CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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 #:	0000
Drug Name:	JETREA™ (Ocriplasmin)
Indication(s):	Treatment of Symptomatic Vitreomacular Adhesion including Macular Hole
Applicant:	ThromboGenics, Inc.
Date(s):	Submitted: 04/17/2012 PDUFA date: 10/16/2012
Review Priority:	Priority
Biometrics Division:	DBIV
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Keywords:
BLA, Superiority, Symptomatic Vitreomacular Adhesion (VMA), Macular Hole, Posterior Vitreous Detachment (PVD)

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1 EXECUTIVE SUMMARY

Conclusions and Recommendations

In this submission, the Applicant seeks approval of ocriplasmin for the treatment of symptomatic vitreomacular adhesion (VMA) including macular hole. The Applicant submitted two pivotal studies: study TG-MV-006, and study TG-MV-007. Both studies TG-MV-006 and TG-MV-007 were randomized, double masked, multi-center, and vehicle-controlled superiority trials to investigate the safety and efficacy of a single intravitreal injection of ocriplasmin 125µg in patients with symptomatic VMA (i.e. focal VMA leading to symptoms).

In both studies TG-MV-006 and TG-MV-007, ocriplasmin 125 µg showed statistical superiority over placebo in achieving the primary efficacy endpoint, resolution of focal VMA at post-injection Day 28, as determined by masked CRC evaluation of OCT scans.

In the Full Analysis Set, in study TG-MV-006, more patients treated with ocriplasmin had resolution of VMA at Day 28, compared with placebo: 27.9% versus 13.1%, respectively, with absolute difference between treatment groups of 14.8% (95% CI: 6.0% – 23.5%, P=0.003); and in study TG-MV-007, 25.3% versus 6.2% with absolute difference of 19.1% (95% CI: 11.6% – 26.7%, P<0.001).

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

The Applicant seeks labeling claim of treatment of VMA (b) (4)

FTMHC was a secondary endpoint (among many other secondary endpoints, see Section 3.2.2 for detailed listing of additional secondary endpoints) for a subset of the overall study population. As the Applicant stated in the SAP: "No adjustments were made for multiple comparisons or multiple endpoints for the additional secondary endpoints. Statistical comparisons for these additional secondary efficacy endpoints were of a supportive nature only and were interpreted as such". Without proper multiplicity adjustment for this secondary endpoint (FTMHC), the study results of FTMHC might not have adequate statistical evidence to support the efficacy of ocriplasmin for FTMHC in patients with FTMH at baseline. If Bonferroni correction method is used for multiplicity adjustment for testing at least 5 secondary endpoints, the significance level would be 0.01 for two-sided tests. Using 0.01 as the significance level for a two-sided test, the results for FTMHC endpoint at Month 6 are not statistically significant for study TG-MV-007 (p-value=0.005 for Study TG-MV-006, and 0.354 for Study TG-MV-007).

To support the indication for the treatment of FTMH, we recommend that the Applicant conduct at least one more pivotal study in patients with FTMH at baseline and using FTMHC as the primary efficacy endpoint.

Brief Overview of Clinical Studies

Studies TG-MV-006 and TG-MV-007 were identically designed efficacy/safety studies. They were multicenter, randomized, placebo-controlled, double-masked, 6-month studies that investigated the safety and efficacy of a single intravitreal injection of ocriplasmin 125µg in patients with symptomatic VMA (*i.e.* focal VMA leading to symptoms). The 2 trials were identical in design (except for treatment 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 of America [USA] and TG-MV-007 conducted in the European Union [EU] and USA). A placebo intravitreal injection of vehicle was chosen over a sham injection to maintain the double-masked design of the studies and ensure that the study treatment procedures would be identical. The planned sample size was 320 patients for each study.

For both studies, 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. The primary endpoint is also more simply referred to as VMA resolution at Day 28, since the CRC could not classify the response as a success unless VMA was completely absent. Any patients 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 with the Food and Drug Administration (FDA) 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.

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.

Study TG-MV-007 enrolled a total of 326 patients from 48 study sites in the EU and U.S: 245 randomized to receive ocriplasmin, and 81 randomized to receive placebo.

Statistical Issues and Findings

Other than lack of multiplicity adjustment for the FTMHC endpoint noted above, there are no major statistical issues for both studies. And the following table summarizes the study results of the primary and key secondary efficacy endpoints.

Table 1: Summary of the Primary and Key Secondary Efficacy Endpoints (FAS, LOCF)

Primary Efficacy Endpoint: VMA								
	TG-MV-006				TG-MV-007			
	Placebo	**Ocriplasmin**	**Difference (95% CI)**	**p-value**	**Placebp**	**Ocriplasmin**	**Difference (95% CI)**	**p-value**
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

Key Secondary Endpoint: Total Posterior Vitreous Detachment (PVD)								
	TG-MV-006				TG-MV-007			
	Placebo	Ocriplasmin	Difference (95% CI)	p-value	Placebo	Ocriplasmin	Difference (95% CI)	p-value
N	107	219			81	245		
n (%)	7 (6.5)	36 (16.4)	9.9 (3.1, 16.7)	0.014	0	26 (10.6)	10.6 (6.8, 14.5)	<0.001

Source: Table 10 and 11 of the Applicant's AC Meeting Briefing Package

The improvement in the primary and key secondary efficacy endpoints was not reflected as improvement in patients' visual acuity. As shown in the following table, compared to placebo treated patients, more ocriplasmin treated patients had worsening of Best Corrected Visual Acuity (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. So far, the reason of more ocriplasmin treated patients having worsening of BCVA is still unclear.

Table 2: Categorical Change 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.

2 INTRODUCTION

2.1 Overview

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 agerelated macular degeneration (AMD).

The only available treatment option for symptomatic VMA so far is major eye surgery (i.e. vitrectomy), whereby any adhesions are manually dissected from the macular surface and the vitreous humor is aspirated from the eye. However, this approach has several inherent limitations including the risk of complications (such as retinal tear/detachment and cataract), and cost and complexity that limit its usefulness and/or outcome for treatment of certain conditions. The complexity and risk of complications are at least in part related to the difficulty of the microsurgical separation of persistent posterior vitreous adhesions to the retina. A less invasive and less traumatic treatment option for this potentially sight-threatening condition would therefore represent a significant advance in care.

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. Ocriplasmin is a recombinant human protein derived from the yeast *Pichia pastoris*. It is a truncated form of human plasmin, with retained protease activity. In vitro and in vivo assessment of plasmin and ocriplasmin demonstrate activity against substrates important in the vitreous structure and vitreoretinal interface, including fibronectin and laminin.

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

2.2 Data Sources

The Applicant's study reports and datasets for studies TG-MV-006, and TG-MV-007 are available on the CBER EDR at \\CBER-FS3\M\ECTD_SUBMISSIONS\STN125422\0000.

The analysis results of the primary end the key secondary endpoint using multiple imputation methods to impute missing data are located at:
\\cber-fs3\m\eCTD_Submissions\STN125422\0004

The revised tables and forest plots for the results of subgroup analyses are located at: \\Cber-fs3\m\eCTD_Submissions\STN125422\0007

The Applicant's Advisory Committee (AC) meeting briefing package is located at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM313091.pdf

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submission is relatively easy to navigate. All the datasets (raw and derived) were submitted with detailed definition of each variable. All the SAS codes for producing the study results were submitted. Results of the primary and key secondary endpoints can be reproduced by the statistical reviewer. The final statistical analysis plan (SAP) was submitted prior to un-blinding of the study. The analysis performed by the Applicant followed the statistical analysis plan (SAP), and was complete and thorough.

3.2 Evaluation of Efficacy

3.2.1 Study Design

Studies TG-MV-006 and TG-MV-007 were identically designed efficacy/safety studies. They were multicenter, randomized, placebo-controlled, double-masked, 6-month studies that investigated the safety and efficacy of a single intravitreal injection of ocriplasmin 125µg in patients with symptomatic VMA (*i.e.* focal VMA leading to symptoms). The primary efficacy endpoint for both studies was the proportion of patients with non-surgical resolution of focal VMA at Day 28 post-injection (or simply referred to as VMA resolution at Day 28) in the study eye.

In both studies, subjects who met the criteria for enrollment were randomly assigned to receive a single 125µg ocriplasmin or placebo intravitreal injection. The randomization allocation ratio of was 2:1 in TG-MV-006 and 3:1 in TG-MV-007. For study TG-MV-006, the original allocation ratio was 3:1 (ocriplasmin:placebo). Per a recommendation by FDA, this ratio was modified to 2:1 (ocriplasmin:placebo) in Protocol Amendment 1. Both studies were 6-month studies with up to 7 visits: Baseline; Injection Day; 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 to be combined at the Investigator's discretion.

At Baseline both eyes were examined (full ophthalmic exam, B-scan ultrasound, OCT and fundus photography). If both eyes met the inclusion criteria, the eye with the worst BCVA was chosen as the study eye. For safety assessments, adverse events (AEs) were collected for both the study eye and non-study eye.

A Data Monitoring Committee (DMC) was established for the TG-MV-006 and TG-MV-007 studies for the purpose of reviewing safety data. After reviewing safety data at each meeting, the DMC recommended continuing enrollment with no protocol modifications.

The DMC conducted formal reviews of available safety data at 4 pre-specified times:
1. After 25% of the subjects in 1 of the studies completed the Day 14 visit (or withdrew).
2. After 50% of the subjects in 1 of the studies completed the Day 14 visit (or withdrew).
3. After all subjects in both studies completed the Day 28 visit (or withdrew).
4. After all subjects in both studies completed the study (or withdrew).

The formal masked review DMC meetings were conducted on 09 Apr 2009, 03 Jun 2009, and 08 Feb 2010. The 4th formal meeting held on 28 Aug 2010 was a safety review after database lock of unmasked data, and was the final close out meeting. In addition, two ad hoc meetings were held on 03 Mar 2010 and 03 May 2010.

3.2.2 Statistical Methodologies

Studies TG-MV-006 and TG-MV-007 were two identically designed pivotal studies. The statistical methodologies were the same for both studies. The primary endpoint and key secondary endpoint was evaluated using the full analysis set (FAS), which included all randomized subjects who received study treatment (ocriplasmin or placebo). 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.

Efficacy Endpoints

The primary endpoint of both studies was the proportion of subjects in the Full Analysis Set with VMA resolution in the study eye at Day 28, as determined by masked Central Reading Center OCT evaluation. All subjects who had creation of an anatomical defect (i.e. retinal hole, retinal detachment) that resulted in decrease of vision or required additional intervention were counted as treatment failures for the primary endpoint.

The key secondary endpoint was the proportion of subjects with total PVD at Day 28, as determined by masked Investigator assessment of B-scan ultrasound.

Additional secondary efficacy parameters defined in the statistical analysis plan (SAP) were

- Proportion of subjects not requiring vitrectomy, both through day 28 and at anytime during the study (through Month 6); and this endpoint for the subgroup of patients where the need for vitrectomy was indicated at baseline by the investigator
- Proportion of macular holes that close without vitrectomy as determined by CRC; all macular holes that close regardless of vitrectomy status
- Achievement of ≥1, ≥ 2 or ≥ 3 lines improvement in Best Corrected Visual Acuity (BCVA) without need for vitrectomy by study visit (Days 7, 14, 28, Month 3 and 6); the analysis be repeated by baseline BCVA groups
- Improvement of BCVA by study visit; analysis be repeated by baseline BCVA groups
- Improvement in VFQ-25 by Month 6

Efficacy Analysis Populations

There were four analysis populations for both studies: Full Analysis Set (FAS), FAS in subjects with focal VMA, Per Protocol (PP) set, and safety set. The FAS included all randomized subjects who received treatment with study drug (ocriplasmin and placebo). Data were analyzed according to subject treatment group randomized, regardless of treatment actually received. FAS in subjects with focal VMA included all FAS subjects who had symptomatic focal VMA to begin with at Baseline as determined by masked Central Reading Center OCT evaluation. The Per-Protocol Set included the FAS excluding subjects where a deviation was of sufficient concern to warrant exclusion. Decisions regarding data exclusion from the Per-Protocol Set were taken prior to unmasking the randomization code (masked review) and documented appropriately. The FAS was the primary population for all analyses of Baseline/demographic and efficacy data.

The safety population consisted of randomized and treated patients. For safety analyses, patients were included in the treatment group to which they were actually treated.

Analysis of Primary Efficacy Endpoints

Success on the primary endpoint was defined as outlined in the Central Reading Center OCT Data Interpretation document. The document was finalized prior to unmasking. Vitreous separation was evaluated using the following scores:

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 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
ON: Optic Nerve							

Success was defined as a resolution from Baseline to the Day 28 visit in the CRC evaluated OCT. The following categories of progression, as defined by the CRC, were consistent with "resolution of focal VMA" for the primary endpoint:

Baseline to Day 28	Baseline to Day 28	Baseline to Day 28
1 to 0	2 to 0	4 to 0
1 to 3	2 to 3	4 to 3
1 to 5	2 to 5	4 to 5

The primary endpoint and key secondary endpoint was evaluated using the FAS. Missing data was imputed using the last observation carried forward (LOCF) approach. The proportion of subjects meeting the endpoint was tabulated by randomized treatment group and the treatment groups were compared using Fisher's exact test. The two-sided 95% CIs for the difference between the 2 groups and the exact odds ratio were also calculated.

In the event that statistical significance with $p<0.05$ was achieved for the primary endpoint for the FAS, the second priority was to determine the resolution of focal VMA in all randomized subjects who received treatment with study drug and had focal VMA at Baseline as determined by masked Central Reading Center OCT evaluation. This population was to be evaluated separately and excluded subjects with either no focal VMA or undetermined focal VMA status at Baseline as they, by definition, did not have the possibility to be a success for the primary endpoint of VMA resolution.

The methods for this primary analysis with second priority were to be the same as those for the primary analysis of the primary endpoint for the FAS.

Additional supportive analyses of the primary efficacy endpoint were evaluated using the full analysis set and the per-protocol sets with the observed cases (OC) approach with missing data excluded and worst case approach for handling missing data.

Analysis of the Key Secondary Efficacy Endpoint

The key secondary endpoint of this study was the proportion of subjects with total PVD at Day 28, as determined by masked Investigator assessment of B-scan ultrasound.

The proportion of subjects with total PVD at Day 28, as determined by masked Investigator assessment of B-scan ultrasound, were tabulated by treatment group. The treatment groups were compared using Fisher's exact test. The two-sided 95% CI for the difference between the 2 groups and the exact odds ratio were also calculated.

The analysis was performed with subjects with total PVD at Baseline included as failures (no total PVD) and repeated excluding subjects with total PVD at Baseline.

Similar analyses were performed using the observed case (OC) and worst case approaches for handling missing data. Note that, per the protocol, subjects who achieved total PVD at 2 consecutive visits were no longer required to have a B-scan ultrasound at subsequent visits. As such, a subject with missing data for Day 28 who had total PVD at Days 7 and 14 was considered as a success in the OC and worst case summaries.

The formal statistical testing of the key secondary efficacy endpoint was to be evaluated if statistical significance ($p<0.05$) was achieved in the analysis of the primary efficacy endpoint for the entire FAS and the subset of the FAS with VMA at Baseline. Analyses of the remaining secondary endpoints were considered supportive or exploratory. The results of those endpoints were described with nominal 95% CIs and nominal p-values without any statistical significance statements.

Analysis of Other Secondary Efficacy Endpoints

For all the other secondary efficacy endpoints, summaries were prepared using the FAS with LOCF approach. No adjustments were made for multiple comparisons or multiple endpoints for the additional secondary endpoints. According to the statistical analysis plan (SAP) of both studies, statistical comparisons for these additional secondary efficacy endpoints were of a supportive nature only and were interpreted as such. The results were evaluated at the two-sided 5% level of significance.

Determination of Sample Size

Assuming a primary endpoint event rate of 27.5% in the 125μg dose group and 10% in the placebo group, a sample size of 320 subjects achieved over 90% power with a 2-sided alpha of 0.05. This specification applied to the original randomization ratio of 3:1. Following Protocol Amendment 1 (IND serial 0036 dated 28 Jan 2009), the randomization ratio was changed to 2:1, per a recommendation by the FDA. The total planned sample size was not amended.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study TG-MV-006

A total of 326 subjects were randomized into the study (107, placebo; 219, ocriplasmin). Of these, most (91.4%) subjects completed the study. By treatment group, 9/107 (8.4%) of subjects in the placebo group and 19/219 (8.7%) of subjects in the ocriplasmin group were discontinued from the study. The most common reasons for discontinuation were 'withdrew consent' (3.7%, placebo; 3.7%, ocriplasmin) and 'lost to follow-up' (2.8%, placebo; 2.7%, ocriplasmin). Four subjects (2 per treatment group) were discontinued due to an AE; an additional 3 subjects (all in the ocriplasmin group) died before completing the study. Disposition of all enrolled patients is shown in Table 3.

Table 3: Study TG-MV-006 Subject Disposition

	Placebo	Ocriplasmin	Total
Subjects Randomized	107	219	326
Completed Study, n (%)	98 (91.6%)	200 (91.3%)	298 (91.4%)
Discontinued from Study, n (%)	9 (8.4%)	19 (8.7%)	28 (8.6%)
Adverse events	2 (1.9%)	2 (0.9%)	4 (1.2%)
Protocol Violation	0	0	0
Withdrew Consent	4 (3.7%)	8 (3.7%)	12 (3.7%)

Lost to Follow-up	3 (2.8%)	6 (2.7%)	9 (2.8%)
Death	0	3 (1.4%)	3 (0.9%)
Other	0	0	0

Source: Applicant's study TG-MV-006 report Table 4

All randomized subjects (N=326) were included in the Safety Set and the Full Analysis Set (Table 4). One subject (Subject 631002) was randomized to the placebo group but was inadvertently treated with ocriplasmin. Therefore, this subject is counted in the placebo group for the Full Analysis Set and in the ocriplasmin group for the Safety Set.

A total of 306 (93.9%) subjects, 99 (92.5%) in the placebo group and 207 (94.5%) in the ocriplasmin group, were included in the Full Analysis Set for subjects with focal VMA at Baseline. These subjects had a pre-treatment determination of focal VMA made by the Investigator during Screening and confirmed by subsequent masked CRC review. The Per-Protocol Set consisted of 283 (86.8%) subjects, with 94 (87.9%) in the placebo group and 189 (86.3%) in the ocriplasmin group.

Table 4: Study TG-MV-006 Analysis Populations

Data Set	Placebo	Ocriplasmin	Total
Safety Set	106	220	326
Full Analysis Set (FAS)	107	219	326
FAS for Subject with Focal VMA at Baseline	99 (92.5%)	207 (94.5%)	306 (93.9%)
Per-Protocol Set	94 (87.9%)	189 (86.3%)	283 (86.8%)

Source: Applicant's study TG-MV-006 report Table 5

The summaries of baseline demographic characteristics are presented in the following table. Other than higher percentage of females were observed in the ocriplasmin group (67.6%) compared with the placebo group (55.1%), there was no marked difference in the baseline characteristics between the two treatment groups.

Table 5: Study TG-MV-006 Demographic Characteristics

	Placebo (N=107)	Ocriplasmin (N=219)	Total (N=326)
Gender, n (%)			
Male	48 (44.9%)	71 (32.4%)	119 (36.5%)
Female	59 (55.1%)	148 (67.6%)	207 (63.5%)
Age (years)			
MEAN (SD)	71.1 (10.04)	71.5 (10.25)	71.3 (10.17)
MEDIAN	70.0	72.0	71.0
RANGE	24, 96	18, 93	18, 96
Race, n (%)			
White	97 (90.7%)	195 (89.0%)	292 (89.6%)
Black	4 (3.7%)	13 (5.9%)	17 (5.2%)
Asian	2 (1.9%)	6 (2.7%)	8 (2.5%)
Other	4 (3.7%)	5 (2.3%)	9 (2.8%)

Ethnicity, n (%)			
Non-Hispanic	98 (91.6%)	204 (93.2%)	302 (92.6%)
Hispanic	9 (8.4%)	15 (6.8%)	24 (7.4%)
Baseline Diagnosis, n (%)			
FTMH	32 (29.9%)	57 (26.0%)	89 (27.3%)
Vitreomacular Traction (Including DR)	75 (70.0%)	162 (74.0%)	237 (72.7%)
Baseline Ocular Characteristics, n (%)			
Epiretinal Membrane	35 (32.7%)	86 (39.3%)	121 (37.1%)
Pseudophakic	29 (27.1%)	91 (41.6%)	120 (36.8%)
Type (Diamter) of Focal VMA, n/N (%)			
>1500µm	19/99 (19.2%)	47/207 (22.7%)	66/306 (21.6%)
≤1500µm	74/99 (74.7%)	145/207 (70.0%)	219/306 (71.6%)
Could not Determine	6/99 (6.1%)	15/207 (7.2%)	21/306 (6.9%)
Expected Need for Vitrectomy, n (%)			
Yes	85 (79.4%)	174 (79.5%)	259 (79.4%)
No	22 (20.6%)	44 (20.1%)	66 (20.2%)
Missing	0	1 (0.5%)	1 (0.3%)
Total PVD at Baseline, n (%)			
Yes	0	1 (0.5%)	1 (0.3%)
No	107 (100.0%)	218 (99.5%)	325 (99.7%)
BCVA (Letter Score)			
MEAN (SD)	65.3 (9.83)	64.5 (10.86)	
MEDIAN	67.0	67.0	
RANGE	38, 82	20, 85	

Source: Applicant's study TG-MV-006 report Table 6

Study TG-MV-007

A total of 326 (81, placebo; 245, ocriplasmin) subjects were randomized into the study across Europe (179, 54.9%) and USA (147, 45.1%). Of these, most (94.8%) subjects completed the study. By treatment group, 7/81 (8.6%) placebo subjects and 10/245 (4.1%) ocriplasmin subjects were discontinued from the study. The most common reasons for discontinuation were withdrawn consent (4.9%, placebo; 2.0%, ocriplasmin) and loss to follow-up (2.5%, placebo; 0.8%, ocriplasmin). Two subjects in the ocriplasmin treatment group were discontinued due to an AE, and one subject in the ocriplasmin group died before completing the study.

Table 6: Study TG-MV-007 Subject Disposition

	Placebo	**Ocriplasmin**	**Total**
Subjects Randomized	81	245	326
Completed Study, n (%)	74 (91.4%)	235 (95.9%)	309 (94.8%)
Discontinued from Study, n (%)	7 (8.6%)	10 (4.1%)	17 (5.2%)
Adverse events	0	2 (0.8%)	2 (0.6%)
Investigator Decision	1 (1.2%)	0	1 (0.3%)
Withdrew Consent	4 (4.9%)	5 (2.0%)	9 (2.8%)
Lost to Follow-up	2 (2.5%)	2 (0.8%)	4 (1.2%)
Death	0	1 (0.4%)	1 (0.3%)

Source: Applicant's study TG-MV-007 report Table 4

All randomized subjects (N=326) were included in the Safety Set and the Full Analysis Set. A total of 310 (95.1%) subjects, 77 (95.1%) in the placebo group and 233 (95.1%) in the ocriplasmin group, were included in the Full Analysis Set for subjects with focal VMA at Baseline. These subjects had a pre-treatment determination of focal VMA made by the Investigator during Screening which was confirmed by subsequent masked CRC review. The Per-Protocol Set consisted of 285 (87.4%) subjects, with 71 (87.7%) in the placebo group and 214 (87.3%) in the ocriplasmin group.

Table 7: Study TG-MV-007 Analysis Populations

Data Set	Placebo	Ocriplasmin	Total
Safety Set	81	245	326
Full Analysis Set (FAS)	81	245	326
FAS for Subject with Focal VMA at Baseline	77 (95.1%)	233 (95.1%)	310 (95.1%)
Per-Protocol Set	71 (87.7%)	214 (87.3%)	285 (87.4%)

Source: Applicant's study TG-MV-007 report Table 5

The summaries of baseline demographic characteristics are presented in the following table. There was no marked difference in the baseline characteristics between the two treatment groups.

Table 8: Study TG-MV-007 Demographic Characteristics

	Placebo (N=81)	Ocriplasmin (N=245)	Total (N=326)
Gender, n (%)			
Male	25 (30.9%)	79 (32.2%)	104 (31.9%)
Female	56 (69.1%)	166 (67.8%)	222 (68.1%)
Age (years)			
MEAN (SD)	70.2 (10.85)	72.6 (7.56)	72.0 (8.54)
MEDIAN	72.0	73.0	73.0
RANGE	32, 97	23, 89	23, 97
Race, n (%)			
White	77 (95.1%)	233 (95.1%)	310 (95.1%)
Black	2 (2.5%)	10 (4.1%)	12 (3.7%)
Asian	2 (2.5%)	2 (0.8%)	4 (1.2%)
Other	0	0	0
Ethnicity, n (%)			
Non-Hispanic (USA)	32 (39.5%)	103 (42.0%)	135 (41.4%)
Hispanic (USA)	4 (4.9%)	8 (3.3%)	12 (3.7%)
Not Specified (non-USA)	45 (55.6%)	134 (54.7%)	179 (54.9%)
Baseline Diagnosis, n (%)			
FTMH	15 (18.5%)	49 (20.0%)	64 (19.6%)
Vitreomacular Traction (Including DR)	66 (81.5%)	196 (80.0%)	262 (80.4%)
Baseline Ocular Characteristics, n (%)			
Epiretinal Membrane	33 (40.7%)	98 (40.0%)	131 (40.2%)
Pseudophakic	24 (29.6%)	81 (33.1%)	105 (32.2%)

Type (Diamter) of Focal VMA, n/N (%)			
>1500µm	22/77 (28.6%)	55/233 (23.6%)	77/310 (24.8%)
≤1500µm	49/77 (63.6%)	169/233 (72.5%)	218/310 (70.3%)
Could not Determine	6/77 (7.8%)	9/233 (3.9%)	15/310 (4.8%)
Expected Need for Vitrectomy, n (%)			
Yes	67 (82.7%)	222 (90.6%)	289 (88.7%)
No	14 (17.3%)	23 (9.4%)	37 (11.3%)
Total PVD at Baseline, n (%)			
Yes	0	0	0
No	81 (100.0%)	245 (100.0%)	326 (100.0%)
BCVA (Letter Score)			
N	80	245	
MEAN (SD)	64.9 (11.58)	63.4 (13.69)	
MEDIAN	66.5	67.0	
RANGE	9, 82	8, 88	

Source: Applicant's study TG-MV-007 report Table 6

3.2.4 Results and Conclusions

3.2.4.1 Primary Efficacy Endpoint

The following table presents the primary efficacy outcome of different analysis sets for both studies TG-MV-006 and TG-MV-007 and the integrated results.

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

Statistical Reviewer's Comments:

In both studies TG-MV-006 and TG-MV-007, ocriplasmin 125 µg showed statistical superiority over placebo in achieving the primary efficacy endpoint, resolution of focal VMA at post-injection Day 28, as determined by masked CRC evaluation of OCT scans.

In the Full Analysis Set, in TG-MV-006, more patients treated with ocriplasmin had resolution of VMA at Day 28, compared with placebo: 27.9% versus 13.1%, respectively, with absolute

difference between treatment groups of 14.8% (95% CI: 6.0%–23.5%, *P*=0.003); and in study TG-MV-007, 25.3% versus 6.2% with absolute difference of 19.1% (95% CI: 11.6%–26.7%, *P*<0.001).

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 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 ≤ 1500um at Baseline (TG-MV-006, 74.7%; TG-MV-007, 63.6%). According to the medical reviewer, it is not clear why there is such large difference in the placebo rates in these two studies.

At the pre-BLA meeting, the Agency requested that the analysis of the endpoint VMA resolution at Day 28 also be performed with cases of creation of anatomical defect irrespective of loss of vision or intervention counted as failures for this endpoint. As explained earlier, this analysis was identical to the primary analysis.

The following table shows the proportion of patients who achieved resolution of VMA for both studies and also for integrated results at all post-injection study visits through Month 6.

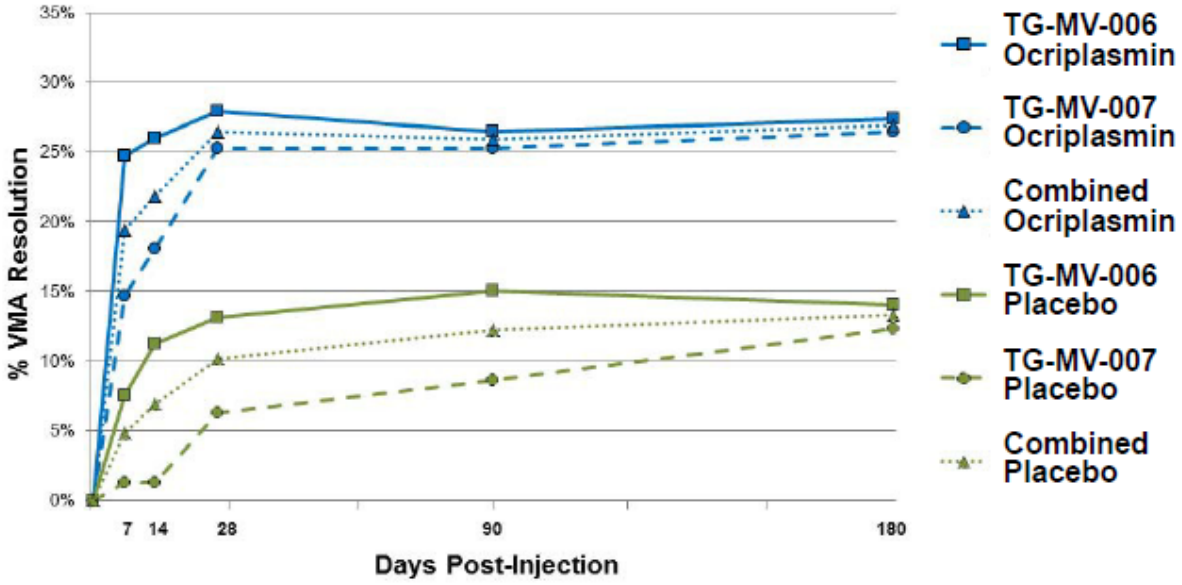
Table 10: Summary and Analysis of Nonsurgical Resolution of Focal VMA by Study Visit (FAS, LOCF)

	TG-MV-006				TG-MV-007				Combined Analysis			
	PL N=107	Ocri N=219	Difference (95% CI)	p-value	PL N=81	Ocri N=245	Difference (95% CI)	p-value	PL N=188	Ocri N=464	Difference (95% CI)	p-value
	n (%)	n (%)			n (%)	n (%)			n (%)	n (%)		
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.

The following figure depicts the above table.

Figure 1: Proportion of Patients who Achieved Resolution of VMA over Time



Source: Figure 19 of the Applicant's AC Meeting Briefing Package

Statistical Reviewer's Comments:

The above table and figure show that majority patients in both groups achieved VMA resolution by Day 28. At all the study visits after baseline, ocriplasmin 125 µg had more patients compared with placebo in achieving VMA resolution until Month 6. For both studies, the treatment difference remains consistent from Day 28 till Month 6.

3.2.4.2 Key Secondary Endpoint

The following table presents the key secondary efficacy endpoint outcome for both studies and the integrated results. For study TG-MV-006, for each dataset, the proportion of subjects with total PVD at Day 28, excluding subjects with total PVD at Baseline as graded by ultrasound, was very similar to that described below when the single subject (Subject 615003, ocriplasmin group) with total PVD at Baseline as graded by ultrasound was considered as a failure. For study TG-MV-007, for each dataset, the proportion of subjects with total PVD at Day 28, excluding subjects with total PVD at Baseline as graded by ultrasound, was identical to that described above, given the fact that there were no subjects in either treatment group with total PVD at Baseline.

Table 11: Patients with Total Posterior Vitreous Detachment at Day 28 in the Study Eye (Key Secondary Efficacy Endpoint, 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 (%)	7 (6.5)	36 (16.4)	9.9 (3.1, 16.7)	0.014	0	26 (10.6)	10.6 (6.8, 14.5)	<0.001	7 (3.7)	62 (13.2)	9.6 (5.5, 13.8)	<0.001
Modified Full Analysis Set												
N	99	207			77	233			176	440		
n (%)	6 (6.1)	30 (14.5)	8.4 (1.7, 15.1)	0.037	0	24 (10.3)	10.3 (6.4, 14.2)	0.001	6 (3.4)	54 (12.3)	8.9 (4.8, 12.9)	<0.001
Per-Protocol Set												
N	94	189			71	214			165	403		
n (%)	6 (6.4)	28 (14.8)	8.4 (1.4, 15.5)	0.051	0	24 (11.2)	11.2 (7.0, 15.4)	<0.001	6 (3.6)	52 (12.9)	9.3 (4.9, 13.6)	<0.001

Source: Table 11 of the Applicant's AC Meeting Briefing Package

Statistical Reviewer's Comments:

In both studies TG-MV-006 and TG-MV-007, ocriplasmin 125 μg showed statistical superiority over placebo in achieving the key secondary endpoint, patients with total PVD at post-injection Day 28, as determined by masked investigator-certified assessment of B-scan ultrasound.

In the Full Analysis Set, in TG-MV-006, more patients treated with ocriplasmin had total PVD at Day 28, compared with placebo: 16.4% versus 6.5%, respectively, with absolute difference between treatment groups of 9.9% (95% CI: 3.1%–16.7%, *P*=0.014); and in study TG-MV-007, 10.6% versus 0.0% with absolute difference of 10.6% (95% CI: 6.8%–14.5%, *P*<0.001). The treatment difference was similar for both studies at about 10%.

3.2.4.3 Selected Secondary Endpoints

3.2.4.3.1 Full Thickness Macular Hole Closure (FTMHC)

A total of 89 patients in the TG-MV-006 study had FTMH at Baseline (26.0%, ocriplasmin; 29.9%, placebo) and 64 patients in TG-MV-007 had FTMH at Baseline (20.0%, ocriplasmin; 18.5%, placebo). The following table presents the proportion of patients in the Full Analysis Set who achieved non-surgical FTMHC in the study eye by Day 28 and Month 6 (without vitrectomy) for both studies and the integrated analysis.

Table 12: Proportion of patients who achieved non-surgical FTMHC in the study eye by Day 28 and Month 6 (FAS, LOCF)

	TG-MV-006				TG-MV-007				Combined Analysis			
Without Vitrectomy												
	PL (N=32)	Ocri (N=57)	Difference (95% CI)	p-value	PL (N=15)	Ocri (N=49)	Difference (95% CI)	p-value	PL (N=47)	Ocri (N=106)	Difference (95% CI)	p-value
By Day 28	4 (12.5)	25 (43.9)	31.4 (14.1, 48.6)	0.002	1 (6.7)	18 (36.7)	30.1 (11.6, 48.5)	0.028	5 (10.6)	43 (40.6)	29.9 (17.1, 42.8)	<0.001
By Month 6	5 (15.6)	26 (45.6)	30.0 (11.9, 48.0)	0.005	3 (20.0)	17 (34.7)	14.7 (-9.5, 38.9)	0.354	8 (17.0)	43 (40.6)	23.5 (9.3, 37.8)	0.004

Source: Applicant's AC Meeting Briefing Package

Statistical Reviewer's Comments:

In both studies TG-MV-006 and TG-MV-007, ocriplasmin 125 µg had more patients who achieved non-surgical FTMHC over placebo.

In the TG-MV-006 study, the proportion of patients in the Full Analysis Set who achieved non-surgical FTMHC by Month 6 was higher in the ocriplasmin group (45.6%, 26/57) compared with the placebo group (15.6%, 5/32), an absolute difference of 30% (95% CI: 11.9%, 48.0%; p=0.005). This difference was not as marked in the TG-MV-007 study, wherein the proportion of patients who achieved non-surgical FTMHC by Month 6 was 34.7% (17/49) in the ocriplasmin group and 20.0% (3/15) in the placebo group, an absolute difference of 14.7% (95% CI: −9.5%, 38.9%; p=0.354).

The Applicant seeks labeling claim of treatment of VMA (b) (4)

(b) (4)

FTMHC was a secondary endpoint (among many other secondary endpoints, see Section 3.2.2 for detailed listing of additional secondary endpoints) for a subset of the overall study population. As the Applicant stated in the SAP: "No adjustments were made for multiple comparisons or multiple endpoints for the additional secondary endpoints. Statistical comparisons for these additional secondary efficacy endpoints were of a supportive nature only and were interpreted as such". Without proper multiplicity adjustment for this secondary endpoint (FTMHC), the study results of FTMHC might not have adequate statistical evidence to support the efficacy of ocriplasmin for FTMHC in patients with FTMH at baseline. If Bonferroni correction method is used for multiplicity adjustment for testing at least 5 secondary endpoints, the significance level would be 0.01 for two-sided tests. Using 0.01 as the significance level for a two-sided test, the results for FTMHC endpoint at Month 6 are not statistically significant for study TG-MV-007 (p-value=0.005 for Study TG-MV-006, and 0.354 for Study TG-MV-007). The Applicant needs at least one more pivotal study focusing only on patients with FTMH at baseline and using FTMHC as the primary efficacy endpoint to support a new indication for the treatment of FTMH.

3.2.4.3.2 Best Corrected Visual Acuity (BCVA)

Although the categorical improvement from baseline of BCVA at Month 6 seems to favor the ocriplasmin treated group, it is observed that in study TG-MV-006, more patients in the ocriplasmin treated group had ≥ 2-line or 3-line **worsening** in BCVA compared with the placebo group at Month 6 (as seen in the following table). 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) with a treatment difference of 5.4% and 95% CI of (1.1%, 9.7%). And in the combined analysis, the proportion of patients with a ≥3 lines (15 letters) worsening in the visual acuity was also

higher in the ocriplasmin treated group compared with the placebo group (5.6% versus 3.2%, respectively) with a treatment difference of 2.4% and 95% CI of (-0.9%, 5.7%).

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 table shows categorical worsening from baseline in BCVA at Month 6 for patients with or without vitrectomy in each individual study and the combined analysis.

In Study TG-MV-006, for patients with vitrectomy, the proportion of patients with a ≥3 lines (15 letters) worsening in the visual acuity was again much higher in the ocriplasmin treated group compared with the placebo group (20.0% versus 6.5%, respectively) with a treatment difference of 13.5% and 95% CI of (-1.0%, 28.1%); for patients without vitrectomy, the proportion of patients with a ≥3 lines (15 letters) worsening in the visual acuity was still higher in the ocriplasmin treated group compared with the placebo group (4.0% versus 0.0%, respectively) with a treatment difference of 4.0% and 95% CI of (-1.1%, 6.9%).

In the combined analysis, for patients with vitrectomy, the proportion of patients with a ≥3 lines (15 letters) worsening in the visual acuity was also higher in the ocriplasmin treated group compared with the placebo group (15.9% versus 6.1%, respectively) with a treatment difference of 9.7% and 95% CI of (-0.6%, 20.1%).

Table 14: Categorical Worsening from Baseline in BCVA at Month 6 with or without Vitrectomy (TG-MV-006, TG-MV-007, and Combined Analysis; FAS, LOCF)

With Vitrectomy												
	TG-MV-006				TG-MV-007				Combined Analysis			
	PL N=31	Ocri N=45	Difference [a] (95% CI)	p-value [b]	PL N=19 [c]	Ocri N=37	Difference (95% CI)	p-value [b]	PL N=50 [c]	Ocri N=82	Difference (95% CI)	p-value [b]
≥ 2-line Worsening in BCVA												
Month 6	3 (9.7)	10 (22 2)	12.5 (-3.5, 28.5)	0.219	3 (16.7)	5 (13.5)	-3.2 (-23.6, 17.3)	>0.999	6 (12.2)	15 (18.3)	6.0 (-6.4, 18.5)	0.347

≥ 3-line Worsening in BCVA												
Month 6	2 (6.5)	9 (20.0)	13.5 (-1.0, 28.1)	0.183	1 (5.6)	4 (10.8)	5.3 (-9.3, 19.8)	>0.999	3 (6.1)	13 (15.9)	9.7 (-0.6, 20.1)	0.087
Without Vitrectomy												
	TG-MV-006				**TG-MV-007**				**Combined Analysis**			
	PL N=76	**Ocri N=174**	**Difference (95% CI)** [a]	**p-value** [b]	**PL N=62** [c]	**Ocri N=208**	**Difference (95% CI)**	**p-value** [b]	**PL N=138** [c]	**Ocri N=382**	**Difference (95% CI)**	**p-value** [b]
≥ 2-line Worsening in BCVA												
Month 6	2 (2.6)	12 (6 9)	4.3 (-4.3, 9.5)	0.239	3 (4.8)	9 (4.3)	-0.5 (-6.5, 5.5)	>0.999	5 (3.6)	21 (5.5)	2.0 (-2.0, 6.0)	0.134
≥ 3-line Worsening in BCVA												
Month 6	0 (0.0)	7 (4.0)	4.0 (-1.1, 6.9)	0.105	3 (4.8)	6 (2.9)	-2.0 (-7.8, 3.9)	0.433	3 (2.2)	13 (3.4)	1.2 (-2.0, 4.3)	0.191

[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:

The following graphs show the proportion of patients with a ≥3 lines (15 letters) worsening in BCVA at Month 6 for all patients, for patients with vitrectomy, and for patients without vitrectomy in each individual study and the combined analysis.

Figure 2: Proportion of Patients with ≥3 lines Worsening in BCVA at Month 6

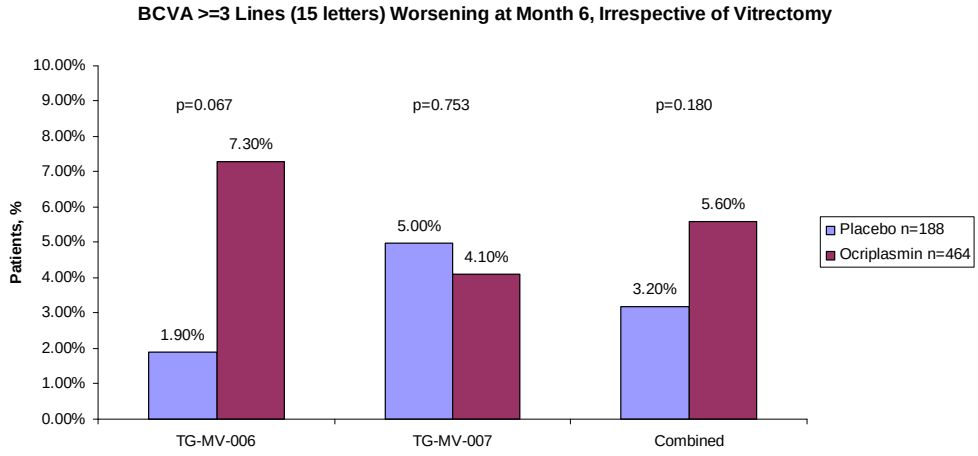


Figure 3: Proportion of Patients with ≥3 lines Worsening in BCVA at Month 6 (With Vitrectomy)

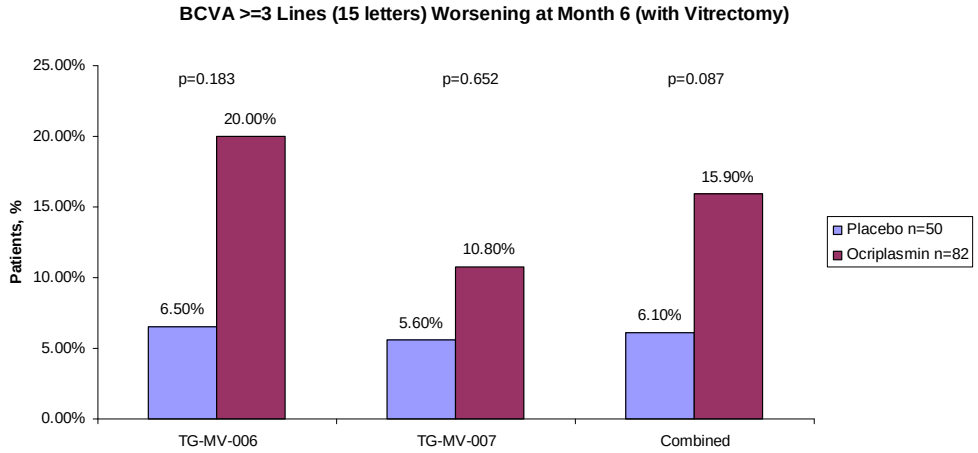
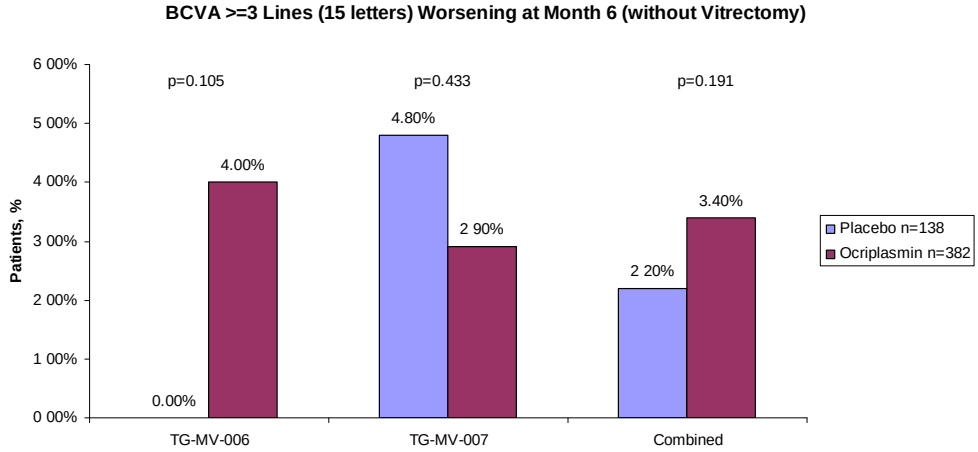


Figure 4: Proportion of Patients with ≥3 lines Worsening in BCVA at Month 6 (Without Vitrectomy)



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. As shown in the following table, 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).

Table 15: Summary of Mean Change from Baseline in BCVA over Time (TG-MV-006, TG-MV-007, Combined Analysis; FAS, LOCF)

	TG-MV-006			TG-MV-007			Combined Analysis		
	PL	Ocri	p-value[b]	PL	Ocri	p-value[b]	PL	Ocri	p-value[b]
Baseline	**n=107**	**n=219**		**n=80**	**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

	TG-MV-006			TG-MV-007			Combined Analysis		
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)	2.6 (6.64)	0.823	2.0 (5.38)	1.4 (8.24)	0.293
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	—

[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 12 of the Applicant's AC Briefing Package.

3.2.4.4 Sensitivity Analysis Results Using Multiple Imputation Method for Missing Data

Per the request of the statistical reviewer, the Applicant performed additional sensitivity analysis by using multiple imputation methods for imputing the missing values of the primary and key secondary endpoint.

The probabilities for assignment of success or failure for observations with missing data were based on modified observed conditional probabilities. For days 14 and 28, probabilities assigned were based on the observed probability of success or failure given a success or failure at the prior visit. For day 7, probabilities were based on the observed success/failure rate for the study and treatment. To account for some observed conditional probabilities of 0.0 and 1.0, the probabilities were adjusted slightly prior to imputation. According to the Applicant's SAS code, the modified conditional probability was calculated using the formula ((count+0.5)/(denominator+1))×100.

The point estimates, confidence intervals, and p-values presented in the following table are based on results using 100 iterations for the imputations. Missing data were imputed based on the conditional probabilities of success or failure using the observed probabilities within study and treatment.

Table 16: Applicant's Analysis Results of Primary and Key Secondary Efficacy Endpoints Using Multiple Imputation Methods for Missing Values (Studies TG-MV-006 and TG-MV-007)

	TG-MV-006			TG-MV-007		
	Treatment Difference	**95% CI**	**p-value**	**Treatment Difference**	**95% CI**	**p-value**
VMA	13.5%	(4.3%, 22.7%)	0.004	19.2%	(10.5%, 27.8%)	<0.001
Total PVD	12.2%	(4.2%, 20.1%)	0.003	8.8%	(2.1%, 15.4%)	0.010

Source: Summary of Applicant's submitted results.

In addition, the Applicant also performed sensitivity analyses using observed cases only, and worst value carried forward for missing values, all these analyses results were consistent with the results of the primary analysis.

3.3 Evaluation of Safety

The following tables summarized deaths happened during the drug development process.

Table 17: Summary of Deaths During the Drug Development

Treatment	**Study / Patient Number**	**Age**	**Gender**	**Race**	**AE Resulting in Death (MeDRA Preferred Term)**
Sham Injection	TG-MV-002/ 0113101	74	M	White	Cardiac Arrest
Sham Injection	TG-MV-002/ 081102	82	M	White	Intestinal obstruction
Ocriplasmin 75µg	TG-MV-003/ 101021	75	M	White	Myocardial infarction
Ocriplasmin 125µg	TG-MV-006/ 603008	81	F	White	Cerebral hemorrhage
Ocriplasmin 125µg	TG-MV-006/ 622012	84	F	White	Lung neoplasm malignant
Ocriplasmin 125µg	TG-MV-006/ 632008	83	F	White	Cardiac failure congestive
Ocriplasmin 125µg	TG-MV-007/ 721008	76	F	White	Brian cancer metastatic
Ocriplasmin 125µg	TG-MV-007/ 775003	88	F	White	Lung neoplasm malignant

Source: Appendix C of the Applicant's AC Meeting Briefing Package

For the pivotal 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 (125 µg) 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.

Table 18 shows the study eye AEs reported by at least 2% of ocriplasmin-treated patients in the randomized, placebo-controlled studies and for all studies during the drug development process (including Phase I and Phase II studies) combined.

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

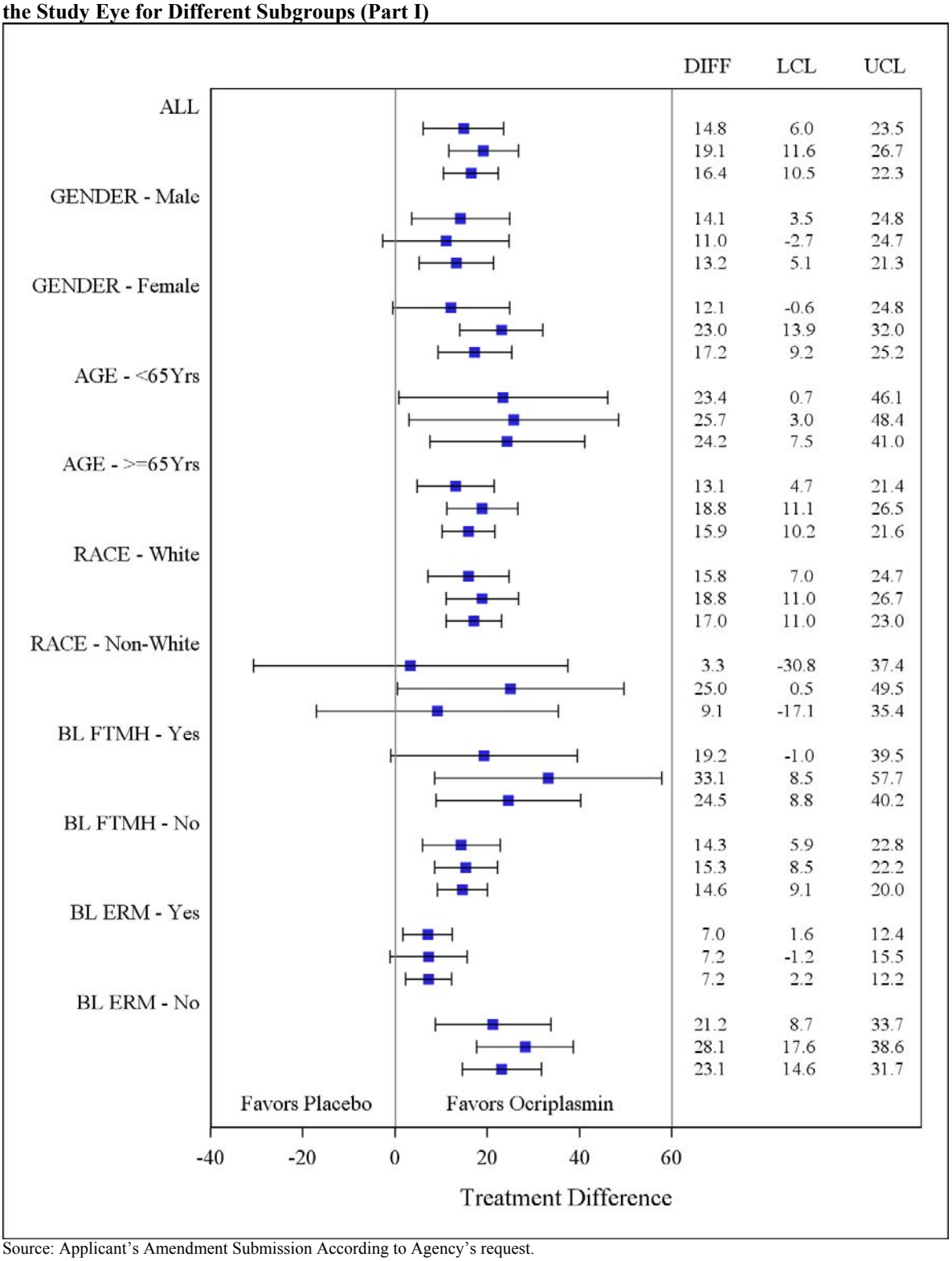
Please see the review of the medical officer for details of the safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Other Special/Subgroup Populations

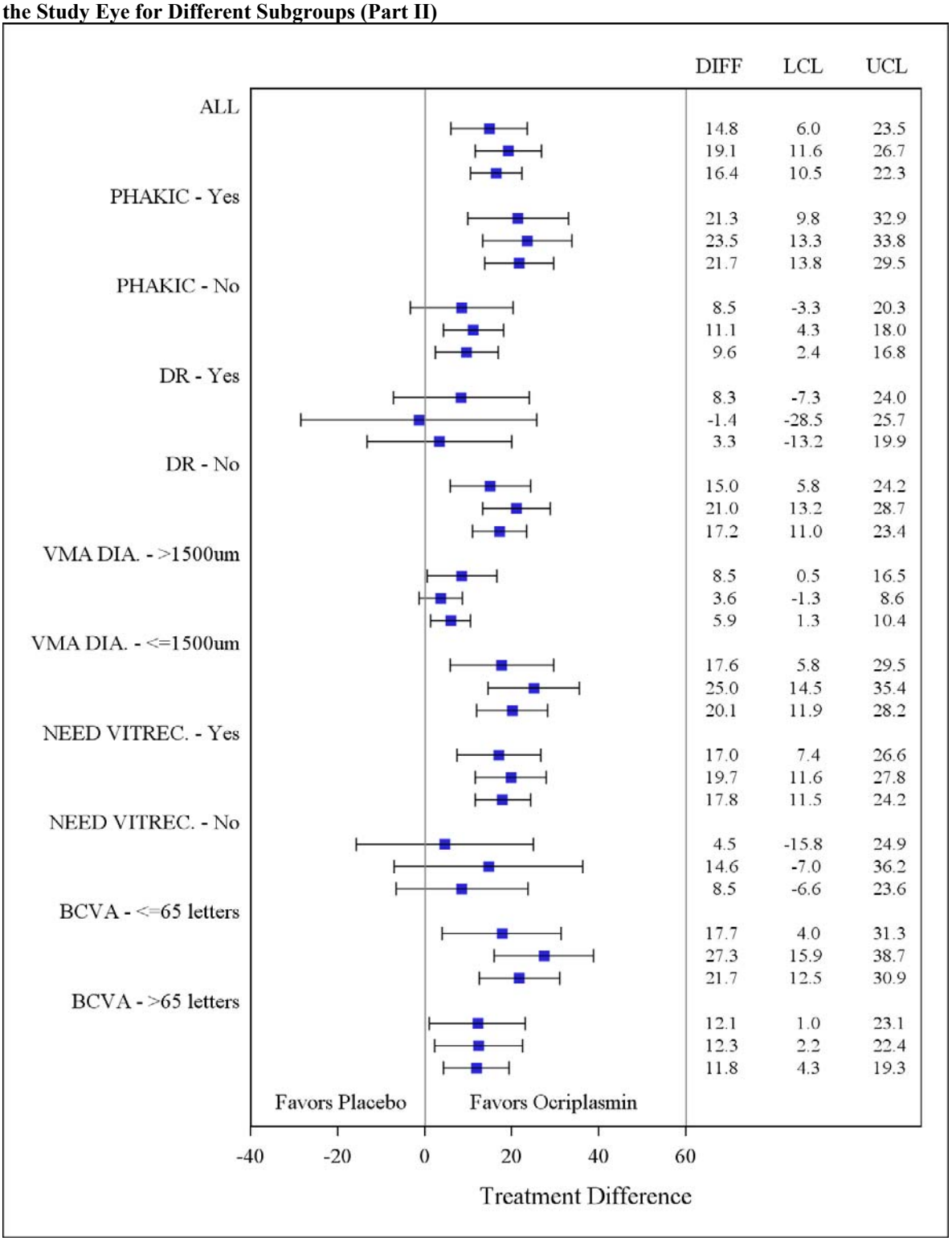
The primary endpoint was analyzed by different subgroups for both study TG-MV-006 and TG-MV-007. The following forest plots showed the treatment difference in the proportion of patients with VMA resolution in the study eye at Day 28 for different subgroups. In the plots, the top line of each subgroup is the treatment difference of this subgroup for study TG-MV-006, the middle line is for study TG-MV-007, and the bottom line is for the integrated results. In general, for both studies, there were no marked differences in the efficacy results among the various subpopulations (see plots).

Figure 5: Forest Plot – Treatment Difference in the Proportion of Patients with VMA Resolution at Day 28 in the Study Eye for Different Subgroups (Part I)



Source: Applicant's Amendment Submission According to Agency's request.

Figure 6: Forest Plot – Treatment Difference in the Proportion of Patients with VMA Resolution at Day 28 in the Study Eye for Different Subgroups (Part II)



Source: Applicant's Amendment Submission According to Agency's request.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Other than lack of multiplicity adjustment for the FTMHC endpoint noted below (see Section 5.4), there are no major statistical issues for both studies. And the following table summarizes the study results of the primary and key secondary efficacy endpoints.

Table 19: Summary of the Primary and Key Secondary Efficacy Endpoints (FAS, LOCF)

Primary Efficacy Endpoint: VMA								
	TG-MV-006				**TG-MV-007**			
	Placebo	**Ocriplasmin**	**Difference (95% CI)**	**p-value**	**Placebp**	**Ocriplasmin**	**Difference (95% CI)**	**p-value**
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
Key Secondary Endpoint: Total PVD								
	TG-MV-006				**TG-MV-007**			
	Placebo	**Ocriplasmin**	**Difference (95% CI)**	**p-value**	**Placebo**	**Ocriplasmin**	**Difference (95% CI)**	**p-value**
N	107	219			81	245		
n (%)	7 (6.5)	36 (16.4)	9.9 (3.1, 16.7)	0.014	0	26 (10.6)	10.6 (6.8, 14.5)	<0.001

Source: Table 10 and 11 of the Applicant's AC Meeting Briefing Package

The improvement in the primary and key secondary efficacy endpoint was not reflected as improvement in patients' visual acuity. As shown in the following table, 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. So far, the reason of more ocriplasmin treated patients having worsening of BCVA is still unclear.

Table 20: Categorical Change 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 (95% CI)** [a]	**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

5.2 Collective Evidence

In both studies TG-MV-006 and TG-MV-007, ocriplasmin 125 µg showed statistical superiority over placebo in achieving the primary efficacy endpoint, resolution of focal VMA at post-injection Day 28, as determined by masked CRC evaluation of OCT scans; and also in achieving the key secondary efficacy endpoint, patients with total PVD at post-injection Day 28, as determined by masked investigator-certified assessment of B-scan ultrasound.

In the Full Analysis Set, in TG-MV-006, more patients treated with ocriplasmin had resolution of VMA at Day 28, compared with placebo: 27.9% versus 13.1%, respectively, with absolute difference between treatment groups of 14.8% (95% CI: 6.0% – 23.5%, P=0.003); and in study TG-MV-007, 25.3% versus 6.2% with absolute difference of 19.1% (95% CI: 11.6% – 26.7%, P<0.001).

For the key secondary efficacy endpoint, in the Full Analysis Set, in TG-MV-006, more patients treated with ocriplasmin had total PVD at Day 28, compared with placebo: 16.4% versus 6.5%, respectively, with absolute difference between treatment groups of 9.9% (95% CI: 3.1%–16.7%, P=0.014); and in study TG-MV-007, 10.6% versus 0.0% with absolute difference of 10.6% (95% CI: 6.8%–14.5%, P<0.001). The treatment difference was similar for both studies at about 10%.

5.3 Conclusions and Recommendations

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

5.4 Labeling Recommendations

The Applicant seeks labeling claim of treatment of VMA (b) (4)

FTMHC was a secondary endpoint (among many other secondary endpoints, see Section 3.2.2 for detailed listing of additional secondary endpoints) for a subset of the overall study population. As the Applicant stated in the SAP: "No adjustments were made for multiple comparisons or multiple endpoints for the additional secondary endpoints. Statistical comparisons for these additional secondary efficacy endpoints were of a supportive nature only and were interpreted as such". Without proper multiplicity adjustment for this secondary endpoint (FTMHC), the study results of FTMHC might not have adequate statistical evidence to support the efficacy of

ocriplasmin for FTMHC in patients with FTMH at baseline. If Bonferroni correction method is used for multiplicity adjustment for testing at least 5 secondary endpoints, the significance level would be 0.01 for two-sided tests. Using 0.01 as the significance level for a two-sided test, the results for FTMHC endpoint at Month 6 are not statistically significant for study TG-MV-007 (p-value=0.005 for Study TG-MV-006, and 0.354 for Study TG-MV-007).

To support the indication for the treatment of FTMH, we recommend that the Applicant conduct at least one more pivotal study in patients with FTMH at baseline and using FTMHC as the primary efficacy endpoint.

The Applicant also presented in the label the favorable results of categorical improvement from baseline of BCVA. As shown in Table 20, compared to placebo treated patients, more ocriplasmin treated patients had worsening of BCVA as well as improvement of BCVA at Month 6; consequently; therefore, the statistical reviewer does not recommend putting the results of categorical improvement from baseline of BCVA in the labeling.

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/s/

YUNFAN DENG
09/21/2012

YAN WANG
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I concur.