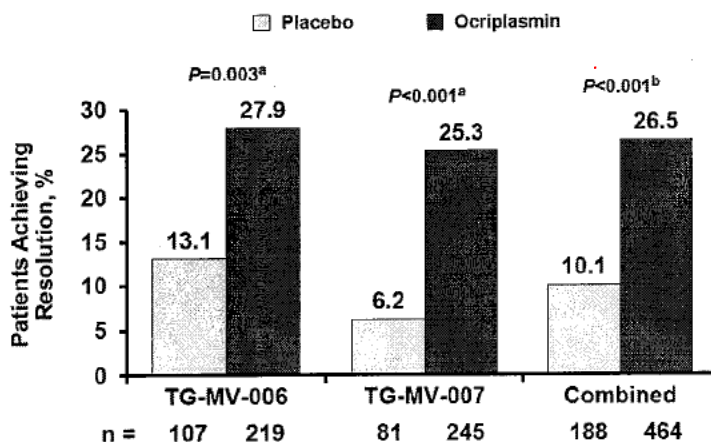
- The **Full Analysis Set** included all randomized patients who received treatment with investigational drug (ocriplasmin or placebo). The Full Analysis Set was the primary population for the efficacy analyses.
- A **Modified Full Analysis Set**, was defined as all randomized patients who received treatment with investigational drug and who were judged by the investigator as having symptomatic VMA at screening which was confirmed at Baseline by masked CRC OCT evaluation (excluded patients who did not have VMA at baseline, e.g. had only macular hole)
- The **Per-Protocol Set** included the Full Analysis Set excluding patients where a deviation was of sufficient concern to warrant exclusion. Decisions regarding data exclusion from the Per-Protocol Set were made prior to unmasking the randomization code (masked review). Patients for whom the actual treatment received did not match the randomized treatment were excluded from the Per-Protocol Set.

Table 10: Summary and Analysis of Nonsurgical Resolution of Focal VMA by Study Visit (FAS, LOCF)

	TG-MV-006				TG-MV-007				Combined Analysis			
	PL N=107 n (%)	Ocri N=219 n (%)	Difference (95% CI)	p-value	PL N=81 n (%)	Ocri N=245 n (%)	Difference (95% CI)	p-value	PL N=188 n (%)	Ocri N=464 n (%)	Difference (95% CI)	p-value
Day 7	8 (7.5)	54 (24.7)	17.2 (9.6, 24.8)	<0.001	1 (1.2)	36 (14.7)	13.5 (8.4, 18.5)	<0.001	9 (4.8)	90 (19.4)	14.6 (9.9, 19.3)	<0.001
Day 14	12 (11.2)	57 (26.0)	14.8 (6.5, 23.2)	0.002	1 (1.2)	44 (18.0)	16.7 (11.4, 22.1)	<0.001	13 (6.9)	101 (21.8)	14.9 (9.6, 20.1)	<0.001
Day 28	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	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)	<0.001
Month 3	16 (15.0)	58 (26.5)	11.5 (2.6, 20.5)	0.024	7 (8.6)	62 (25.3)	16.7 (8.5, 24.9)	<0.001	23 (12.2)	120 (25.9)	13.6 (7.5, 19.8)	<0.001
Month 6	15 (14.0)	60 (27.4)	13.4 (4.5, 22.2)	0.008	10 (12.3)	65 (26.5)	14.2 (5.1, 23.2)	0.009	25 (13.3)	125 (26.9)	13.6 (7.3, 20.0)	<0.001

Source: Table 14.2.1.4 of the Applicant's TG-MV-006 Study Report, and Table 14.2.1.4 of the Applicant's TG-MV-007 Study Report.

Figure 5. Primary Efficacy Endpoint: Proportion of Patients with VMA Resolution at Day 28 (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)



Abbreviation: VMA, vitreomacular adhesion.

^aFisher's exact test; ^bCochran-Mantel-Haenszel test, stratified by study.

Note: Full Analysis Set included all randomized patients who received treatment; data analyzed according to randomized patient-treatment group regardless of treatment actually received.

Data on file, ThromboGenics.

Drs. Harris and Deng note the placebo event rate of VMA resolution in TG-MV-006 was approximately twice that observed in TG-MV-007. The Applicant gave a number of possible explanations, such as less epiretinal membranes, more MH patients in the placebo group at baseline (TG-MV-006, 29.9%; TG-MV-007, 18.5%), less ERM cases at baseline (TG-MV-006, 32.7%; TG-MV-007, 40.7%) or a higher proportion of patients with a VMA diameter $\leq 1500\mu\text{m}$ at baseline (TG-MV-006, 74.7%; TG-MV-007, 63.6%). While not statistically significant, it is unclear why there is a large difference in the placebo rates in these two trials.

In addition to requesting approval of treatment of VMA, the applicant requested the indication of treating macular hole. The reviewers do not recommend approval of FTMHC because the latter was based on a secondary endpoint and not adjusted for multiplicity. After adjustment only study 006 shows significance $p=0.005$, while study 007 does not show a significant outcome with $p=0.354$.

The applicant's submission notes that "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. In the submission, the results of those endpoints were described with nominal 95% CIs and nominal p-values without any statistical significance statements. There were a total of six predefined exploratory endpoints (note: BCVA was tested at ≥ 2 and ≥ 3 lines) proposed in the phase 3 studies.

Finally it was noted that the outcome for posterior vitreous detachment (PVD) was statistically significant in both studies

(b) (4)

(b) (4)

Dr. Harris notes that “the current standard of treatment for patients who present with VMT is “watchful waiting” for those patients whose symptoms remain stable or vitrectomy if there is progression in retinal traction or progressive decrease in vision. Ocriplasmin was developed as an alternative for an invasive procedure which carries risks such as retinal tears/detachments, endophthalmitis, etc. The requirement to have vitrectomy surgery is not totally mitigated in those patients who are successfully treated with ocriplasmin. Based on the phase 3 trials, approximately 20% of patients successfully treated with ocriplasmin may require vitrectomy surgery.” (Table 9 and Table 10)

Table 9: Proportion of Patients who received a Vitrectomy in the Study Eye by Month 6 (TG-MV-006, TG-MV-007 and Integrated Studies: Full Analysis Set)

Time Point	TG-MV-006				TG-MV-007				Integrated Studies			
	PL (N=107) n (%)	Ocriplasmin (N=219) n (%)	Difference (95% CI) ^a	p-value ^b	PL (N=81) n (%)	Ocriplasmin (N=245) n (%)	Difference (95% CI) ^a	p-value ^b	PL (N=188) n (%)	Ocriplasmin (N=464) n (%)	Difference (95% CI) ^a	p-value ^b
By Month 6	31 (29.0)	45 (20.5)	-8.4 (-18.5, 1.7)	0.096	19 (23.5)	37 (15.1)	-8.4 (-18.6, 1.9)	0.091	50 (26.6)	82 (17.7)	-8.9 (-16.1, -1.7)	0.016

Reference: Table 2.3.1, Module 5.3.5.3

CI=confidence interval; PL=placebo

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

^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.

Table 10: Proportion of Patients who received a Vitrectomy in the Study Eye as of Month 6 by Outcome of the Primary Efficacy Endpoint (Integrated Studies: Full Analysis Set)

Treatment Group	Success on Efficacy Endpoint		Failure on Efficacy Endpoint		Difference (95% CI) ^a	Effect of Efficacy Endpoint	
	N	n (%)	N	n (%)		p-value ^b	Odds Ratio (95% Wald CI)
Ocriplasmin	123	25 (20.3)	341	57 (16.7)	-3.6 (-11.7, 4.5)	0.649	1.117 (0.695, 1.795)
Placebo	19	4 (21.1)	169	46 (27.2)	6.2 (-13.4, 25.7)		

Reference: Table 2.3.15 (post-hoc) and Table 2.3.19 (post-hoc), Module 5.3.5.3

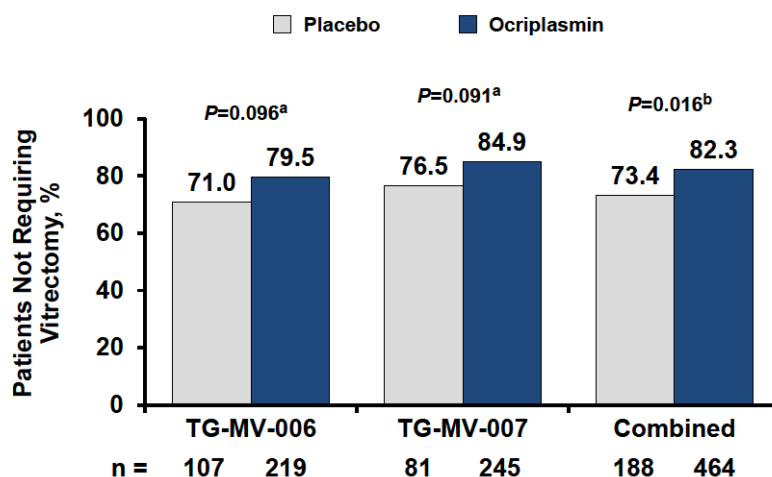
CI=confidence interval

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

^b P-value is from Type 3 analysis of effects from multivariate logistic regression.

As seen in Figure 26 below, more ocriplasmin patients did not need vitrectomy by Month 6 compared to placebo patients (82.3% vs. 73.4%)

Figure 26. Proportion of Patients Not Requiring Vitrectomy at Month 6 (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)



^aFisher's exact test; ^bCochran-Mantel-Haenszel test, stratified by study.
Data on file, ThromboGenics.

Applicant's AC briefing material, page 83

The geriatric population has been studied in these clinical trials. The mean age of the patients in the two Phase 3 trials was 72.0 years and 70.7 years for the JETREA and vehicle groups, respectively. In the pivotal studies, 384 and 145 patients were ≥ 65 years and of these 192 and 73 patients were ≥ 75 years in the JETREA and vehicle groups, respectively. No statistically significant difference in efficacy was seen.

Comment:

The clinical and statistical reviewers concluded that ocriplasmin was effective for the treatment of VMA and recommend approval of the application. A summary of the efficacy findings is included in Section 14 of the labeling.

8. Safety

The safety evaluation is summarized in the reviews by Drs. Harris, Boyd, and Chambers and information on some adverse events in also captured in the statistical review by Drs. Deng and Wang.

Safety was evaluated in 741 patients who received ocriplasmin and 247 control patients. This included the 465 ocriplasmin and 187 vehicle treated patients from the two Phase 3 studies.

Serious nonfatal ADRs of the eye occurred in 37/465 (8%) ocriplasmin and 20/187 (10.7%) placebo patients. Dropouts and discontinuations were seen in 29/465 (6.2%) of ocriplasmin and 16/187 (8.6%) placebo patients, most of these were due to patients withdrawing consent or being lost to follow up.

The most commonly reported adverse reactions are presented in the table below, and show that these events were reported more frequently with ocriplasmin than the vehicle. Dr. Harris

discusses that 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 drug's 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. Some events occurred proximal to the injection and resolved.

Of note, the concern about adverse events of worsening in BCVA is discussed in detail in the section below.

Table 18: Summary of Ocular AE in the Study Eye for at Least 2% of Patients in Phase 2, Randomized, Placebo-Controlled Studies (TG-MV-006 and TG-MV-007) and All Completed Studies (Safety Set)

System Organ Class Preferred Term Category	Phase 3, Randomized, Placebo- Controlled Studies		Completed Studies	
	Placebo n=187	Ocriplasmin 125µg n=465	Control ^a n=247	Ocriplasmin Any Dose n=741
Study Eye AEs, n (%)				
Vitreous floaters	14 (7.5)	78 (16.8)	18 (7.3)	119 (16.1)
Conjunctival hemorrhage	24 (12.8)	68 (14.6)	49 (19.8)	129 (17.4)
Eye pain	11 (5.9)	61 (13.1)	19 (7.7)	90 (12.1)
Photopsia	5 (2.7)	55 (11.8)	7 (2.8)	66 (8.9)
Vision blurred	6 (3.2)	39 (8.4)	7 (2.8)	47 (6.3)
Macular hole (new or worsening)	18 (9.6)	31 (6.7)	19 (7.7)	50 (6.7)
Visual acuity reduced	8 (4.3)	29 (6.2)	8 (3.2)	41 (5.5)
Retinal edema	2 (1.1)	25 (5.4)	2 (0.8)	32 (4.3)
Visual impairment ^b	2 (1.1)	25 (5.4)	2 (0.8)	27 (3.6)
Macular edema	3 (1.6)	19 (4.1)	10 (4.0)	43 (5.8)
Intraocular pressure increased	10 (5.3)	18 (3.9)	17 (6.9)	65 (8.8)
Anterior chamber cells	5 (2.7)	17 (3.7)	12 (4.9)	57 (7.7)
Photophobia ^c	0	17 (3.7)	0	25 (3.4)
Ocular discomfort	2 (1.1)	13 (2.8)	4 (1.6)	17 (2.3)
Vitreous detachment	2 (1.1)	12 (2.6)	2 (0.8)	13 (1.8)
Iritis	0	12 (2.6)	0	12 (1.6)
Cataract	8 (4.3)	11 (2.4)	12 (4.9)	34 (4.6)
Dry eye	2 (1.1)	11 (2.4)	2 (0.8)	14 (1.9)
Conjunctival hyperemia	4 (2.1)	10 (2.2)	6 (2.4)	25 (3.4)
Metamorphopsia	1 (0.5)	10 (2.2)	1 (0.4)	14 (1.9)

Source: Table 22 of the Applicant's AC Meeting Briefing Package

8.1 Adverse Reactions of Special Interest

Best Corrected Visual Acuity

Then looking at the combined analysis, over time, there is a mean change from baseline of two letters for placebo treated patients and three letters in ocriplasmin treated patients at Month 6, as shown in Table 12 and Figure 28

Table 12. Change from Baseline in BCVA Letter Score by Study Visit, Irrespective of Vitrectomy (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)

Visit	TG-MV-006			TG-MV-007			Combined Analysis		
	Placebo	Ocriplasmin 125µg	P value ^a	Placebo	Ocriplasmin 125µg	P value ^a	Placebo	Ocriplasmin 125µg	P value ^a
Baseline	n=107	n=219		n=80 ^b	n=245		n=188	n=464	
Mean letter score (SD)	65.3 (9.83)	64.5 (10.86)	—	64.9 (11.58)	63.4 (13.69)	—	65.1 (10.59)	63.9 (12.43)	—
Median letter score	67.0	67.0	—	66.5	67.0	—	67.0	67.0	—
Day 7									
Mean change from BL (SD)	1.2 (5.81)	0.1 (8.12)	0.183	1.7 (5.05)	-0.9 (8.09)	0.008	1.4 (5.49)	-0.4 (8.11)	0.005
Median change from BL	1.0	0.0	—	1.0	0.0	—	1.0	0.0	—
Day 14									
Mean change from BL (SD)	2.6 (5.14)	1.4 (9.60)	0.165	1.3 (5.62)	1.4 (6.82)	0.863	2.0 (5.38)	1.4 (8.24)	0.293
Median change from BL	3.0	2.0	—	1.0	1.0	—	2.0	2.0	—
Day 28									
Mean change from BL (SD)	2.6 (6.50)	2.6 (10.58)	0.950	2.8 (6.13)	2.6 (6.64)	0.823	2.7 (6.33)	2.6 (8.71)	0.861
Median change from BL	2.0	3.0	—	2.0	2.0	—	2.0	2.0	—
Month 3									
Mean change from BL (SD)	1.6 (12.09)	3.8 (10.50)	0.111	2.3 (8.00)	3.4 (7.75)	0.273	1.9 (10.52)	3.6 (9.14)	0.048
Median change from BL	2.0	3.0	—	2.0	3.0	—	2.0	3.0	—
Month 6									
Mean change from BL (SD)	2.8 (9.89)	3.5 (12.30)	0.732	2.1 (9.49)	3.6 (10.35)	0.218	2.5 (9.71)	3.6 (11.30)	0.303
Median change from BL	2.0	3.0	—	2.0	3.0	—	2.0	3.0	—

Abbreviations: ANOVA, analysis of variance; BCVA, best corrected visual acuity; BL, baseline; SD, standard deviation.

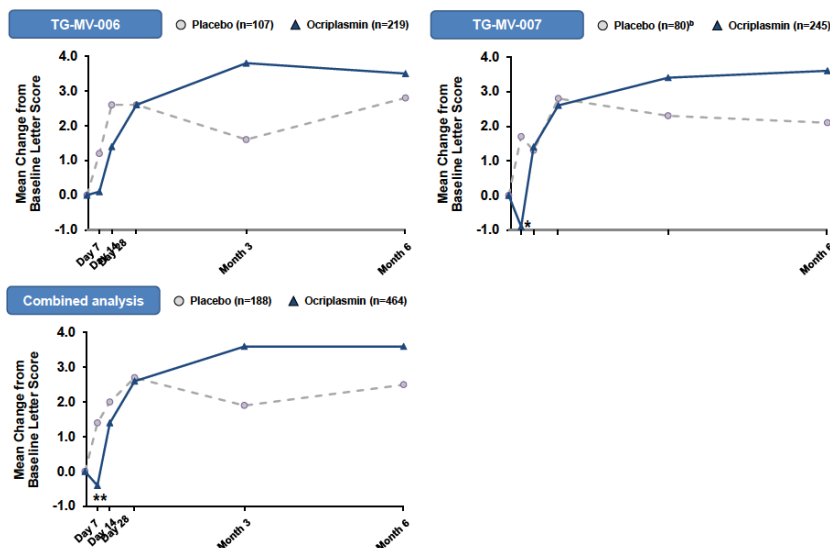
^aFor individual studies, treatment groups were compared with respect to change from baseline using ANOVA model with factors for treatment and baseline visual acuity category (<65 letters, 65–75 letters, >75 letters); for the combined analysis, the model also included a factor for study.

^bThe number of patients in the treatment group is 81; change from baseline was calculated on n = 80.

Data on file, ThromboGenics.

Applicant's AC briefing material, pages 85-86

Figure 28. Mean Change in BCVA Over Time (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)^a



Abbreviation: BCVA, best corrected visual acuity.

^a*P=0.008; **P=0.005.

^aTreatment groups were compared with respect to change from baseline using analysis of variance model with factors for treatment and baseline visual acuity category (< 65 letters, 65–75 letters, >75 letters); for the combined analysis, the model also included a factor for study.

^bThe number of patients in the treatment group is 81; change from baseline was calculated on n = 80.

Data on file, ThromboGenics.

In the table and figure above, the modest 2 to 3 letter increase in BCVA seems to favor the ocriplasmin group. However, the mean change in BCVA over time for the population as a whole in these studies does not provide a granular look at the information, and can be potentially misleading. When BCVA is examined in more detail in Table 13 below, it shows that while more ocriplasmin patients benefit in gaining ≥ 2 lines of visual acuity and ≥ 3 lines of visual acuity, there is another group that actually has worsening in BCVA by ≥ 2 lines or ≥ 3 lines. The top two rows in the table show the improvement in BCVA seen in both studies and the combined analysis. The bottom two rows in the table show the worsening in BCVA. The rate of ≥ 3 lines worsening in BCVA is higher for ocriplasmin vs. vehicle in Study 006 (7.3% vs. 1.9% in 3 line loss) and the combined analysis (5.6% vs. 3.2%) but this is not seen in Study 007 (4.1% vs. 5%).

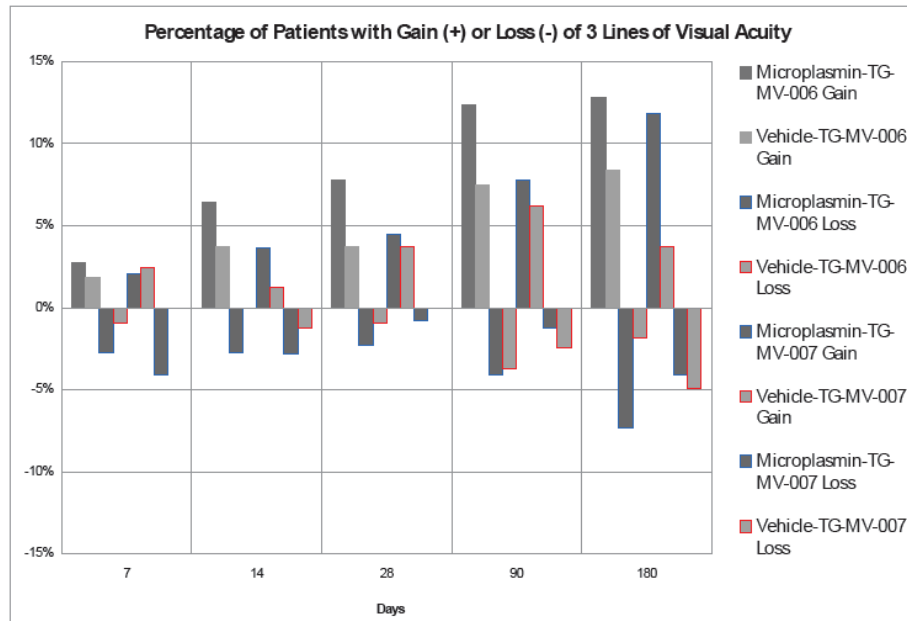
The clinical reviewers examined in great detail the information on BCVA, and looked at the individual patients who had ≥ 2 lines worsening of BCVA.

Table 13: Categorical Improvement from Baseline in BCVA at Month 6, Irrespective of Vitrectomy (TG-MV-006, TG-MV-007, and Combined Analysis; FAS, LOCF)

	TG-MV-006				TG-MV-007				Combined Analysis			
	PL N=107	Ocri N=219	Difference ^a (95% CI)	P-value ^b	PL N=81 ^c	Ocri N=245	Difference (95% CI)	P-value ^b	PL N=188 ^c	Ocri N=464	Difference (95% CI)	P-value ^b
≥ 2-line Improvement in BCVA												
Month 6	18 (16.8)	66 (30.1)	13.3 (4.0, 22.7)	0.010	14 (17.5)	64 (26.1)	8.6 (-1.4, 18.6)	0.133	32 (17.1)	130 (28.0)	10.9 (4.1, 17.7)	0.003
≥ 3-line Improvement in BCVA												
Month 6	9 (8.4)	28 (12.8)	4.4 (-2.5, 11.2)	0.270	3 (3.8)	29 (11.8)	8.1 (2.3, 13.9)	0.049	12 (6.4)	57 (12.3)	5.9 (1.3, 10.5)	0.024
≥ 2-line Worsening in BCVA												
Month 6	5 (4.7)	22 (10.0)	5.4 (-0.3, 11.0)	0.133	6 (7.5)	14 (5.7)	-1.8 (-8.2, 4.7)	0.594	11 (5.9)	36 (7.8)	1.9 (-2.3, 6.0)	0.352
≥ 3-line Worsening in BCVA												
Month 6	2 (1.9)	16 (7.3)	5.4 (1.1, 9.7)	0.067	4 (5.0)	10 (4.1)	-0.9 (-6.3, 4.5)	0.753	6 (3.2)	26 (5.6)	2.4 (-0.9, 5.7)	0.180

^a The difference is the absolute difference and CIs between treatment groups are based on the normal approximation.
^b p-value from Fisher's Exact test for each individual study; and P-value from CMH test for combined analysis, stratified by study.
^c One patient did not have baseline BCVA measurement in Study TG-MV-007; therefore, the denominator in this analysis is 80 for placebo group, and 187 for the combined analysis.
Source: Table 14 of the Applicant's AC briefing package.

The following Figure provides a more granular presentation of the variability in gain or loss of 3 lines in visual acuity at Day 7 through Day 180 (Month 6) visits, and shows that while some patients in both trials, both arms, had gains in BCVA (bars above the 0% line), there was a larger % of patients in the ocriplasmin arms of Study 6 who had 3 lines loss at each of the study visits. In Study 7, the 3 line or greater loss in BCVA was seen at Days 7,14, and 28, but not at Month 3 and Month 6.



The above Table and figure present the categorical changes in 2 lines or 3 lines of visual acuity for the patients from Study 006 and 007, regardless of whether or not they had resolution of VMA. Therefore, the association between success or failure on the primary endpoint (resolution of the VMA or failure to resolve the VMA, respectively) and changes in visual acuity were examined further (Appendix C) and tabulated. As seen in the two tables below, patients who had resolution of VMA had a larger increase in 2 or 3 line of gain in visual acuity compared to those who did not resolve VMA in both arms, and ocriplasmin patients had somewhat higher rates than placebo patients, even among patients who did not resolve their VMA.

Categorical Increase in Visual Acuity at Month 6 in TG-MV-006 and 007 (See Appendix C)

		Ocriplasmin	Placebo
VMA resolved	≥2 lines improvement	55/123 (44.7%)	4/19 (21.1%)
	≥3 lines improvement	25/123 (20.3%)	3/19 (15.8%)
VMA not resolved	≥2 lines improvement	75/341 (22%)	28/169 (16.7%)
	≥3 lines improvement	32/341 (9.4%)	9/169 (5.4%)

On the other hand, decreases in visual acuity were similar in ocriplasmin and placebo patients who had resolution of VMA, however, in patients who did not have resolution of VMA, a somewhat higher rate of ocriplasmin patients lost 2 or 3 lines of vision compared to the placebo patients.

Caterogical Decrease in Visual Acuity at Month 6 in TG-MV-006 and 007
(See Appendix C)

		Ocriplasmin	Placebo
VMA resolved	≥2 lines decrease	6/123 (4.9%)	1/19 (5.3%)
	≥3 lines decrease	3/123 (2.4%)	1/19 (5.3%)
VMA not resolved	≥2 lines decrease	30/341 (8.8%)	11/169 (6.5%)
	≥3 lines decrease	23/341 (6.7%)	6/169 (3.6%)

To better understand the information on decreases in visual acuity, the reviewers requested and the applicant submitted details on all patients who had ≥ 2 lines worsening of BCVA (see complete listing in Appendix B). There were 11/188 (5.9%) placebo patients and 36/464 (7.8%) ocriplasmin patients from the two Phase 3 trials who had ≥ 2 lines worsening of BCVA, including 5.6% (26/464) ocriplasmin subjects and 3.2% (6/188) placebo subjects who experienced ≥ 3 lines of worsening visual acuity.

The medical officer reviewed these cases and concluded that 32/47 (68%) of subjects showed that the likely reason for the decrease in visual acuity was VMT progression and/or macular hole progression. This was noted in 27/36 (75%) of ocriplasmin subjects and 5/11 (45.5%) of placebo subjects. Other conditions associated with decreased visual acuity in these patients included: macular atrophy, myopic degeneration, subretinal fluid, flattened fovea, poor fovea contour, foveal remodeling, surface wrinkling retinopathy, chorioretinal degeneration, cataract, and corneal opacity. (Appendix B)

Comment:

As discussed internally, it is possible that the higher proportion of ocriplasmin (6.7% vs 3.6% placebo) patients with ≥ 3 lines decrease may be due to the partial treatment effect of ocriplasmin which was associated with some degree of VMA release but without complete VMA resolution. The partial release may have resulted in greater vitreomacular traction (VMT) and greater decrease in visual acuity compared to the placebo arm. In this trial the patients were not followed past Month 6; therefore whether the remaining VMA will resolve spontaneously or whether these patients will undergo vitrectomy subsequently is not known. It is likely; however, that these patients would receive further follow-up and intervention as clinically warranted, and once the adhesion is released, they may stabilize or resolve the visual changes. (See Appendix A). In addition, during the discussion it was noted that the other retinal changes may be related or associated with the VMA.

In the tables above, rates of improvement or worsening of visual acuity based on whether patients had had resolution of VMA (successful outcome on primary endpoint) or not, are presented. In the table below, information on patients who did not have vitrectomy is presented, showing the improvement in BCVA in patients without vitrectomy is consistently higher in patients given ocriplasmin in each of the trials and in the combined analysis.

BLA 125422 JETREA (ocriplasmin) Intravitreal Injection, 2.5 mg/mL
Indication: treatment of symptomatic vitreomacular adhesions

Table 13. Categorical Improvement from Baseline in BCVA at Month 6 without Vitrectomy (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)

Time Point	TG-MV-006				TG-MV-007				Combined Analysis			
	Placebo (n=107) n (%)	Ocriplasmin (n=219) n (%)	Difference (95% CI) ^a	P value ^b	Placebo (n=81) ^c n (%)	Ocriplasmin (n=245) n (%)	Difference (95% CI) ^a	P value ^b	Placebo (N=188) ^d n (%)	Ocriplasmin (N=464) n (%)	Difference (95% CI) ^a	P value ^b
Non-surgical ≥2-line Improvement in BCVA^e												
Month 6	12 (11.2)	56 (25.6)	14.4 (6.0, 22.7)	0.002	9 (11.1)	54 (22.0)	10.9 (2.3, 19.5)	0.035	21 (11.2)	110 (23.7)	12.5 (6.6, 18.5)	<0.001
Non-surgical ≥3-line Improvement in BCVA^e												
Month 6	7 (6.5)	23 (10.5)	4.0 (-2.2, 10.2)	0.310	0	22 (9.0)	9.0 (5.4, 12.6)	0.002	7 (3.7)	45 (9.7)	6.0 (2.2, 9.8)	0.008
Non-surgical ≥3-line Improvement from Baseline or Improvement to ≥85 Letters^e												
Month 6	9 (8.4)	31 (14.2)	5.7 (-1.3, 12.7)	0.154	3 (3.7)	31 (12.7)	8.9 (3.1, 14.8)	0.021	12 (6.4)	62 (13.4)	7.0 (2.3, 11.6)	0.009

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval.

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

^bP value from Fisher's exact test for individual studies; P value from Cochran-Mantel-Haenszel test for the combined analysis, stratified by study.

^cOne patient did not have baseline BCVA measurement; however, this patient had a vitrectomy during the study and therefore did not meet the endpoint based on this criterion; therefore, this patient was included in the denominator for this analysis (81 for the placebo group).

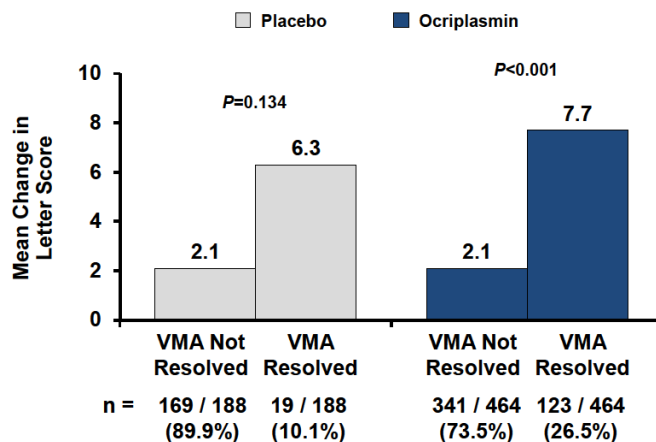
^dOne patient did not have baseline BCVA measurement; however, this patient had a vitrectomy during the study and therefore did not meet the endpoint based on this criterion; therefore, this patient was included in the denominator for this analysis (188 for the placebo group).

^eFor patients who did not have a vitrectomy during the study, non-surgical categorical improvement is defined as values observed at Month 6 or carried forward from previous visits if data are missing; data for patients with an on-study vitrectomy are included up to the date of vitrectomy; patients are considered as failures post-vitrectomy.

Data on file, ThromboGenics.

When looking at the change from baseline in BCVA over time, at Day 28 the improvement in mean BCVA is greater in patients who resolved VMA than in patients who did not resolve VMA. Patients who resolved VMA had a mean of 7.7 letters gain with ocriplasmin and 6.3 letters gain with vehicle. In patients without VMA resolution, the mean letter gain is 2.1 in patients whose VMA did not resolve, regardless of treatment arm. (Figure 9)

Figure 9. Improvement in Mean BCVA at Month 6 by Resolution of VMA at Day 28 (Combined Analysis: Full Analysis Set)



Abbreviation: BCVA, best corrected visual acuity; VMA, vitreomacular adhesion.

For individual studies, treatment groups are compared with respect to the change from baseline using analysis of variance model with factors for treatment and baseline visual acuity category (<65, 65-75, >75); for combined analysis, the model also includes a factor for study.

Data on file, ThromboGenics.

The rate of visual acuity reduction (3.2%, 1.5%, 2.8%, 6.4%, and 9.1%) increased with higher doses of ocriplasmin (control, 25 µg, 75 µg, 125 µg and 175 µg) respectively, suggesting a dose response (source Table 2.3.6, page 1027/4521 of ISS).

		Control (I) (N=247)		25 µg (N=67)		50 µg (N=10)		75 µg (N=71)		125 µg (N=582)		175 µg (N=11)		
Category	Preferred Term	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E	
	Study Eye Event	12	(4.9%)	13	12	(17.9%)	13	0	0	14	(19.7%)	18	31	
	Non-Study Eye Event	0		0	0		0	0	0	0		0	0	
Vision blurred	Study Eye Event	9	(3.6%)	12	3	(4.5%)	4	0	0	3	(4.2%)	3	44	
	Non-Study Eye Event	7	(2.8%)	8	3	(4.5%)	3	0	0	2	(2.8%)	2	42	
Macular oedema	Study Eye Event	4	(1.6%)	4	1	(1.5%)	1	0	0	1	(1.4%)	1	6	
	Non-Study Eye Event	10	(4.0%)	12	5	(7.5%)	6	0	0	12	(16.9%)	13	27	
Cataract	Study Eye Event	10	(4.0%)	12	5	(7.5%)	6	0	0	10	(14.1%)	11	27	
	Non-Study Eye Event	0		0	0		0	0	0	2	(2.8%)	2	2	
Visual acuity reduced	Study Eye Event	12	(4.9%)	12	6	(9.0%)	6	2	(20.0%)	2	10	(14.1%)	11	21
	Non-Study Eye Event	12	(4.9%)	12	5	(7.5%)	5	2	(20.0%)	2	8	(11.3%)	9	19
Study Eye Event	Study Eye Event	0		0	1	(1.5%)	1	0	0	2	(2.8%)	2	2	
	Non-Study Eye Event	9	(3.6%)	9	1	(1.5%)	1	0	0	2	(2.8%)	2	38	
Study Eye Event	Study Eye Event	8	(3.2%)	8	1	(1.5%)	1	0	0	2	(2.8%)	2	37	
	Non-Study Eye Event	1	(0.4%)	1	0		0	0	0	0		3	3	

Lens Subluxation

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 one week later with no reported lens subluxation. In addition, subluxation was seen in 3 animal species as described in the Pharmacology/ Toxicology section above, therefore a warning will be included in labeling about the potential risk of this toxicity.

Dyschromatopsia

Dyschromatopsia was reported in 16 of 820 patients (2.0%). This adverse reaction was rarely reported in the Phase 3 trials, but was described in the safety update. 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.

Retinal Breaks

The medical officer noted that the majority of retinal tears and retinal detachments occurred during or after vitrectomy and were seen in 8/187 (4.3%) placebo and 9/465 (1.9%) of ocriplasmin patients. However, 2 (0.4%) retinal detachments occurred in the ocriplasmin group and 1 (0.5%) retinal tear in the placebo group before vitrectomy.

Cataracts

The rate was lower in the ocriplasmin group.

Other analyses

The rate of vision alterations, vitreous floaters, photopsia and eye pain were numerically higher in females than males in both treatment groups.

The rate of vision alteration, retinal/macular edema, intraocular inflammation, eye pain, vitreous floaters and photopsia were numerically higher in younger (<65 years) patients treated with ocriplasmin than older (≥ 65 years) patients. Vision alteration was reported more frequently in younger patients (<65 years) (24.5%, 11.4%) than older patients (≥ 65 years) (14.1%, 1.4%) treated with ocriplasmin 125 µg or placebo, respectively, in the Phase 3 trials

and consistently the rates were higher in the ocriplasmin arm compared to the placebo arm. Similar findings were observed for subgroup analyses by age <75, ≥ 75 years.

Phakic patients who received ocriplasmin were more likely to have vision alteration, retinal edema, vitreous floaters and photopsia than pseudophakic patients.

One case of accidental overdose of 0.250 mg ocriplasmin (twice the recommended dose) has been reported. The patient had a decrease in BCVA of 21 letters (ETDRS score) from baseline that returned to within 9 letters of baseline during the study. The patient also had mild conjunctival hyperemia, eye inflammation and miosis which resolved with corticosteroid eye drops.

Safety Update

The 120 day safety update covered the period from April 2011 to May 2012, and included a summary of completed and ongoing studies

- TG-MV-008 – uncontrolled trial of 0.125 mg injection, terminated. Most of the dyschromatopsia cases were reported from this trial.
- TG-MV-005 – ongoing controlled trial of VMA associated with AMD
- TG-MV-009 – ongoing comparative trial in pediatric patients scheduled for vitrectomy
- TG-MV-012 – follow up of visual function in 24 patients previously in studies 006 and 007
- TG-MV-014 – Phase 3 sham-controlled trial in VMA/VMT /MH patients (177 treated as of May 2012)
- JSEI-TGAMD-001b – Phase 3 placebo-controlled single-center trial in VMA and AMD
- 10-EI-0186b – Single center uncontrolled trial in VMA, MH in uveitis patients

15 day alert reports included: visual decrease by 32 letters overnight, lens dislocation (4 month old infant), and one patient with retinal toxicity, macular hole, retinal vasculitis, and impaired pupillary reflex.

Comment:

The adverse reactions were reviewed. The reviewers concluded that the benefits outweigh the risks and recommend approval of the application. The adverse reaction findings of the safety analysis will be included in the warnings, precautions and adverse reactions section of labeling, as appropriate.

The applicant proposed to include the favorable results of categorical improvement in BCVA from baseline. However, as shown in the analysis of BCVA, while more ocriplasmin patients had improvements (mainly in the VMA resolved group), more ocriplasmin patients had decrease in visual acuity particularly in the VMA not resolved subset, mainly due to progression of disease. Therefore, the statistical reviewer does not recommend putting the results of categorical improvement from baseline of BCVA in the labeling. Instead, the labeling includes a table and figure that show the rates of patients with improvements in BCVA and rates of patients with decrease in BCVA.

9. Advisory Committee Meeting

The application was discussed before the Dermatologic and Ophthalmic Drugs Advisory Committee on July 26, 2012. Based on the Quick Notes by Yvette Waples of the Advisors and Consultants Staff, the committee voted unanimously (10 vs. 0) that 0.125 mg of ocriplasmin demonstrated efficacy in the treatment of vitreomacular adhesions (VMA), although some commented on a desire to see a greater effect size. The committee also voted unanimously that the benefits outweighed the risks for VMA. For the treatment of macular holes associated with VMA, the vote was Yes=7 and No=3; and regarding treatment of any macular holes, the vote was No=8, Yes=1, and Abstain=1 because there were no data presented on treatment of all MH regardless of the presence of VMA. Six members voted No regarding the need for additional safety studies before approval, while three members were interested to further information; some members requested there be post-marketing studies to further evaluate the safety of ocriplasmin on the retina, including optical coherence tomography (OCT) data. Recommendations regarding labeling included stating “for single use in one eye only,” keeping the word “symptomatic” in the indication, and providing information for patients in labeling. Further information and transcripts are available at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicalOphthalmicDrugsAdvisoryCommittee/ucm280522.htm>

10. Pediatrics

Efficacy and safety in pediatrics have not been established. Vitreomacular adhesion occurs infrequently in pediatric patients; however, the company is conducting a pediatric trial, TG-MV-009, titled “The MIC (Microplasmin In Children),” using ocriplasmin in conjunction with vitrectomy. Trial enrollment was recently completed and the study report is pending, therefore the application was presented before the Pediatric Review Committee on October 3, 2012 and the recommendation was made to defer submission of pediatric studies because the application is ready for approval. The full study report is expected to be submitted in December 2012.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection – OBP and OC

The drug substance facility was inspected (b) (4) by Mary Farbman and Reyes Candau-Chacon. Six issues were cited on Form 483. Other facilities were inspected later, and the final TB-EER per Mahesh Ramanadham was entered in DARRTS (b) (4). The TB-EER overall recommendation was that there were no pending or ongoing compliance actions that prevent approval of this BLA. There was also a request for a PMC for information required under the regulation and therefore against CDER policy. (See Division Director Review #2 dated October 17, 2012 for details.)

11.2 Office of Scientific Investigation (OSI) Audits

OSI inspected four investigators from Studies 006 and 007 each of whom enrolled between 14 to 20 subjects. Three investigators were considered to be NAI and one investigator was classified VAI. An FDA Form 483 was issued that nausea vomiting that occurred in two patients during a fluorescein angiography procedure was not reported, one patient’s final visit was at 35 days instead of between 25-31 days after treatment, discrepancies were noted in data

recorded on source documents and electronic case report forms. These discrepancies were addressed by the investigator during the FDA inspection. The overall conclusion and recommendation from OSI/DGCPC is that based on the inspectional findings above, efficacy and safety data obtained from these sites can be considered reliable in support of the application.

11.3 Debarment Certification

ThromboGenics certified that they had not used services of any debarred individual [as required under FD&C Act Section 306].

11.4 Financial Disclosure

The medical officer concluded that Thrombogenics has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for ocriplasmin. There was one investigator who participated in the Phase 3 safety and efficacy trials that disclosed financial ties to the sponsor.

11.5 Other Regulatory Issues

None identified.

12. Labeling

The package insert and carton and container labeling were reviewed as applicable by the Division, DMEPA, OPDP/DPDP and OBP, and two labeling meetings where all reviewers and consultants were invited were held on October 2 and October 3, 2012 during which labeling recommendations were discussed and the majority of labeling content was finalized. For example, there was discussion of the importance of including that the vial contained 0.5 mg ocriplasmin in 0.2 mL solution, but also of including the information that the concentration is 2.5 mg/mL; therefore, this information was included in the relevant parts of labeling, as recommended and discussed by OBP, DMEPA and DTOP. Other discussion covered topics such as animal findings of subluxation and information to be included in Section 14.

- **Package insert (PI):** The PI is written in PLR format and has been reviewed each discipline, and includes the recommendations made by these groups.
- **Carton and Container Labels:** The labels have been reviewed by OBP and DMEPA.
- **Proprietary Name:** The proposed proprietary name Jetrea was reviewed and found acceptable by DMEPA on July 25, 2012 and a letter stating that the name is acceptable was issued by Dr. Holquist of DMEPA on July 25, 2012.
- **Proper Name:** The proper name for this biologic is “ocriplasmin,” as recommended in the OBP/DTP labeling review.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The BLA is recommended for *Approval*, given that two Phase 3 trials showed the product is safe and effective for the treatment of symptomatic vitreomacular adhesion (VMA). The Advisory Committee members recommended unanimously that efficacy had been demonstrated and that the benefits outweighed the risks. The review team also is recommending approval. Manufacturing site inspections were completed (b) (4) (see Section 11.1).

For this biologic product, the following licensing and product information provided by OBP/DTP needs to be included in the approval letter:

LICENSING

We have approved your BLA for Jetrea (ocriplasmin) Intravitreal Injection effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Jetrea under your existing Department of Health and Human Services U.S. License No. 1866. Jetrea is indicated for treatment of symptomatic vitreomacular adhesion.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture ocriplasmin drug substance at Fujifilm Diosynth Biotechnologies UK Ltd in Billingham, Cleveland TS23 1LH and drug product at (b) (4). You may label your product with the proprietary name, Jetrea, and will market it in 2.5 mg/mL Intravitreal Injection.

DATING PERIOD

The dating period for Jetrea (ocriplasmin) shall be 18 months from the date of manufacture when stored at -20°C. The date of manufacture shall be defined as the (b) (4) of the formulated drug product. The dating period for your drug substance shall be (b) (4) from the date of manufacture when stored at (b) (4).

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 501.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Jetrea (ocriplasmin) to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Jetrea, or in the manufacturing facilities, will require the submission of information to your biologics

license application for our review and written approval, consistent with 21 CFR 601.12.

13.2 Risk Benefit Assessment

Two Phase 3 controlled clinical trials demonstrated that JETREA is safe and effective in the treatment of symptomatic vitreomacular adhesion (VMA). The dose is a single intravitreal injection of 125µg of ocriplasmin, delivered in 0.1 mL of diluted drug product.

The trials were superiority trials; in both ocriplasmin 125µg was superior to the vehicle control. The effect size, however, was noted to be modest and the DODAC members expressed a hope to see a greater effect size.

FAS population	Ocriplasmin	Placebo	P value
TG-MV-006	61/219 (27.9%)	14/107 (13.1%)	0.003
TG-MV-007	62/245 (25.3%)	5/81 (6.2%)	<0.001
Overall	123/464 (26.5%)	19/188 (10.1%)	<0.001

Although one might consider whether different dosing or dosage regimens could achieve a greater effect size, such studies may be challenging or not feasible because nonclinical studies in monkeys showed that repeat doses (a second dose) were associated with subluxation in all monkeys due to ocriplasmin, a proteolytic enzyme in the serine protease category.

Resolution of VMA is a structural endpoint, however, the relationship between the structural endpoint and visual acuity was reviewed, and the findings are summarized in Appendix A of this document.

Ocriplasmin is not recommended for the treatment of full thickness macular holes (FTMH) associated with VMA. The percentage of macular hole closures was statistically greater in one of the two trials; however, in the protocol, this endpoint was considered supportive or exploratory with no prespecified statistical plan.

The safety profile of ocriplasmin, in context of the efficacy shown, was acceptable. The rate of serious ocular events was not higher (was somewhat lower) in the ocriplasmin arm and the rates of dropouts and discontinuations were also not higher (was somewhat lower) in the ocriplasmin arm. Overall, there was a difference noted in the rate of adverse events, many were numerically higher in the ocriplasmin arm, many were related to the procedure and resolved.

However, proportionally 7.8% of ocriplasmin patients compared to 5.9% of vehicle patients had 2 or more lines of decrease in BCVA. Examination of these patients and their OCT showed this worsening was related to progression of the VMA and MH. In patients who had resolution of VMA, the decrease in vision was not different (5.3% in vehicle control and 4.9% in ocriplasmin). The rates in patients who did not resolve VMA were 5.9% vehicle and 8.8% ocriplasmin. Information on ocular adverse reactions is included in labeling.

13.3 Recommendation for other Postmarketing Requirements and Commitments

The following PMRs and PMCs will be included in the *Approval* letter:

a) Post-Marketing Requirement

1. TG-MV-009, titled “The MIC (Microplasmin In Children) Trial: A Randomized, Placebo-controlled, double-masked, Clinical Trial of Intravitreal Microplasmin in Infants and Children Scheduled for Vitrectomy.”

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

b) Post-Marketing Commitments

For the PMC’s below, on October 2, 2012 the applicant submitted a timetable for the completion of each of the PMC’s.

2. 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.

Final Report Submission: 03/13

3. 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.”

Interim Report Submission: 12/12

Final Report Submission: 04/13

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

Final Report Submission: 12/12

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

Final Report Submission: 12/17

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

Final Report Submission: 12/15

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

Final Report Submission: 03/13

8. 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)

Final Report Submission: 03/13

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

Final Report Submission: 03/13

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

Final Report Submission: 10/12

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

Final Report Submission: 08/13

12. 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.

Final Report Submission: 03/13

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

Final Report Submission: 06/13

14. 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.

Final Report Submission: 03/13

15. 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.

Final Report Submission: 12/12

16. 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.

Final Report Submission: 12/13

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

Final Report Submission: 03/13

18. 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.

Final Report Submission: 12/13

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

Final Report Submission: 03/13

20. 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.

Final Report Submission: 03/13

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

Final Report Submission: 03/13

22. 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.

Final Report Submission: 03/13

23. 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.

Final Report Submission: 03/13

24. Validate the efficacy of the (b) (4) (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 (b) (4) (b) (4) should be filed in subsequent Annual Reports.

Final Report Submission: 03/13

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

Final Report Submission: 03/13

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

Final Report Submission: 03/13

APPENDIX A:

Summary of evaluation of vitreomacular adhesions, vitreomacular traction, posterior vitreous detachment and visual symptoms, notably visual acuity

Introduction

As the eye ages, the vitreous body undergoes a process of liquefaction and collapse.

“In the normal aging eye, the vitreous body undergoes liquefaction (synchysis) resulting in liquid pockets within the vitreous gel. This predisposes the gel to collapse with separation of the posterior vitreous cortex from the retinal surface (syneresis). Incomplete posterior detachment with persistent cortical attachment of the macula may lead to tractional retinal distortion and macular edema, with resultant vision loss, metamorphopsia, micropsia, and photopsia. Diagnosis of vitreomacular traction (VMT) by bio microscopy may be challenging, particularly when the area of vitreoretinal attachment is broad. Optical coherence tomography (OCT) better defines the vitreoretinal relationships in eyes with VMT and also documents concomitant epimacular membrane and macular edema. Although spontaneous vitreoretinal separation may yet occur, VMT tends to progress over time. Pars plana vitrectomy is effective in releasing the VMT with visual improvement in some cases.”²

Autopsy studies have shown that the incidence of posterior vitreous detachment (PVD) is approximately 63% by the eighth decade of life.³

This posterior vitreous detachment usually occurs as an acute event with the vitreous completely separating from the posterior retina.⁴ In some cases, the posterior vitreous detachment is incomplete and vitreoretinal adhesions remain. These persistent adhesions are most clinically relevant when they occur in the macula (i.e., vitreomacular adhesions (VMA)) and/or over blood vessels. Thus, VMA results from incomplete posterior vitreous separation which results in persistent anterior-posterior traction on the macula.

Vitreoretinal traction (VMT) at the macula has been associated with cystoid macular edema which causes symptoms of decreased visual acuity (VA), metamorphopsia and photopsia, patients usually present with varying of these visual complaints. Patients’ symptoms may remain stable with some patients eventually having the VMA spontaneously detach. A subgroup of patients will have worsening traction and deteriorating visual acuity.⁵

Natural History

The natural history of vitreomacular traction is not well documented in the literature despite being first recognized by Reese in 1967.⁶ Four researchers who have studied this natural history have used various methods for observing the retinal changes that occur. Hickichi *et.al.*⁷ used biomicroscopy with a 58.6 diopter lens, Larsson used OCT-2 images and Odrobina *et.al.*

² Sonmez, K et al. Vitreomacular traction syndrome. *Retina* 2008; 28(9):1207-1214.

³ Uchino E, Uemura A. Initial Stages of Posterior Vitreous Detachment in healthy eyes of Older Persons Evaluated by Optical Coherence Tomography. *Arch Ophthalmol* 2001;119:1475-1479.

⁴ Hikichi T, Yoshida A. Course of Vitreomacular Traction Syndrome. *Am J Ophthalmol* 1995;119:55-61.

⁵ Ibid

⁶ Reese A, Jones I. Macular Changes Secondary to Vitreous Traction. *Am J Ophthalmol* 1997;51:544-9.

⁷ Hikichi T, Yoshida A. Course of Vitreomacular Traction Syndrome. *Am J Ophthalmol* 1995;119:55-61.

used high-resolution spectral-domain OCT (SOCT). Recently, with the advent of researchers investigating the use of enzymatic vitreolysis, Stalmans *et. al.* used OCT images to study the natural course of VMA compared to intravitreal microplasmin injections. In addition to reporting on the anatomic/morphologic appearance of the vitreous and retina, the authors also comment on the patients visual acuity changes over the period of observation.

Hikichi *et. al.* retrospectively studied patients to determine the natural history of vitreomacular traction. In this study 53 eyes with symptomatic traction were enrolled and had a mean follow up of 60 months. The results from this paper are:

- 43/53 (81%) of eyes had cystoid changes at baseline
- 29/43 (67%) had cystoid changes that persisted during follow-up
- 34/53 (64%) of subjects had visual acuity decreased by ≥ 2 Snellen lines from baseline
- 1/53 (<1%) developed a macular hole during follow-up
- 6/53 (11%) developed complete posterior vitreous detachment (all 6 had resolution of cystoid changes)
- None of the 6 eyes that had complete PVD had decrease in visual acuity during the follow up; whereas 34/47 (72%) of eyes with persistent vitreous traction had decrease in vision (see Figure 1) Two eyes with VA better than 20/100 at baseline had a final VA of 20/30. The four eyes with initial VA of worse than 20/100 had a final VA of 20/100 or 20/200. Therefore, it was hypothesized that the recovery of VA depends on the degree of macular damage when the release occurs.
- In 6/6 eyes where vitreous traction on the macula was released, cystoid changes resolved as noted above (although degenerative sequelae of cystoid macular degeneration remained in 4 eyes). Of the remaining 47 eyes with persistent vitreous traction, 42/47 (89%) had cystoid changes on final examination,
- The number of eyes with resolved cystoid changes or stable visual acuity was significantly higher when complete vitreomacular separation occurred (6/6) than when it did not with resolved cystoid changes in (3/37 [8%]) and stable VA in 13/47 [28%]).
- Hikichi et al state, “early traction release is thought to improve the visual acuity more effectively in eyes with vitreomacular traction syndrome.”
- Conclusion: most symptomatic eyes with persistent vitreomacular traction syndrome have a further decrease in visual acuity. Complete vitreomacular separation, which occurs infrequently in eyes with the disorder, allows resolution of cystoid changes and improvement in visual acuity.

Larsson⁸ used optical coherence tomography (OCT) to evaluate the macula before and after vitrectomy in 11 patients with VMT. While this study was designed to evaluate patients undergoing surgical intervention, the authors waited 3 months after diagnosis before performing surgery to evaluate the natural history of the disease. In this study, 11 eyes were diagnosed with VMT using OCT, and found to have traction and increased macular thickness. The mean duration of visual deterioration for these patients was 5 months (2-12 months). The patients were told there was a slight chance their condition would resolve spontaneously and given the option for immediate vitrectomy or waiting 12 weeks. All chose to wait the 12 weeks. During the 12 weeks (3 months) before vitrectomy was performed, none of the patients

⁸ Larsson J. Vitrectomy in Vitreomacular Traction Syndrome Evaluated by Ocular Coherence Tomography (OCT) Retinal Mapping. *Acta Ophthalmol Scand* 2004;82:691-694.

had an improvement in visual acuity or decrease in retinal thickness, in other words, there was no spontaneous improvement in these 11 patients. The results after vitrectomy was performed are summarized in the “Current Treatment” section below.

Odrobina *et.al.*⁹ conducted a retrospective observational study of idiopathic symptomatic VMT in 19 patients using spectral-domain (S)OCT to estimate the natural course of vitreomacular traction (VMT) disorder. The average observational period was 8 ± 4.4 months. Patients who had decreased visual acuity or metamorphopsia and at least two follow up visits were included in the study.

- Mean baseline VA was 0.4 ± 0.3 which improved to a mean final VA was 0.3 ± 0.32 ¹⁰
 - The article does not break down VA on follow up for the 9 patients who had spontaneous resolution vs. the 10 patients who had persistent VMT
- 9/19 (47%) had complete resolution of VMA (total vitreous detachment), in these eyes there were no epiretinal membrane (ERM) and horizontal vitreous surface adhesion was 180 ± 84 microns
- 6/19 (32%) had complete resolution of intraretinal cystoid spaces, these were ones with total vitreous detachment
- In 10/19 (53%) of eyes with persistent VMT the mean maximal horizontal vitreous surface adhesion was 600 ± 385 microns, and 6 of these had ERM. In one of these ERM developed during follow up
- 2/19 (10%) eyes with macular holes at baseline spontaneously closed
- 2/19 (10%) eyes developed macular holes during the observational period
- In 3 eyes, macular morphology and vitreous adhesion did not change.
- The authors noted that in these 19 patients, those whose eyes had less surface adhesion and no ERM resolved spontaneously, and commented that eyes with higher vitreous surface adhesion or coexisting ERM should perhaps have vitrectomy.
- The authors also comment that they had less ERM in their trial (26%) compared to other reports with 50%-83%, and the spontaneous resolution may be higher when there is less ERM.

Stalmans *et.al.*¹¹ conducted a prospective trial in 60 patients comparing sham injection (natural history) to enzymatic vitreolysis with 3 different doses of microplasmin. Twelve patients were enrolled in the sham group and followed for 180 days. Enrolled patients had VMA on OCT with macular thickening. In following the natural history of the disease in patients in the sham group it was noted that:

- 1/12 (8%) had spontaneous resolution of VMA at 1 month
- 3 sham patients had vitrectomy by day 180, the reason for vitrectomy in VMA patients was macular hole (MH)
- 2/9 (11.1%) had spontaneous resolution of VMA at 6 months
- 12 sham treated patients
 - 0/9 (0%) had increase in VA at month 6 if no vitrectomy

⁹ Odrobina D, Michalewska Z. Long Term Evaluation of Vitreomacular Traction Disorder in Spectral Domain Optical Coherence Tomography. *Retina* 2011;31:324-331.

¹⁰ Logarithm of the minimum angle of resolution

¹¹ Stalmans P, Delaey C. Intravitreal Injection of Microplasmin for Treatment of Vitreomacular Adhesion. *Retina* 2010;30:1122-1127

- 2/3 (67%) had ≥ 3 lines VA improvement after having a vitrectomy¹²

In summary, based on this limited natural history data, it would appear that without treatment, 11% -47% of VMA will spontaneously resolve, 0%-10% of patients may be at risk for developing macular holes. In patients with VMA, 72% (34/47) of eyes with persistent vitreous traction had decrease in vision, while patients who had spontaneous PVT resolution (complete PVD) did not have further decline in vision and some had improvement in VA; the improvement was more likely if the baseline VA was better than 20/100. Patients with complete PVD generally had resolution of macular edema and this happened infrequently in patients with persistent VMA.

Current Treatment – Patient Outcomes

The current standard of treatment for patients who present with VMT is “watchful waiting” since some cases may resolve when the posterior detachment completes and since the only current treatment is surgical which carries risks of retinal breaks, detachments and glaucoma among others. Surgery is currently indicated if there is progression in vitreous traction as noted on OCT and if vision decreases to 20/60 or worse.¹³

Four surgical series by Smiddy, Mac Donald, Koerner and Melberg have evaluated the effect of surgically relieving the VMA on visual function in 95 eyes.

Smiddy et al¹⁴ performed pars plana vitrectomy in 16 patients with partial posterior vitreous detachment with persistent vitreomacular attachment (VMA). These patients had vitreomacular traction and decreased visual acuity, most often 20/200. Symptoms had been present for 1-12 months in duration. Postoperatively, 5 patients had unchanged visual acuity and 11 (69%) patients had an improvement in their visual acuity (see table). The postoperative visual acuity was within one Snellen line of the preoperative level in 6 eyes, two-three lines better in 6 eyes, four-seven lines better in 4 eyes. Cystic macular changes were seen in 12 eyes at entry, although the authors do not report on the follow-up findings.

MacDonald et al¹⁵ reported on 20 consecutive eyes that underwent vitrectomy and posterior hyaloid-epiretinal membrane stripping for reduced vision caused by vitreomacular traction syndrome (VTS); the patients were followed for 6-36 months (median 13 months). All of these patients had symptoms of reduced or distorted vision. Release of vitreomacular traction resulted in improvement in vision of 2 or more lines in 15/20 (75%) patients and 8/20 patients obtained visual acuity of 20/50 or better. Sixteen patients had macular edema at entry; it persisted postoperatively in 3 patients.

¹² Based on the study report for TG-MV-004 from which this paper was written

¹³ Yanoff M, Duker J.(2009). Ophthalmology 3rd ed. St. Louis, MO: Mosby.

Carpineto P, Antonio L. Diagnosing and Treating Vitreomacular Adhesion. *European Ophthalmic Review* 2011;5:69-73.

¹⁴ Smiddy W, Michels, R. Vitrectomy for Macular Traction Caused by Incomplete Vitreous Separation. *Arch Ophthalmol* 1988;106:624-628.

¹⁵ McDonald H, Johnson, R. Surgical Results in the Vitreomacular Traction Syndrome. *Ophthalmology* 1994;101:1397-1403.

Koerner et al¹⁶ performed vitrectomy on 50 patients with VTS; the indication was progressive deterioration in VA or symptoms of metamorphopsia or disturbance in binocular reading. Postoperatively visual acuity was improved in 60% of patients; and VA of 20/40 went from 18% of patients preoperatively to 49% postoperatively. Better outcome was seen in patients whose preoperative VA was 20/100 or better, than those with VA worse than 20/100. Koerner et al also refer to the publication by Gaudric et al and state those authors also found that poorer post-operative visual results are obtained in patients with preoperative VA 20/200 or worse compared to patients with VA above 20/200, suggesting release of VMA that affects visual acuity should not be delayed too long.

Melberg et al¹⁷ reported on 9 patients with symptomatic decrease in visual acuity and macular traction retinal detachment and VTS who had pars plana vitrectomy and retinal reattachment. Complete retinal reattachment was achieved in 7/9. VA was improved in 4, stable in 4 and worse in 1 eye.

In the above studies, the pre-op visual acuity in these patients was < 20/100 in 60-78%, and improved by at least two lines in 44-77% and had a final visual acuity of > 20/100 in 44-88% of cases.

In the Larsson study discussed above previously, patients underwent vitrectomy after a 3 month period of “watchful waiting”. Six months after surgical release of the VMA, 10 of 11 patients had an improvement of two or more lines in vision, the mean improvement in VA was 3.1 lines and central macular thickness decreased from 609µm to 243 µm.

Manually dissecting the vitreous adhesion away from the macular surface allows the retina to return to its normal anatomical state so that vision can be restored. In the above studies, patients with symptomatic VMA manifested by decreased vision and metamorphopsia had pars plana vitrectomy performed, and visual improvement ranged from 44% (with retinal reattachment) to 75%.

COMMENT:

In summary, from the natural history series, persistent VMA/PVT is associated with a decrease in VA in many of the patients, and when there is spontaneous resolution of the VMA, or when there is surgical release of the VMA, the VA tends to stabilize and/or improve in many (although not all) patients. This series of publication demonstrates that there is an association between the structural findings associated with VMA and the functional impact on the patients' visual acuity; many patients develop decrease in visual acuity along with metamorphopsia, etc., with VMA, while after spontaneous resolution or surgical vitrectomy, many patients have stabilization or improvement in vision. These findings suggest that in the absence of spontaneous resolution of PVT, either surgical or chemical (enzymatic) release of the VMA/PVT is likely to have clinical benefit on visual acuity in at least some patients. Early traction release appears to be more effective in yielded visual acuity improvement, while persistent VMT leads to macular damage and declining VA. Thus eyes with VA worse than

¹⁶ Koerner F, Garweg J. Vitrectomy for Macular Pucker and Vitreomacular Traction syndrome. *Doc Ophthalmol.* 1999;97:449-458.

¹⁷ Melberg N, Williams D. Vitrectomy for Vitreomacular Traction syndrome with Macular Detachment. *Retina* 1995;15:192-197.

20/100 tend to have less VA improvement after vitrectomy compared to eyes with VA better than 20/100 at baseline.

Current Investigations of Associated Pathologies

There is growing evidence that supports the fact that abnormalities at the vitreoretinal interface may play a role in other ocular diseases such as age-related macular degeneration (AMD). Several studies have described the relationship between the posterior vitreous and macula in AMD and have suggested that VMA plays an important role in the development of exudative AMD (Sebag). Research groups have postulated that persistent attachment of the posterior vitreous cortex to the macula may be a risk factor for the development of exudative AMD due to traction inducing chronic low-grade inflammation, impairing oxygenation and/or exposing the macula to cytokines (e.g., VEGF).

Krebs *et. al.* conducted a prospective, observational case series of 163 eyes comparing patients with exudative AMD to those with non-exudative AMD and controls. The results showed that there was a higher incidence of persistent vitreomacular adhesions diagnosed by OCT in patients with exudative AMD compared with normal eyes and eyes with non-exudative AMD. VMA was present in 36% of patients with exudative AMD, 7% of those with non-exudative AMD and 10% of controls.

Lee *et.al.* (2008) retrospectively reviewed the OCT and fluorescein angiography (FA) images in 251 patients with unilateral AMD. VMA was present in 56 patients (22%). The findings from the study were that CNV was present in (44/53, 83%) of eyes with vitreomacular adhesion and only in (6/53, 11%) of eyes without vitreomacular adhesion. It was also noted that the location of VMA was located over the area of the CNV in all of the exudative eyes.

In addition, Lee *et. al* (2010) studied the AMD/VMA relationship in a study conducted to evaluate the effect of OCT documented VMA on the outcome of anti-VEGF treatment for exudative AMD. A total of 148 eyes of newly diagnosed exudative AMD patients were treated with anti VEGF treatment and followed for a minimum of 1 year. In this study the mean BCVA decreased over time in patients with VMA compared to those without traction. These authors postulate that chronic traction forces may antagonize the effect of anti-VEGF treatment for AMD. This would lend support to the theory that traction exposes the macula to cytokines such as VEGF as proposed by several authors.

Benefit of Restoring Retinal Anatomy

Persistent vitreomacular adhesions which occur due to incomplete posterior vitreous traction have been associated with cystoid macular edema, decreased visual acuity, metamorphopsia and photopsia. Recent studies have also suggested that VMA plays a significant role in other ocular diseases such as age-related macular degeneration. It is the mechanical and biochemical processes that occur at the vitreoretinal interface that have been implicated in the pathologies associated with VMA. The goal of treatment is to relieve the traction by manually dissecting the vitreous adhesion away from the macular surface thereby allowing the retina to return to its normal anatomical state so that vision can be restored. Studies have shown that relieving this traction results in decrease macular edema and increase in visual acuity. Some authors report that the improvement in vision is greater when the preoperative VA is above 20/200; suggesting that waiting for spontaneous resolution to occur may not be warranted if

there is continuing decrease in visual acuity. In addition there is recent work that suggests that relieving this traction also may have additional benefits in diseases such as AMD.

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APPENDIX B

≥ 2-Line Loss in BCVA at Month 6– Phase 3 Studies

Patient ID	Trt ¹⁾	Age	Sex	FTMH ¹⁾	ERM ¹⁾	VMA ¹⁾	Visual Acuity ²⁾						Reason for decrease
						Resolution ³⁾	BL	D7	D14	D28	M3	M6	
601005	O	61	F	No	Yes	No	66	66	67	67	70	55	VMT progression
601006	O	76	M	No	Yes	No	73	75	77	67	72	68	Transcription error
601015	O	79	F	No	Yes	No	79	79	72	78	59	63	VMT progression
605005	O	79	M	No	Yes	No	68	63	58	66	64	55	VMT progression
605011	O	69	F	Yes	Yes	No	75	70	60	65	55	60	MH progression
609014	P	79	M	Yes	No	No	65	66	63	64	51	54	MH progression
609015	O	76	F	No	No	No	52	56	52	50	40	33	MH progression
612010	O	81	M	No	Yes	No	71	68	67	65	61	60	VMT progression
613002	O	67	M	No	Yes	Yes	50	44	54	16	16	16	VMT progression & AMD
614011	P	74	M	Yes	No	No	57	60	61	59	22	0	Ischemic optic neuropathy
615007	O	66	M	No	No	No	51	55	55	56	51	33	Macular Atrophy
615008	P	63	F	Yes	No	Yes	73	73	72	65	66	61	Thickened Macula
615009	O	74	M	No	Yes	No	69	65	65	61	57	50	Myopic Degeneration/ VMT progression
618005	O	78	F	No	No	No	76	61	56	62	75	66	Subretinal Fluid
622004	O	71	F	Yes	No	No	59	60	57	60	61	31	Macular Atrophy
622017	O	63	F	Yes	No	Yes	60	50	41	41	39	39	MH progression
624001	P	71	M	Yes	No	No	73	74	77	73	75	55	MH progression/ Flattened Fovea
627003	O	68	F	Yes	No	No	58	56	54	55	25	25	MH progression
628003	O	81	M	No	No	No	74	73	72	74	68	58	MH progression
628004	O	85	F	Yes	No	No	50	50	52	52	52	35	Chorioretinal degeneration
635003	P	86	M	No	No	No	53	28	57	29	50	42	VMT progression
639001	O	59	F	Yes	Yes	No	70	58	58	58	58	42	MH progression/ Flattened Fovea
640003	O	70	M	No	Yes	No	52	54	54	54	42	36	Cataract and VMT progression
640004	O	62	F	--4)	Yes	No	70	81	76	65	68	57	VMT progression
642003	O	84	F	No	Yes	No	74	69	66	63	52	59	VMT progression
643011	O	62	F	No	No	No	70	71	0	0	62	0	Vision Unknown

BLA 125422 JETREA (ocriplasmin) Intravitreal Injection, 2.5 mg/mL
Indication: treatment of symptomatic vitreomacular adhesions

Patient ID	Trt ¹⁾	Age	Sex	FTMH ¹⁾	ERM ¹⁾	Resolution ³⁾	BL	D7	D14	D28	M3	M6	for decrease
644002	O	76	M	No	Yes	No	69	68	71	67	70	59	VMT progression
706016	P	64	F	Yes	No	No	63	64	63	62	52	46	MH progression
710004	O	67	F	Yes	Yes	No	57	56	68	59	57	39	Corneal opacity/ MH progression
716009	O	72	F	No	No	No	79	82	82	77	83	55	VMT to macular hole
719003	O	65	M	No	Yes	No	77	66	69	73	64	66	VMT progression/SWR
719007	P	78	F	Yes	No	No	65	63	63	67	63	19	Cataract
721006	P	74	F	No	Yes	No	65	67	67	66	58	54	Poor Fovea Contour
727001	O	82	F	No	No	No	65	2	46	53	65	10	VMT to MH
728002	O	78	F	No	No	No	78	68	74	76	68	63	VMT progression/ AMD
728003	P	75	F	Yes	No	No	69	55	56	56	49	49	MH progression
728004	O	70	F	Yes	No	Yes	44	45	37	40	49	30	MH progression
730007	O	71	M	No	Yes	No	75	46	65	55	57	39	VMT to MH
731001	O	75	F	No	No	No	80	76	69	71	81	41	Cataract/ Poor Fovea Contour
731005	O	76	F	No	Yes	Yes	88	87	86	84	87	72	VMT to macular hole
733002	O	75	M	No	Yes	No	52	52	51	53	51	29	VMT progression
733003	O	89	M	No	Yes	No	47	43	40	43	38	28	VMT progression
776001	O	73	F	Yes	No	Yes	57	57	42	42	49	43	MH progression
781001	O	75	F	No	No	Yes	53	33	34	46	52	42	Foveal remodeling
781008	O	79	F	No	No	No	76	69	77	71	77	58	Cataract
782004	P	66	M	No	No	No	82	78	77	78	73	70	*SWR IS/OS discontinuity
792016	P	77	M	No	No	No	61	61	61	56	50	34	Serous Detachment

¹⁾ O: Ocriplasmin; P: Placebo; FTMH: full thickness macular hole VMA: Vitreomacular adhesion;
ERM: Epiretinal membrane (presence at baseline);

²⁾ BL: Baseline; D: Day; M: Month

³⁾ VMA resolution at Day 28 (LOCF)

⁴⁾ Unreadable

FTMH: Full thickness macular hole (presence at baseline)

* Surface Wrinkling Retinopathy

APPENDIX C

Summary of Categorical Change from Baseline in Visual Acuity, patients who had a **DECREASE** in at Least 2 Lines, and in at Least 3 lines, by Study Visit and Response to Primary Endpoint (resolution of VMA) – Pooled TG-MV-006/007¹⁸

Table 2.6.17.2 Summary of Categorical Change from Baseline [1] in Visual Acuity by Study Visit and Response to Primary Endpoint – Study Eye Comparisons Between Subgroups by Treatment Missing Data Imputed Using LOCF (Full Analysis Set)

Pooled TG-MV-006/007

Change Visit	Microplasmin			
	Success on Primary Endpoint (N=123) n (%)	Failure on Primary Endpoint (N=341) n (%)	Difference (95% CI) [2]	p-value [3]
Decline (Decreased Lines Read)				
Subjects with At Least 2 Lines (10 Letters) Decline				
Post-Injection Day 7	16 (13.0)	24 (7.0)	-6.0 (-12.5, 0.6)	0.041
Post-Injection Day 14	9 (7.3)	17 (5.0)	-2.3 (-7.5, 2.8)	0.328
Post-Injection Day 28	5 (4.1)	11 (3.2)	-0.8 (-4.8, 3.1)	0.690
Post-Injection Month 3	5 (4.1)	21 (6.2)	2.1 (-2.2, 6.4)	0.359
Post-Injection Month 6	6 (4.9)	30 (8.8)	3.9 (-0.9, 8.8)	0.150
Subjects with At Least 3 Lines (15 Letters) Decline				
Post-Injection Day 7	5 (4.1)	11 (3.2)	-0.8 (-4.8, 3.1)	0.645
Post-Injection Day 14	5 (4.1)	8 (2.3)	-1.7 (-5.6, 2.1)	0.322
Post-Injection Day 28	3 (2.4)	4 (1.2)	-1.3 (-4.2, 1.7)	0.346
Post-Injection Month 3	3 (2.4)	9 (2.6)	0.2 (-3.0, 3.4)	0.861
Post-Injection Month 6	3 (2.4)	23 (6.7)	4.3 (0.5, 8.1)	0.069

Source: Listing 16.2.6.1

Pooled TG-MV-006/007

Change Visit	Placebo			
	Success on Primary Endpoint (N=19) n (%)	Failure on Primary Endpoint (N=169) n (%)	Difference (95% CI) [2]	p-value [3]
Decline (Decreased Lines Read)				
Subjects with At Least 2 Lines (10 Letters) Decline				
Post-Injection Day 7	1 (5.3)	3 (1.8)	-3.5 (-13.7, 6.8)	0.294
Post-Injection Day 14	0	3 (1.8)	1.8 (-0.2, 3.8)	0.651
Post-Injection Day 28	0	5 (3.0)	3.0 (0.4, 5.5)	0.441
Post-Injection Month 3	1 (5.3)	11 (6.5)	1.3 (-9.4, 12.0)	0.730
Post-Injection Month 6	0	11 (6.5)	6.5 (2.8, 10.3)	0.272
Subjects with At Least 3 Lines (15 Letters) Decline				
Post-Injection Day 7	0	1 (0.6)	0.6 (-0.6, 1.8)	0.698
Post-Injection Day 14	0	1 (0.6)	0.6 (-0.6, 1.8)	0.796
Post-Injection Day 28	0	1 (0.6)	0.6 (-0.6, 1.8)	0.698
Post-Injection Month 3	1 (5.3)	5 (3.0)	-2.3 (-12.7, 8.1)	0.638
Post-Injection Month 6	0	6 (3.6)	3.6 (0.8, 6.4)	0.446

Source: Listing 16.2.6.1

[1] Baseline is the last non-missing value prior to administration of study drug.

[2] The difference and confidence intervals between subgroups are based on the percentage of successes.

[3] For individual studies, p-values are from Fisher's exact test, comparing subgroups. For pooled studies, p from Cochran-Mantel-Haenszel test, stratified by study.

[4] For individual studies, exact odds ratio and confidence interval are obtained from logistic regression with randomized

treatment. For pooled studies, the model includes randomized treatment and study.

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¹⁸ Source: Summary of Clinical Efficacy 3.2.2.4.2., Table 2.6.17.2, Module 5.3.5.3

APPENDIX C - continued

Summary of Categorical Change from Baseline in Visual Acuity, patients who had a **INCREASE** in at Least 2 Lines, and in at Least 3 lines, by Study Visit and Response to Primary Endpoint (resolution of VMA) – Pooled TG-MV-006/007¹⁹

Table 2.6.17.2 Summary of Categorical Change from Baseline [1] in Visual Acuity by Study Visit and Response to Primary Endpoint – Study Eye Comparisons Between Subgroups by Treatment Missing Data Imputed Using LOCF (Full Analysis Set)

Pooled TG-MV-006/007

Change Visit	Microplasmin			
	Success on Primary Endpoint (N=123)	Failure on Primary Endpoint (N=341)	Difference (95% CI) [2]	p-value [3]
	n (%)	n (%)		
Improvement (Increased Lines Read)				
Subjects with At Least 2 Lines (10 Letters) Improvement				
Post-Injection Day 7	10 (8.1)	24 (7.0)	-1.1 (-6.6, 4.4)	0.744
Post-Injection Day 14	19 (15.4)	29 (8.5)	-6.9 (-14.0, 0.1)	0.031
Post-Injection Day 28	33 (26.8)	46 (13.5)	-13.3 (-22.0, -4.7)	<0.001
Post-Injection Month 3	47 (38.2)	63 (18.5)	-19.7 (-29.3, -10.2)	<0.001
Post-Injection Month 6	55 (44.7)	75 (22.0)	-22.7 (-32.5, -12.9)	<0.001
Subjects with At Least 3 Lines (15 Letters) Improvement				
Post-Injection Day 7	3 (2.4)	8 (2.3)	-0.1 (-3.3, 3.1)	0.965
Post-Injection Day 14	8 (6.5)	15 (4.4)	-2.1 (-7.0, 2.8)	0.379
Post-Injection Day 28	13 (10.6)	15 (4.4)	-6.2 (-12.0, -0.3)	0.016
Post-Injection Month 3	25 (20.3)	21 (6.2)	-14.2 (-21.7, -6.6)	<0.001
Post-Injection Month 6	25 (20.3)	32 (9.4)	-10.9 (-18.7, -3.2)	0.002

Source: Listing 16.2.6.1

Pooled TG-MV-006/007

		Placebo			
Change		Success on Primary Endpoint (N=19)	Failure on Primary Endpoint (N=169)	Difference (95% CI) [2]	p-value [3]
Visit		n (%)	n (%)		
Improvement (Increased Lines Read)					
Subjects with At Least 2 Lines (10 Letters) Improvement					
	Post-Injection Day 7	4 (21.1)	7 (4.2)	-16.9 (-35.5, 1.7)	0.002
	Post-Injection Day 14	5 (26.3)	5 (3.0)	-23.3 (-43.3, -3.4)	<0.001
	Post-Injection Day 28	6 (31.6)	10 (6.0)	-25.6 (-46.8, -4.4)	<0.001
	Post-Injection Month 3	4 (21.1)	23 (13.7)	-7.4 (-26.4, 11.7)	0.373
	Post-Injection Month 6	4 (21.1)	28 (16.7)	-4.4 (-23.6, 14.8)	0.620
Subjects with At Least 3 Lines (15 Letters) Improvement					
	Post-Injection Day 7	1 (5.3)	3 (1.8)	-3.5 (-13.7, 6.8)	0.294
	Post-Injection Day 14	3 (15.8)	2 (1.2)	-14.6 (-31.1, 1.9)	<0.001
	Post-Injection Day 28	2 (10.5)	5 (3.0)	-7.6 (-21.6, 6.5)	0.100
	Post-Injection Month 3	2 (10.5)	11 (6.5)	-4.0 (-18.3, 10.3)	0.546
	Post-Injection Month 6	3 (15.8)	9 (5.4)	-10.4 (-27.2, 6.3)	0.122

Source: Listing 16.2.6.1

[1] Baseline is the last non-missing value prior to administration of study drug.

[2] The difference and confidence intervals between subgroups are based on the percentage of successes.

[3] For individual studies, p-values are from Fisher's exact test, comparing subgroups. For pooled studies, p from Cochran-Mantel-Haenszel test, stratified by study.

[4] For individual studies, exact odds ratio and confidence interval are obtained from logistic regression with randomized treatment. For pooled studies, the model includes randomized treatment and study.

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¹⁹ Source: Summary of Clinical Efficacy 3.2.2.4.2., Table 2.6.17.2, Module 5.3.5.3

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/s/

RENATA ALBRECHT
10/17/2012

EDWARD M COX
10/17/2012

Medical Officer's Review of BLA 125-422
M.O. Review #3

BLA 125-422

Submission: 10/05/2012

Review Completed: 10/09/2012

Proposed Tradename:

Jetrea

Established Name:

ocriplasmin

Applicant:

Thrombogenics
101 Wood Avenue South, 6th Floor
Iselin, NJ 08830

Proposed Indication:

Treatment of Vitreomacular Adhesion
including Macular Holes

**Dosage Form and
Route of Administration:**

ophthalmic intravitreal injection

Submitted:

1.) Listing of Visual Acuity and Selected
Adverse Events for Subjects with \geq 2-line
Loss in BCVA at 6 Month

2.) Listing of Visual Acuity and Baseline
and Month 6 Macular Hole Status for
subjects with \geq 2-line Loss in BCVA at 6
Month for in Phase 3 Studies

Reviewer's Comments:

This review is in follow-up to question raised during the BLA wrap-up meeting. Further qualification of subjects with \geq 2-line Loss in BCVA was requested in terms of baseline macular hole status and the relationship between vision loss and adverse event reports of inflammation.

≥ 2-Line Loss in BCVA – Phase 3 Studies

Patient ID	Trt ¹⁾	Age	Sex	FTMH ¹⁾	FTMH at month 6	ERM ¹⁾	VMA ¹⁾ Resolution ²⁾	Visual Acuity ³⁾						Reason for decrease	Qualifying Event ⁵⁾
								BL	D7	D14	D28	M3	M6		
601005	O	61	F	No	Yes	Yes	No	66	66	67	67	70	55	VMT progression	--
601006	O	76	M	No	No	Yes	No	73	75	77	67	72	68	Transcription error	--
601015	O	79	F	No	No	Yes	No	79	79	72	78	59	63	VMT progression	--
605005	O	79	M	No	No	Yes	No	68	63	58	66	64	55	VMT progression	--
605011	O	69	F	Yes	Yes	Yes	No	75	70	60	65	55	60	MH progression	--
609014	P	79	M	Yes	Yes	No	No	65	66	63	64	51	54	MH progression	--
609015	O	76	F	No	Yes	No	No	52	56	52	50	40	33	MH progression	--
612010	O	81	M	No	No	Yes	No	71	68	67	65	61	60	VMT progression	--
613002	O	67	M	No		Yes	Yes	50	44	54	16	16	16	VMT progression & AMD	--
614011	P	74	M	Yes		No	No	57	60	61	59	22	0	Ischemic optic neuropathy	--
615007	O	66	M	No	No	No	No	51	55	55	56	51	33	Macular Atrophy	--
615008	P	63	F	Yes	No	No	Yes	73	73	72	65	66	61	Thickened Macula	--
615009	O	74	M	No	No	Yes	No	69	65	65	61	57	50	Myopic Degeneration/ VMT progression	Macular edema
618005	O	78	F	No		No	No	76	61	56	62	75	66	Subretinal Fluid	Retinal edema, subretinal fluid
622004	O	71	F	Yes		No	No	59	60	57	60	61	31	Macular Atrophy	--
622017	O	63	F	Yes		No	Yes	60	50	41	41	39	39	MH progression	--

Patient ID	Trt ¹⁾	Age	Sex	FTMH ¹⁾	FTMH at month 6	ERM ¹⁾	VMA ¹⁾ Resolution ²⁾	Visual Acuity ³⁾						Reason for decrease	Qualifying Event ⁵⁾
								BL	D7	D14	D28	M3	M6		
624001	P	71	M	Yes	No	No	No	73	74	77	73	75	55	MH progression/ Flattened Fovea	Macular edema, cystoid macular edema
627003	O	68	F	Yes		No	No	58	56	54	55	25	25	MH progression	--
628003	O	81	M	No	Yes	No	No	74	73	72	74	68	58	MH progression	--
628004	O	85	F	Yes	No	No	No	50	50	52	52	52	35	Chorioretinal degeneration	--
635003	P	86	M	No	unreadable	No	No	53	28	57	29	50	42	VMT progression	--
639001	O	59	F	Yes	No	Yes	No	70	58	58	58	58	42	MH progression/ Flattened Fovea	--
640003	O	70	M	No	unreadable	Yes	No	52	54	54	54	42	36	Cataract and VMT progression	--
640004	O	62	F	-- ⁴⁾	unreadable	Yes	No	70	81	76	65	68	57	VMT progression	--
642003	O	84	F	No	No	Yes	No	74	69	66	63	52	59	VMT progression	--
643011	O	62	F	No	No	No	No	70	71	0	0	62	0	Vision Unknown	--
644002	O	76	M	No	No	Yes	No	69	68	71	67	70	59	VMT progression	--
706016	P	64	F	Yes	Yes	No	No	63	64	63	62	52	46	MH progression	--
710004	O	67	F	Yes	No	Yes	No	57	56	68	59	57	39	Corneal opacity/ MH progression	--
716009	O	72	F	No	Yes	No	No	79	82	82	77	83	55	VMT to macular hole	--
719003	O	65	M	No	No	Yes	No	77	66	69	73	64	66	VMT progression/SWR	--

Patient ID	Trt ¹⁾	Age	Sex	FTMH ¹⁾	FTMH at month 6	ERM ¹⁾	VMA ¹⁾ Resolution ²⁾	Visual Acuity ³⁾						Reason for decrease	Qualifying Event ⁵⁾
								BL	D7	D14	D28	M3	M6		
719007	P	78	F	Yes	No	No	No	65	63	63	67	63	19	Cataract	--
721006	P	74	F	No	No	Yes	No	65	67	67	66	58	54	Poor Fovea Contour	--
727001	O	82	F	No	Yes	No	No	65	2	46	53	65	10	VMT to MH	--
728002	O	78	F	No	No	No	No	78	68	74	76	68	63	VMT progression/ AMD	--
728003	P	75	F	Yes		No	No	69	55	56	56	49	49	MH progression	--
728004	O	70	F	Yes	Yes	No	Yes	44	45	37	40	49	30	MH progression	--
730007	O	71	M	No	Yes	Yes	No	75	46	65	55	57	39	VMT to MH	--
731001	O	75	F	No	No	No	No	80	76	69	71	81	41	Cataract/ Poor Fovea Contour	--
731005	O	76	F	No	No	Yes	Yes	88	87	86	84	87	72	VMT to macular hole	--
733002	O	75	M	No	No	Yes	No	52	52	51	53	51	29	VMT progression	--
733003	O	89	M	No	No	Yes	No	47	43	40	43	38	28	VMT progression	--
776001	O	73	F	Yes	Yes	No	Yes	57	57	42	42	49	43	MH progression	--
781001	O	75	F	No	No	No	Yes	53	33	34	46	52	42	Foveal remodeling	--
781008	O	79	F	No	No	No	No	76	69	77	71	77	58	Cataract	--
782004	P	66	M	No	No	No	No	82	78	77	78	73	70	*SWR IS/OS discontinuity	--
792016	P	77	M	No	No	No	No	61	61	61	56	50	34	Serous Detachment	--

1)

O: Ocriplasmin; P: Placebo; VMA: Vitreomacular adhesion; ERM: Epiretinal membrane (presence at baseline);

3) BL: Baseline; D: Day; M: Month

²⁾ VMA resolution at Day 28 (LOCF)

⁴⁾ Unreadable

⁵⁾ Adverse events of macular edema, retina edema and iritis

FTMH: Full thickness macular hole (presence at baseline), * Surface Wrinkling Retinopathy

Reviewer's comments:

In the phase 3 studies there were 3/47 subjects that had ≥ 2 lines of visual acuity loss who also reported an adverse event related to inflammation (i.e. retinal edema, macular edema, and iritis).

Sixteen of forty-seven (16/47, 34%) subjects that had ≥ 2 lines of visual acuity loss had a macular hole at baseline. Eleven of these sixteen subjects (69%) lost vision due to progression in the size of the macular hole. Six of the thirty-one subjects (6/31, 19%) who did not have a macular hole at baseline developed a hole causing ≥ 2 lines of visual acuity loss.

Jennifer D. Harris, M.D.
Medical Officer

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/s/

JENNIFER D HARRIS
10/11/2012

WILLIAM M BOYD
10/11/2012

Medical Officer's Review of BLA 125-422
120-Day Safety Update

BLA 125-422

Submission: 8/16/2012

Review Completed: 9/12/2012

Proposed Tradename:

Jetrea

Generic Name:

ocriplasmin

Sponsor:

Thrombogenics
101 Wood Avenue South, 6th Floor
Iselin, NJ 08830

Proposed Indication:

Treatment of Vitreomacular Adhesion
including Macular Holes

**Dosage Form and
Route of Administration:**

ophthalmic intravitreal injection

Submitted:

1.) 120 Day Safety Update summarizing
safety data from the ocriplasmin clinical
development program from 01 April 2011 to
31 May 2012

2.) Data Summary of \geq 2-line Loss in
BCVA at 6 Month for in Phase 3 Studies

BLA 125-422 was submitted on 16 April 2012. The data cut-off date for the BLA was March 31, 2011. This 120-Day Safety Update Report summarizes the safety data for ocriplasmin from 01 April 2011 to 31 May 2012. The data summary of patients with \geq 2-line Loss in BCVA was submitted at the request of the Agency.

Clinical Study Completed During the Reporting Period

Study ID	No. Ctrs. Initiated/Enrolled	Design	Indication/Route/Regimen	Entered/Completed	Duration	Sex (M/F) Age range (yrs) Race
TG-MV-008	1 EU/ 1 EU	Phase 2 single center, open-label study	Vitreomacular traction including macular hole Single intravitreal injection ocriplasmin 0.125mg	30 / 17	6 months	4/13 53 to 80 yrs 17 White

Reviewer Comments:

Preliminary safety data from study TG-MV-008 was included in the original BLA submission and addressed in the M.O. review. The Clinical Study Report Synopsis has been provided in this 120-day Safety Update. This study was an open-label study that was terminated early when it was concluded that there was no more to be gained scientifically from further enrollment in a single-center, uncontrolled open-label trial.

Based on the M.O. review, the majority of cases of dyschromatopsia were reported from this trial and another uncontrolled open-label clinical study TG-MV-010 that were conducted in the same (single) center where the intravitreal injections were administered by the same investigator. See section on Dyschromatopsia/ERG changes on page 7.

Clinical Studies Ongoing During the Reporting Period

Study ID	No. Ctrs. Initiated / Enrolled	Design / Control	Indication Route Regimen	Planned Enrollment Total By Treatment	Duration ^a
TG-MV-005	16 USA, 16 EU / 8 USA, 13 EU	Phase 2 multicenter, randomized, sham-injection controlled, double-masked study	Vitreomacular adhesion associated with AMD Single intravitreal injection: ocriplasmin 0.125mg sham-injection	100 75 25	12 months
TG-MV-009	1 USA / 1 USA	Phase 2 single center, randomized, placebo-controlled, double-masked study	Infants and children with premature retinopathy scheduled for vitrectomy Single intravitreal injection ocriplasmin 0.175mg placebo	24 16 8	6 months
TG-MV-012	1 USA, 1 EU / 1 USA, 1 EU	Phase 2 follow-up study in 2 centers to assess visual function in a subset of patients who have previously participated in studies TG-MV-006 and TG-MV-007.	Patients who have previously participated in the TG-MV-006 and TG-MV-007 ocriplasmin studies. No treatment administered in this study	24 N/A	1 visit

TG-MV-014	25 USA / 25 USA	Phase 3b, randomized, sham-controlled, double-masked, multicenter	Patients with symptomatic vitreomacular adhesion (vitreomacular traction) including macular hole Single intravitreal injection: ocriplasmin 0.125mg sham-injection	210 140 70	24 months
JSEI-TG-AMD-001 ^b	1 USA / 1 USA	Phase 3 single center, placebo-controlled study	Vitreomacular adhesion associated with neovascular AMD Single intravitreal injection ocriplasmin 0.125mg placebo	30 20 10	12 months

Study ID	No. Ctrs. Initiated / Enrolled	Design / Control	Indication Route Regimen	Planned Enrollment Total By Treatment	Duration
10-EI-0186 ^b	1 USA / 1 USA	Phase 1-2 single-center, open-label, uncontrolled study	Vitreomacular adhesion associated with macular edema in uveitis patients Single intravitreal injection ocriplasmin 0.125mg	5 5	6 months

^a Duration of post-injection observation period

^b Investigator-initiated study

15-Day Alert Reports Submitted During the Reporting Period

Treatment	Study	Country	Patient ID	Verbatim	MedDRA Preferred Term
Ocriplasmin	TG-MV-005	UK	531005	Decreased vision 32 letters drop overnight	Visual acuity reduced
Ocriplasmin	TG-MV-009	USA	901023	Zonular dehiscence	Lens dislocation
Ocriplasmin	TG-MV-014	USA	1401001	Photoreceptor toxicity Worsening of macular hole Stage 4 Vasculitis Relative afferent pupillary defect ^a	Retinal toxicity Macular hole Retinal vasculitis Pupillary reflex impaired

^a Reported as 'reserve' afferent pupillary defect

Reviewer Comments:

The adverse events reported in the 15-day reports are consistent with the adverse events reviewed in the BLA.

Deaths

Study/ Patient Number	Age	Gender	Treatment	MedDRA Preferred Term / Verbatim
TG-MV-005/554003	88 yrs	F	Ocriplasmin 0.125mg or sham	Myocardial infarction / Myocardial infarction
TG-MV-009/901023/901024 ^a	6 mo	M	Ocriplasmin 0.175mg or placebo	Convulsion / Seizures Device malfunction / Ventriculoperitoneal shunt malfunction Device malfunction / Ventriculoperitoneal shunt malfunction Encephalopathy / Encephalopathy

^a The same infant was randomized twice within the same study, once as patient 901023 and once under patient number 901024 (this was permitted by the study protocol)

Serious Adverse Events

Study / Patient Number	Age (yrs)	Gender	Treatment	MedDRA Preferred Term / Verbatim
TG-MV-005/527005	87	F	Ocriplasmin 0.125mg or sham	Blindness transient / Raised IOP transient visual loss immediately after intravitreal injection Intraocular pressure increased / Raised IOP transient visual loss immediately after intravitreal injection
TG-MV-005/531005	72	F	Ocriplasmin 0.125mg or sham	Visual acuity reduced / Decreased vision 32 letters drop overnight
TG-MV-005/533008	83	F	Ocriplasmin 0.125mg or sham	Urinary tract infection / Urinary tract infection
TG-MV-005/541003	80	M	Ocriplasmin 0.125mg or sham	Visual acuity reduced / Severe vision loss
TG-MV-005/551005	82	M	Ocriplasmin 0.125mg or sham	Vocal cord neoplasm / spinocellular carcinoma of left vocal cords Vocal cordectomy / Vocal cord surgery
TG-MV-005/561006	81	F	Ocriplasmin 0.125mg or sham	Cystitis / Cystitis Dizziness postural / Orthostatism
TG-MV-005/571003	68	F	Ocriplasmin 0.125mg or sham	Vascular pseudoaneurysm / Pseudo-aneurysm left femoral artery

Study/Patient Number	Age (yrs)	Gender	Treatment	MedDRA Preferred Term / Verbatim
TG-MV-005/574006	74	F	Ocriplasmin 0.125mg or sham	Cataract operation / Cataract extraction with intraocular lens
TG-MV-005/575002	80	F	Ocriplasmin 0.125mg or sham	Retinal detachment / Tractional retinal detachment, study eye
TG-MV-005/580005	81	M	Ocriplasmin 0.125mg or sham	Rectal hemorrhage/Rectal bleeding Joint injury / Left knee injury due to fall
TG-MV-005/580006	82	M	Ocriplasmin 0.125mg or sham	Urosepsis/Urosepsis
TG-MV-005/583002	79	M	Ocriplasmin 0.125mg or sham	Brain cancer metastatic/Metastatic brain cancer
TG-MV-005/586001	63	F	Ocriplasmin 0.125mg or sham	Shoulder arthroplasty/Right shoulder replacement surgery for right shoulder pain
TG-MV-009/901020	8	M	Ocriplasmin 0.175mg or placebo	Pneumonia aspiration/Aspiration pneumonia with hypoxemia Apnea / Obstructive and central apnea
TG-MV-009/901023	4 mo	M	Ocriplasmin 0.175mg ^{a,b}	Lens dislocation/Zonular dehiscence

Study/Patient Number	Age (yrs)	Gender	Treatment	MedDRA Preferred Term / Verbatim
TG-MV-014/ 1401001	62	F	Ocriplasmin 0.125mg or sham	Retinal toxicity/Photoreceptor toxicity Macular hole/Worsening of macular hole Stage 4 Retinal vasculitis / Vasculitis Pupillary reflex impaired/Relative afferent pupillary defect ^c
TG-MV-014/ 1403008	66	F	Ocriplasmin 0.125mg or sham	Macular hole/Worsening from baseline of macular hole from Stage 2 to Stage 3
TG-MV-014/ 1408003	59	F	Ocriplasmin 0.125mg or sham	Vitreous adhesions/Vitreomacular traction, worsening
TG-MV-014/ 1409017	76	F	Ocriplasmin 0.125mg or sham	Vitreous adhesions/Worsening of vitreomacular traction syndrome

TG-MV-014/ 1411001	59	F	Ocriplasmin 0.125mg or sham	Intraocular pressure increased/Elevated IOP
TG-MV-014/ 1415010	71	F	Ocriplasmin 0.125mg or sham	Macular hole/Increase in macular hole to Stage 3
TG-MV-014/ 1416002	60	F	Ocriplasmin 0.125mg or sham	Retinal detachment/Retinal detachment
TG-MV-014/ 1416011	65	F	Ocriplasmin 0.125mg or sham	Intraocular pressure increased/Elevated intraocular pressure post study procedure

Study / Patient Number	Age (yrs)	Gender	Treatment	MedDRA Preferred Term / Verbatim
TG-MV-014/ 1419014	65	F	Ocriplasmin 0.125mg or sham	Macular hole/Worsening of macular hole, vitrectomy scheduled
TG-MV-014/ 1420004	67	M	Ocriplasmin 0.125mg or sham	Macular hole/Worsening of macular hole from Stage 2 to Stage 3, PPV surgery scheduled for 6FEB12
TG-MV-014/ 1420007	83	F	Ocriplasmin 0.125mg or sham	Inguinal hernia/Inguinal hernia
TG-MV-014/ 1421006	67	F	Ocriplasmin 0.125mg or sham	Vitreous adhesions/Worsening of vitreomacular traction Retinal detachment / Partial/single retinal detachment
TG-MV-014/ 1423002	67	F	Ocriplasmin 0.125mg or sham	Macular hole/Stage 3 macular hole
TG-MV-014/ 1424015	56	F	Ocriplasmin 0.125mg or sham	Cellulitis/Cellulitis of right hand from cat bite
JSEI-TG-AMD- 001/008 ^b	72	M	Ocriplasmin 0.125mg or placebo	Visual acuity reduced/Sudden loss of visual acuity

^a Case was unmasked for expedited regulatory reporting

^b Although the investigator considered this event to be non-serious, the Sponsor assessed the case as serious based on the event being considered medically important afferent pupillary defect

^c Reported as 'reserve' afferent pupillary defect

^d Although the investigator considered this event to be unlikely related to study treatment, the Sponsor assessed the case as possibly related

Adverse Events Leading to Discontinuation

Study / Patient Number	Age	Gender	Treatment	MedDRA Preferred Term / Verbatim
TG-MV-005/ 583002	79 yrs	M	Ocriplasmin 0.125mg or sham	Brain cancer metastatic / Metastatic brain cancer
TG-MV-005/ 554003	88 yrs	F	Ocriplasmin 0.125mg or sham	Myocardial infarction / Myocardial infarction
TG-MV-009/ 901023/901024	6 mo	M	Ocriplasmin 0.175mg	Device malfunction / Ventriculoperitoneal shunt malfunction Encephalopathy / Encephalopathy

Reviewer Comments:

These studies were ongoing during the reporting period and therefore the blind had not been broken. The study drug adverse events cannot be determined with the exception of patient TG-MV-009/901023 who received 0.175mg of ocriplasmin. This case was discussed in the M.O. review for the BLA. The types of adverse event reported in this blinded data are consistent with those from the original BLA review.

Dyschromatopsia and ERG changes

ERGs were prospectively obtained in 2 early Phase 2 studies (TG-MV-001 and TG-MV-002).

TG-MV-001 was an open-label, dose ranging study. Ocriplasmin was administered to patients before planned vitrectomy for vitreomacular traction, diabetic macular edema, and macular hole. ERGs were obtained at baseline, on post-injection Day 7 and on post-operative Day 28.

TG-MV-002 was a randomized, sham-injection controlled, double-masked, ascending dose study with diabetic macular edema. ERGs were obtained at baseline and 1 month after ocriplasmin injection. None of the ERG changes reported in either study were reported as adverse events. Because no signal related to ERG findings was identified in the early Phase 2 studies, routine ERGs were not obtained in Phase 3 studies (TG-MV-006 and TG-MV-007).

Following the Phase 3 studies, dyschromatopsia and ERG abnormalities were reported in 2 single center open-label Phase 2 studies (TG-MV-008 and TG-MV-010), conducted at the same site. The TG-MV-008 protocol was subsequently amended specifying ERGs measurements for all patients participating in the study.

In addition, color vision testing for all patients and an ERG sub-study in the ongoing masked TG-MV-014 study was instituted.

Dyschromatopsia and ERG Abnormalities from Completed Studies

Study	Patient ID	Dyschromatopsia			ERG Abnormality			Visual Acuity (ETDRS ^a Score)			VMA ^a resolution
		Present	Resolved at Final Study Visit	As of 31 May 2012	Present	Resolved at Final Study Visit	As of 31 May 2012	Baseline	End of Study ^b	Change from Baseline	Day 28
TG-MV-006	614002	√	Ongoing ^c	No further follow-up ^c	-- ^d	--	--	55	54	-1	No
TG-MV-006	614010	√	Ongoing	No follow-up expected ^e	--	--	--	74	85	+11	Yes
TG-MV-006	638002	√	√	--	--	--	--	63	83	+20	Yes
TG-MV-007	717005	√	√	--	√	Not assessed	No follow-up ERG	80	88	+8	Yes
TG-MV-007	794005	√	√	--	--	--	--	60	75	+15	Yes
TG-MV-008	801001	√	√	--	√	Ongoing	No follow-up ERG	67	84	+17	Yes
TG-MV-008	801002	√	Ongoing	Resolved ^f	√	Ongoing	Ongoing; no further follow-up expected	49	44	-5	Yes
TG-MV-008	801003	√	√	--	√	√	--	63	78	+15	Yes
TG-MV-008	801004	√	√	--	√	Not assessed	No follow-up ERG	62	66	+4	Yes
TG-MV-008	801009	√	√	--	√	√	--	60	78	+18	Yes
TG-MV-008	801011	√	√	--	√	√	--	75	87	+12	Yes

TG-MV-008	801014	√	√	--	√	√	--	61	85	+24	No
TG-MV-008	801016	--	--	--	√	√	--	72	73	+1	No
TG-MV-008	801017	--	--	--	√	√	--	60	71	+11	No

Study	Patient ID	Dyschromatopsia			ERG Abnormality			Visual Acuity (ETDRS Score)			VMA ^a resolution
		Present	Resolved at Final Study Visit	As of 31 May 2012	Present	Resolved at Final Study Visit	As of 31 May 2012	Baseline	End of Study	Change from Baseline	Day 28
TG-MV-010	101402	√	Ongoing	Resolved ^g	--	--	--	84	≈83 ^h	-1	N/A ⁱ
TG-MV-010	101403	√	√	--	--	--	--	95	95	0	N/A
TG-MV-010	101503	√	√	--	--	--	--	90	≈85	-5	N/A
TG-MV-010	101504	√	√	--	--	--	--	85	≈83	-2	N/A

^a ETDRS: Early Treatment Diabetic Retinopathy Study; VMA: Vitreomacular adhesion

^b This is not the end-of-study value, but the most recent value

^c Patient died 18 months after the injection date, 15 months after the last study visit (cause of death unknown)

^d Not present

^e Pat is considered lost to follow-up after the end of the study

^f Reported as resolved at a post-study contact 28 months after injection

^g Reported as resolved at a post-study contact 11 months after injection

^h Received after 31 May 2012 - data is from follow-up contact dated 27 June 2012

ⁱ Not applicable

The unshaded areas show the status at the cut-off date for the BLA submission; the grey-shaded areas show the status as per the date of 31 May 2012

Reviewer Comments:

*Based on the submitted data, 16/517 (3%) of patients had dyschromatopsia and 10/517 (1.9%) had ERG changes in the completed trials. All patients with dyschromatopsia and ERG changes were in the ocriplasmin treated group. 12/16 (75%) patients with dyschromatopsia and 6/10 (60%) of patients with ERG changes had resolution of these events by the end of the study. **Note:** 2 patients that had ERG changes did not receive a follow-up assessment to determine resolution. None of the patients with dyschromatopsia and/or ERG changes had any clinically meaningful loss of visual acuity. 12/18 (66.7%) had improvement in visual acuity with 9 (50%) patients having an increase of ≥ 2 lines.*

In addition to the patient listed above, Phase 2 studies TG-MV-001 and TG-MV-002 were reviewed retrospectively and it was noted that an additional 9 patients had changes from baseline in their ERG. Six (6) of these changes were noted after vitrectomy so it can not be determine if this is related to surgery or to the drug. The other 3 were obtained using non standard ERG equipment per the Optic Nerve Research Center and none of the patients reported dyschromatopsia or and adverse event that could be related to ERG changes.

Dyschromatopsia and/or Clinically Significant ERG Changes from Ongoing Studies TG-MV-014 and TG-MV-005

Patient ID	Dyschromatopsia	Clinically Significant ERG Change	Visual Acuity (ETDRS Score)		
	Present	Present	Baseline	Most Recent Visit	Change from Baseline
541003*	Not available	Not available	76	72	-4
1401001	√	√	57	55	-2
1402001	√	√	57	79	+22
1402015	--a	√	73	76	+3
1403001	√	--	63	63	0
1403005	√	--	72	69	-3
1403006	√	--	59	71	+12
1403009	√	--	55	77	+22
1403010	√	--	58	60	+2
1408002	√	--	52	50	-2
1408004	√	--	68	70	+2
1408007	√	--	56	64	+8
1408011	√	--	48	49	+1
1408015	√	--	61	61	0
1409001	√	--	55	46	-9

1409002	√	--	71	72	+1
1409008	√	--	67	78	+11
1409010	√	--	68	64	-4
1409016	√	--	75	76	+1
1409018	√	--	52	49	-3
1410003	√	--	53	62	+9
141008	√	--	58	66	+8
1415007	√	--	69	82	+13
1415008	√	--	63	60	-3
1415010	√	--	56	60	+4
1416001	--	√	73	82	+9
1416002	--	√	75	83	+8

Patient ID	Dyschromatopsia	Clinically Significant ERG Change	Visual Acuity (ETDRS Score)		
	Present	Present	Baseline	Most Recent Visit	Change from Baseline
1416003	--	√	77	90	+13
1416008	√	√	60	72	+12
1416011	--	√	52	56	+4
1416015	√	√	70	67	-3
1416019	--	√	61	52	-9
1418003	√	--	57	70	+13
1419011	√	--	53	57	+4
142002	√	--	62	55	-7
142004	√	--	48	53	+5
142006	√	--	66	90	+24
142007	√	--	46	55	+9
142009	√	--	48	56	+8
1420011	√	--	72	75	+3
1421001	√	--	53	50	-3
1424002	√	--	54	75	+21
1425005	--	√	72	73	+1

*Not present

*This patient was from the ongoing masked exudative AMD study TG-MV-005. This patient was included in the list because for acute transient vision loss and had a post injection ERG obtained that was reported as a general reduction in amplitudes and delayed implicit times in all rings. All other patients are from the ongoing ERG sub-study form TG-MV-014.

As of 31 May 2012, 177 patients have been treated in the ongoing masked study TG-MV-014. Of these, it was estimated that 118 patients have received ocriplasmin injection and 59 patients were sham-treated. There have been 35 cases of dyschromatopsia and 11 cases of clinically significant ERG changes reported to date. Clinically significant ERG changes were defined as a 40% change from baseline or a 30% change from the previous visit. This criterion was established by the central ERG Reader for this study based on review of the literature. The frequency of dyschromatopsia and ERG changes in each treatment group cannot be determined since the study is ongoing and masked.

≥ 2-Line Loss in BCVA – Phase 3 Studies

Patient ID	Trt ¹⁾	Age	Sex	FTMH ¹⁾	ERM ¹⁾	VMA ¹⁾	Visual Acuity ²⁾						Reason for decrease
						Resolution ³⁾	BL	D7	D14	D28	M3	M6	
601005	O	61	F	No	Yes	No	66	66	67	67	70	55	VMT progression
601006	O	76	M	No	Yes	No	73	75	77	67	72	68	Transcription error
601015	O	79	F	No	Yes	No	79	79	72	78	59	63	VMT progression
605005	O	79	M	No	Yes	No	68	63	58	66	64	55	VMT progression
605011	O	69	F	Yes	Yes	No	75	70	60	65	55	60	MH progression
609014	P	79	M	Yes	No	No	65	66	63	64	51	54	MH progression
609015	O	76	F	No	No	No	52	56	52	50	40	33	MH progression
612010	O	81	M	No	Yes	No	71	68	67	65	61	60	VMT progression
613002	O	67	M	No	Yes	Yes	50	44	54	16	16	16	VMT progression & AMD
614011	P	74	M	Yes	No	No	57	60	61	59	22	0	Ischemic optic neuropathy
615007	O	66	M	No	No	No	51	55	55	56	51	33	Macular Atrophy
615008	P	63	F	Yes	No	Yes	73	73	72	65	66	61	Thickened Macula
615009	O	74	M	No	Yes	No	69	65	65	61	57	50	Myopic Degeneration/ VMT progression
618005	O	78	F	No	No	No	76	61	56	62	75	66	Subretinal Fluid
622004	O	71	F	Yes	No	No	59	60	57	60	61	31	Macular Atrophy
622017	O	63	F	Yes	No	Yes	60	50	41	41	39	39	MH progression
624001	P	71	M	Yes	No	No	73	74	77	73	75	55	MH progression/ Flattened Fovea
627003	O	68	F	Yes	No	No	58	56	54	55	25	25	MH progression
628003	O	81	M	No	No	No	74	73	72	74	68	58	MH progression

Patient ID	Trt ¹⁾	Age	Sex	FTMH ¹⁾	ERM ¹⁾	VMA ¹⁾	Visual Acuity ²⁾						Reason for decrease
						Resolution ³⁾	BL	D7	D14	D28	M3	M6	
628004	O	85	F	Yes	No	No	50	50	52	52	52	35	Chorioretinal degeneration
635003	P	86	M	No	No	No	53	28	57	29	50	42	VMT progression
639001	O	59	F	Yes	Yes	No	70	58	58	58	58	42	MH progression/ Flattened Fovea
640003	O	70	M	No	Yes	No	52	54	54	54	42	36	Cataract and VMT progression
640004	O	62	F	-- ⁴⁾	Yes	No	70	81	76	65	68	57	VMT progression
642003	O	84	F	No	Yes	No	74	69	66	63	52	59	VMT progression
643011	O	62	F	No	No	No	70	71	0	0	62	0	Vision Unknown
644002	O	76	M	No	Yes	No	69	68	71	67	70	59	VMT progression
706016	P	64	F	Yes	No	No	63	64	63	62	52	46	MH progression
710004	O	67	F	Yes	Yes	No	57	56	68	59	57	39	Corneal opacity/ MH progression
716009	O	72	F	No	No	No	79	82	82	77	83	55	VMT to macular hole
719003	O	65	M	No	Yes	No	77	66	69	73	64	66	VMT progression/SWR
719007	P	78	F	Yes	No	No	65	63	63	67	63	19	Cataract
721006	P	74	F	No	Yes	No	65	67	67	66	58	54	Poor Fovea Contour
727001	O	82	F	No	No	No	65	2	46	53	65	10	VMT to MH
728002	O	78	F	No	No	No	78	68	74	76	68	63	VMT progression/ AMD
728003	P	75	F	Yes	No	No	69	55	56	56	49	49	MH progression
728004	O	70	F	Yes	No	Yes	44	45	37	40	49	30	MH progression
730007	O	71	M	No	Yes	No	75	46	65	55	57	39	VMT to MH
731001	O	75	F	No	No	No	80	76	69	71	81	41	Cataract/ Poor Fovea Contour
731005	O	76	F	No	Yes	Yes	88	87	86	84	87	72	VMT to macular hole
733002	O	75	M	No	Yes	No	52	52	51	53	51	29	VMT progression
733003	O	89	M	No	Yes	No	47	43	40	43	38	28	VMT progression
776001	O	73	F	Yes	No	Yes	57	57	42	42	49	43	MH progression
781001	O	75	F	No	No	Yes	53	33	34	46	52	42	Foveal remodeling

Patient ID	Trt ¹⁾	Age	Sex	FTMH ¹⁾	ERM ¹⁾	VMA ¹⁾ Resolution ³⁾	Visual Acuity ²⁾						Reason for decrease
							BL	D7	D14	D28	M3	M6	
781008	O	79	F	No	No	No	76	69	77	71	77	58	Cataract
782004	P	66	M	No	No	No	82	78	77	78	73	70	*SWR IS/OS discontinuity
792016	P	77	M	No	No	No	61	61	61	56	50	34	Serous Detachment

¹⁾ O: Ocriplasmin; P: Placebo; VMA: Vitreomacular adhesion; ERM: Epiretinal membrane (presence at baseline);

²⁾ BL: Baseline; D: Day; M: Month

³⁾ VMA resolution at Day 28 (LOCF)

⁴⁾ Unreadable

FTMH: Full thickness macular hole (presence at baseline)

* Surface Wrinkling Retinopathy

Reviewer's Comments:

There were 47/652 (7.2%) of subjects who had a ≥ 2 line decrease in vision at the end of the phase 3 studies. There was a slightly higher percentage of patients in the ocriplasmin group versus placebo [36/464 (7.8%) versus 11/188 (5.9%)] who experience this decrease in vision.

The majority of vision loss occurred in those patient who did not have resolution of their VMA [40/47 (85%)]. Of the 7/47 (14.9%) of patients who did have resolution of their VMA; six (6) of these patients were in the ocriplasmin group.

OCT's for 32/47 (68%) of subjects showed that the likely reason for the decrease in vision was VMT progression and/or macular hole progression. This was noted in 27/36 (75%) of ocriplasmin subjects and 5/11 (45.5%) of placebo subjects.

Reviewer's Comments/Recommendation:

The adverse event data submitted in this report for the completed studies is consistent with the safety data reviewed in the original BLA. There are no new safety signals raised in this update.

The dyschromatopsia and ERG data submitted show that these events appear not to have an adverse effect on visual acuity and are transient in nature as the majority resolve without intervention.

The majority of patients with ≥ 2 line decrease in vision in the trials are due to VMT progression and/or macular hole progression. Based on the action of the drug, this may

be due to a partial release of the adhesion which would potentially result in worsening traction with pulling leading to increase macular hole size.

Jennifer D. Harris, M.D.
Medical Officer

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/s/

JENNIFER D HARRIS
09/26/2012

WILLIAM M BOYD
09/26/2012

CLINICAL REVIEW

Application Type N
Application Number(s) BLA 125-422, IND 100,370
Priority or Standard Priority

Submit Date(s) 4/17/2012
Received Date(s) April 17, 2012
PDUFA Goal Date 10/17/2012
Division / Office OAP/DTOP

Reviewer Name(s) Jennifer D. Harris, M.D.
Review Completion Date August 16, 2012

Established Name Ocriplasmin intravitreal
injection, 2.5 mg/mL
(Proposed) Trade Name Jetrea
Therapeutic Class
Applicant Thrombogenics, Inc.

Formulation(s) solution
Dosing Regimen Intravitreal injection
Indication(s) Treatment of vitreomacular
adhesion (VMA) (b) (4)

Intended Population(s) Patients with symptomatic
vitreomacular adhesions

APPEARS THIS WAY ON ORIGINAL



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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Ocriplasmin 125µg is recommended for approval for the treatment of symptomatic vitreomacular adhesions (b) (4)

1.2 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) and for the pre-planned secondary endpoint of induction of posterior vitreous detachment (PVD). 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.

Persistent vitreomacular adhesions which occur due to incomplete posterior vitreous traction have been associated with cystoid macular edema, decreased visual acuity, metamorphopsia and photopsia. Recent studies have also suggested that VMA plays a significant role in other ocular diseases such as age-related macular degeneration. It is the mechanical and biochemical processes that occur at the vitreoretinal interface that have been implicated in the pathologies associated with VMA. The goal of treatment is to relieve the traction by manually dissecting the vitreous adhesion away from the macular surface thereby allowing the retina to return to its normal anatomical state so that vision can be restored. Studies have shown that relieving this traction results in decrease macular edema and increase in visual acuity. Some authors report that the improvement in vision is greater when the preoperative VA is better than 20/200; suggesting that waiting for spontaneous resolution to occur may not be warranted if there is continuing decrease in visual acuity. In addition there is recent work that suggests that relieving this traction also may have additional benefits in diseases such as AMD. A more in depth review of the literature is contained in appendix 9.1.

*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 the sponsor that were considered supportive or exploratory with no prespecified statistical plan in place to determine statistical significance.*

Overall, 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.

However, 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). Overall, 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 sponsor. 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. A determination cannot be made based on the data available why the rate of decrease vision in approximately twice as high in the drug group compared to placebo. Further data would need to be gathered to make this determination; however, the risk of this safety finding does not outweigh the potential patient benefits of this product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

N/A – REMS is not recommended for this product.

1.4 Recommendations for Postmarket Requirements and Commitments

The sponsor currently is conducting an efficacy trial in patients ≤ 16 as an adjunct to conventional vitrectomy. The results of this study should be submitted to this application as a postmarketing requirement.

2 Introduction and Regulatory Background

2.1 Product Information

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 0.5mg of ocriplasmin in 0.4 ml (1.25 mg/mL) solution for intravitreal injection after dilution with 0.9% (w/v) sodium chloride solution. 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 symptomatic VMA including macular hole 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 abnormal vitreoretinal interface focal points thereby resolving or reducing the complications associated with VMA.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no pharmacological treatments for symptomatic VMA. The only current treatment for this condition is surgery (vitrectomy).

2.3 Availability of Proposed Active Ingredient in the United States

There are no approved ocriplasmin products in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

There are no specific safety issues that warrant special attention.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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 resulting in the phase 3 clinical protocols. 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.

The BLA for ocriplasmin (125-403) was originally submitted to the Agency on 12/22/2011. This was subsequently withdrawn on 1/31/2012 to align the sponsors manufacturing schedules with the pre-approval inspection timeline. It was renumbered as BLA 125-422.

2.6 Other Relevant Background Information

Ocriplasmin is not marketed in any other country.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was of sufficient quality to allow for a substantive review with only minimal additional clinical information required from the sponsor.

3.2 Compliance with Good Clinical Practices

All completed studies in this submission were conducted in compliance with the Declaration of Helsinki, the International Conference on harmonization (ICH Good Clinical Practice (GCP) guidelines and the applicable governmental regulatory requirements.

3.3 Financial Disclosures

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

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	(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)			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)			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.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The study drug contained (b) (4) of study drug ((b) (4) ocriplasmin). The placebo had the same components and concentrations of the study drug with exception of the ocriplasmin.

Components	Concentration	Function
Microplasmin	2.5mg/mL	Active Ingredient
Mannitol	3.75mg/mL	(b) (4)
Citric Acid (b) (4)	1.051mg/mL	
Water	(b) (4)	

Source: Table 2 Applicant's Clinical Overview

4.2 Clinical Microbiology

N/A – this is no an anti-infective product.

4.3 Preclinical Pharmacology/Toxicology

See Pharm/Tox review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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 abnormal vitreoretinal interface focal points thereby resolving or reducing the complications associated with VMA.

4.4.2 Pharmacodynamics

See biopharmaceutics review.

4.4.3 Pharmacokinetics

See biopharmaceutics review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

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	Single intravitreal injection of ocriplasmin	36/38

	pharmacokinetic trial prior to pars plana vitrectomy	Dose / time before vitrectomy: 125µg/5-30min; 125µg/31-60min; 125µg/2-4h; 125µg/24h; 125µg/7d; no ocriplasmin treatment	
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

5.2 Review Strategy

The clinical development program involves 10 studies, including 8 Phase 2 studies (TG-MV-001, TG-MV-002, TG-MV-003, TG-MV-004, TG-MV-005, TG-MV-008, TG-MV-009 and TG-MV-010) and 2 Phase 3 studies (TG-MV-006 and TG-MV-007). Five of the Phase 2 studies were not included in this document either because they were ongoing as of the cut-off date for the summary (TG-MV-005, TG-MV-008, TG-MV-009) or it was an uncontrolled safety study (TG-MV-001) or a pharmacokinetic study (TG-MV-010).

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.

5.3 Discussion of Individual Studies/Clinical Trials

Clinical Protocol – Studies TG-MV-006 and TG-MV-007

Primary objective: To evaluate the safety and efficacy of intravitreal microplasmin 125µg dose in subjects with focal vitreomacular adhesion.

Trial design: Multicenter, randomized, placebo controlled, double-masked, trial in which subjects were randomized to either microplasmin or placebo intravitreal injection.

If at any point after 4 weeks from time of study drug injection, the underlying condition did not improved (i.e., the adhesion has not been relieved), the Investigator could proceed to vitrectomy at his/her discretion. Additionally, if before this time, the BCVA in the study eye worsened by > 2 lines, or the underlying condition worsened, the Investigator could proceed to vitrectomy at his/her discretion.

Sample Size: 326 subjects/study

VMA status was categorized by the CRC using 1 of 7 categories.

0	1	2	3	4	5	6	7
No visible vitreous separation	Vitreous attached from fovea to ON; separated elsewhere	Vitreous attached at fovea and ON and separated between; may be separated outside	Vitreous attached only at ON or at ON and elsewhere, but not attached at fovea	Vitreous attached only at Fovea	Vitreous visible with complete separation and no attachment	Vitreous separation visible somewhere but unable to determine state of separation	Unable to determine state of separation

Focal VMA was defined by 3 of the 7 categories:

- Vitreous attached from fovea to optic nerve separated elsewhere
- Vitreous attached at fovea and optic nerve and separated between; may be separated outside
- Vitreous attached only at fovea

Inclusion Criteria:

- Male or female subjects aged ≥ 18
- Presence of focal vitreomacular adhesion (i.e., central vitreal adhesion within 6mm OCT field surrounded by elevation of the posterior vitreous cortex) that in the opinion of the

Investigator is related to decreased visual function (such as metamorphopsia, decreased visual acuity, or other visual complaint)

- BCVA of 20/25 or worse in study eye
- BCVA of 20/800 or better in the non-study eye
- Written informed consent obtained from the subject prior to inclusion in the trial

Exclusion Criteria:

- Any evidence of proliferative retinopathy (including PDR or other ischemic retinopathies involving vitreoretinal vascular proliferation) or exudative AMD or retinal vein occlusion in the study eye
- Subjects with any vitreous hemorrhage or any other vitreous opacification which precludes either of the following: visualization of the posterior pole by visual inspection OR adequate assessment of the macula by either OCT and/or fluorescein angiogram in the study eye
- Subjects with macular hole diameter > 400µm in the study eye
- Aphakia in the study eye
- High myopia (more than 8D) in study eye (unless prior cataract extraction or refractive surgery that makes refraction assessment unreliable for myopia severity approximation, in which case axial length >28 mm is an exclusion).
- Subjects with history of rhegmatogenous retinal detachment in either eye
- Subjects who have had ocular surgery, laser photocoagulation treatment, or intravitreal injection(s) in the study eye in the prior three months
- Subjects who have had laser photocoagulation to the macula in the study eye at any time
- Subjects with pseudo-exfoliation, Marfan's syndrome, phacodonesis or any other finding in the investigator's opinion suggesting lens/zonular instability
- Subjects who have had a vitrectomy in the study eye at any time.
- Subjects with uncontrolled glaucoma in the study eye (defined as intraocular pressure \geq 26 mm Hg in spite of treatment with anti-glaucoma medication)
- Subjects who are pregnant or of child-bearing potential not utilizing an acceptable form of contraception. Acceptable methods of birth control include intrauterine device, oral, implanted, or injected contraceptives, and barrier methods with spermicide.
- Subjects who, in the Investigators view, will not complete all visits and investigations
- Subjects who have participated in an investigational drug trial within the past 30 days
- Subjects who have previously participated in this trial

Primary Efficacy Endpoint

Proportion of subjects with nonsurgical resolution of focal vitreomacular adhesion at day 28, as determined by masked Central Reading Centre (CRC) OCT evaluation. Any patients that had creation of an anatomical defect (i.e., retinal hole, retinal detachment) that resulted in loss of

vision or that required additional intervention were not counted as successes on this primary endpoint.

Secondary Efficacy Endpoints

- Proportion of subjects with total PVD at day 28, as determined by masked investigator assessment of B-scan ultrasound.
- Proportion of subjects not requiring vitrectomy
- Proportion of macular holes that close without vitrectomy as determined by CRC
- Achievement of ≥ 2 and ≥ 3 lines improvement in Best Corrected Visual Acuity (BCVA) without need for vitrectomy
- Improvement in BCVA
- Improvement in VFQ-25

Safety Endpoints

Post-injection complications (including adverse events, worsening visual acuity, worsening macular edema, vitreous hemorrhage, retinal tear or detachments, increase in ocular inflammation and IOP increases)

Study Schedule

This was a 6 month study with a total of 7 visits: Baseline, Injection Day (Day 0), Post-Injection Day 7, Post-Injection Day 14, Post-Injection Day 28, Post-Injection Month 3 and Post-Injection Month 6. Baseline and Injection Day visits were combined at the Investigator's discretion.

	Baseline	Injection Day	Post- Injection Day 7	Post- Injection Day 14	Post- Injection Day 28	Post- Injection Month 3	Post- Injection Month 6
Visit Number	V #1	V #2	V #3	V #4	V #5	V #6	V #7
Visit Day (visit window)	BL ^a	0	7 (± 2d)	14 (±3d)	28 (± 3d)	90 (± 1w)	180 (±2w)
Assessments							
Consent	X						
Demography, medical and ocular history	X						
Full ophthalmologic exam ^{b, c}	X	X	X	X	X	X	X
Pregnancy test ^d	X						
Study drug / placebo injection		X ^e					
B-scan ultrasound ^c	X	X ^f	X	X	X ^g	X ^g	X ^g
OCT ^c	X	X ^f	X	X	X	X	X
VFQ-25	X						X
Fundus Photography ^c	X						X
Fluorescein Angiogram ^h	X						X
AE/SAE reporting		X	X	X	X	X	X

^a Baseline visit had to be performed within 2 weeks of Visit 2. At the discretion of the Investigator, Visit 1 and Visit 2 could have been combined.

^b Full ophthalmologic exam included: vision with ETDRS chart, manifest refraction, intraocular pressure, slit-lamp examination and dilated fundus examination. The same slit-lamp machine and lighting conditions were used across study visits for a given subject.

^c At Baseline, full ophthalmologic exam, B-scan ultrasound, OCT and fundus photography were performed in both eyes; at other study visits, these exams were performed only in study eye.

^d Was performed in non-menopausal female subjects.

^e Post-injection, IOP measurement and indirect ophthalmologic examination was performed by the Investigator to exclude retinal non-perfusion or other complications.

^f If Baseline examination was performed >48 hrs prior to injection, B-scan ultrasound and OCT examination had to be repeated in the study eye.

^g If total PVD NOT present at prior 2 consecutive visits, then B-Scan ultrasound was performed in the study eye.

^h FA was performed in both eyes at Baseline visit, and repeated in study eye at Visit 7.

Abbreviations used – Optical Coherence Tomography (OCT), Visual Function Questionnaire (VFQ), Adverse Event (AE), Serious Adverse Event (SAE), Early Treatment Diabetic Retinopathy Study (ETDRS)

Analysis sets

Safety Set

Consisted of all subjects who received treatment with study drug (ocriplasmin and placebo). The Safety Set was the primary population for all safety analyses.

Full Analysis Set (FAS)

The FAS included all randomized subjects who received treatment with study drug (ocriplasmin and placebo). The FAS was the primary population for all analyses of Baseline/demographic and efficacy data.

Modified Full Analysis Set (FAS)

Defined as all randomized subjects who received treatment with study drug and had symptomatic focal VMA to begin with at Baseline as determined by masked Central Reading Center OCT evaluation.

Per-Protocol Set

The Per-Protocol Set included the FAS excluding subjects where a deviation was of sufficient concern to warrant exclusion.

Data Set	TG-MV-006 ^a			TG-MV-007			Integrated Studies		
	Placebo	Ocriplasmin	Total	Placebo	Ocriplasmin	Total	Placebo	Ocriplasmin	Total
Patients randomized (N)	107	219	326	81	245	326	188	464	652
Full Analysis Set (n, %)	107 (100)	219 (100)	326 (100)	81 (100)	245 (100)	326 (100)	188 (100)	464 (100)	652 (100)
Modified Full Analysis Set (n, %)	99 (92.5)	207 (94.5)	306 (93.9)	77 (95.1)	233 (95.1)	310 (95.1)	176 (93.6)	440 (94.8)	616 (94.5)
Per-Protocol Set (n, %)	94 (87.9)	189 (86.3)	283 (86.8)	71 (87.7)	214 (87.3)	285 (87.4)	165 (87.8)	403 (86.9)	568 (87.1)

Reference: [Table 1.1, Module 5.3.5.3](#)

^a One patient (Patient 631002) inadvertently received ocriplasmin instead of placebo. Since patients in the Full Analysis Set were analyzed according to the intent-to-treat principle, this patient was counted in the placebo group for the analysis of efficacy.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

6.1.1 Methods

Description of the clinical trial design is contained in section 5.3.

6.1.2 Demographics

Characteristic	TG-MV-006			TG-MV-007			Integrated Studies		
	Placebo (N=107)	Ocriplasmin (N=219)	Total (N=326)	Placebo (N=81)	Ocriplasmin (N=245)	Total (N=326)	Placebo (N=188)	Ocriplasmin (N=464)	Total (N=652)
Gender, n (%)									
Male	48 (44.9)	71 (32.4)	119 (36.5)	25 (30.9)	79 (32.2)	104 (31.9)	73 (38.8)	150 (32.3)	223 (34.2)
Female	59 (55.1)	148 (67.6)*	207 (63.5)	56 (69.1)	166 (67.8)	222 (68.1)	115 (61.2)	314 (67.7)	429 (65.8)
Age (yrs)									
Mean (SD)	71.1 (10.04)	71.5 (10.25)	71.3 (10.17)	70.2 (10.85)	72.6 (7.56)	72.0 (8.54)	70.7 (10.38)	72.1 (8.94)	71.7 (9.39)
Median	70.0	72.0	71.0	72.0	73.0	73.0	71.0	72.0	72.0
Min, max	24, 96	18, 93	18, 96	32, 97	23, 89	23, 97	24, 97	18, 93	18, 97
Race, n (%)									
White	97 (90.7)	195 (89.0)	292 (89.6)	77 (95.1)	233 (95.1)	310 (95.1)	174 (92.6)	428 (92.2)	602 (92.3)
Black	4 (3.7)	13 (5.9)	17 (5.2)	2 (2.5)	10 (4.1)	12 (3.7)	6 (3.2)	23 (5.0)	29 (4.4)
Asian	2 (1.9)	6 (2.7)	8 (2.5)	2 (2.5)	2 (0.8)	4 (1.2)	4 (2.1)	8 (1.7)	12 (1.8)
Other	4 (3.7)	5 (2.3)	9 (2.8)	0	0	0	4 (2.1)	5 (1.1)	9 (1.4)
Ethnicity, n (%)									
Non-Hispanic (USA)	98 (91.6)	204 (93.2)	302 (92.6)	32 (39.5)	103 (42.0)	135 (41.4)	130 (69.1)	307 (66.2)	437 (67.0)
Hispanic (USA)	9 (8.4)	15 (6.8)	24 (7.4)	4 (4.9)	8 (3.3)	12 (3.7)	13 (6.9)	23 (5.0)	36 (5.5)
Not specified (non-USA)	0	0	0	45 (55.6)	134 (54.7)	179 (54.9)	45 (23.9)	134 (28.9)	179 (27.5)
Baseline Diagnosis, n (%)^a									
FTMH	32 (29.9)	57 (26.0)	89 (27.3)	15 (18.5)	49 (20.0)	64 (19.6)	47 (25.0)	106 (22.8)	153 (23.5)
VMT (including DR)	75 (70.0)	162 (74.0)	237 (72.7)	66 (81.5)	196 (80.0)	262 (80.4)	141 (75.0)	358 (77.2)	499 (76.5)

Characteristic	TG-MV-006			TG-MV-007			Integrated Studies		
	Placebo (N=107)	Ocriplasmin (N=219)	Total (N=326)	Placebo (N=81)	Ocriplasmin (N=245)	Total (N=326)	Placebo (N=188)	Ocriplasmin (N=464)	Total (N=652)
Baseline Ocular Characteristics, n (%)^b									
ERM	35 (32.7)	86 (39.3)	121 (37.1)	33 (40.7)	98 (40.0)	131 (40.2)	68 (36.2)	184 (39.7)	252 (38.7)
Pseudophakic	29 (27.1)	91 (41.6)*	120 (36.8)	24 (29.6)	81 (33.1)	105 (32.2)	53 (28.2)	172 (37.1)*	225 (34.5)
DR	7 (6.5)	12 (5.5)	19 (5.8)	8 (9.9)	18 (7.3)	26 (8.0)	15 (8.0)	30 (6.5)	45 (6.9)
Type (Diameter) of Focal VMA, n/N (%)^c									
> 1500µm	19/99 (19.2)	47/207 (22.7)	66/306 (21.6)	22/77 (28.6)	55/233 (23.6)	77/310 (24.8)	41/176 (23.3)	102/440 (23.2)	143/616 (23.2)
≤ 1500µm	74/99 (74.7)	145/207 (70.0)	219/306 (71.6)	49/77 (63.6)	169/233 (72.5)	218/310 (70.3)	123/176 (69.9)	314/440 (71.4)	437/616 (70.9)
Could not determine	6/99 (6.1)	15/207 (7.2)	21/306 (6.9)	6/77 (7.8)	9/233 (3.9)	15/310 (4.8)	12/176 (6.8)	24/440 (5.5)	36/616 (5.8)
Expected Need for Vitrectomy, n (%)^d									
Yes	85 (79.4)	174 (79.5)	259 (79.4)	67 (82.7)	222 (90.6)	289 (88.7)	152 (80.9)	396 (85.3)	548 (84.0)
No	22 (20.6)	44 (20.1)	66 (20.2)	14 (17.3)	23 (9.4)	37 (11.3)	36 (19.1)	67 (14.4)	103 (15.8)
Missing	0	1 (0.5)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
Total PVD at Baseline, n (%)									
Yes	0	1 (0.5)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
No	107 (100.0)	218 (99.5)	325 (99.7)	81 (100.0)	245 (100.0)	326 (100.0)	188 (100.0)	463 (99.8)	651 (99.8)

Characteristic	TG-MV-006			TG-MV-007			Integrated Studies		
	Placebo (N=107)	Ocriplasmin (N=219)	Total (N=326)	Placebo (N=81)	Ocriplasmin (N=245)	Total (N=326)	Placebo (N=188)	Ocriplasmin (N=464)	Total (N=652)
BCVA (Letter Score)									
Mean (SD)	65.3 (9.83)	64.5 (10.86)	64.8 (10.53)	64.9 (11.58)	63.4 (13.69)	63.8 (13.20)	65.1 (10.59)	63.9 (12.43)	64.3 (11.94)
Median	67.0	67.0	67.0	66.5	67.0	67.0	67.0	67.0	67.0
Min, max	38, 82	20, 85	20, 85	9, 82	8, 88	8, 88	9, 82	8, 88	8, 88

Reference: Table 1.2.1, Table 2.2.1.1, Table 2.2.2.1 and Table 2.2.2.2, Module 5.3.5.3

BCVA=best corrected visual acuity; DR=diabetic retinopathy; ERM=epiretinal membrane; FTMH=full thickness macular hole; PVD=posterior vitreous detachment; SD=standard deviation; USA=United States of America; VMA=vitreomacular adhesion; VMT=vitreomacular traction

^a denotes a statistically significant difference between treatment groups.

^b Based on CRC review of pre-treatment OCT. All cases other than FTMH were considered to be VMT.

^c Patients could have had > 1 baseline ocular characteristic.

^d Percentages are based on total number of patients in the Modified Full Analysis Set.

^e Yes / no answer for the question asked of the investigator prior to randomization: "If no improvement in this patient's condition, do you think you would proceed to vitrectomy?"

6.1.3 Subject Disposition

Patient Disposition (TG-MV-006 and TG-MV-007)

	TG-MV-006			TG-MV-007		
	Placebo	Ocriplasmin	Total	Placebo	Ocriplasmin	Total
Patients randomized (N)	107	219	326	81	245	326
Completed study, n (%)	98 (91.6)	200 (91.3)	298 (91.4)	74 (91.4)	235 (95.9)	309 (94.8)
Discontinued from study, n (%)	9 (8.4)	19 (8.7)	28 (8.6)	7 (8.6)	10 (4.1)	17 (5.2)
Adverse event	2 (1.9)	2 (0.9)	4 (1.2)	0	2 (0.8) ^a	2 (0.6)
Investigator decision	0	0	0	1 (1.2)	0	1 (0.3)
Withdrew consent	4 (3.7)	8 (3.7)	12 (3.7)	4 (4.9)	5 (2.0)	9 (2.8)
Lost to follow-up	3 (2.8)	6 (2.7)	9 (2.8)	2 (2.5)	2 (0.8)	4 (1.2)
Death	0	3 (1.4)	3 (0.9)	0	1 (0.4)	1 (0.3)

Note: One patient (Patient 631002, TG-MV-006) was randomized to placebo but was inadvertently treated with ocriplasmin instead of placebo.

^a One patient (Patient 721008, TG-MV-007) discontinued due to metastatic brain cancer and subsequently died. This patient is not counted as discontinuing due to death in this table.

Data Set	TG-MV-006*			TG-MV-007		
	Placebo	Ocriplasmin	Total	Placebo	Ocriplasmin	Total
Patients randomized (N)	107	219	326	81	245	326
Full Analysis Set (n, %)	107 (100)	219 (100)	326 (100)	81 (100)	245 (100)	326 (100)
Modified Full Analysis Set (n, %)	99 (92.5)	207 (94.5)	306 (93.9)	77 (95.1)	233 (95.1)	310 (95.1)
Per-Protocol Set (n, %)	94 (87.9)	189 (86.3)	283 (86.8)	71 (87.7)	214 (87.3)	285 (87.4)

*One patient (Patient 631002) inadvertently received ocriplasmin instead of placebo. Since patients in the Full Analysis Set were analyzed according to the intent-to-treat principle, this patient was counted in the placebo group for the analysis of efficacy

6.1.4 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

CI=confidence interval; PL=placebo; VMA=vitreomacular adhesion

^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.

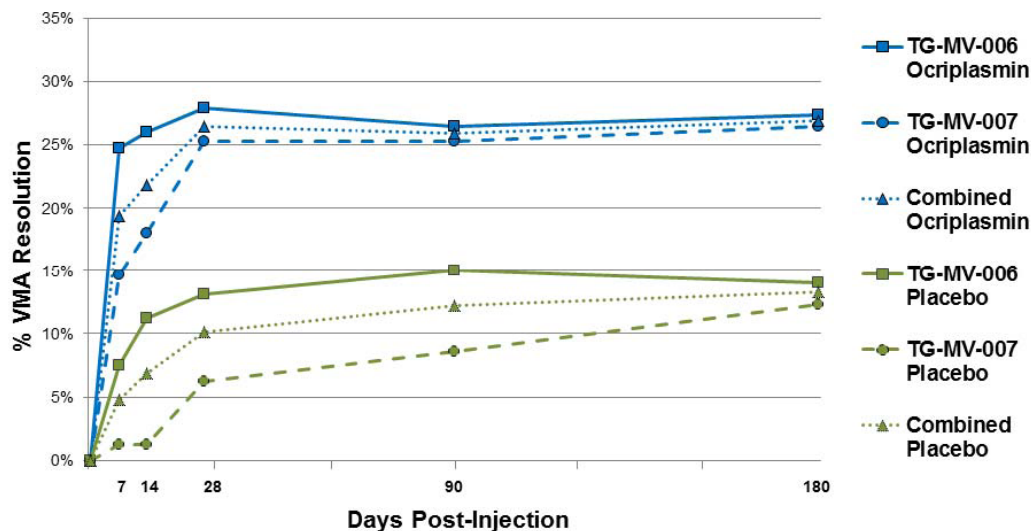
Reviewer Comments:

Ocriplasmin is statistically superior to placebo in both of the phase 3 trials for all of the analysis sets. While the drug response rate appears consistent in both trials, the placebo event rate is twice as high in Study 006 compared to 007. The applicant postulates that this could have resulted from factors such as more patients with macular holes, less epiretinal membrane cases and higher proportion of patients with VMA diameter $\leq 1500\mu\text{m}$ in study 006. Some studies have shown that spontaneous resolution of VMA occurs more often in patients with VMA diameter $\leq 1500\mu\text{m}$ and in those without associated ERM; however, this effect should also be seen in the drug group not just in the placebo group. While not statistically significant, it is unclear why there is such a large discrepancy in the placebo rates in these two trials.

A review of the baseline demographic characteristics of placebo patients in both studies does not reveal differences that would explain this outcome. The number of placebo patients with FTMH at baseline is similar and there is only 1 patient with an epiretinal membrane at baseline. There

are 14/14 (100%) of placebo patients in TG-MV-006 with $VMA \leq 1500\mu m$ at baseline versus 4/5 (80%) in study TG-MV-007.

Proportion of Patients with VMA Resolution in the Study Eye (TG-MV-006, TG-MV-007 and Integrated Studies: Full Analysis Set)



Reviewer Comments:

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.

6.1.5 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

Reviewer's Comments:

Per the Applicant's submission "The primary endpoint comparison was performed with an alpha level of 0.05 as treatment efficacy was characterized by a single primary efficacy endpoint between 2 treatment groups." 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.

6.1.6 Other Endpoints

Exploratory Endpoints

- Proportion of subjects not requiring vitrectomy
- Proportion of full-thickness macular holes (FTMHs) that closed without vitrectomy as determined by CRC
- Achievement of ≥ 2 and ≥ 3 lines improvement in best corrected visual acuity (BCVA) without need for vitrectomy
- Improvement in BCVA
- Improvement in the National Eye Institute (NEI) 25-Item Visual Function Questionnaire (VFQ-25)

Reviewer's Comments:

The NEI VFQ-25 is not considered a qualified endpoint by the Agency; therefore, the results for this endpoint have not been presented as part of this review.

Efficacy Results for Exploratory Endpoints (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
Proportion of Patients who received a Vitrectomy by Month 6							
31/107 (29.0)	45/219 (20.5)	-8.4 (-18.5, 1.7)	0.096	19/81 (23.5)	37/245 (15.1)	-8.4 (-18.6, 1.9)	0.091
Proportion of Patients with Non-Surgical \geq 2-line Improvement in BCVA at Month 6							
12/107 (11.2)	56/219 (25.6)	14.4 (6.0, 22.7)	0.002	9/81 (11.1)	54/245 (22.0)	10.9 (2.3, 19.5)	0.035
Proportion of Patients with Non-Surgical \geq 3-line Improvement in BCVA at Month 6							
7/107 (6.5)	23/219 (10.5)	4.0 (-2.2, 10.2)	0.310	0/81	22/245 (9.0)	9.0 (5.4, 12.6)	0.002

Source: Table 5 of the Applicant's Clinical Overview

^a The (absolute) difference and CIs between treatment groups are based on the proportion of successes (variable: VMA resolution, total PVD, improvement in BCVA), the proportion of patients with FTMH closure (variable: non-surgical FTMH closure) or the proportion of patients who received vitrectomy (variable: vitrectomy)

^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

Reviewer's comments:

Per the Applicant's submission "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 total of 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.

FTMH Results

Reviewer's comments: FTMH was an exploratory endpoint in both of the phase 3 trials. Efficacy for this endpoint was not demonstrated. This section is being added to the review to further explore the results since this is an indication that the sponsor is seeking in addition to VMA resolution.

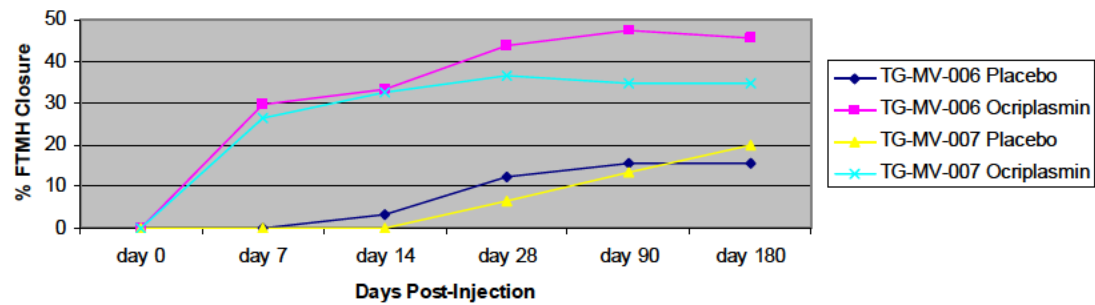
Efficacy Results for FTMH Endpoint (TG-MV-006 and TG-MV-007)

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

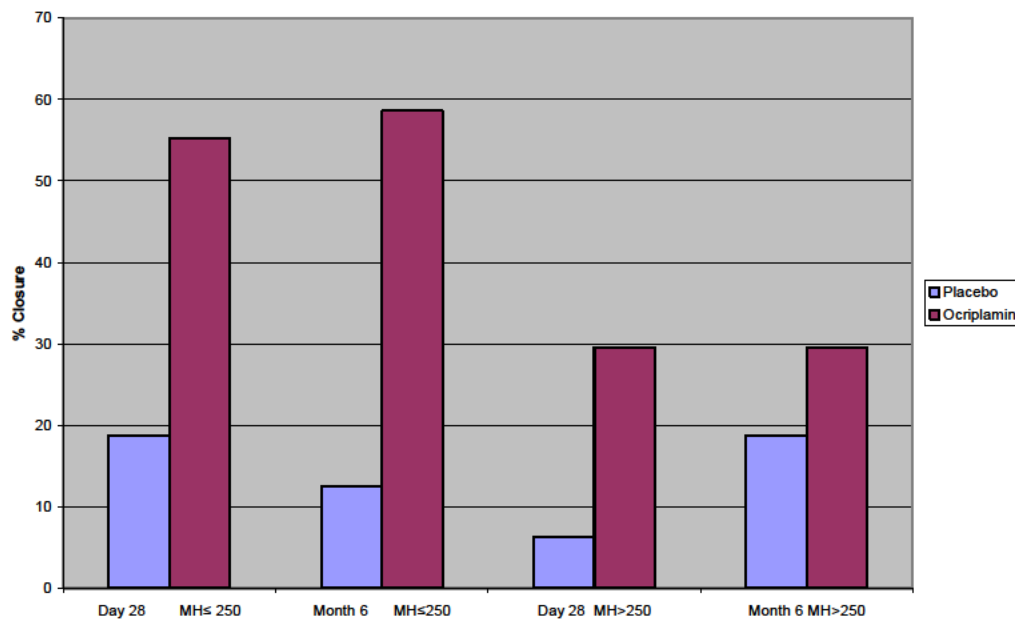
^a The (absolute) difference and CIs between treatment groups are based on the proportion of patients with FTMHC.

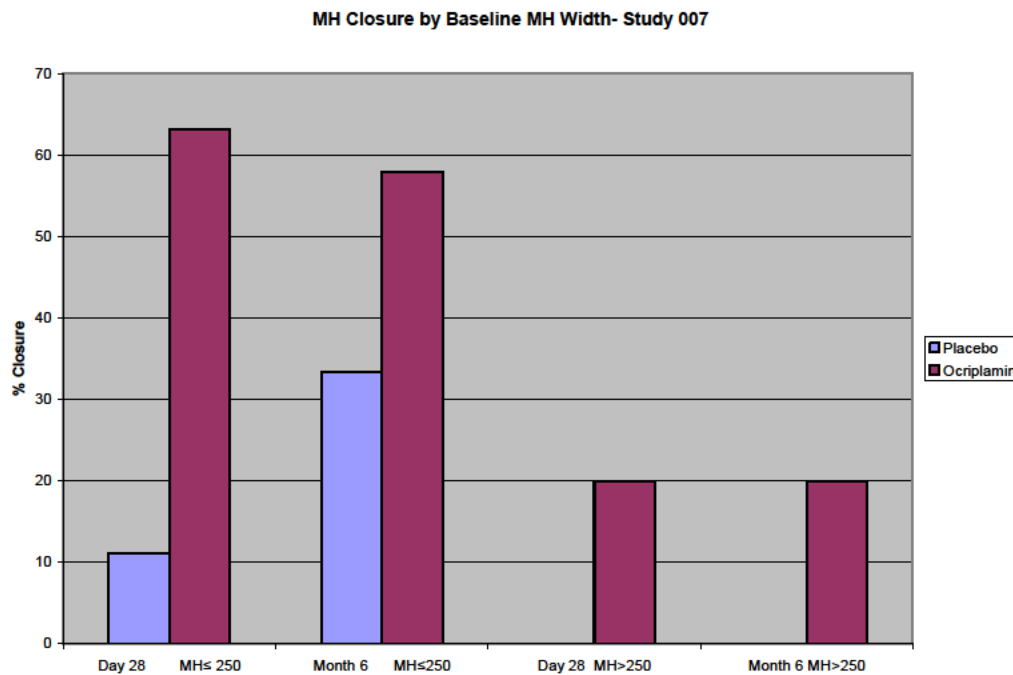
^b For individual studies, p-value is from Fisher's exact test, comparing placebo and ocriplasmin. For pooled studies, p-value is from Cochran-Mantel-Haenszel test comparing placebo and ocriplasmin, stratified by study.

Proportion of Patients with Non-Surgical FTMH Closure in the Study Eye (TG-MV-006 and TG-MV-007)



MH Closure by Baseline MH Width - Study-006



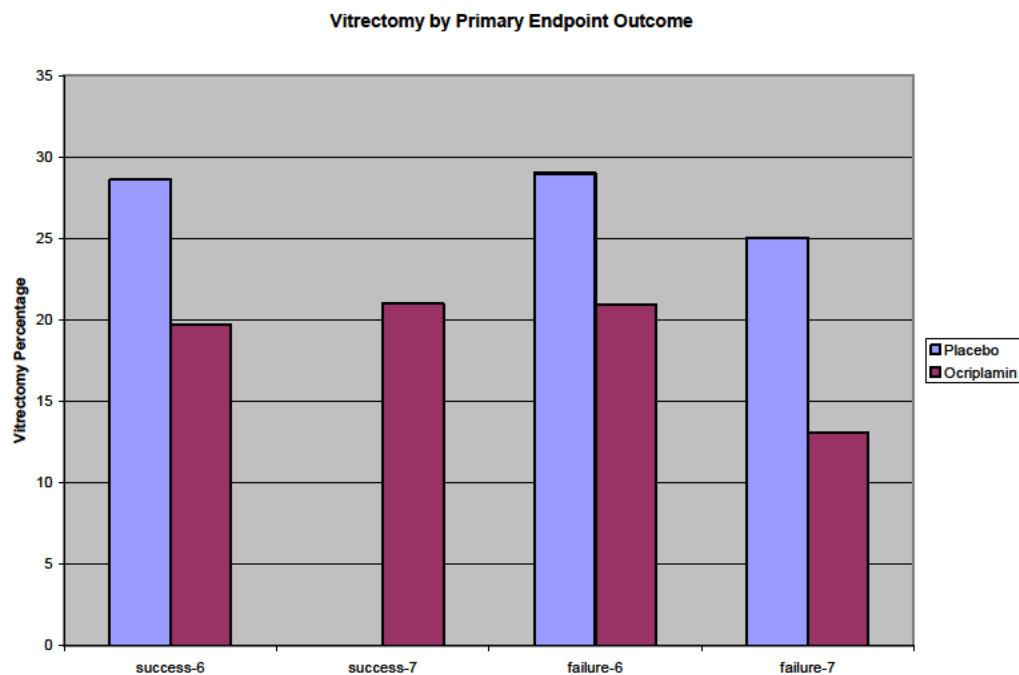


Reviewer's Comments:

*The percentage of macular hole closure in both of the phase 3 trials is numerically greater in the ocriplasmin treated patients compared to placebo. This difference was **not** statistically significant. Macular holes with widths $\leq 250\mu\text{m}$ closed at a higher rate than larger holes.*

Vitrectomy

The current standard of treatment for patients who present with VMT is "watchful waiting" for those patients whose symptoms remain stable or vitrectomy if there is progression in retinal traction or progressive decrease in vision. Ocriplasmin was developed as an alternative for an invasive procedure which carries risks such as retinal tears/detachments, endophthalmitis, etc. The requirement to have vitrectomy surgery is not totally mitigated in those patients who successfully treated with ocriplasmin. Based on the phase 3 trials, approximately 20% of patients successfully treated with ocriplasmin may require vitrectomy surgery.



Visual Acuity Results

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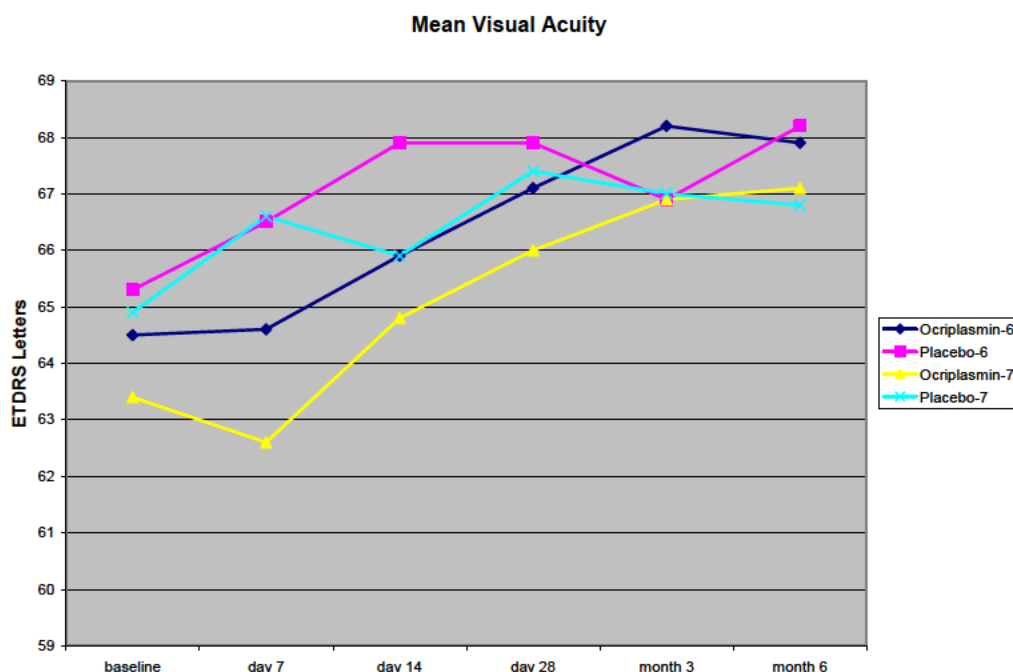
One subject did not have a BCVA measurement at Baseline; therefore, the denominator used in this analysis is 80 for the placebo group.

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

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

Reviewer's Comments:

*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).*



Reviewer's Comments:

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).

6.1.7 Subpopulations

The following subgroups (Baseline demographics and ocular characteristics) were evaluated:

Gender (male vs. female)

Age (≤ 65 vs. > 65)

Race (white vs. non-white)

Baseline FTMH

Baseline ERM

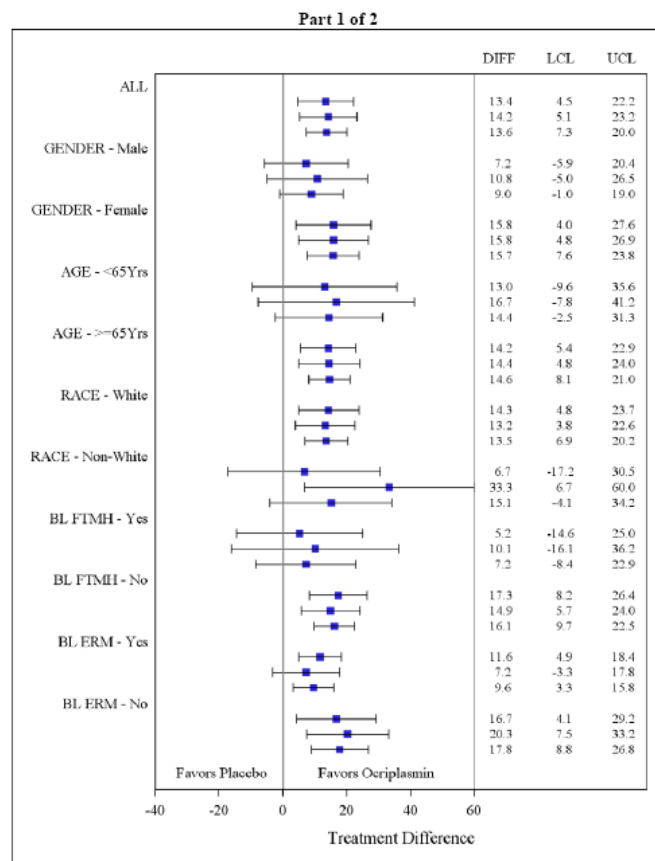
Lens status (phakic versus pseudophakic)

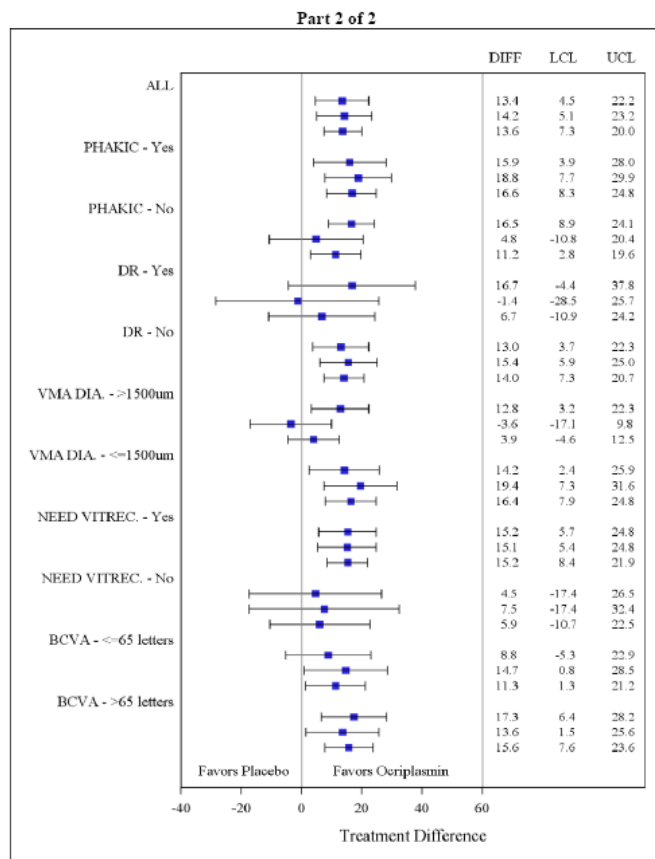
Baseline Diabetic Retinopathy

Type of VMA ($>1500\mu\text{m}$ versus $\leq 1500\mu\text{m}$ diameter)

Baseline BCVA subgroups (>65 letters versus ≤ 65 letters).

Forest Plot for the Treatment Difference in the Proportion of Patients with VMA Resolution in the Study Eye at Month 6 without Creation of an Anatomical Defect (TG-MV-006, TG-MV-007 and Integrated Studies - Full Analysis Set)





Reviewers Comments: Overall, the results for these subgroups were consistent with the primary analysis results.

Analysis of Clinical Information Relevant to Dosing Recommendations

There are no additional dosing recommendations.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

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.

Reviewer's comments:

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. Tolerance and withdrawal effects are not considered to be a concern for single-use ocriplasmin.

Additional Efficacy Issues/Analyses

There are no additional efficacy issues requiring review.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A total of 10 sponsor studies and 2 investigator-initiated studies have been conducted for administered ocriplasmin. Seven (7) of those studies were completed at the time of the data cut-of date.

Study ID	No. Ctrs. Initiated / Enrolled	Design / Control	Indication Route Regimen	Total Enrollment (Planned / Actual) By Treatment (Entered/Completed)	Duration ^a
UNCONTROLLED STUDIES					
TG-MV-001	4 EU / 4 EU	Phase 2 multicenter, open-label, uncontrolled trial with ascending dose / exposure time in 6 sequential cohorts in patients with vitreomacular traction (VMT) maculopathy	VMT maculopathy Single intravitreal injection ocriplasmin dose / time before vitrectomy: ocriplasmin 25µg/1h ocriplasmin 25µg/24h ocriplasmin 25µg/7d ocriplasmin 50µg/24h ocriplasmin 75µg/24h ocriplasmin 125µg/24h	60/61 ^b 10/10 10/10 10/9 10/9 12/11 ^b 9/9	6m
TG-MV-010	1 EU / 1 EU	Phase 2 single center, ascending-exposure time pharmacokinetic trial prior to pars plana vitrectomy (PPV)	Pharmacokinetics Single intravitreal injection ocriplasmin dose / time before vitrectomy: ocriplasmin 125µg/5-30min ocriplasmin 125µg/31-60min ocriplasmin 125µg/2-4h ocriplasmin 125µg/24h ocriplasmin 125µg/7d no ocriplasmin treatment	36/38 9/9 9/8 8/8 4/4 4/4 4/4	6w

Study ID	No. Ctrs. Initiated / Enrolled	Design / Control	Indication Route Regimen	Total Enrollment (Planned / Actual) By Treatment (Entered/Completed)	Duration
CONTROLLED STUDIES					
TG-MV-002		Phase 2 multicenter, randomized, sham-injection controlled, double-masked, ascending-dose, dose-range-finding study in patients with diabetic macular edema	Diabetic macular edema Single intravitreal injection ocriplasmin 25µg ocriplasmin 75µg ocriplasmin 125µg sham injection	60/51 8/8 15/15 15/14 13/11	12m

TG-MV-003	19 USA / 19 USA	Phase 2 multicenter, randomized, placebo-controlled, double-masked, parallel-group, dose-ranging study in patients undergoing vitrectomy	Non-proliferative vitreoretinal disease Single intravitreal injection ocriplasmin 25µg ocriplasmin 75µg ocriplasmin 125µg placebo	120/125 29/26 33/29 32/32 31/30	6m
TG-MV-004	4 EU / 3 EU	Phase 2 multicenter, randomized, sham-injection controlled, double-masked, ascending-dose, dose-range-finding trial in patients with VMT	VMT Single intravitreal injection ^c ocriplasmin 75µg ocriplasmin 125µg ocriplasmin 175µg sham injection	60/61 12/12 25/25 ^d 13/11 12/12 ^e	6m

Study ID	No. Ctrs. Initiated / Enrolled	Design / Control	Indication Route Regimen	Total Enrollment (Planned / Actual) By Treatment (Entered/Completed)	Duration
TG-MV-006	44 USA / 42 USA	Phase 3 multicenter, randomized, placebo-controlled, double-masked study in patients with symptomatic vitreomacular adhesions ([VMA] i.e. focal VMA leading to symptoms)	Symptomatic VMA Single intravitreal injection ocriplasmin 125µg placebo	320/326 220/201 ^f 106/97	6m
TG-MV-007	50 USA, EU / 48 USA, EU	Phase 3 multicenter, randomized, placebo-controlled, double-masked study in patients with symptomatic VMA (i.e. focal VMA leading to symptoms)	Symptomatic VMA Single intravitreal injection ocriplasmin 125µg placebo	320/326 245/235 81/74	6m

^a Duration of post-injection observation period.

^b One patient (2504) withdrew consent prior to treatment and was replaced. One patient (2606) was allocated to Cohort 6 (125µg) but was treated with the dose for Cohort 5 (75µg).

^c In Cohort 4 only, patients who did not achieve resolution of VMT by Post-Injection Day 28 could receive up to 2 open-label injections of ocriplasmin 125µg at monthly intervals.

^d One patient randomized to ocriplasmin 175µg received an injection of approximately 129µg due to a dilution error during study drug preparation. This patient was counted with the ocriplasmin 125µg group. In Cohort 4, 9 patients each received 2 open-label injections with ocriplasmin 125µg.

^e In Cohort 4, 2 patients who received sham-injection during the controlled period of the study each received 2 open-label injections with ocriplasmin 125µg.

^f Patient 631002 was randomized to placebo and was treated with ocriplasmin. This patient was included in the ocriplasmin 125µg group for safety and in the placebo group for efficacy.

7.1.2 Categorization of Adverse Events

MedDRA nomenclature was used to code adverse events. The number and percent of patients reporting adverse events was tabulated based on the system organ class and preferred term. Summary table were generated for all adverse events regardless of causality as well as for treatment-related adverse events.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

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).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Study	Ocriplasmin						Placebo	Sham	No Treatment
	25µg	50µg	75µg	125µg	175µg	Any Dose			
TG-MV-001	30	10	11	9	0	60	0	0	0
TG-MV-003	29	0	33	32	0	94	31	0	0
TG-MV-010	0	0	0	34	0	34	0	0	4
Subtotal ^a	59	10	44	75	0	188	31	0	4
TG-MV-002	8	0	15	15	0	38	0	13	0
TG-MV-004	0	0	12	27	11	50	0	12	0
TG-MV-006	0	0	0	220	0	220	106	0	0
TG-MV-007	0	0	0	245	0	245	81	0	0
Subtotal ^b	8	0	27	507	11	553	187	25	0

Total	67	10	71	582	11	741	218	25	4
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a Subtotal for pre-planned vitrectomy studies

b Subtotal for studies without pre-planned vitrectomy

Demographic and Baseline Characteristics (Safety Set)

	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo (N=187)		Ocriclasmin 125µg (N=465)		Control ^a N=247		Ocriclasmin Any Dose (N=741)	
Gender [n (%)]								
Male	73	(39.0%)	150	(32.3%)	98	(39.7%)	259	(35.0%)
Female	114	(61.0%)	315	(67.7%)	149	(60.3%)	482	(65.0%)
Race [n(%)]								
White	173	(92.5%)	429	(92.3%)	228	(92.3%)	633	(85.4%) ^b
Black	6	(3.2%)	23	(4.9%)	9	(3.6%)	29	(3.9%)
Asian	4	(2.1%)	8	(1.7%)	5	(2.0%)	13	(1.8%)
Other	4	(2.1%)	5	(1.1%)	5	(2.0%)	6	(0.8%)
Geographic region [n (%)]								
United States	142	(75.9%)	331	(71.2%)	173	(70.0%)	425	(57.4%)
Europe	45	(24.1%)	134	(28.8%)	74	(30.0%)	316	(42.6%)
BMI [n (%)]								
< 25	69	(36.9%)	148	(31.8%)	88	(35.6%)	223	(30.1%)
≥ 25	118	(63.1%)	314	(67.5%)	155	(62.8%)	479	(64.6%)
Age (years) at Baseline								
n	187		465		247		741	
Mean (SD)	70.7	(10.39)	72.0	(8.94)	70.0	(10.32)	70.0	(9.56)
Median	71.0		72.0		70.0		70.0	
Min - Max	24-97		18-93		24-97		18-93	
Age Group [n (%)]								
<65 years	42	(22.5%)	81	(17.4%)	60	(24.3%)	190	(25.6%)
≥ 65 years	145	(77.5%)	384	(82.6%)	187	(75.7%)	551	(74.4%)
<75 years	114	(61.0%)	273	(58.7%)	160	(64.8%)	494	(66.7%)
≥ 75 years	73	(39.0%)	192	(41.3%)	87	(35.2%)	247	(33.3%)

	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo (N=187)		Ocriclasmin 125µg (N=465)		Control N=247		Ocriclasmin Any Dose (N=741)	
Baseline Diagnosis [n (%)] ^c								
Full thickness macular hole ^d								
Yes	47	(25.1%)	105	(22.6%)	48	(19.4%)	114	(15.4%)
No	133	(71.1%)	332	(71.4%)	136	(55.1%)	356	(48.0%)
Unknown / not collected	7	(3.7%)	28	(6.0%)	63	(25.5%)	271	(36.6%)
Diabetic retinopathy								
Yes	15	(8.0%)	31	(6.7%)	29	(11.7%)	78	(10.5%)
No	172	(92.0%)	434	(93.3%)	218	(88.3%)	663	(89.5%)
Epiretinal membrane ^e								
Yes	67	(35.8%)	183	(39.4%)	68	(27.5%)	189	(25.5%)
No	119	(63.6%)	267	(57.4%)	122	(49.4%)	294	(39.7%)
Unknown / not collected	1	(0.5%)	15	(3.2%)	57	(23.1%)	258	(34.8%)
Lens status ^f								
Phakia	134	(71.7%)	293	(63.0%)	153	(61.9%)	363	(49.0%)
Pseudophakia	53	(28.3%)	172	(37.0%)	59	(23.9%)	190	(25.6%)
Not characterized	0		0		35	(14.2%)	188	(25.4%)
Vitrectomy expected if no improvement [n (%)] ^g								
Yes	151	(80.7%)	397	(85.4%)				
No	36	(19.3%)	67	(14.4%)				

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

^b Race was not recorded in [TG-MV-001](#); therefore, race is missing for 60 (8.1%) patients.

^c Patients may be included in multiple baseline diagnosis categories as appropriate.

^d FTMH status at Baseline was recorded only for [TG-MV-002](#), [TG-MV-004](#), [TG-MV-006](#) and [TG-MV-007](#).

^e ERM status at Baseline was recorded only for [TG-MV-002](#), [TG-MV-004](#), [TG-MV-006](#) and [TG-MV-007](#).

^f Lens status was characterized for all studies except [TG-MV-001](#), [TG-MV-003](#) and [TG-MV-010](#).

^g Yes / no answer for the question asked of the investigator prior to randomization: "If no improvement in this patient's condition, do you think you would proceed to vitrectomy?" Recorded for [TG-MV-006](#) and [TG-MV-007](#) only.

7.2.2 Explorations for Dose Response

Dose response was evaluated in 3 Phase 2 studies, TG-MV-002, TG-MV-003 and TG-MV-004. Doses of ocriclasmin evaluated included 25µg, 75µg, 125µg and 175µg. The 125µg dose was associated with the most efficacy in both studies with no additional benefit was observed with the 175µg dose or repeat injections of 125µg. Ocriclasmin was administered at one dose level

(125µg) for each of the phase 3 studies. No dose response information was obtained during the phase 3 trials.

Special Animal and/or In Vitro Testing

No special toxicology studies were conducted with ocriplasmin.

7.2.4 Routine Clinical Testing

The routine clinical testing required to evaluate the safety concerns of intravitreally administered products (i.e. biomicroscopy, funduscopy, visual acuity, etc) were adequately addressed in the design and conduct of the trials for this product.

7.2.5 Metabolic, Clearance, and Interaction Workup

No formal studies have been conducted with ocriplasmin in patients with renal or hepatic impairment.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

N/A – there are no other approved intravitreally injected products in this drug class.

7.3 Major Safety Results

7.3.1 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	(b) (4)	Lung neoplasm malignant
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Reviewers Comments:

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.

7.3.2 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.

Reviewers Comments:

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

7.3.3 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.

^d Deaths 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".

Reviewers Comments:

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.

7.3.4 Significant Adverse Events

Adverse events related to dropouts/discontinuations are presented in section 7.3.3. There were no other significant adverse events identified.

7.3.5 Submission Specific Primary Safety Concerns

N/A-There are no submission specific safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse Events Reported at a Rate of $\geq 1\%$ for Patients Treated with Ocriplasmin 125 μ g in the Placebo-Controlled Studies (Safety Set)

System Organ Class Preferred Term Category	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo N=187		Ocriplasmin 125 μ g 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 AEs⁽²⁾								
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%)

System Organ Class Preferred Term Category	Pivotal Placebo-Controlled Studies		All Studies Combined	
	Placebo N=187	Ocriplasmin 125µg N=465	Control ⁽¹⁾ N=247	Ocriplasmin Any Dose N=741
Vitreous detachment	3 (1.6%)	13 (2.8%)	3 (1.2%)	14 (1.9%)

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

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

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

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

Reviewers Comments:

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. The visual acuity data discussed previously in the efficacy section would possibly suggest that these adverse events may be transient and cause no long term harm to the retina; however, this conclusion can not be made definitively based on the data available.

Dyschromatopsia and Lens Subluxation

The applicant has requested the inclusion of dyschromatopsia and lens subluxation in the warnings and precautions section of the label. Although these events were not noted in the adverse events of the phase 3 trials, their potential occurrence should be relayed to practitioners and patients.

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.

7.4.2 Laboratory Findings

Clinical laboratory tests were performed at Baseline and on Post-Injection Day 28 for 1 Phase 2 study (TG-MV-001). In this study, 30 patients were treated with ocriplasmin 25µg, 10 patients were treated with ocriplasmin 50µg, 11 patients were treated with 75µg and 9 patients were treated with ocriplasmin 125µg.

Clinically significant laboratory abnormalities were reported as AEs for 3 (10.0%) patients treated with ocriplasmin 25µg and 1 (11.1%) patient treated with ocriplasmin 125µg. In patients treated with ocriplasmin 25µg, the laboratory abnormalities mapped to preferred terms of leucocytosis, diabetes mellitus inadequate control and blood bilirubin increased. The patient treated with ocriplasmin 125µg had hepatic enzyme increased (alkaline phosphatase, aspartate aminotransferase [AST], alanine aminotransferase [ALT] and total bilirubin) attributed to preexistent osteomyelofibrosis. None of these events required treatment and all resolved by the last study visit.

In pivotal placebo-controlled studies, the incidence of individual preferred terms for laboratory abnormalities was less than 0.5% in both treatment groups and none was considered a suspected ADR.

7.4.3 Vital Signs

Vital sign measurements were not required in studies that evaluated ocriplasmin following intravitreal injection.

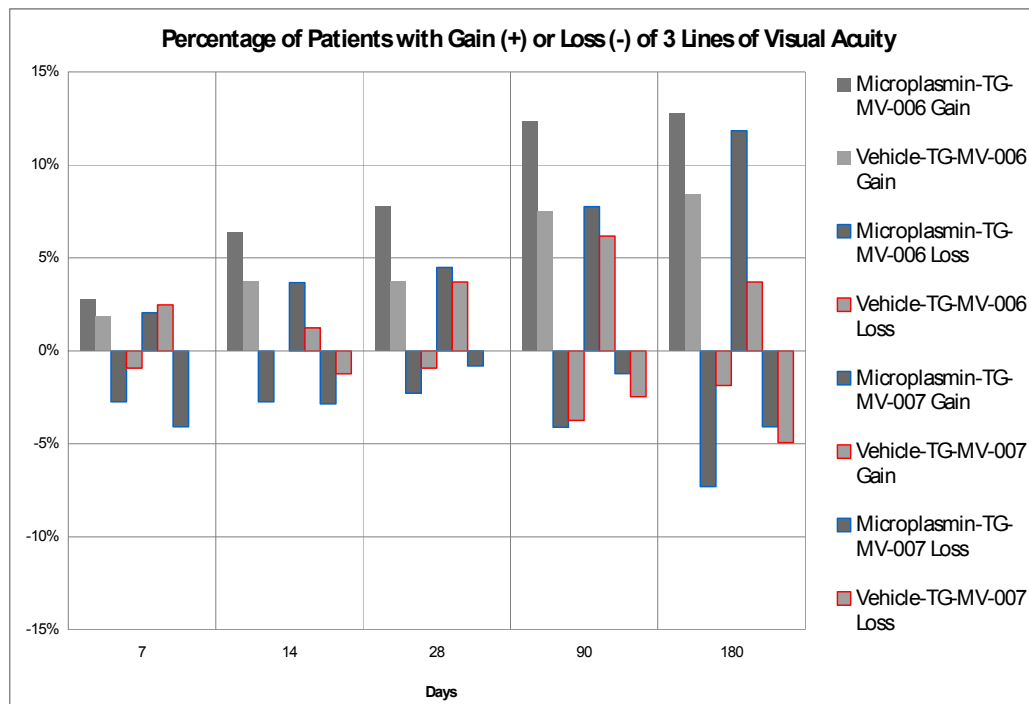
Physical Findings

Ocular examinations were performed at all study visits except for fundus photography and fluorescein angiography, which were done at Baseline and Month 6. These examinations included evaluation of the following:

- BCVA, refraction
- IOP measurement
- Slit lamp examination
- Dilated retinal examinations
- OCT
- Fundus photography
- Fluorescein angiography

BCVA

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.



Reviewer's Comments:

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. A determination cannot be made based on the data available why the rate of decrease vision in approximately twice as high in the drug group compared to placebo.

IOP Measurement

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

Retinal Breaks

Preferred Term	Pivotal Placebo-Controlled Studies						All Studies Combined					
	Placebo N=187			Ocriplasmin 125µg N=465			Control ^a N=247			Ocriplasmin Any Dose N=741		
	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.

Reviewer's Comments:

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

Preferred Term	Pivotal Placebo-Controlled Studies						All Studies Combined					
	Placebo N=187			Ocriplasmin 125µg N=465			Control ^a N=247			Ocriplasmin Any Dose N=741		
	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.

Reviewer's Comments:

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

7.4.4 Electrocardiograms (ECGs)

ECG measurements were not required in studies that evaluated ocriplasmin following intravitreal injection.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies conducted for this development program.

7.4.6 Immunogenicity

There were no systemic antibody assays done during the ophthalmic development of ocriplasmin. There were no differences noted among subjects treated with ocriplasmin and controls for systemic or ocular allergy-type reactions.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A single injection of 125µg was used in the clinical trials. Systemic drug concentration was not determined in this study. Therefore, the relationship between response and drug concentration could not be evaluated. Only 1 dose of active drug was used in this study; therefore, analysis of drug-dose relationship is not applicable.

7.5.2 Time Dependency for Adverse Events

Preferred Term	Pivotal Placebo-Controlled Studies						All Studies Combined					
	Placebo N=187			Ocriclasmin 125µg N=465			Control ¹ N=247			Ocriclasmin Any Dose N=741		
	n	%	E	n	%	E	n	%	E	n	%	E
Suspected ADRs												
Vitreous floaters	14	(7.5%)	15	78	(16.8%)	85	18	(7.3%)	19	119	(16.1%)	131
0-7 Days	5	(2.7%)	6	60	(12.9%)	60	5	(2.0%)	6	89	(12.0%)	90
8-EOS	9	(4.8%)	9	18	(3.9%)	25	13	(5.3%)	13	30	(4.0%)	41
Eye pain	11	(5.9%)	11	61	(13.1%)	68	19	(7.7%)	22	90	(12.1%)	103
0-7 Days	6	(3.2%)	6	49	(10.5%)	53	10	(4.0%)	11	69	(9.3%)	74
8-EOS	5	(2.7%)	5	12	(2.6%)	15	9	(3.6%)	11	21	(2.8%)	29
Photopsia	5	(2.7%)	5	55	(11.8%)	60	7	(2.8%)	7	66	(8.9%)	71
0-7 Days	2	(1.1%)	2	47	(10.1%)	50	2	(0.8%)	2	57	(7.7%)	60
8-EOS	3	(1.6%)	3	8	(1.7%)	10	5	(2.0%)	5	9	(1.2%)	11
Vision blurred	6	(3.2%)	7	39	(8.4%)	41	7	(2.8%)	8	47	(6.3%)	49
0-7 Days	1	(0.5%)	2	30	(6.5%)	31	1	(0.4%)	2	32	(4.3%)	33
8-EOS	5	(2.7%)	5	9	(1.9%)	10	6	(2.4%)	6	15	(2.0%)	16
Visual acuity reduced	8	(4.3%)	8	29	(6.2%)	30	8	(3.2%)	8	41	(5.5%)	42
0-7 Days	0		0	19	(4.1%)	20	0		0	27	(3.6%)	28
8-EOS	8	(4.3%)	8	10	(2.2%)	10	8	(3.2%)	8	14	(1.9%)	14
Visual impairment	2	(1.1%)	2	25	(5.4%)	27	2	(0.8%)	2	27	(3.6%)	29
0-7 Days	0		0	15	(3.2%)	15	0		0	16	(2.2%)	16
8-EOS	2	(1.1%)	2	10	(2.2%)	12	2	(0.8%)	2	11	(1.5%)	13
Retinal oedema	2	(1.1%)	2	25	(5.4%)	28	2	(0.8%)	2	32	(4.3%)	35
0-7 Days	0		0	17	(3.7%)	19	0		0	19	(2.6%)	21
8-EOS	2	(1.1%)	2	8	(1.7%)	9	2	(0.8%)	2	13	(1.8%)	14
Macular oedema	3	(1.6%)	4	19	(4.1%)	19	10	(4.0%)	12	43	(5.8%)	47
0-7 Days	0		0	3	(0.6%)	3	0		0	4	(0.5%)	4
8-EOS	3	(1.6%)	4	16	(3.4%)	16	10	(4.0%)	12	39	(5.3%)	43
Anterior chamber cell	5	(2.7%)	5	17	(3.7%)	18	12	(4.9%)	13	57	(7.7%)	66
0-7 Days	1	(0.5%)	1	12	(2.6%)	12	3	(1.2%)	3	25	(3.4%)	26
8-EOS	4	(2.1%)	4	5	(1.1%)	6	9	(3.6%)	10	32	(4.3%)	40
Photophobia	0		0	17	(3.7%)	17	0		0	25	(3.4%)	25
0-7 Days	0		0	15	(3.2%)	15	0		0	22	(3.0%)	22
8-EOS	0		0	2	(0.4%)	2	0		0	3	(0.4%)	3

Preferred Term	Pivotal Placebo-Controlled Studies						All Studies Combined					
	Placebo N=187			Ocricplasmin 125µg N=465			Control N=247			Ocricplasmin Any Dose N=741		
	n	%	E	n	%	E	n	%	E	n	%	E
Ocular discomfort	2	(1.1%)	2	13	(2.8%)	13	4	(1.6%)	4	17	(2.3%)	17
0-7 Days	2	(1.1%)	2	8	(1.7%)	8	2	(0.8%)	2	11	(1.5%)	11
8-EOS	0		0	5	(1.1%)	5	2	(0.8%)	2	6	(0.8%)	6
Vitreous detachment	2	(1.1%)	2	12	(2.6%)	13	2	(0.8%)	2	13	(1.8%)	14
0-7 Days	0		0	7	(1.5%)	7	0		0	8	(1.1%)	8
8-EOS	2	(1.1%)	2	5	(1.1%)	6	2	(0.8%)	2	5	(0.7%)	6
Iritis	0		0	12	(2.6%)	13	0		0	12	(1.6%)	13
0-7 Days	0		0	9	(1.9%)	9	0		0	9	(1.2%)	9
8-EOS	0		0	3	(0.6%)	4	0		0	3	(0.4%)	4
Dry eye	2	(1.1%)	2	11	(2.4%)	11	2	(0.8%)	2	14	(1.9%)	14
0-7 Days	1	(0.5%)	1	4	(0.9%)	4	1	(0.4%)	1	5	(0.7%)	5
8-EOS	1	(0.5%)	1	7	(1.5%)	7	1	(0.4%)	1	9	(1.2%)	9
Metamorphopsia	1	(0.5%)	1	10	(2.2%)	10	1	(0.4%)	1	14	(1.9%)	14
0-7 Days	0		0	7	(1.5%)	7	0		0	8	(1.1%)	8
8-EOS	1	(0.5%)	1	3	(0.6%)	3	1	(0.4%)	1	6	(0.8%)	6
Retinal degeneration	1	(0.5%)	1	8	(1.7%)	8	1	(0.4%)	1	11	(1.5%)	11
0-7 Days	0		0	0		0	0		0	0		0
8-EOS	1	(0.5%)	1	8	(1.7%)	8	1	(0.4%)	1	11	(1.5%)	11
Eyelid oedema	1	(0.5%)	1	7	(1.5%)	7	8	(3.2%)	8	22	(3.0%)	24
0-7 Days	0		0	3	(0.6%)	3	1	(0.4%)	1	9	(1.2%)	9
8-EOS	1	(0.5%)	1	4	(0.9%)	4	7	(2.8%)	7	13	(1.8%)	15
Retinal pigment epitheliopathy	0		0	7	(1.5%)	7	4	(1.6%)	4	24	(3.2%)	24
0-7 Days	0		0	0		0	0		0	0		0
8-EOS	0		0	7	(1.5%)	7	4	(1.6%)	4	24	(3.2%)	24
Macular degeneration	1	(0.5%)	1	6	(1.3%)	6	1	(0.4%)	1	13	(1.8%)	14
0-7 Days	0		0	0		0	0		0	0		0
8-EOS	1	(0.5%)	1	6	(1.3%)	6	1	(0.4%)	1	13	(1.8%)	14
Miosis	0		0	5	(1.1%)	5	0		0	5	(0.7%)	5
0-7 Days	0		0	5	(1.1%)	5	0		0	5	(0.7%)	5
8-EOS	0		0	0		0	0		0	0		0

Preferred Term	Pivotal Placebo-Controlled Studies						All Studies Combined					
	Placebo N=187			Ocricplasmin 125µg N=465			Control N=247			Ocricplasmin Any Dose N=741		
	n	%	E	n	%	E	n	%	E	n	%	E
Scotoma	0		0	5	(1.1%)	5	0		0	5	(0.7%)	5
0-7 Days	0		0	2	(0.4%)	2	0		0	2	(0.3%)	2
8-EOS	0		0	3	(0.6%)	3	0		0	3	(0.4%)	3
Corneal abrasion	0		0	5	(1.1%)	5	1	(0.4%)	1	7	(0.9%)	7
0-7 Days	0		0	4	(0.9%)	4	0		0	6	(0.8%)	6
8-EOS	0		0	1	(0.2%)	1	1	(0.4%)	1	1	(0.1%)	1
Ocular hyperaemia	1	(0.5%)	1	4	(0.9%)	4	1	(0.4%)	1	14	(1.9%)	18
0-7 Days	1	(0.5%)	1	3	(0.6%)	3	1	(0.4%)	1	9	(1.2%)	9
8-EOS	0		0	1	(0.2%)	1	0		0	5	(0.7%)	9
Conjunctival irritation	0		0	4	(0.9%)	4	0		0	4	(0.5%)	4
0-7 Days	0		0	3	(0.6%)	3	0		0	3	(0.4%)	3
8-EOS	0		0	1	(0.2%)	1	0		0	1	(0.1%)	1
Diplopia	0		0	4	(0.9%)	4	0		0	4	(0.5%)	4
0-7 Days	0		0	0		0	0		0	0		0
8-EOS	0		0	4	(0.9%)	4	0		0	4	(0.5%)	4
Visual field defect	1	(0.5%)	1	3	(0.6%)	3	1	(0.4%)	1	4	(0.5%)	4
0-7 Days	0		0	2	(0.4%)	2	0		0	2	(0.3%)	2
8-EOS	1	(0.5%)	1	1	(0.2%)	1	1	(0.4%)	1	2	(0.3%)	2
Pupils unequal	0		0	3	(0.6%)	3	0		0	3	(0.4%)	3
0-7 Days	0		0	2	(0.4%)	2	0		0	2	(0.3%)	2
8-EOS	0		0	1	(0.2%)	1	0		0	1	(0.1%)	1

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

Reference: [Table 2.4.1.2](#), [Table 2.4.3.2](#)

Reviewer's Comments:

The majority of adverse events occurred during the first 7 days after ocular injection. Many of the adverse events occurring at a higher rate during the first 7 days are those commonly

associated with intraocular injections such as floaters, eye pain, blurred vision, iritis photophobia and ocular discomfort. Macular edema appears to be a later complication associated with injection of ocriplasmin. In the phase 3 trial this adverse events occurred 6 times the rate ≥ 8 days after surgery compared to ≤ 7 days after surgery.

7.5.3 Drug-Demographic Interactions

The following demographic and disease interactions were analyzed: gender (female vs. male); age (<65 years vs. ≥ 65 years; <75 years vs. ≥ 75 years); BMI (<25 kg/m² vs. ≥ 25 kg/m²); lens status at baseline (phakic vs. pseudophakic); baseline DR status (DR present vs. no DR present); baseline FTMH status (FTMH present vs. no FTMH present) and baseline ERM status (ERM present vs. no ERM present).

Subgroup Analysis by Gender (Safety Set)

Category / Preferred Term	Male		Female		Female / Male ARR ^a	Female / Male RR ^b
	Placebo (N=73) n %	Ocriplasmin 125µg (N=150) n %	Placebo (N=114) n %	Ocriplasmin 125µg (N=315) n %		
Vision alteration	4 (5.5%)	23 (15.3%)	10 (8.8%)	71 (22.5%)	1.4	0.9
Retinal / macular oedema	2 (2.7%)	11 (7.3%)	3 (2.6%)	33 (10.5%)	1.7	1.5
Intraocular inflammation	1 (1.4%)	10 (6.7%)	6 (5.3%)	23 (7.3%)	0.4	0.3
Eye pain ^c	4 (5.5%)	15 (10.0%)	9 (7.9%)	59 (18.7%)	2.4	1.3
Vitreous floaters	3 (4.1%)	17 (11.3%)	11 (9.6%)	61 (19.4%)	1.4	0.7
Photopsia	1 (1.4%)	7 (4.7%)	4 (3.5%)	48 (15.2%)	3.5	1.3

^a Attributable Risk Ratio

^b Relative Risk

^c Includes the preferred terms Eye pain and Ocular discomfort

The rate of vision alterations, vitreous floaters, photopsia and eye pain were numerically higher in females than males in both treatment groups.

Subgroup Analysis by Age (<65, ≥ 65) (Safety Set)

Category / Preferred Term	<65 years		≥ 65 years		≥ 65 / <65 ARR ^a	≥ 65 / <65 RR ^b
	Placebo (N=42)	Ocriplasmin 125µg (N=81)	Placebo (N=145)	Ocriplasmin 125µg (N=384)		
	n %	n %	n %	n %		
Vision alteration	4 (9.5%)	22 (27.2%)	10 (6.9%)	72 (18.8%)	0.7	1.0
Retinal / macular oedema	0 (0.0%)	12 (14.8%)	5 (3.4%)	32 (8.3%)	0.3	Undefined
Intraocular inflammation	2 (4.8%)	13 (16.0%)	5 (3.4%)	20 (5.2%)	0.2	0.5
Eye pain ^c	6 (14.3%)	14 (17.3%)	7 (4.8%)	60 (15.6%)	3.6	2.7
Vitreous floaters	2 (4.8%)	18 (22.2%)	12 (8.3%)	60 (15.6%)	0.4	0.4
Photopsia	1 (2.4%)	17 (21.0%)	4 (2.8%)	38 (9.9%)	0.4	0.4

^a Attributable Risk Ratio

^b Relative Risk

^c Includes the preferred terms Eye pain and Ocular discomfort.

Subgroup Analysis by Age (<75, ≥ 75) (Safety Set)

Category / Preferred Term	<75 years		≥ 75 years		≥ 75 / <75 ARR ^a	≥ 75 / <75 RR ^b
	Placebo (N=114)	Ocriplasmin 125µg (N=273)	Placebo (N=73)	Ocriplasmin 125µg (N=192)		
	n %	n %	n %	n %		
Vision alteration	13 (11.4%)	67 (24.5%)	1 (1.4%)	27 (14.1%)	1.0	4.7
Retinal / macular oedema	4 (3.5%)	33 (12.1%)	1 (1.4%)	11 (5.7%)	0.5	1.2
Intraocular inflammation	6 (5.3%)	23 (8.4%)	1 (1.4%)	10 (5.2%)	1.2	2.3
Eye pain ^c	13 (11.4%)	50 (18.3%)	0 (0.0%)	24 (12.5%)	1.8	Undefined
Vitreous floaters	8 (7.0%)	53 (19.4%)	6 (8.2%)	25 (13.0%)	0.4	0.6
Photopsia	3 (2.6%)	43 (15.8%)	2 (2.7%)	12 (6.3%)	0.3	0.4

^a Attributable Risk Ratio

^b Relative Risk

^c Includes the preferred terms Eye pain and Ocular discomfort.

The rate of vision alteration, retinal/macular edema, intraocular inflammation, eye pain, vitreous floaters and photopsia were numerically higher in younger (<65 years) patients treated with ocriplasmin than older (≥ 65 years) patients treated with ocriplasmin or placebo patients of each age group. Similar findings were observed for subgroup analyses by age <75, ≥ 75 years.

Subgroup Analysis by Race (Safety Set)

Category / Preferred Term	Caucasian		Non-Caucasians		Caucasian / Non- Caucasian ARR ^a	Caucasian / Non- Caucasian RR ^b
	Placebo (N=173)	Ocriplasmin 125µg (N=429)	Placebo (N=14)	Ocriplasmin 125µg (N=36)		
	n %	n %	n %	n %		
Vision alteration	12 (6.9%)	88 (20.5%)	2 (14.3%)	6 (16.7%)	5.7	2.5
Retinal / macular oedema	5 (2.9%)	42 (9.8%)	0 (0.0%)	2 (5.6%)	1.2	Undefined
Intraocular inflammation	7 (4.0%)	29 (6.8%)	0 (0.0%)	4 (11.1%)	0.3	Undefined
Eye pain ^c	13 (7.5%)	67 (15.6%)	0 (0.0%)	7 (19.4%)	0.4	Undefined
Vitreous floaters	12 (6.9%)	73 (17.0%)	2 (14.3%)	5 (13.9%)	-25.2	2.5
Photopsia	4 (2.3%)	50 (11.7%)	1 (7.1%)	5 (13.9%)	1.4	2.6

^a Attributable Risk Ratio

^b Relative Risk

^c Includes the preferred terms Eye pain and Ocular discomfort.

Due to the small sample size of non-Caucasians, no clear effect of the variable race on the incidence of AEs was observed.

Subgroup Analysis by BMI (Safety Set)

Category / Preferred Term	<25 kg/m ²		≥ 25 kg/m ²		≥ 25 / <25 ARR ^a	≥ 25 / <25 RR ^b
	Placebo (N=69)	Ocriplasmin 125µg (N=148)	Placebo (N=118)	Ocriplasmin 125µg (N=314)		
	n %	n %	n %	n %		
Vision alteration	4 (5.8%)	33 (22.3%)	10 (8.5%)	61 (19.4%)	0.7	0.6
Retinal / macular oedema	1 (1.4%)	18 (12.2%)	4 (3.4%)	26 (8.3%)	0.5	0.3
Intraocular inflammation	2 (2.9%)	13 (8.8%)	5 (4.2%)	19 (6.1%)	0.3	0.5
Eye pain ^c	4 (5.8%)	25 (16.9%)	9 (7.6%)	49 (15.6%)	0.7	0.7
Vitreous floaters	3 (4.3%)	24 (16.2%)	11 (9.3%)	54 (17.2%)	0.7	0.5
Photopsia	2 (2.9%)	19 (12.8%)	3 (2.5%)	36 (11.5%)	0.9	1.0

^a Attributable Risk Ratio

^b Relative Risk

^c Includes the preferred terms Eye pain and Ocular discomfort.

No consistent trends for effect of BMI were observed.

Drug-Disease Interactions

No formal studies have been conducted with ocriplasmin in patients with renal or hepatic impairment.

Subgroup Analysis by Lens Status at Baseline (Safety Set)

Category / Preferred Term	Phakia		Pseudophakia		Phakia / Pseudophakia ARR ^a	Phakia / Pseudophakia RR ^b
	Placebo (N=134)	Ocriplasmin 125µg (N=293)	Placebo (N=53)	Ocriplasmin 125µg (N=172)		
	n %	n %	n %	n %		
Vision alteration	11 (8.2%)	67 (22.9%)	3 (5.7%)	27 (15.7%)	1.5	1.0
Retinal / macular oedema	4 (3.0%)	31 (10.6%)	1 (1.9%)	13 (7.6%)	1.3	0.9
Intraocular inflammation	6 (4.5%)	21 (7.2%)	1 (1.9%)	12 (7.0%)	0.5	0.4
Eye pain ^c	12 (9.0%)	44 (15.0%)	1 (1.9%)	30 (17.4%)	0.4	0.2
Vitreous floaters	8 (6.0%)	55 (18.8%)	6 (11.3%)	23 (13.4%)	6.1	2.6
Photopsia	3 (2.2%)	40 (13.7%)	2 (3.8%)	15 (8.7%)	2.3	2.7

^a Attributable Risk Ratio

^b Relative Risk

^c Includes the preferred terms Eye pain and Ocular discomfort.

Phakic patients who received ocriplasmin were more likely to have vision alteration, retinal edema, vitreous floaters and photopsia than pseudophakic patients.

Subgroup Analysis by Diabetic Retinopathy Status at Baseline (Safety Set)

Category / Preferred Term	DR		No DR		No DR / DR ARR ^a	No DR / DR RR ^b
	Placebo (N=15)	Ocriplasmin 125µg (N=31)	Placebo (N=172)	Ocriplasmin 125µg (N=434)		
	n %	n %	n %	n %		
Vision alteration	0 (0.0%)	2 (6.5%)	14 (8.1%)	92 (21.2%)	2.0	Undefined
Retinal / macular oedema	1 (6.7%)	1 (3.2%)	4 (2.3%)	43 (9.9%)	-2.2	9.0
Intraocular inflammation	0 (0.0%)	2 (6.5%)	7 (4.1%)	31 (7.1%)	0.5	Undefined
Eye pain ^c	0 (0.0%)	6 (19.4%)	13 (7.6%)	68 (15.7%)	0.4	Undefined
Vitreous floaters	0 (0.0%)	2 (6.5%)	14 (8.1%)	76 (17.5%)	1.4	Undefined
Photopsia	0 (0.0%)	3 (9.7%)	5 (2.9%)	52 (12.0%)	0.9	Undefined

^a Attributable Risk Ratio

^b Relative Risk

^c Includes the preferred terms Eye pain and Ocular discomfort.

Due to the small sample size in some of the groups, no clear effect of the variable DR /No DR on the incidence of AEs was observed.

Subgroup Analysis by Macular Hole Status at Baseline (Safety Set)

Category / Preferred Term	FTMH		No FTMH		No FTMH / FTMH ARR ^a	No FTMH / FTMH RR ^b
	Placebo (N=47)	Ocriplasmin 125µg (N=105)	Placebo (N=133)	Ocriplasmin 125µg (N=332)		
	n %	n %	n %	n %		
Vision alteration	6 (12.8%)	35 (33.3%)	7 (5.3%)	56 (16.9%)	0.7	1.2
Retinal / macular oedema	2 (4.3%)	12 (11.4%)	3 (2.3%)	28 (8.4%)	0.9	1.4
Intraocular inflammation	6 (12.8%)	7 (6.7%)	1 (0.8%)	23 (6.9%)	-1.1	16.5
Eye pain ^c	7 (14.9%)	22 (21.0%)	6 (4.5%)	50 (15.1%)	1.7	2.4
Vitreous floaters	4 (8.5%)	21 (20.0%)	10 (7.5%)	54 (16.3%)	0.6	0.9
Photopsia	2 (4.3%)	16 (15.2%)	3 (2.3%)	35 (10.5%)	0.8	1.3

^a Attributable Risk Ratio

^b Relative Risk

^c Includes the preferred terms Eye pain and Ocular discomfort.

Vision alteration and eye pain occurred more frequently in patients with FTMH at baseline in both placebo and ocriplasmin groups. Intraocular inflammation occurred more frequently in placebo-treated patients with FTMH than without FTMH, while intraocular inflammation occurred at a similar frequency among ocriplasmin-treated patients with and without FTMH.

Subgroup Analysis by Epiretinal Membrane Status at Baseline (Safety Set)

Category / Preferred Term	ERM present		ERM absent		ERM absent / present ARR ^a	ERM absent / present RR ^b
	Placebo (N=67)	Ocriplasmin 125µg (N=183)	Placebo (N=119)	Ocriplasmin 125µg (N=267)		
	n %	n %	n %	n %		
Vision alteration	5 (7.5%)	28 (15.3%)	9 (7.6%)	63 (23.6%)	2.1	1.5
Retinal / macular oedema	1 (1.5%)	15 (8.2%)	4 (3.4%)	26 (9.7%)	0.9	0.5
Intraocular inflammation	0 (0.0%)	12 (6.6%)	7 (5.9%)	18 (6.7%)	0.1	Undefined
Eye pain ^c	3 (4.5%)	24 (13.1%)	9 (7.6%)	49 (18.4%)	1.3	0.8
Vitreous floaters	3 (4.5%)	24 (13.1%)	11 (9.2%)	50 (18.7%)	1.1	0.7
Photopsia	0 (0.0%)	11 (6.0%)	5 (4.2%)	42 (15.7%)	1.9	Undefined

^a Attributable Risk Ratio

^b Relative Risk

^c Includes the preferred terms Eye pain and Ocular discomfort.

Vision alteration, photopsia, vitreous floaters and eye pain occurred more frequently in ocriplasmin-treated patients without ERM than with ERM.

7.5.5 Drug-Drug Interactions

No formal interaction studies have been performed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies for ocriplasmin have not been conducted.

7.6.2 Human Reproduction and Pregnancy Data

There are no clinical data for the use of ocriplasmin in pregnant and breast-feeding women.
There are no data on the effect of ocriplasmin on fertility.

7.6.3 Pediatrics and Assessment of Effects on Growth

Studies in pediatric patients are currently ongoing. Completion of the studies will be requested in a PMR.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

One case of accidental overdose of 0.250 mg ocriplasmin (twice the recommended dose) has been reported. The patient had a decrease in BCVA of 21 letters (ETDRS score) from baseline that returned to within 9 letters of baseline during the study.

Non-clinical studies examining the abuse/dependence potential or the withdrawal/rebound effects of ocriplasmin.

In clinical studies there were no adverse events suggestive of withdrawal or rebound effects. Tolerance and withdrawal effects would not be considered to be an issue for single-use ocriplasmin.

7.7 Additional Submissions / Safety Issues

See separate M.O. 120 day Safety Update review.

8 Postmarket Experience

Ocriplasmin is not marketed in any country.

9 Appendices

9.1 Literature Review/References

Introduction

As the eye ages, the vitreous body undergoes a process of liquefaction and collapse.

Sonmez et al write, “In the normal aging eye, the vitreous body undergoes liquefaction (synchysis) resulting in liquid pockets within the vitreous gel.¹ This predisposes the gel to collapse with separation of the posterior vitreous cortex from the retinal surface (syneresis). Incomplete posterior detachment with persistent cortical attachment of the macula may lead to tractional retinal distortion and macular edema, with resultant vision loss, metamorphopsia, micropsia, and photopsia. Diagnosis of vitreomacular traction (VMT) by bio microscopy may be challenging, particularly when the area of vitreoretinal attachment is broad. Optical coherence tomography (OCT) better defines the vitreoretinal relationships in eyes with VMT and also documents concomitant epimacular membrane and macular edema. Although spontaneous vitreoretinal separation may yet occur, VMT tends to progress over time. Pars plana vitrectomy is effective in releasing the VMT with visual improvement in some cases.”

Autopsy studies have shown that the incidence of posterior vitreous detachment (PVD) is approximately 63% by the eighth decade of life.²

This posterior vitreous detachment usually occurs as an acute event with the vitreous completely separating from the posterior retina.³ In some cases, the posterior vitreous detachment is incomplete and vitreoretinal adhesions remain. These persistent adhesions are most clinically relevant when they occur in the macula (i.e., vitreomacular adhesions (VMA)) and/or over blood vessels. Thus, VMA results from incomplete posterior vitreous separation which results in persistent anterior-posterior traction on the macula.

Vitreoretinal traction (VMT) at the macula has been associated with cystoid macular edema which causes symptoms of decreased visual acuity (VA), metamorphopsia and photopsia. Patients usually present with varying visual complaints. Patients’ symptoms may remain stable

1 Sonmez, K et al. Vitreomacular traction syndrome. *Retina* 2008; 28(9):1207-1214.

2 Uchino E, Uemura A. Initial Stages of Posterior Vitreous Detachment in healthy eyes of Older Persons Evaluated by Optical Coherence Tomography. *Arch Ophthalmol* 2001;119:1475-1479.

3 Hikichi T, Yoshida A. Course of Vitreomacular Traction Syndrome. *Am J Ophthalmol* 1995;119:55-61.

with some patients eventually having the VMA spontaneously detach. A subgroup of patients will have worsening traction and deteriorating visual acuity. 4

Natural History

The natural history of vitreomacular traction is not well documented in the literature despite being first recognized by Reese in 1967. ⁵ Four researchers who have studied this natural history have used various methods for observing the retinal changes that occur. Hickichi *et.al.* used biomicroscopy with a 58.6 diopter lens, Larsson used OCT-2 images and Odrobina *et.al.* used high-resolution spectral-domain OCT (SOCT). Recently, with the advent of researchers investigating the use of enzymatic vitreolysis, Stalmans *et. al.* used OCT images to study the natural course of VMA compared to intravitreal microplasmin injections. In addition to reporting on the anatomic/morphologic appearance of the vitreous and retina, the authors also comment on the patients visual acuity changes over the period of observation.

Hikichi *et.al.* retrospectively studied patients to determine the natural history of vitreomacular traction. In this study 53 eyes with symptomatic traction were enrolled and had a mean follow up of 60 months. The results from this paper are:

- 43/53 (81%) of eyes had cystoid changes at baseline
29/43 (67%) had cystoid changes that persisted during follow-up
- 34/53 (64%) of subjects had visual acuity decreased by ≥ 2 Snellen lines from baseline
- 1/53 (<1%) developed a macular hole during follow-up
- 6/53 (11%) developed complete posterior vitreous detachment (all 6 had resolution of cystoid changes)
- None of the 6 eyes that had complete PVT resolution had decrease in visual acuity during the follow up; whereas 34/47 (72%) of eyes with persistent vitreous traction had decrease in vision (see Figure 1)
- In 6/6 eyes where vitreous traction on the macula was released, cystoid changes resolved as noted above (although degenerative sequelae of cystoid macular degeneration remained in 4 eyes. Of the remaining 47 eyes with persistent vitreous traction, 42/47 (89%) had cystoid changes on final examination,
- The number of eyes with resolved cystoid changes or stable visual acuity was significantly higher when complete vitreomacular separation occurred (6/6) than when it did not with resolved cystoid changes in (3/37 [8%]) and stable VA in 13/47 [28%]).

4 Hikichi T, Yoshida A. Course of Vitreomacular Traction Syndrome. *Am J Ophthalmol* 1995;119:55-61.

5 Reese A, Jones I. Macular Changes Secondary to Vitreous Traction. *Am J Ophthalmol* 1997;51:544-9.

- Conclusion: most symptomatic eyes with vitreomacular traction syndrome underwent a further decrease in visual acuity. Complete vitreomacular separation, which occurs infrequently in eyes with the disorder, allows resolution of cystoid changes and improvement in visual acuity.

Larsson⁶ used optical coherence tomography (OCT) to evaluate the macula before and after vitrectomy in 11 patients with VMT. While this study was designed to evaluate patients undergoing surgical intervention, the authors waited 3 months after diagnosis before performing surgery to evaluate the natural history of the disease. In this study, 11 eyes were diagnosed with VMT using OCT, and found to have traction and increased macular thickness. The mean duration of visual deterioration for these patients was 5 months (2-12 months). The patients were told there was a slight chance their condition would resolve spontaneously and given the option for immediate vitrectomy or waiting 12 weeks. All chose to wait the 12 weeks. During the 12 weeks (3 months) before vitrectomy was performed, none of the patients had an improvement in visual acuity or decrease in retinal thickness, in other words, there was no spontaneous improvement in these 11 patients. The results after vitrectomy was performed are summarized in the section below.

Odrobina *et.al.*⁷ conducted a retrospective observational study of idiopathic symptomatic VMT in 19 patients using spectral-domain (S)OCT to estimate the natural course of vitreomacular traction (VMT) disorder. The average observational period was 8 months (\pm 4.4 months). Patients who had decreased visual acuity or metamorphopsia and at least two follow up visits were included in the study

- Mean baseline VA was 0.4 ± 0.3 which improved to a mean final VA was 0.3 ± 0.32
 - The article does not break down VA on follow up for the 9 patients who had spontaneous resolution vs. the 10 patients who had persistent VMT
- 9/19 (47%) had complete resolution of VMA (total vitreous detachment), in these eyes there were no epiretinal membrane (ERM) and horizontal vitreous surface adhesion was 180 ± 84 microns
- In 10/19 (53%) of eyes with persistent VMT the mean maximal horizontal vitreous surface adhesion was 600 ± 385 microns, and 6 of these had ERM. In one of these ERM developed during follow up
- 6/19 (32%) had complete resolution of intraretinal cystoid spaces
- 2 eyes with macular holes at baseline spontaneously closed
- 2/19 (10%) eyes developed macular holes during the observational period
- In 3 eyes, macular morphology and vitreous adhesion did not change.

6 Larsson J. Vitrectomy in Vitreomacular Traction Syndrome Evaluated by Ocular Coherence Tomography (OCT) Retinal Mapping. *Acta Ophthalmol Scand* 2004;82:691-694.

7 Odrobina D, Michalewska Z. Long Term Evaluation of Vitreomacular Traction Disorder in Spectral Domain Optical Coherence Tomography. *Retina* 2011;31:324-331.

- The authors noted that eyes with less surface adhesion and no ERM resolved spontaneously, and commented that eyes with higher vitreous surface adhesion or coexisting ERM should perhaps have vitrectomy.
- The authors also comments that they had less ERM in their trial (26%) compared to other reports with 50%-83%, and the spontaneous resolution may be higher when there is less ERM.

Stalmans *et.al.*⁸ conducted a prospective trial in 60 patients comparing sham injection (natural history) to enzymatic vitreolysis with microplasmin. Twelve patients were enrolled in the sham group and followed for 180 days. Enrolled patients had VMA on OCT with macular thickening. In following the natural history of the disease in patients in the sham group it was noted that:

- 1/12 (8%) had spontaneous resolution of VMA at 1 month
- 3 sham patients had vitrectomy by day 180, the reason for vitrectomy was macular hole (MH)
- 2/9 (11.1%) had spontaneous resolution of VMA at 6 months
- 0/9 (0%) had increase in VA at month 6

In summary, based on this limited natural history data, it would appear that without treatment, 11% -47% of VMA will spontaneously resolve, 0%-10% of patients may be at risk for developing macular holes, and the incidence of decrease in macular edema is 0%-32%. In patients with VMA, 72% (34/47) of eyes with persistent vitreous traction had decrease in vision, while patients who had spontaneous PVT resolution did not have decline in vision.

Current Treatment – Patient Outcomes

The current standard of treatment for patients who present with VMT is “watchful waiting” since some cases may resolve when the posterior detachment completes and since the only current treatment is surgical which carries risks of retinal breaks, detachments and glaucoma among others.⁹ Surgery is currently indicated if there is progression in vitreous traction as noted on OCT and if vision decreases to 20/60 or worse.¹⁰

Four surgical series by Smiddy, Mac Donald, Koerner and Melberg have evaluated the effect of surgically relieving the VMA on visual function in 95 eyes.

8 Stalmans P, Delaey C. Intravitreal Injection of Microplasmin for Treatment of Vitreomacular Adhesion. *Retina* 2010;30:1122-1127

9 Yanoff M, Duker J.(2009). Ophthalmology 3rd ed.) St. Louis, MO: Mosby.

Carpineto P, Antonio L. Diagnosing and Treating Vitreomacular Adhesion. *European Ophthalmic Review* 2011;5:69-73.

10 Yanoff M, Duker J.(2009). Ophthalmology 3rd ed.) St. Louis, MO: Mosby.

Carpineto P, Antonio L. Diagnosing and Treating Vitreomacular Adhesion. *European Ophthalmic Review* 2011;5:69-73.

Smiddy et al¹¹ performed pars plana vitrectomy in 16 patients with partial posterior vitreous detachment with persistent vitreomacular attachment (VMA). These patients had vitreomacular traction and decreased visual acuity, most often 20/200. Symptoms had been present for 1-12 months in duration. Postoperatively, 5 patients had unchanged visual acuity and 11 (69%) patients had an improvement in their visual acuity (see table). The postoperative visual acuity was within one Snellen line of the preoperative level in 6 eyes, two-three lines better in 6 eyes, four-seven lines better in 4 eyes. Cystic macular changes were seen in 12 eyes at entry, although the authors do not report on the follow-up findings.

MacDonald et al¹² reported on 20 consecutive eyes that underwent vitrectomy and posterior hyaloid-epiretinal membrane stripping for reduced vision caused by vitreomacular traction syndrome (VTS); the patients were followed for 6-36 months (median 13 months). All of these patients had symptoms of reduced or distorted vision. Release of vitreomacular traction resulted in improvement in vision of 2 or more lines in 15/20 (75%) patients and 8/20 patients obtained visual acuity of 20/50 or better. Sixteen patients had macular edema at entry; it persisted postoperatively in 3 patients.

Koerner et al¹³ operated on 50 patients with VTS; the indication was progressive deterioration in VA or symptoms of metamorphopsia or disturbance in binocular reading. Postoperatively visual acuity was improved in 60% of patients; and VA of 20/40 went from 18% of patients preoperatively to 49% postoperatively. Authors cite Gaudric et al and state that significantly poorer visual results are obtained for preoperative VA 20/200 or worse compared to ones above 20/200, suggesting release of VMA affecting visual acuity should not be delayed too long.

Melberg et al¹⁴ reported on 9 patients with symptomatic decrease in visual acuity and macular traction retinal detachment and VTS who had pars plana vitrectomy and retinal reattachment. Complete retinal reattachment was achieved in 7/9. VA was improved in 4, stable in 4 and worse in 1 eye.

In the above studies, the pre-op visual acuity in these patients was < 20/100 in 60-78%, and improved by at least two lines in 44-77% and had a final visual acuity of > 20/100 in 44-88% of cases.

In the Larsson study discussed above previously, patients underwent vitrectomy after a 3 month period of "watchful waiting". Six months after surgical release of the VMA, 10 of 11 patients

11 Smiddy W, Michels R. Vitrectomy for Macular Traction Caused by Incomplete Vitreous Separation. *Arch Ophthalmol* 1988;106:624-628.

12 McDonald H, Johnson R. Surgical Results in the Vitreomacular Traction Syndrome. *Ophthalmology* 1994;101:1397-1403.

13 Koerner F, Garweg J. Vitrectomy for Macular Pucker and Vitreomacular Traction syndrome. *Doc Ophthalmol*. 1999;97:449-458.

14 Melberg N, Williams D. Vitrectomy for Vitreomacular Traction syndrome with Macular Detachment. *Retina* 1995;15:192-197.

had an improvement of two or more lines in vision, the mean improvement in VA was 3.1 lines and central macular thickness decreased from 609 μ m to 243 μ m.

Manually dissecting the vitreous adhesion away from the macular surface allows the retina to return to its normal anatomical state so that vision can be restored. In the above studies, patients with symptomatic VMA manifested by decreased vision and metamorphopsia had pars plana vitrectomy performed, and visual improvement ranged from 44% (with retinal reattachment) to 75%.

In summary, from the natural history series, persistent VMA/PVT is associated with a decrease in VA in many of the patients, and when there is spontaneous resolution of the VMA, or when there is surgical release of the VMA, the VA tends to stabilize and/or improve in many (although not all) patients. This series of publication demonstrates that there is an association between the structural findings associated with VMA and the functional impact on the patients' visual acuity; many patients develop decrease in visual acuity along with metamorphopsia, etc., with VMA, while after spontaneous resolution or surgical vitrectomy, many patients have stabilization or improvement in vision. These findings suggest that in the absence of spontaneous resolution of PVT, either surgical or chemical (enzymatic) release of the VMA/PVT is likely to have clinical benefit on visual acuity in at least some patients.

Current Investigations of Associated Pathologies

There is growing evidence that supports the fact that abnormalities at the vitreoretinal interface may play a role in other ocular diseases such as age-related macular degeneration (AMD). Several studies have described the relationship between the posterior vitreous and macula in AMD and have suggested that VMA plays an important role in the development of exudative AMD (Sebag). Research groups have postulated that persistent attachment of the posterior vitreous cortex to the macula may be a risk factor for the development of exudative AMD due to traction inducing chronic low-grade inflammation, impairing oxygenation and/or exposing the macula to cytokines (e.g., VEGF).

Krebs *et. al.* conducted a prospective, observational case series of 163 eyes comparing patients with exudative AMD to those with non-exudative AMD and controls. The results showed that there was a higher incidence of persistent vitreomacular adhesions diagnosed by OCT in patients with exudative AMD compared with normal eyes and eyes with non-exudative AMD. VMA was present in 36% of patients with exudative AMD, 7% of those with non-exudative AMD and 10% of controls.

Lee *et.al.* (2008) retrospectively reviewed the OCT and fluorescein angiography (FA) images in 251 patients with unilateral AMD. VMA was present in 56 patients (22%). The findings from the study were that CNV was present in (44/53, 83%) of eyes with vitreomacular adhesion and only in (6/53, 11%) of eyes without vitreomacular adhesion. It was also noted that the location of VMA was located over the area of the CNV in all of the exudative eyes.

In addition, Lee *et. al* (2010) studied the AMD/VMA relationship in a study conducted to evaluate the effect of OCT documented VMA on the outcome of anti-VEGF treatment for exudative AMD. A total of 148 eyes of newly diagnosed exudative AMD patients were treated with anti VEGF treatment and followed for a minimum of 1 year. In this study the mean BCVA decreased over time in patients with VMA compared to those without traction. These authors postulate that chronic traction forces may antagonize the effect of anti-VEGF treatment for AMD. This would lend support to the theory that traction exposes the macula to cytokines such as VEGF as proposed by several authors.

Benefit of Restoring Retinal Anatomy

Persistent vitreomacular adhesions which occur due to incomplete posterior vitreous traction have been associated with cystoid macular edema, decreased visual acuity, metamorphopsia and photopsia. Recent studies have also suggested that VMA plays a significant role in other ocular diseases such as age-related macular degeneration. It is the mechanical and biochemical processes that occur at the vitreoretinal interface that have been implicated in the pathologies associated with VMA. The goal of treatment is to relieve the traction by manually dissecting the vitreous adhesion away from the macular surface thereby allowing the retina to return to its normal anatomical state so that vision can be restored. Studies have shown that relieving this traction results in decrease macular edema and increase in visual acuity. Some authors report that the improvement in vision is greater when the preoperative VA is above 20/200; suggesting that waiting for spontaneous resolution to occur may not be warranted if there is continuing decrease in visual acuity. In addition there is recent work that suggests that relieving this traction also may have additional benefits in diseases such as AMD.

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9.2 Labeling Recommendations

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

9.3 Advisory Committee Meeting

An Advisory Committee meeting was held for ocriplasmin on July 26 2012. A synopsis of the outcome of this meeting follows.

1) **VOTE:** Has substantial evidence been provided to demonstrate that ocriplasmin 125µg 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 125µg 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. Please see the transcript for details of the Committee discussion.*

2)

2) **VOTE:** Has substantial evidence been provided to demonstrate that ocriplasmin 125µg 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 125µg 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. Please see the transcript for details of the Committee discussion.*

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. Please see the transcript for details of the Committee discussion.*

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: *In summary, although the majority agreed that no additional studies are needed prior to approval, the committee suggested post-marketing studies to be conducted to further address the safety of ocriplasmin's effect on the retina, including the need for additional optical coherence tomography (OCT) data.*

Please see the transcript for details of the Committee discussion.

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. Please see the transcript for details of the Committee discussion.*

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*

All Adverse Drug Reactions (ADRs) were ocular events, which is consistent with the route of administration, rapid inactivation, and limited systemic bioavailability. Most ADRs were non-serious, mild in intensity, had an onset 0-7 days post-injection, resolved within 2-3 weeks and were not considered to be clinically significant. The majority of the ADRs were consistent with induction of posterior vitreous detachment (PVD), such as vitreous floaters and photopsia; or were due to inflammation/irritation resulting from the injection procedure and / or the drug.

Table 1 summarizes the ADRs from the pivotal placebo-controlled studies in at least 2% of patients treated with JETREA that occurred anytime post-injection, and the corresponding incidence of these ADRs with an onset 0-7 days post-injection.

Table 1: Adverse Drug Reactions Reported for at Least 2% of Patients Treated with JETREA (Cumulative Post-Injection) in Pivotal Placebo-Controlled Studies and the Corresponding Incidences of these ADRs with an Onset of 0-7 Days

	ADRs with Onset 0-7 Days Post-Injection		Cumulative Post-Injection ADRs	
Adverse Reactions	Placebo (n=187) Percentage	Ocriplasmin 0.125 mg (n=465) Percentage	Placebo (n=187) Percentage	Ocriplasmin 0.125 mg (n=465) Percentage
Vitreous floaters	2.7	12.9	7.5	16.8
Eye pain	3.2	10.5	5.9	13.1
Photopsia	1.1	10.1	2.7	11.8
Vision blurred	0.5	6.5	3.2	8.4
Visual acuity reduced	0	4.1	4.3	6.2
Visual impairment	0	3.2	1.1	5.4
Subretinal fluid	0	3.7	1.1	5.4
Macular edema	0	0.6	1.6	4.1
Photophobia	0	3.2	0	3.7
Anterior chamber cell	0.5	2.6	2.7	3.7
Ocular discomfort	1.1	1.7	1.1	2.8
Iritis	0	1.9	0	2.6
Vitreous detachment	0	1.5	1.1	2.6
Dry eye	0.5	0.9	1.1	2.4
Metamorphopsia	0	1.5	0.5	2.2

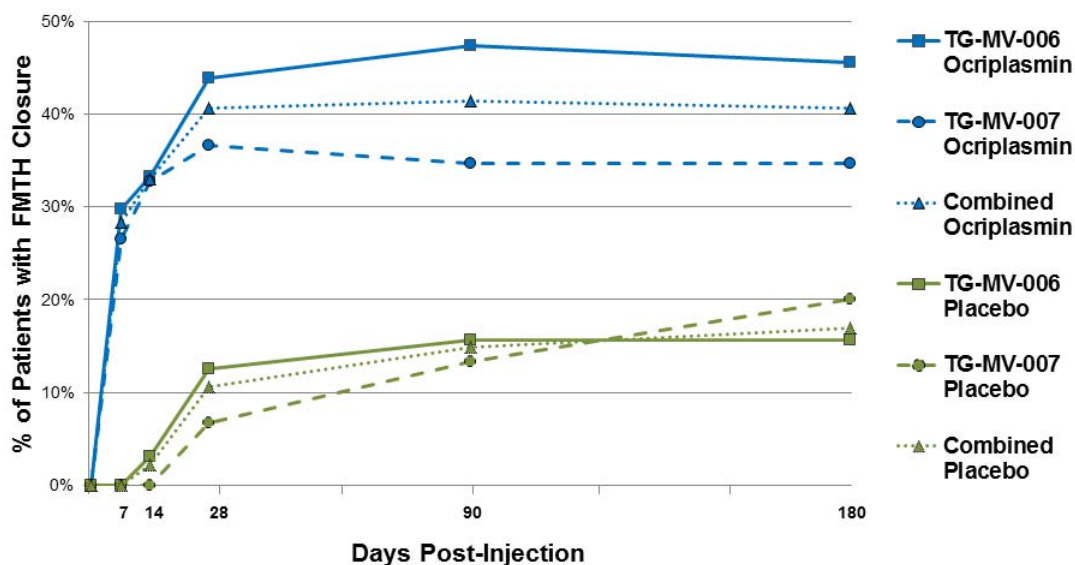
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In the integrated Full Analysis Set, 47 (25.0%) patients in the placebo group and 106 (22.8%) patients in the ocriplasmin group had full thickness macular hole (FTMH) at Baseline. Of these, the proportion of patients who achieved FTMH closure without need for vitrectomy by Day 28 was almost 4-fold higher in the ocriplasmin group (40.6%) compared with the placebo group (10.6%) ($p < 0.001$) (**Figure 8**). The majority (30/44, 68.2%) of patients in the ocriplasmin group who achieved FTMH closure without need for vitrectomy during the study did so by Day 7, compared with no patients in the placebo group. The effect was maintained over time, as 40.6% of ocriplasmin treated patients had FTMH closure without need for vitrectomy at Month 6, representing an absolute difference relative to placebo of 23.5% ($p = 0.004$).

Figure 8: Proportion of Patients with FTMH Closure Without Need for Vitrectomy by Study Visit (Integrated Studies: Full Analysis Set)



$p \leq 0.005$ in TG-MV-006, at all post-injection days, $p \leq 0.028$ in TG-MV-007, up to Day 28 (included), $p \leq 0.004$ in integrated data, at all post-injection days

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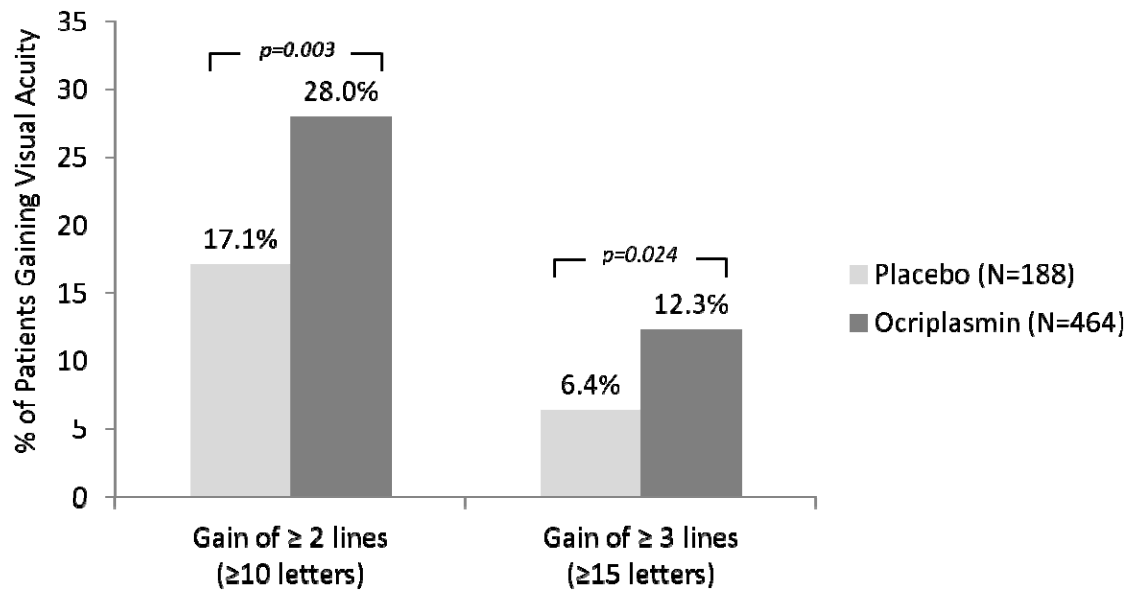
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JETREA treated patients were less likely to require vitrectomy by the end of the study (Month 6) compared with placebo treated patients (17.7% vs. 26.6%, respectively; $p=0.016$).

A higher percentage of JETREA treated patients achieved ≥ 2 or ≥ 3 line improvement in BCVA at Month 6 (28.0 and 12.3%, respectively) compared with patients treated with placebo (17.1% and 6.4%) ($p=0.003$ and $p=0.024$, respectively) (**Figure 9**).

Figure 9: Proportion of Patients Gaining ≥ 2 or ≥ 3 Lines in BCVA Overall (i.e. Irrespective of Vitrectomy) At Month 6 (Integrated Data from Pivotal Studies)



JETREA treated patients were also more likely to achieve these levels of BCVA improvement without needing vitrectomy during the study (**Figure 10**).

Figure 10 Proportion of Patients Gaining ≥ 2 or ≥ 3 Lines in BCVA Without Vitrectomy At Month 6 (Integrated Data from Pivotal Studies)

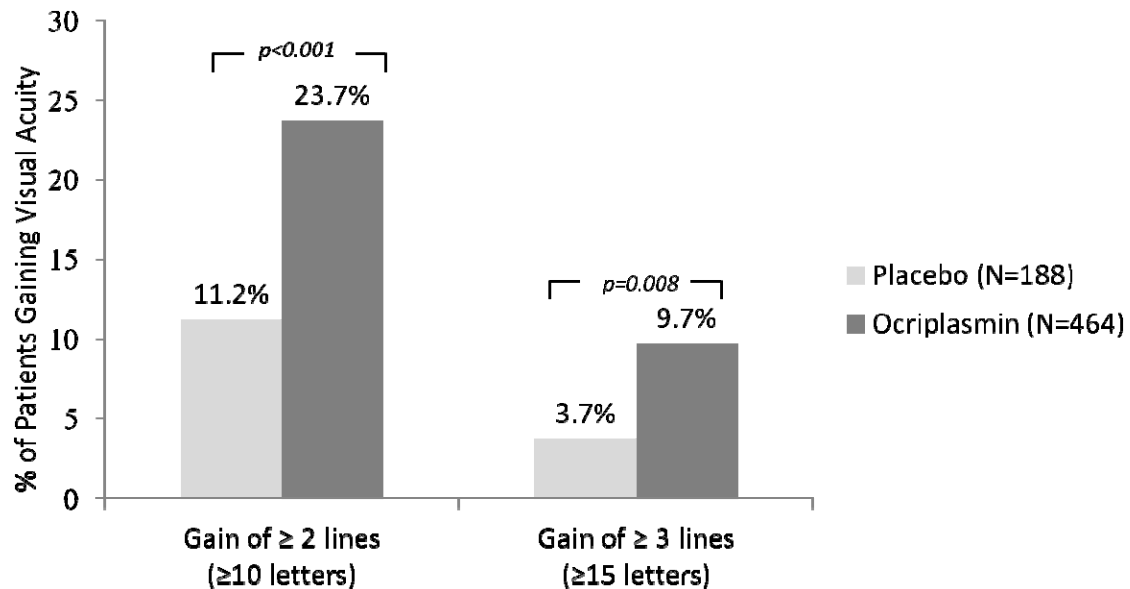


Figure 11 shows that in those patients presenting at baseline with a BCVA $< 20/50$ (*i.e.* < 65 letters), JETREA treated patients were more than 2-fold more likely to gain ≥ 3 lines (≥ 15 letters) in BCVA irrespective of vitrectomy (JETREA 25.1% vs. 11.4% placebo, $p=0.010$).

Figure 11 Results by Baseline BCVA: Proportion of Patients Who Gained ≥ 3 Lines in BCVA At Month 6 Overall (i.e. Irrespective of Vitrectomy) (Integrated Data from Pivotal Studies)

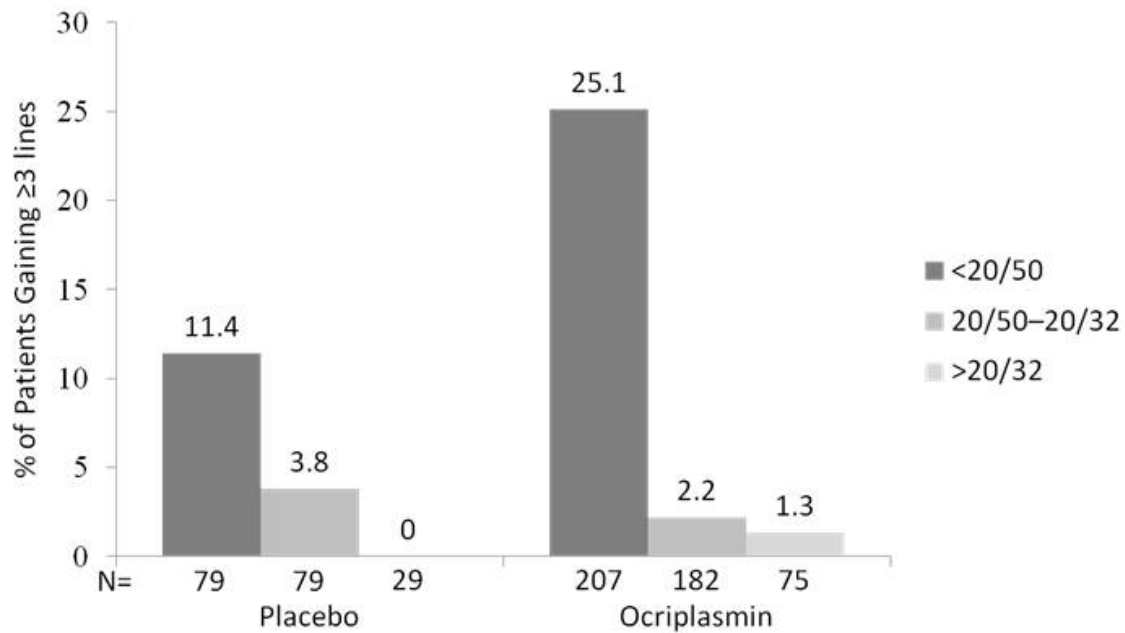
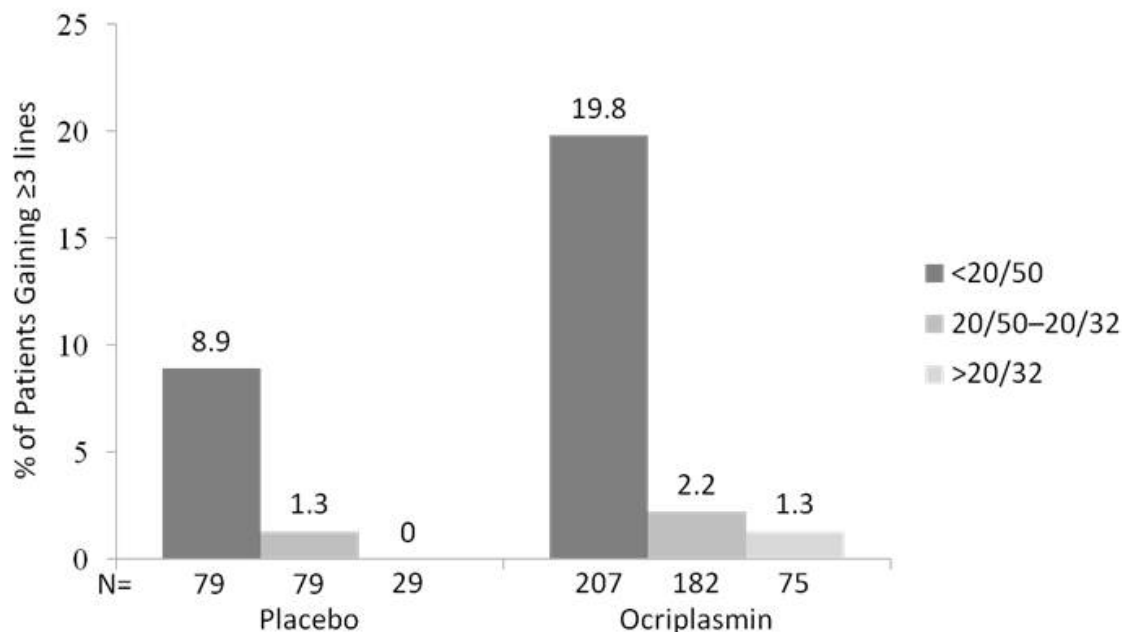


Figure 12 shows that in those patients presenting at baseline with a BCVA $< 20/50$ (i.e. < 65 letters), JETREA treated patients were more than 2-fold more likely to gain ≥ 3 lines (≥ 15 letters) in BCVA without vitrectomy (JETREA 19.8% vs. 8.9% placebo, $p=0.024$).

Figure 12 Results by Baseline BCVA: Proportion of Patients Who Gained ≥ 3 Lines in BCVA At Month 6 Without Vitrectomy (Integrated Data From Pivotal Studies)



At Month 6, 44.7% of the JETREA treated patients who achieved VMA resolution at Day 28 gained ≥ 2 lines in BCVA and 20.3% gained ≥ 3 lines in BCVA. Approximately 77% of patients treated with JETREA who achieved FTMH closure without vitrectomy at Month 6 gained ≥ 2 lines in BCVA at Month 6, and 51.2% gained ≥ 3 lines in BCVA at Month 6.

A larger proportion of patients without an epiretinal membrane (ERM) achieved VMA resolution, regardless of the treatment received. However, JETREA injection increased the proportion of patients who achieved VMA resolution compared with placebo injection in patients both with ERM (8.7% vs. 1.5%, JETREA vs. placebo, respectively; $p=0.046$) or without ERM (37.4% vs. 14.3%, JETREA vs. placebo, respectively; $p<0.001$).

JETREA had a positive effect on vision-related health status as measured with the National Eye Institute Visual Function Questionnaire 25 (VFQ 25). In the integrated analysis, improvements in each sub-scale score, as well as the composite score, were numerically better in the JETREA group compared with the placebo group. A notable difference in favor of JETREA was observed for improvement in the general vision sub-scale score (6.1 JETREA vs. 2.1 placebo, $p=0.024$).

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/s/

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09/26/2012

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