U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 125422
Supplement #:	25
Drug Name:	Jetrea™ (ocriplasmin)
Indication(s):	Treatment of symptomatic vitreomacular adhesion
Applicant:	ThromboGenics, Inc.
Date(s):	Submitted: 12/19/2013 PDUFA date: 06/20/2014
Review Priority:	Standard 6 Months for Pediatric Supplement
Biometrics Division:	DBIV
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Keywords: pediatric, total macular posterior vitreous detachment (PVD), vitrectomy

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1 EXECUTIVE SUMMARY

JETREA® (ocriplasmin) solution for intravitreal injection was approved on October 17, 2012 by FDA for the treatment of symptomatic vitreomacular adhesion (VMA) in adults. This supplement Biologics License Application (sBLA) includes the results from a pediatric study (TG-MV-009) for the safety and efficacy of ocriplasmin administered as an intravitreal injection in pediatric subjects scheduled for vitrectomy. This submission intends to fulfill the pediatric study request under the Pediatric Research Equity Act (PREA) (21 U.S.C.355c) as a postmarketing requirement. Furthermore, based on the clinical data, the applicant proposed revised labeling for JETREA®.

Study TG-MV-009 was a single center, randomized, vehicle-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.

Twenty-two (22) subjects participated in the study; 20 subjects were treated in one eye (13 subjects treated with ocriplasmin and 7 subjects treated with placebo), one subject had two eyes treated with ocriplasmin, and one subject had one eye treated with ocriplasmin and one eye treated with placebo. Therefore, a total of 24 eyes (16 ocriplasmin; 8 placebo) from 22 subjects were evaluated in the study. Each treated eye was randomized independently to a study treatment; and each treated eye was given a unique subject number regardless whether a subject had one eye or two eyes treated.

The primary efficacy endpoint was the proportion of eyes with total macular posterior vitreous detachment (PVD) (to the vascular ridge in eyes with Retinopathy of Prematurity [ROP]) at the beginning of vitrectomy or after application of suction during vitrectomy, as assessed by masked surgeon under operating microscope. The primary endpoint was evaluated using the Full Analysis Set (FAS) with missing data imputed with the last observation carried forward (LOCF) method. The FAS included all randomized study eye, and were analyzed according to the treatment group randomized.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Symptomatic vitreomacular adhesion (VMA) is a condition in which partial, posterior vitreous detachment (PVD) exists, wherein the remaining focal VMA leads to symptoms, with patients developing decreased visual acuity (VA), metamorphopsia, central visual field defect and / or complications. Focal VMA may result in macular hole (MH) formation and some forms of cystoid macular oedema. Additionally, focal VMA is associated with a worse prognosis in various conditions, including diabetic retinopathy (DR) and age related macular degeneration (AMD). Treatment option for symptomatic VMA before the approval of JETREA® (ocriplasmin) was eye surgery (i.e. vitrectomy), whereby any adhesions are manually dissected from the macular surface and the vitreous humor is aspirated from the eye.

Ocriplasmin is a recombinant human protein derived from the yeast *Pichia pastoris*. It is a truncated form of human plasmin, with retained protease activity. The applicant developed ocriplasmin as a potential pharmacologic agent that can facilitate the induction of a PVD, which may help avoiding surgical intervention of VMA. The original BLA125422 for ocriplasmin was approved by the Agency on October 17, 2012 for the treatment of symptomatic VMA in adults as an intravitreal injection.

2.1.2 History of Drug Development

In the approval letter for the original BLA, the Agency requested the applicant to assess the safety and effectiveness of the product for the claimed indication in pediatric patients under the Pediatric Research Equity Act (PREA) (21 U.S.C.355c) as a postmarketing requirement.

In accordance with the PREA request, the applicant conducted study TG-MV-009 to evaluate the safety and preliminary efficacy of intravitreal ocriplasmin 175µg dose in pediatric subjects scheduled for vitrectomy. The statistical reviewer was not aware of any discussion between the applicant and the Agency regarding the clinical trial design for this pediatric study.

2.1.3 Studies Reviewed

One single-center pediatric study (Study TG-MV-009) was submitted in this sBLA. Key information of this study is presented in the following table.

Table 1: Key Information for Study TG-MV-009

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
TG-MV-009	*Phase 2, single-center, randomized, double-masked, vehicle-controlled factorial design*	*Single intravitreal injection of 175 µg 30 to 60 minutes prior to the planned start of vitrectomy*	*Six (6) months post injection*	*Ocriplasmin: 16* *Vehicle: 8*	*Children 16 years of age or younger who were candidates for conventional 2-port or 3-port pars plana vitrectomy*[a]

[a] Pars plana vitrectomy is a general term for a group of operations accomplished in the deeper part of the eye, all of which involve removing some or all of the vitreous—the eye's clear internal jelly
Source: Statistical Reviewer's Summary

2.2 Data Sources

The data sources for this review mainly came from the applicant's study report for Study TG-MV-009. The study report is available at:
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The applicant submitted SAS datasets electronically; the datasets are available at:
\\cdsesub1\bla\eCTD_Submissions\STN125422\0051\m5\datasets\tg-mv-009\analyses\legacy\datasets

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the submitted data were in good quality with definition of each variable. Results of the primary efficacy endpoints can be reproduced by the statistical reviewer with minor data manipulation. The final statistical analysis plan (SAP) for this study was submitted.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study TG-MV-009 was a single center, randomized, vehicle-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.

Eligible pediatric subjects were randomized to receive a single intravitreal injection of 175 µg ocriplasmin or placebo in a 2:1 ratio. According to the applicant, if both eyes met eligibility criteria, each eye was randomized independently; however, both eyes could not be treated at the same time. For a subject who had both eyes treated, the applicant gave a unique subject number for each eye.

The applicant-defined key inclusion criteria for the study were: 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. Subjects who were diagnosed with Stage 1, 2, 3, or 5 ROP at the time of surgery were excluded; but subjects with Stage 4 ROP could be included.

Evaluation of safety and efficacy were performed at Baseline; Injection / Operative Day (within 2 weeks of Baseline or combined with Baseline); Post-Injection Day 1; Post-Injection Day 7; Post-Injection Day 28; Post-Injection Month 3; and Post-Injection Month 6. A schedule of assessments was presented in the following table. Specifically, grading of the posterior vitreous detachment (PVD) under the operating microscope by the masked surgeon was performed prior to study drug administration and prior to (before suction was applied) and after suction during vitrectomy. PVD is a condition of the eye in which the vitreous membrane separates from the retina. The PVD grades were defined by the applicant as follows:

- 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

The applicant stated that this study was performed primarily for safety reasons, but had a single primary efficacy endpoint of the proportion of eyes with total macular PVD (to the vascular ridge in eyes with ROP) at the beginning of vitrectomy (prior to suction) or after application of suction during vitrectomy, as assessed by masked surgeon observation under an operating microscope. According to the Case Report Form (CRF), besides grading of PVD, the surgeon also needed to report his/her judgment regarding the present or absent of total macular PVD. Therefore, subjects who had PVD grades of Grade 0, Grade 1, or Grade 2 might still be deemed as having total macular PVD assessing by the masked surgeon.

Secondary efficacy endpoints included vitreous liquefaction at the beginning of vitrectomy, immediate postoperative retinal re-attachment / macular re-attachment, presence of proliferative vitreoretinopathy on follow-up, and ROP classification during follow-up (Day 28, 3, and 6 months).

The safety endpoints included adverse events, ocular interventions, change in intraocular pressure (IOP) from baseline, and abnormalities from slit lamp examination findings and retinal examination.

Table 2: Schedule of Assessments

	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)
Source: Table 3 of applicant's Study TG-MV-003 report.

3.2.2 Statistical Methodologies

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 during vitrectomy, as assessed by masked surgeon observation under operating microscope. Eyes with total macular PVD at either the beginning of vitrectomy (prior to suction) or after suction were considered as successes on the endpoint. Eyes that had total macular PVD prior to study drug treatment were considered as failures on the primary efficacy analyses. In addition, all eyes

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.

The primary endpoint was evaluated using the Full Analysis Set (FAS) with missing data imputed using the last observation carried forward (LOCF) method. The FAS included all randomized study eye, and were analyzed according to the treatment group randomized. The number and percentage of eyes meeting the endpoint were tabulated by randomized treatment group, and the treatment groups were compared using Fisher's exact test. As part of sensitivity analyses, primary analyses were performed in the observed case (OC) and in the FAS using the worst case (WC) approach.

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3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Twenty-two (22) subjects participated in the study; 20 subjects were treated in one eye, and two (2) subjects were treated in both eyes. Therefore, a total of 24 eyes (16 ocrisplasmin; 8 placebo) were evaluated in the study. Each treated eye was randomized independently to a study treatment; and each treated eye was given a unique subject number regardless whether a subject had one eye or two eyes treated. For the two subjects who were treated in both eyes, the first subject was randomized to receive ocriplasmin in one eye and placebo in the other eye; the second subjects was randomized to receive ocriplasmin in both eyes.

One subject treated with ocriplasmin in both eyes (Subject 901023/901024) died due to non-ocular AEs the Investigator considered unrelated to study drug (ventriculoperitoneal shunt malfunction and encephalopathy). The onset for both of these AEs was Post-Injection Day 52; and death occurred on Post-Injection Day 98.

All randomized study eyes (N=24) were included in the safety population and the FAS. All study eyes were treated with the study drug to which they were randomized.

Table 3: Study TG-MV-009 Analysis Population

	Placebo (N=8)	Ocriplasmin (N=16)	Total (N=24)
Safety Population	8	16	24
Full Analysis Set	8	16	24

Source: Table 5 of Study TG-MV-009 report.

As presented in the following table, demographics and ocular baseline characteristics were generally consistent between the two treatment groups.

Table 4: Study TG-MV-009 Demographic and Baseline Characteristics

Characteristics	Placebo (N=8)	Ocriplasmin (N=16)	Total (N=24)
	n (%)	n (%)	n (%)
Gender			
Male	7	13	20
Female	1	3	4
Age			
Mean (Std)	8.0 (6.61)	6.1 (6.40)	6.8 (6.39)
Median	9.0	4.0	6.5
Min, Max	0, 16	0, 16	0, 16
Race			
White/Caucasian	5	13	18
Black/African American	2	1	3
Asian	0	1	1
Other	1	1	2
Hispanic Origin			
Yes	0	0	0
No	8	16	24
Estimated Gestational Age (weeks) at Birth			
Mean (Std)	33.0 (7.93)	33.5 (6.93)	33.3 (7.11)
Median	36.0	37.0	37.0
Min, Max	24, 40	23, 41	23, 41
Underlying Condition/reason for Vitrectomy			
ROP	1	4	5
ROP Stage 4A	0	1	1
ROP Stage 4B	1	3	4
Trauma	1	0	1
Other	6	12	18
Retinal Detachment	3	9	12
Vitreous haemorrhage	1	0	1
Angle closure glaucoma	1	0	1
Preretinal proliferation with contraction	1	0	1
Proliferative vitreoretinopathy	0	1	1
Retinal fold	0	1	1
Macular hole	0	1	1

Source: Table 6 of Study TG-MV-009 report.

3.2.4 Results and Conclusions

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3.3 Evaluation of Safety

All subjects in both treatment groups had at least one AE. For the ocriplasmin group, 124/147 (84.4%) adverse events (AEs) were ocular AEs, with 15/16 study eyes having at least 1 ocular AE. Of the ocular AEs, 117/124 (94.4%) events occurred in the study eye, and 8/124 events occurred in the non-study eye. Non-ocular events accounted for 15.6% of all AEs.

For the placebo group, 49/63 (77.8%) AEs were ocular AEs, with 8/8 study eyes having at least 1 ocular AE. Of the ocular AEs, 46/49 (93.9%) and 3/49 (6.1%) occurred in the study eye and the non-study eye, respectively. Non-ocular events accounted for 22.2% of all AEs.

One subject treated with ocriplasmin in both eyes had non-ocular SAEs with a fatal outcome. The Investigator considered the SAEs leading to death to be unrelated to study drug. The AEs

with fatal outcome in this premature infant were device malfunction (verbatim: ventriculoperitoneal shunt malfunction) and encephalopathy.

Please refer to the review of the medical reviewer for details of the safety evaluation.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues identified for this study.

5.2 Collective Evidence

(b) (4)

5.3 Conclusions and Recommendations

(b) (4)

5.4 Labeling Recommendations

The applicant proposed to update Section 8.4 Pediatric Use of the label as follows:

> *"A* (b) (4) *single center, randomized, placebo controlled, double masked clinical study to investigate the safety and efficacy of a single intravitreal injection of 0.175 mg ocriplasmin in pediatric subjects as an adjunct to vitrectomy was conducted in 24 eyes* (b) (4) (b) (4)
>
> (b) (4)

The statistical reviewer recommends removal of the two sentences (b) (4) (b) (4) The statistical reviewer recommends this section be revised as follows to report the study results:

"The treatment of ocriplasmin is not recommended for pediatric subjects scheduled for vitrectomy. A single center, randomized, placebo controlled, double masked clinical study to investigate the safety and efficacy of a single intravitreal injection of 0.175 mg ocriplasmin in pediatric subjects as an adjunct to vitrectomy was conducted in 24 eyes. (b) (4)

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/s/

YUNFAN DENG
05/15/2014

YAN WANG
05/15/2014
I concur.