CLINICAL REVIEW

Application Type	(b) (4)
Application Number(s)	BLA 125-422
Priority or Standard	Standard
Submit Date(s)	12/18/2013
Received Date(s)	12/19/2013
PDUFA Goal Date	06/20/2014
Division / Office	OAP/DTOP
Reviewer Name(s)	Jennifer D. Harris, M.D.
Review Completion Date	03/12/2014
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

Template Version: March 6, 2009

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

(b) (4)

1.2 Risk Benefit Assessment

(b) (4)

Overall, there are no statistically significant differences in the rate of common adverse events or serious adverse events in the study eye between the ocriplasmin treated patients and placebo. The safety results of this trial are consistent with those noted in the original BLA review.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

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 (b) (4) 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 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

(b) (4)

2.3 Availability of Proposed Active Ingredient in the United States

Ocriplasmin is an approved product currently marketed 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

Jetrea (oncriplasmin intravitreal injection) 2.5 mg/mL was approved for the treatment of symptomatic vitreomacular adhesion (VMA) in October 2012. At the time of approval, the required pediatric assessment was deferred because the product was ready for approval for use in adults and the ongoing pediatric study (TG-MV-009) had not be completed. This supplement has been submitted to fulfill the pediatric assessment post marketing requirement.

2.6 Other Relevant Background Information

None.

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

The completed study in this submission was 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 investigator who participated in this pediatric clinical trial. There was one investigator who participated in the trial and he has no financial interests to disclose.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The study drug was provided in glass vials containing (b) (4) mL (b) (4) mg) ocriplasmin as a frozen liquid. The placebo had the same components and concentrations, except that no ocriplasmin was included.

Components	Concentration	Function
Ocriplasmin	2.5mg/mL	Active Ingredient
Mannitol	(b) (4)	
Water for injection		

4.2 Clinical Microbiology

N/A – this is not an anti-infective product.

4.3 Preclinical Pharmacology/Toxicology

See Pharm/Tox review for the original BLA 125-422.

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 for original BLA 125-422.

4.4.3 Pharmacokinetics

See biopharmaceutics review for original BLA 125-422.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study ID	Study Design	Route and Regimen	Total Enrollment
TG-MV-009	Phase 2, single center, randomized, placebo-controlled, double-masked study in pediatric subjects scheduled for vitrectomy	Single intravitreal injection of 175µg ocriplasmin or placebo in study eye 30 to 60 minutes before vitrectomy	24 eyes/22 subjects

The clinical studies contained in BLA 125-422 used 125µg of ocriplasmin in adults. This pediatric trial was conducted with 175 µg due to the stronger vitreous attachment in children and the shorter drug exposure time prior to vitrectomy.

5.2 Review Strategy

This supplement contains a single study in pediatric patients scheduled for vitrectomy. The review of this data will allow for pertinent pediatric safety (b) (4) *data to be added to the appropriate sections of the approved product label.*

5.3 Discussion of Individual Studies/Clinical Trials

Protocol: TG-MV-009

Title: The MIC (microplasmin in children) Trial

Study Objective: The objective of this trial was to evaluate the safety and preliminary efficacy of intravitreal ocriplasmin 175µg dose in pediatric subjects scheduled for vitrectomy.

Trial Design: Phase 2, single center, randomized, placebo-controlled, double-masked clinical study to investigate the safety and efficacy of a single intravitreal injection of 175µg ocriplasmin in pediatric subjects scheduled for vitrectomy. Ocriplasmin or placebo was injected in the mid-vitreous 30 to 60 minutes prior to the planned start of vitrectomy.

Sample Size: 24 eyes/22 subjects

Inclusion Criteria

1. Male or female infants or children 16 years of age or younger
2. Subject was a suitable candidate for conventional 2-port or 3-port pars plana vitrectomy
3. Subject with attached vitreous somewhere in posterior pole
4. Subject's parent or guardian was willing and able to comply with follow-up requirements
5. Subject's parent(s) signed the informed parental permission form and, in the case of school age children, the subject signed the assent form

Exclusion Criteria

1. Subject diagnosed with Stage 1, 2, 3, or 5 ROP at the time of surgery
2. Unclear media which precluded assessment of the posterior pole, such as a cataract or vitreal opacity
3. Active parental / guardian drug or alcohol use or dependence that, in the opinion of the site Investigator, would interfere with parent's or guardian's adherence to study requirements
4. Medical problems that made consistent follow-up over the treatment period uncertain
5. Subject participated in an investigational drug or device study in the prior 30 days
6. Subjects who were pregnant

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of eyes with total macular PVD* (to the vascular ridge in eyes with ROP) at the beginning of vitrectomy or after application of suction, as assessed by masked surgeon observation under the operating microscope. Eyes which had creation of an anatomical defect (i.e., retinal hole or retinal detachment) that resulted in decrease of vision or required intervention were counted as treatment failures for the primary endpoint.

* PVD Classification

- Grade 0: No PVD
- Grade 1: Partial PVD with attachment at the optic disc and elsewhere in the posterior pole
- Grade 2: Partial PVD with attachment at either the optic disc or elsewhere in the posterior pole
- Grade 3: Total PVD without disc attachment

Secondary Efficacy Endpoints

- Investigator assessment of vitreous liquefaction at the beginning of vitrectomy
- Immediate postoperative retinal re-attachment / macular re-attachment
- Presence of proliferative vitreoretinopathy on follow-up
- ROP** classification on follow-up (Day 28, 3, and 6 months)

**ROP Classification

- Stage 1:Demarcation line
- Stage 2: Ridge
- Stage 3: Extraretinal fibrovascular tissue
- Stage 4A:Extrafoveal partial retinal detachment
- Stage 4B: Foveal partial retinal detachment
- Stage 5: Total retinal detachment

Safety Endpoints

- Type and incidence of all adverse events
- Type and incidence of ophthalmic adverse events
- Intraocular pressure (IOP) and change in IOP from baseline
- Slit lamp examination findings
- Retinal examination
- Concomitant medication usage and other ocular interventions

Study Schedule

	Baseline	Injection / Operative Day	Post-- Injection Day 1	Post-Injection Day 7	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**	**1**	**7** *(±3d)*	**28** *(± 7d)*	**90** *(± 3w)*	**180** *(± 4w)*
Assessments							
Consent / Assent	X						
Demography, medical and ocular history	X						
Full ophthalmic exam [b, c]	X	X	X	X	X	X	X
Pregnancy test [d]	X						
B-scan Ultrasonography		X [f]					
Study drug / placebo injection		X [a]					
Vitrectomy		X					
Fundus Photography [c, e]	X						X
Fluorescein Angiogram [c, e]	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 ophthalmic exam included: vision where assessable, IOP (tonopen or applanation) where obtainable, slit lamp examination where obtainable and dilated fundus examination.
[c] At Baseline, full ophthalmic exam, and fundus photography / fluorescein angiography were performed in both eyes; at all other visits, these exams were performed only in the study eye(s).
[d] Urine pregnancy test was performed in female subjects of childbearing potential
[e] Fundus photography and fluorescein angiography were performed in both eyes at Baseline and repeated in the study eye at Visit 7.
[f] B-scan Ultrasonography was performed where obtainable prior to study drug injection and then repeated prior to start of vitrectomy
Abbreviations used – Intraocular Pressure (IOP), Adverse Event (AE), Serious Adverse Event (SAE), Day (d), Week (w), Baseline (BL)

Study Analysis Populations

	Placebo (N=8)	Ocriplasmin (N=16)	Total (N=24)
Safety Population [a]	8	16	24
Full Analysis Set [b]	8	16	24
Per-Protocol Set [c]	7	14	21

Reference: Table 14.1.1

Safety Set- all subjects who received treatment with study medication. Study eyes that received the incorrect treatment were to be analyzed based on treatment received. The Safety Set was the primary population for all safety analyses.

Full Analysis Set (FAS) - all randomized study eyes, which were analyzed according to treatment group randomized, regardless of treatment actually received. The FAS was the primary population for all analyses of baseline/demographic and efficacy data.

Per-Protocol Set (PPS) -FAS excluding study eyes and/or data that fell into the following categories and where the violation/deviation was deemed sufficiently serious to warrant exclusion from the analysis:

- Subjects violating inclusion/exclusion criteria
- Subjects (or visits) deviating from the protocol guidelines during the trial (e.g., incorrect timing of measurements, incorrect timing of subject visits)
- Study eyes that had total macular PVD pre-treatment.

Investigators

Site No.	Investigator Name	Sub-Investigator(s) Name	Hospital/Institution Name and Address
901	Antonio Capone, Jr., MD	(b) (6)	Associated Retinal Consultants, PC William Beaumont Medical Building, 3535 W. Thirteen Mile Road, Suite(s) 344 & 606, Royal Oak, MI 48073, United States of America (USA)

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7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety of ocriplasmin in adults patients was evaluated in original BLA 125-422. This supplement evaluated the safety in pediatric patients.

Study ID	Study Design	Route and Regimen	Total Enrollment
TG-MV-009	Phase 2, single center, randomized, placebo-controlled, double-masked study in pediatric subjects scheduled for vitrectomy	Single intravitreal injection of 175µg ocriplasmin or placebo in study eye 30 to 60 minutes before vitrectomy	24 eyes/22 subjects

7.1.2 Categorization of Adverse Events

MedDRA nomenclature was used to code adverse events.

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

N/A – (b) (4)

7.2 Adequacy of Safety Assessments

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

Twenty-four eyes of 22 pediatric patients were exposed to 175µg ocriplasmin for 30 to 60 minutes prior to vitrectomy.

7.2.2 Explorations for Dose Response

N/A – a single dose was evaluated in pediatric patients

7.2.3 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 intravitreously administered products (i.e., biomicroscopy, fundoscopy, 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
ocriplasmin	901023/ 901024	4 month	male	white	(b) (6)	Day 98 post injection	Shunt malfunction and encephalopathy

7.3.2 Nonfatal Serious Adverse Events

Subject	Treatment Group	SAE
901023/901024	Ocriplasmin	Zonular dehiscence
901016	Placebo	Shunt infection
901020	Placebo	Pneumonia, sleep apnea, hypoxia

7.3.3 Dropouts and/or Discontinuations

	Placebo (N=8)	Ocriplasmin (N=16)	Total (N=24)
Eyes Randomised	8	16	24
Completed Study	7	14	21
Discontinued from Study[a]	1	2	3
Reasons for Discontinuation			
Adverse Event	0	0	0
Protocol Violation	0	0	0
Investigator Decision	0	0	0
Withdrew Consent	0	0	0
Lost to Follow-Up	1	0	1
Death[a]	0	2	2
Other	0	0	0

Reference: Table 14.1.1

[a] One subject treated with ocriplasmin in both eyes (Subject 901023 / 901024) died due to non-ocular SAEs the Investigator considered to be unrelated to study drug. According to counting conventions, this individual subject contributed both observations in the ocriplasmin group.

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

System Organ Class Preferred Term Category	Placebo N=8		Ocriplasmin 175µg N=16	
Number of adverse events	**n**	**%**	**n**	**%**
Any event				
Any non-ocular event	4	50%	16	100%
Any ocular event	8	100%	15	93.8%

System Organ Class Preferred Term Category	Placebo N=8		Ocriplasmin 175µg N=16	
Study eye event	8	100%	15	93.8%
Non-study eye event	1	12.5%	4	25%
Ocular AEs[a]				
Eye pain	4	50%	12	75%
Conjunctival hemorrhage	4	50%	7	43.8%
Eyelid edema	5	62.5%	6	37.5%
Maculopathy	3	37.5%	6	37.5%
Anterior chamber cell	3	37.5%	5	31.3%
Anterior chamber flare	3	37.5%	5	31.3%
Conjunctival hyperemia	3	37.5%	3	18.8%
Vitreous hemorrhage	1	12.5%	4	25%
Retinal detachment	0	0	4	25%
Conjunctival edema	1	12.5%	2	12.5%
Corneal epithelium defect	2	25%	1	6.3%
Macular edema	1	12.5%	1	6.3%
Retinal disorder	0	0	3	18.8%
Retinal edema	1	12.5%	2	12.5%
Retinal pigment epitheliopathy	1	12.5%	1	12.5%
Blepharospasm	0	0	2	12.5%
Corneal disorder	1	12.5%	1	6.3%
Corneal edema	1	12.5%	1	6.3%
Cyclitic membrane	0	0	1	6.3%
Hypotony	0	0	2	12.5%
Ocular discomfort	1	12.5%	1	6.3%
Optic atrophy	0	0	2	12.5%
Optic nerve disorder	1	12.5%	1	6.3%
Photophobia	1	12.5%	1	6.3%
Retinal tear	0	0	2	12.5%
Angle closure glaucoma	0	0	1	6.3%
Anterior chamber fibrin	0	0	1	6.3%
Cataract subcapsular	0	0	1	6.3%
Chorioretinal disorder	1	12.5%	0	0
Chromatopsia	1	12.5%	0	0
Ciliary zonular dehiscence	0	0	1	6.3%
Conjunctivitis	0	0	1	6.3%
Corneal opacity	0	0	1	6.3%
Corneal thickening	1	12.5%	0	0
Eye irritation	0	0	1	6.3%
Foreign body sensation	0	0	1	6.3%

System Organ Class Preferred Term Category	Placebo N=8		Ocriplasmin 175µg N=16	
Glaucomatous optic disc atrophy	1	12.5%	0	0
Hyperemia	0	0	1	6.3%
Iris adhesions	0	0	1	6.3%
Iris bombe	0	0	1	6.3%
Iris neovascularization	0	0	1	6.3%
Lacrimal hemorrhage	0	0	1	6.3%
Lens dislocation	0	0	1	6.3%
Macular degeneration	0	0	1	6.3%
Macular hole	0	0	1	6.3%
Optic nerve sheath hemorrhage	0	0	1	6.3%
Pupillary disorder	0	0	1	6.3%
Retinal hemorrhage	0	0	1	6.3%
Retinopathy of prematurity	0	0	1	6.3%
Vision blurred	1	12.5%	0	0
Vitreous adhesions	0	0	1	6.3%
Vitreous disorder	0	0	1	6.3%
Vitreous floaters	0	0	1	6.3%
Infections and infestations				
Shunt infection	1	12.5%	1	6.3%
Sinusitis	0	0	2	12.5%
Upper respiratory tract infection	2	25%	0	0
Otitis media	0	0	1	6.3%
Pneumonia	1	12.5%	0	0
Staphylococcal infection	1	12.5%	0	0
Gastrointestinal disorders				
Constipation	1	12.5%	1	6.3%
Vomiting	0	0	2	12.5%
Nausea	0	0	1	6.3%
Injury, poisoning and procedural complications				
Foreign body in eye	0	0	3	18.8%
Optic nerve injury	0	0	1	6.3%
Retinal scar	0	0	1	6.3%
Investigations				
Intraocular pressure increased	3	37.5%	2	12.5%
Nervous system disorders				
Convulsion	0	0	2	12.5%
Encephalopathy	0	0	2	12.5%
Headache	0	0	2	12.5%

System Organ Class Preferred Term Category	Placebo N=8		Ocriplasmin 175µg N=16	
Respiratory, thoracic and mediastinal disorders				
Bronchopylmonary dysplasia	1	12.5%	1	6.3%
Asthma	0	0	1	6.3%
Dyspnea	1	12.5%	0	0
Hypoxia	1	12.5%	0	0
Sleep apnea	1	12.5%	0	0
General disorders and administration site conditions				
Device malfunction	0	0	2	12.5%
Skin and subcutaneous tissue disorders				
Rash maculo-papular	1	12.5%	1	6.3%
Immune system disorders				
Hypersensitivity	0	0	1	6.3%
Metabolism and nutrition disorders				
Failure to thrive	0	0	1	6.3%

Comment: *Overall, there are no statistically significant differences in the rate of common adverse events or serious adverse events in the study eye between the ocriplasmin treated patients and placebo. The safety results of this trial are consistent with those noted in the original BLA review.*

7.4.2 Laboratory Findings

N/A -the protocol did not require collection of clinical laboratory tests.

7.4.3 Vital Signs

N/A - the protocol did not require collection of vital signs.

7.4.4 Electrocardiograms (ECGs)

N/A -the protocol did not require collection of ECGs.

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.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A single injection of 175µg was used in the clinical trial; therefore, analysis of drug-dose relationship is not applicable.

7.5.2 Time Dependency for Adverse Events

A single injection of 175µg was used in the clinical trial and was removed within 30 to 60 minutes after administration. There was no time dependency of adverse events noted.

7.5.3 Drug-Demographic Interactions

No formal interaction studies have been performed.

7.5.4 Drug-Disease Interactions

No formal interaction studies have been performed.

7.5.5 Drug-Drug Interactions

No formal interaction studies have been performed.

7.6 Additional Safety Evaluations

N/A – no additional safety evaluations were conducted.

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

An assessment of effects on growth has not been conducted as part of this supplement.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no cases of overdose reported in this clinical trial. There were no adverse events suggestive of withdrawal or rebound effects. Tolerance and withdrawal effects would not be considered an issue for single-use ocriplasmin.

7.7 Additional Submissions / Safety Issues

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

8 Postmarket Experience

None.

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

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9.3 Advisory Committee Meeting

N/A

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/s/

JENNIFER D HARRIS
05/12/2014

WILLIAM M BOYD
05/12/2014