

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125422Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

| | |
|--------------------------|---|
| BLA: 125,422 | Submission Date: 04/17/12 |
| Submission Type: | NME, Priority |
| Brand/Code Name: | JETREA® |
| Generic Name: | Ocriplasmin |
| Primary Reviewer: | Yoriko Harigaya, Pharm.D. |
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| OCP Division: | Division of Clinical Pharmacology 4 |
| ORM Division: | Division of Transplant and Ophthalmology Products |
| Sponsor: | ThromboGenics |
| Relevant IND: | 100,370 |
| Formulation; Strength: | Solution for IVT Injection (2.5mg/mL after dilution) |
| Proposed Indication: | Treatment of symptomatic vitreomacular adhesion including macular hole |
| Proposed Dosage Regimen: | Single Dose Intravitreal Injection of 125 µg (0.1 mL of the diluted solution) |

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1 EXECUTIVE SUMMARY

Ocriplasmin (JETREA™) intravitreal injection is a recombinant truncated form of human plasmin obtained from microplasminogen produced in a *Pichia pasoris* expression system by recombinant DNA technology. The current submission is the original BLA for Ocriplasmin with an indication of treatment of patients with symptomatic vitreomacular adhesion (VMA), including macular holes, at a single intravitreal dose of 125 µg (0.1 mL of the diluted 2.5mg/mL solution).

The intravitreal (IVT) pharmacokinetic (PK) profile of ocriplasmin was determined in a clinical Phase 2 Study TG-MV-010 after IVT administration by measuring ocriplasmin activity levels in the vitreous humor in patients with eye disease for which a primary vitrectomy was indicated (n=38). In addition, the systemic PK profile of ocriplasmin was determined in a clinical Study TG-M-001 after intravenous (IV) administration in healthy volunteers (n=62) by measuring ocriplasmin antigen levels, as ocriplasmin was originally developed as a thrombolytic agent for intravascular use (terminated for commercial reasons). To support approval for this indication, the sponsor conducted two Phase 3 Studies TG-MV-006 and TG-MV-007 in patients with symptomatic VMA.

1.1 Recommendation

From a Clinical Pharmacology perspective, the application is acceptable provided that the Sponsor and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

1.2 Labeling Recommendations

Please refer to Section 3.1 for detailed labeling recommendations.

1.3 Phase 4 Requirements

No Phase IV study recommendation.

1.4 Summary of Clinical Pharmacology Findings

The sponsor submitted the study report and datasets for the Phase 2 Study TG-MV-010 evaluating the PK properties of IVT ocriplasmin in the vitreous humor at a single dose of 125µg when administered at different time points prior to planned primary pars plana vitrectomy (PPV).

- All subjects in the ocriplasmin treatment group (n=16) displayed ocriplasmin activity levels in the vitreous humor above LLOQ (<272.37ng/mL) between 0.5 and 4 hours post-dose and below the LLOQ after at least 24 hours post-dose.
- Ocriplasmin appeared to be inactivated mostly via α 2-antiplasmin, and the systemic absorption of ocriplasmin following a single IVT dose is expected to be minimal.
- Safety observations did not suggest a significant risk associated with single dose IVT administration of 125 µg ocriplasmin.

2 QUESTION BASED REVIEW

General Attributes

2.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Ocriplasmin (molecular weight [MW] 27.2kDa), is a truncated form of human plasmin which retains protease activity (Figure 1 and Table 1). Recombinant human ocriplasmin is produced in the transformed yeast *Pichia pastoris* (b) (4)

Ocriplasmin will be supplied in 2mL glass vials containing 0.5 mg ocriplasmin as a frozen liquid. The quantitative composition of the product (1 vial) is provided in Table 2. Each vial should only be used once and for the treatment of a single eye.

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Table 2: Composition of Ocriplasmin

| Components | Concentration | Function |
|------------------------------------|---------------|-------------------|
| ocriplasmin | 2.5mg/mL | active ingredient |
| mannitol | 3.75mg/mL | (b) (4) |
| citric acid (b) (4) | 1.051mg/mL | (b) (4) |
| water for injection Ph. Eur. / USP | (b) (4) | (b) (4) |

2.2 What are the proposed mechanism of action and therapeutic indication?

Ocriplasmin exerts proteolytic effects on collagen, fibronectin, and laminin to produce vitreous liquefaction and detachment from the macula. Ocriplasmin’s proteolytic properties target the architectural components of the vitreous and the adhesion at the vitreoretinal interface, both of which are implicated in the pathogenesis of symptomatic VMA. In addition, ocriplasmin’s proteolytic activity is under control of serine protease inhibitors, α 2-antiplasmin and α 2-macroglobulin.

2.3 What are the proposed dosage and route of administration?

Dosage Form: a sterile, clear, colorless solution for IVT administration after dilution with normal saline (0.9%)

Route of Administration: IVT Injection

Proposed dose: single dose of 125 μ g of ocriplasmin

General Clinical Pharmacology

2.4 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Results of clinical pharmacology studies (TG-MV-010, TG-M-001) were submitted to support the clinical pharmacology of ocriplasmin for patients with symptomatic VMA (Table 3).

Table 3: Clinical Pharmacology Studies

| Type of Study | Study | Objectives | Study Design | Dosage Regimen | Number of Subjects |
|-----------------------------|-----------|---|---|--|--|
| PK and initial tolerability | TG-M-001 | safety and tolerability in ascending doses and preliminary PK and pharmacodynamic (PD) | Placebo controlled; double blind; dose escalation | ocriplasmin; (b) (4) powder, 50mg; single dose; part 1: 0.1, 0.5, 1.0, 2.0mg/kg 15min infusion, part 2: 1.0mg/kg 15min infusion plus 1.0, 2.0, 3.0, 4.0mg/kg 60min infusion, part 3: 1.0mg/kg 15min infusion plus 1.0mg/kg 60min infusion; IV infusion | 60 healthy subjects (40 drug, 20 placebo) |
| PK | TG-MV-010 | PK properties of IVT microplasmin 125mcg dose when administered at different time points prior to planned pars plana vitrectomy (PPV) | open-label; notreatment control; ascending exposure time; single centre | Ocriplasmin solution; 2.5mg/mL, single dose, 125µg; IVT injection | 38 patients scheduled for primary pars plana vitrectomy (34 drug, 4 control) |

2.5 What is the clinical efficacy and safety in patients?

Summary of Clinical Efficacy

Onset of effect of ocriplasmin 125 µg was observed approximately 1 week after injection and the treatment effect was sustained throughout the 6-month study period. VMA resolution rate (approximately 25%; 123/464) and full thickness macular hole (FTMH) closure rate without surgery (approximately 40%; 43/106) at Day 28 in the ocriplasmin 125 µg treatment group were higher compared to the placebo group [approximately 10% for both VMA (19/188) and FTMH closure (5/47)] in the pivotal placebo-controlled studies (Figure 2 and Figure 3). Patients treated with ocriplasmin were less likely to require vitrectomy (approximately 20%) compared to placebo (approximately 30%).

Figure 2: Proportion of Patients with VMA Resolution in the Study Eye (TG-MV-006, TG-MV-007 and Integrated Studies)

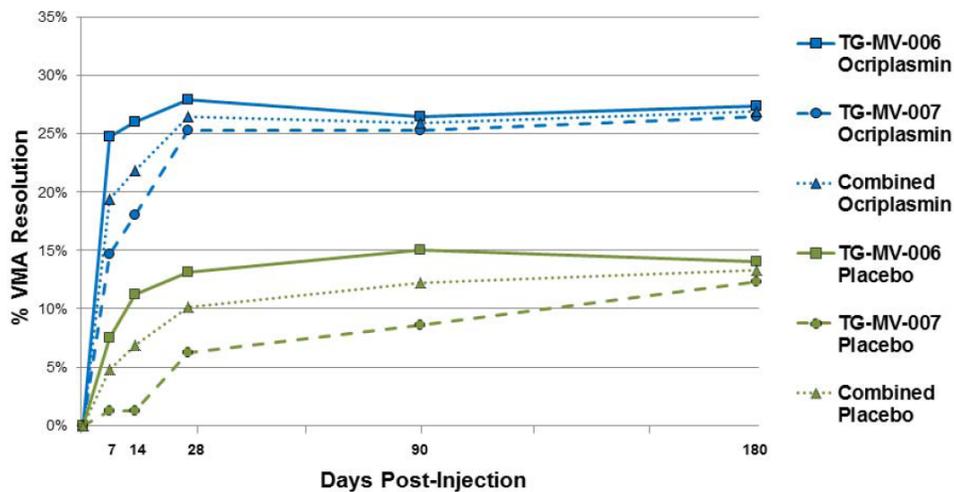
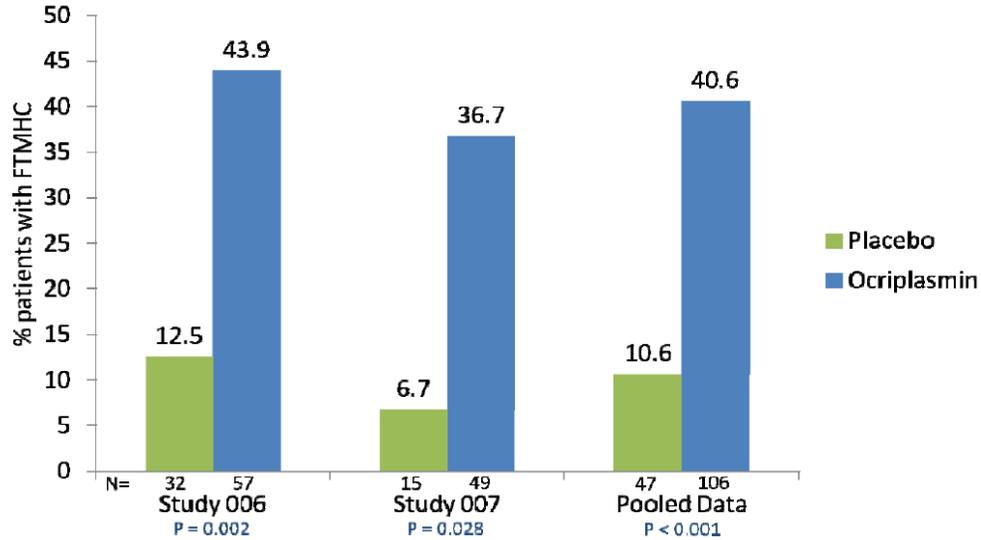
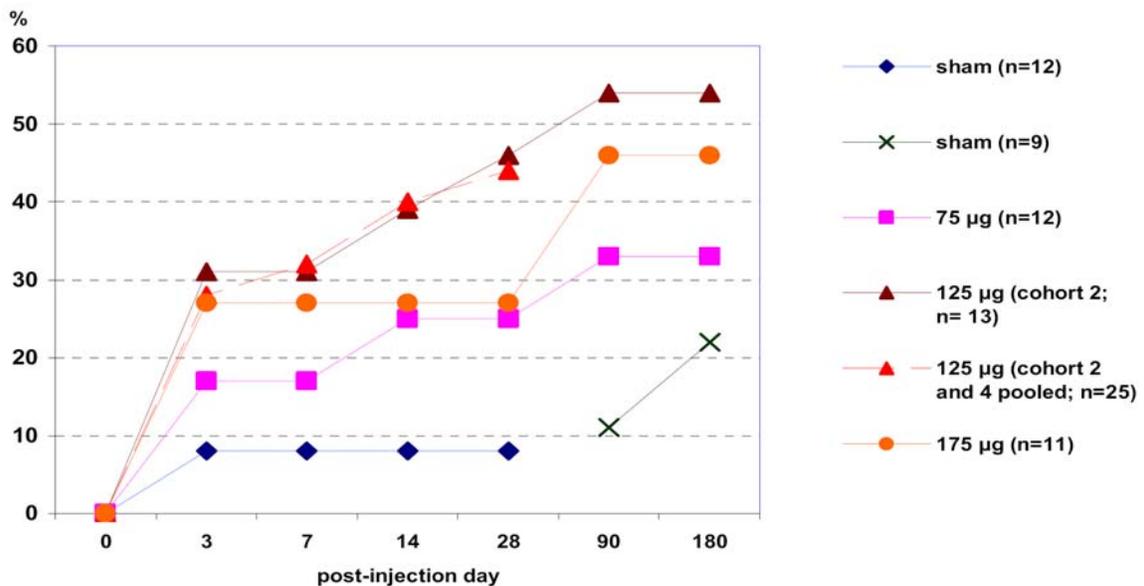


Figure 3: Proportion of Patients with FTMH at Baseline who achieved Non-Surgical FTMH closure (FTMHC) by Day 28 (TG-MV-006, TG-MV-007 and Integrated Studies)



In Study TG-MV-004, the vitreomacular traction (VMT) resolution rates in placebo, 75 µg and 125 µg ocriplasmin treatment groups at Day 180 were increased dose proportionally up to 125 µg (22%, 33% and 54%, respectively). However, no clear difference in VMT resolution rate was observed between the 125 µg group (54% VMT resolution) and the 175 µg group (46% VMT resolution) at Day 180. A plateau in VMT resolution seems to be achieved with 125 µg ocriplasmin (Figure 4).

Figure 4: Proportion of subjects with resolution of VMT (TG-MV-004)



Summary of Clinical Safety

Most of suspected adverse drug reactions were observed at ocular, which is consistent with the route of administration. The most notable safety findings were those related to visual function changes (*i.e.* visual impairment, dyschromatopsia and / or electroretinogram (ERG) changes). The time to onset visual impairment was within a few hours to days of the injection, and they were generally reversible within 2 weeks without intervention.

The incidence rate of visual acuity reduction (1.5%, 2.8%, 6.4%, and 9.1%) was higher at higher doses of ocriplasmin (25 µg, 75 µg, 125 µg and 175 µg, respectively) (Table 4). The significantly higher ($p<0.05$) incidence rates of Vision blurred (7.2%) and Visual impairment (4.5%) were observed with 125 µg ocriplasmin group compared to placebo group (2.8% and 0.8%, respectively).

Vision alteration was reported more frequently in younger patients (<65 years) (24.5%, 11.4%) than older patients (≥ 65 years) (14.1%, 1.4%) treated with ocriplasmin 125 µg or placebo, respectively, in the pivotal placebo-controlled studies (TG-MV-006 and TG-MV-007).

A subset of patients (6/820 [0.7%]) from clinical studies had serious and / or severe acute visual impairment with rapid VMA resolution. In all but 1 case, the acute visual impairment resolved. The lack of resolution was considered by the investigator to be due to this patient's concomitant disease. Many of these acute visual impairments were probably related to the mechanical effects of ocriplasmin-induced pharmacologic vitreolysis / posterior vitreous detachment (PVD).

Other common adverse drug reactions ($\geq 5\%$) observed in subjects treated with 125 µg ocriplasmin were Vitreous floaters (17.4%), Eye pain (11.9%), Photopsia (10.7%) and Retinal oedema (5%). The significantly higher ($p<0.05$) incidence rates of Vitreous floaters (17.4% v.s. 7.3%), Photopsia (10.7% v.s. 2.8%), Retinal edema (5% v.s. 0.8%), Photophobia (3.4% v.s. 0%), Vitreous detachment (2.1% v.s. 0.8%) and Iritis (2.1% v.s. 0%) were observed with 125 µg ocriplasmin group compared to placebo group (Table 4).

Table 4: Suspected Adverse Drug Reactions in the Study Eye Summarized by Ocriplasmin Dose for all Studies Combined. The redline boxes indicate Placebo and 125 µg groups. The events were highlighted in red when the incidence rates of safety events between Placebo and 125 µg groups are significantly different (chi-squared test $p<0.05$).

| Preferred Term | Placebo/Sham (N=247) | | | Ocriciplasmin | | | | | | | | | | | | | | |
|--------------------------------|-------------------------|---------|----|----------------|---------|----|----------------|---------|---|----------------|----------|----|------------------|----------|-----|-----------------|----------|---|
| | n | (%) | E | 25µg (N=67) | | | 50µg (N=10) | | | 75µg (N=71) | | | 125µg (N=582) | | | 175µg (N=11) | | |
| | n | (%) | E | n | (%) | E | n | (%) | E | n | (%) | E | n | (%) | E | n | (%) | E |
| Suspected ADRs | | | | | | | | | | | | | | | | | | |
| Vitreous floaters | 18 | (7.3%) | 19 | 3 | (4.5%) | 3 | 0 | | 0 | 11 | (15.5%) | 12 | 101 | (17.4%) | 111 | 4 | (36.4%) | 5 |
| Eye pain | 19 | (7.7%) | 22 | 11 | (16.4%) | 14 | 0 | | 0 | 9 | (12.7%) | 11 | 69 | (11.9%) | 77 | 1 | (9.1%) | 1 |
| Photopsia | 7 | (2.8%) | 7 | 3 | (4.5%) | 3 | 0 | | 0 | 1 | (1.4%) | 1 | 62 | (10.7%) | 67 | 0 | | 0 |
| Vision blurred | 7 | (2.8%) | 8 | 3 | (4.5%) | 3 | 0 | | 0 | 2 | (2.8%) | 2 | 42 | (7.2%) | 44 | 0 | | 0 |
| Visual acuity reduced | 8 | (3.2%) | 8 | 1 | (1.5%) | 1 | 0 | | 0 | 2 | (2.8%) | 2 | 37 | (6.4%) | 38 | 1 | (9.1%) | 1 |
| Visual impairment | 2 | (0.8%) | 2 | 0 | | 0 | 0 | | 0 | 1 | (1.4%) | 1 | 26 | (4.5%) | 28 | 0 | | 0 |
| Retinal oedema | 2 | (0.8%) | 2 | 1 | (1.5%) | 1 | 0 | | 0 | 2 | (2.8%) | 2 | 29 | (5.0%) | 32 | 0 | | 0 |
| Macular oedema | 10 | (4.0%) | 12 | 5 | (7.5%) | 6 | 0 | | 0 | 10 | (14.1%) | 11 | 27 | (4.6%) | 29 | 1 | (9.1%) | 1 |
| Anterior chamber cell | 12 | (4.9%) | 13 | 12 | (17.9%) | 13 | 0 | | 0 | 14 | (19.7%) | 18 | 31 | (5.3%) | 35 | 0 | | 0 |
| Photophobia | 0 | | 0 | 4 | (6.0%) | 4 | 0 | | 0 | 1 | (1.4%) | 1 | 20 | (3.4%) | 20 | 0 | | 0 |
| Ocular discomfort | 4 | (1.6%) | 4 | 1 | (1.5%) | 1 | 0 | | 0 | 2 | (2.8%) | 2 | 14 | (2.4%) | 14 | 0 | | 0 |
| Vitreous detachment | 2 | (0.8%) | 2 | 0 | | 0 | 0 | | 0 | 1 | (1.4%) | 1 | 12 | (2.1%) | 13 | 0 | | 0 |
| Iritis | 0 | | 0 | 0 | | 0 | 0 | | 0 | 0 | | 0 | 12 | (2.1%) | 13 | 0 | | 0 |
| Dry eye | 2 | (0.8%) | 2 | 0 | | 0 | 0 | | 0 | 1 | (1.4%) | 1 | 13 | (2.2%) | 13 | 0 | | 0 |
| Metamorphopsia | 1 | (0.4%) | 1 | 3 | (4.5%) | 3 | 0 | | 0 | 0 | | 0 | 11 | (1.9%) | 11 | 0 | | 0 |
| Retinal degeneration | 1 | (0.4%) | 1 | 1 | (1.5%) | 1 | 0 | | 0 | 2 | (2.8%) | 2 | 8 | (1.4%) | 8 | 0 | | 0 |
| Eyelid oedema | 8 | (3.2%) | 8 | 7 | (10.4%) | 8 | 0 | | 0 | 3 | (4.2%) | 3 | 12 | (2.1%) | 13 | 0 | | 0 |
| Retinal pigment epitheliopathy | 4 | (1.6%) | 4 | 6 | (9.0%) | 6 | 0 | | 0 | 6 | (8.5%) | 6 | 12 | (2.1%) | 12 | 0 | | 0 |
| Macular degeneration | 1 | (0.4%) | 1 | 3 | (4.5%) | 3 | 1 | (10.0%) | 2 | 3 | (4.2%) | 3 | 6 | (1.0%) | 6 | 0 | | 0 |
| Miosis | 0 | | 0 | 0 | | 0 | 0 | | 0 | 0 | | 0 | 5 | (0.9%) | 5 | 0 | | 0 |
| Scotoma | 0 | | 0 | 0 | | 0 | 0 | | 0 | 0 | | 0 | 5 | (0.9%) | 5 | 0 | | 0 |
| Corneal abrasion | 1 | (0.4%) | 1 | 1 | (1.5%) | 1 | 0 | | 0 | 1 | (1.4%) | 1 | 5 | (0.9%) | 5 | 0 | | 0 |
| Ocular hyperaemia | 1 | (0.4%) | 1 | 4 | (6.0%) | 6 | 0 | | 0 | 2 | (2.8%) | 4 | 8 | (1.4%) | 8 | 0 | | 0 |
| Conjunctival irritation | 0 | | 0 | 0 | | 0 | 0 | | 0 | 0 | | 0 | 4 | (0.7%) | 4 | 0 | | 0 |
| Diplopia | 0 | | 0 | 0 | | 0 | 0 | | 0 | 0 | | 0 | 4 | (0.7%) | 4 | 0 | | 0 |
| Visual field defect | 1 | (0.4%) | 1 | 0 | | 0 | 1 | (10.0%) | 1 | 0 | | 0 | 3 | (0.5%) | 3 | 0 | | 0 |
| Pupils unequal | 0 | | 0 | 0 | | 0 | 0 | | 0 | 0 | | 0 | 3 | (0.5%) | 3 | 0 | | 0 |

Although a single IVT dose of 175µg ocriciplasmin was studied in a small number of patients (n=11) in StudyTG-MV-004, the risk profile of 175µg dose group showed no significant differences compared with 125µg dose group ($p \geq 0.05$).

Pharmacokinetic Characteristics of the Drug

2.6 What are the single dose PK parameters?

Phase 1 – Plasma Ocriciplasmin PK Parameters in Healthy Volunteers Following Single IV Administration (Study TG-M-001)

A single 15 min intravenous (IV) infusion was given at different dose levels in healthy volunteers. C_{max} and AUC parameters did not increase in a dose proportional manner. C_{max} increased in a sub-proportional manner, while AUC(0-t) increased in a supra-proportional manner which may be suggestive of saturation of microplasma elimination mechanisms at high prevailing plasma concentrations (Table 5). Ocriciplasmin was cleared with a half-life of approximately 3.5 to 8 hours following a single dose 15 min IV infusion in healthy volunteers.

Table 5: Plasma Ocriplasmin PK Parameters: Study TG-M-001: Single Dose *via* fast infusion over 15min

| Infusion Dose [Ratio] (mg.kg ⁻¹) | n | Adjusted Geometric Mean | |
|---|---|--|--|
| | | Cmax [Ratio] (ng.ml ⁻¹) | AUC(0-t) [Ratio] (ng.h.ml ⁻¹) |
| F 0.5 [1] | 4 | 12930 [1] | 28190 [1] |
| F 1.0 [2] | 4 | 28270 [2.19] | 106900 [3.79] |
| F 1.5 [3] | 4 | 30860 [2.39] | 122100 [4.33] |
| F 2.0 [4] | 4 | 42290 [3.27] | 214100 [7.59] |

Phase 2 –Ocriplasmin PK Parameters in Patients with Eye Disease Following Single IVT Administration (Study TG-MV-010)

The PK properties of a single 125µg IVT dose of ocriplasmin were evaluated when administered at different time points prior to planned primary pars plana vitrectomy in patients with eye disease. The enzymatic activity of ocriplasmin was assessed to determine the concentration of ocriplasmin in human vitreous fluid. The mean ocriplasmin activity level was 11600, 8109, 2611, 497 ng/mL, and <LLOQ (272.37 ng/mL) in vitreous samples collected at 5-30 min, 31-60 min, 2-4 hours, 24+/-2 hours, 7+/-1 days post-injection, respectively (Figure 5 and Table 6). The maximum IVT ocriplasmin activity level observed at 5-30 min was approximately 22 µg/mL, and 1/8 (12.5%) patients had IVT ocriplasmin activity levels below LLOQ (<272.37 ng/mL) at 5-30 min post-dose. All patients (n=16) had IVT ocriplasmin activity levels above LLOQ between 0.5 and 4 hours post-dose, and 50% of patients (2/4) displayed IVT ocriplasmin activity levels below LLOQ at 24+/-2 hours post-dose. IVT ocriplasmin activity level was not detected at Day 7 post-dose. Inter-individual variability (CV%) at each study visit was 58 to 65% throughout 24 hours post-dose. The mean ocriplasmin activity levels appeared to decrease via a second-order kinetic process in human eyes as this was observed in an *in vitro* study.

Figure 5: Box Plot of Ocriplasmin Activity Levels vs. Time from IVT Injection

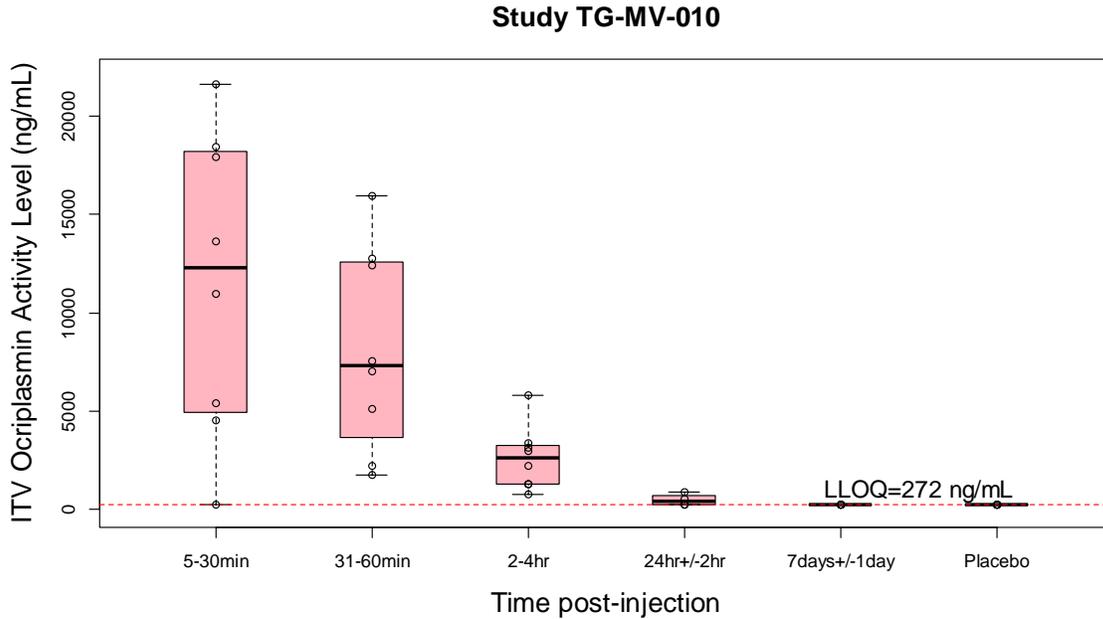


Table 6: Ocriplasmin Activity Levels (ng/mL) Following a Single 125 µg Dose: Study TG-MV-010

| Time post-injection (subjects) | 5-30min (n=8) | 31-60min (n=8) | 2-4hours (n=8) | 24hr +/- 2hr: (n=4) | 7dyas +/- 1day: (n=4) | Placebo (n=4) |
|--------------------------------|---------------|----------------|----------------|---------------------|-----------------------|---------------|
| Minimum | <LLOQ | 1751.0 | 783.3 | <LLOQ | <LLOQ | <LLOQ |
| Mean | 11600.0 | 8109.0 | 2611.0 | 496.5 | <LLOQ | <LLOQ |
| Maximum | 21610.0 | 15970.0 | 5784.0 | 876.1 | <LLOQ | <LLOQ |
| SD | ±7637.4 | ±5181.9 | ±1608.3 | ±288.2 | N/A | N/A |
| CV% | 65 | 64 | 62 | 58 | N/A | N/A |

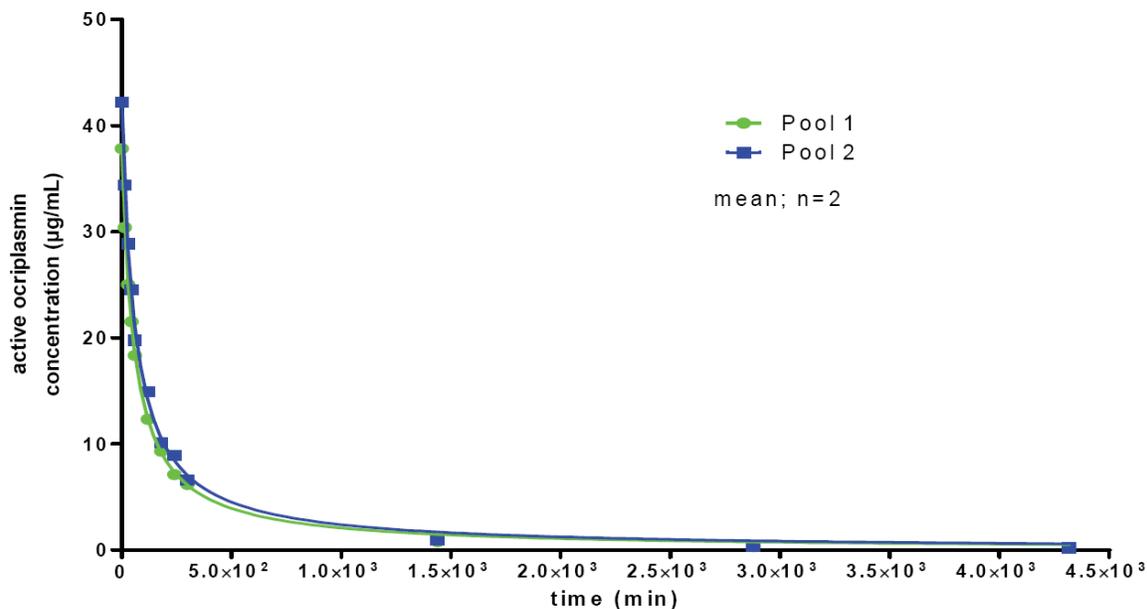
*LLOQ=272.4 ng/mL

2.7 What are the characteristics of drug absorption, distribution and metabolism?

No drug absorption, distribution and metabolism study has been conducted for ocriplasmin. Ocriplasmin is a biologic product, and ocriplasmin is inactivated via auto proteolysis and its interactions with protease inhibitor α 2-antiplasmin or α -macroglobulin.

Concentrations of active ocriplasmin in pooled human vitreous fluid were evaluated in an *in vitro* study following the addition of 125µg ocriplasmin and incubation at +37°C. Approximately 16% of the initial actual concentrations were left after 5 hours incubation. Less than 0.6% of the initial actual concentrations were left after 3 days incubation (Figure 6). Ocriplasmin was inactivated quickly in this *in vitro* study, which is similar to the inactivation observed in patients' eyes in Study TG-MV-010. The result suggests that ocriplasmin is inactivated via α 2-antiplasmin, and the systemic absorption of ocriplasmin following a single dose of IVT injection is expected to be minimal.

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



Immunogenicity

2.8 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

In Study TG-M-001, there was no evidence of a dose-related trend of elevated titres of anti-ocriplasmin antibodies and none of the elevated titres of anti-ocriplasmin antibodies was associated with clinical findings following a single IV dose of ocriplasmin to healthy volunteers.

Analytical Section

2.9 What bioanalytical methods are used to assess concentrations? Are the bioanalytical methods acceptable?

The determination of the concentration of active microplasmin is based on the difference in absorbance (optical density) between the chromogen (p-nitrozniline) formed and the original chromogenic substrate. When microplasmin is incubated at 37°C with a chromogenic substrate, the p-nitroaniline (pNA) moiety of the substrate will be released. The rate of this chromogen formation is proportional to the enzymatic activity of microplasmin and is measured with a spectrophotometer.

Five calibration curves were prepared and analyzed. For each curve, six microplasmin

calibrators were prepared at the following concentrations: 5 nM, 10nM, 20 nM, 40 nM, 70 nM and 100 nM. The limits of quantitation are determined as the lowest/highest concentration of Quality Control (QC) samples for which precision and accuracy are satisfactory.

Acceptance criteria for accuracy and precision are met from 5 nM to 80 nM; however, considering that several individual recoveries are below 70% for the 5 nM level (Table 7). Therefore, the practical range of quantification from 10 nM (272.37 ng/mL) to 80 nM (2178.96 ng/mL) after a ^{(b) (4)} dilution of the vitreous fluid with a ^{(b) (4)} was defined.

Table 7: Bioanalytical Method (optical density) Validation for Ocriplasmin Activity

| | 5 nM | | 10 nM | | 50 nM | | 80 nM | |
|--------------------|-------------------|------------------|-------------------|------------------|-------------------|------------------|-------------------|------------------|
| | Accuracy (% Diff) | Precision (% CV) |
| Intra-assay | 83.5 | 1.7 | 71.4 | 1.5 | 97 | 1 | 90.9 | 1.4 |
| Inter-assay | 66.8 | 20.4 | 80.6 | 11.6 | 94.8 | 2.3 | 94.3 | 3.3 |

3 APPENDIX

3.1 Label Statements

Detailed Labeling Recommendations are follows (The sponsor's changes are given as single underlines and FDA recommended changes are given as double underlines and ~~striketrough~~ for deletions).

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3.2 Individual Study Reviews

Study TG-MV-010

Title: An Open-Label, Ascending-Exposure-Time, Single Center Trial To Evaluate The Pharmacokinetic Properties Of Ocriplasmin IVT Injection In Subjects Scheduled For Primary Pars Plana Vitrectomy

Objective

This study was a Phase 2, open-label, ascending-exposure-time, single centre study to evaluate the PK properties of 125µg ocriplasmin administered as a single intravitreal dose at different time points prior to planned primary pars plana vitrectomy (PPV).

Methods

Patients were allocated to 1 of the following groups in a sequential manner until a group was full, starting with Group 1 and ending with Group 6:

- Group 1: PPV 5-30 minutes after ocriplasmin injection (n=8)
- Group 2: PPV 31-60 minutes after ocriplasmin injection (n=8)
- Group 3: PPV 2-4 hours after ocriplasmin injection (n=8)
- Group 4: PPV 24 hours (± 2 hours) after ocriplasmin injection (n=4)
- Group 5: PPV 7 days (± 1 day) after ocriplasmin injection (n=4)
- Group 6: PPV without prior ocriplasmin injection (control arm) (n=4)

A vitreous sample was obtained at the beginning of primary vitrectomy in patients at various times relative to ocriplasmin injection (post-injection) for the determination of ocriplasmin activity: Group 1 (5-30 minutes); Group 2 (31-60 minutes); Group 3 (2-4 hours); Group 4 (24 hours ± 2 hours); Group 5 (7 days ± 1 day). Patients in Group 6 did not receive an ocriplasmin injection but vitreous samples were evaluated as a control group.

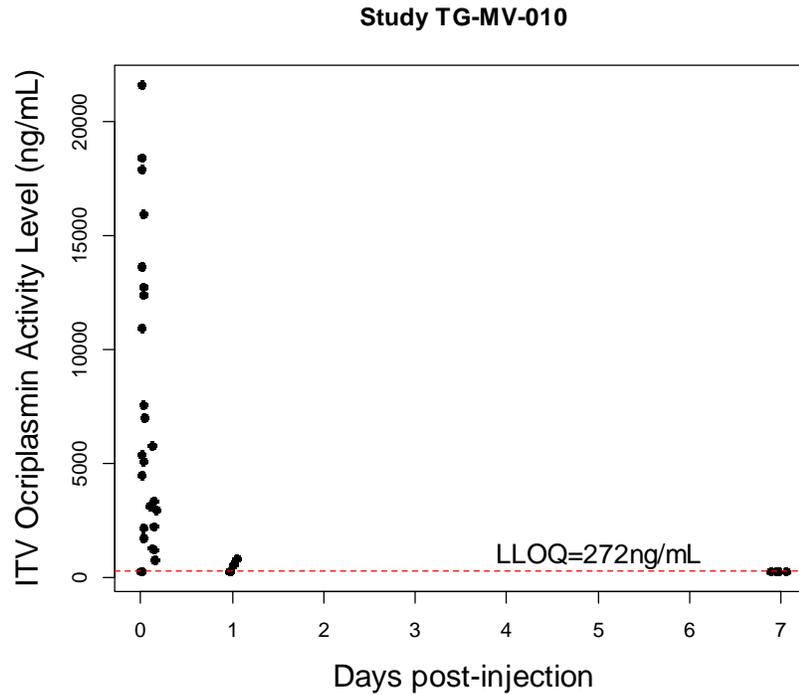
Results

Thirty-eight patients were enrolled in the study. As 2 patients had vitreous samples not suitable for inclusion in the ocriplasmin activity analysis, 2 additional patients were enrolled resulting in 38 patients rather than the planned 36.

The mean ocriplasmin activity level was 11597.7ng/mL in samples collected 5-30 minutes post injection (Group 1). Mean ocriplasmin activity levels decreased with the time from injection to sampling (8108.7ng/mL [31- 60 minutes, Group 2]; 2610.6ng/mL [2-4 hours, Group 3]; 496.5ng/mL [24 hours, Group 4]). 2/4 patients (50.0%) in Group 4 had an ocriplasmin activity level < LLOQ (272ng/mL) (Figure 7).

Ocriplasmin activity levels in vitreous samples collected 7 days post-injection (Group 5) were comparable to the control group (Group 6), and all results in both groups displayed below the LLOQ (< 272ng/mL).

Figure 7 : Scatter Plot of Ocriplasmin Activity Level versus Time from Injection



There were 8/34 subjects (23.5%) with 27 drug-related ocular adverse events during the study. The most common drug-related ocular adverse events included reduced visual acuity (7/34 subjects [20.6%]), vitreous floaters (7/34 subjects [20.6%]), photopsia (5/34 subjects [14.7%]) and chromatopsia (4/34 subjects [11.8%]) (Table 8).

Table 8: Summary of Adverse Events (Study TG-MV-010)

| Category | | Ocriclasmin (N=34) | | | Control (N=4) | | |
|---------------------------|-------------------------|--------------------|---------|--------|---------------|---------|--------|
| | | n | (%) | Events | n | (%) | Events |
| All AEs | Any Event | 21 | (61.8%) | 65 | 3 | (75.0%) | 11 |
| | Any Non-Ocular Event | 5 | (14.7%) | 6 | 2 | (50.0%) | 3 |
| | Any Ocular Event | 19 | (55.9%) | 59 | 2 | (50.0%) | 8 |
| | Any Study Eye Event | 19 | (55.9%) | 57 | 2 | (50.0%) | 8 |
| | Any Non-Study Eye Event | 2 | (5.9%) | 2 | 0 | 0 | 0 |
| Drug-Related AEs | Any Event | 8 | (23.5%) | 27 | 0 | 0 | 0 |
| | Any Ocular Event | 8 | (23.5%) | 27 | 0 | 0 | 0 |
| | Any Study Eye Event | 8 | (23.5%) | 27 | 0 | 0 | 0 |
| | | | | | | | |
| Severe AEs | Any Event | 2 | (5.9%) | 2 | 2 | (50.0%) | 3 |
| | Any Ocular Event | 1 | (2.9%) | 1 | 1 | (25.0%) | 2 |
| | Any Study Eye Event | 1 | (2.9%) | 1 | 1 | (25.0%) | 2 |
| SAEs | Any Event | 2 | (5.9%) | 2 | 2 | (50.0%) | 4 |
| | Any Non-Ocular Event | 2 | (5.9%) | 2 | 1 | (25.0%) | 1 |
| | Any Ocular Event | 0 | 0 | 0 | 1 | (25.0%) | 3 |
| | Any Study Eye Event | 0 | 0 | 0 | 1 | (25.0%) | 3 |
| Discontinued due to an AE | | 0 | 0 | 0 | 0 | 0 | 0 |
| Deaths | | 0 | 0 | 0 | 0 | 0 | 0 |

Reviewer's discussion:

All subjects in the ocriclasmin treatment group (n=16) displayed IVT ocriclasmin activity level above LLOQ (272.37ng/mL) between 0.5 and 4 hours post-dose and below the LLOQ after at least 24 hours post-dose.

Ocriclasmin appeared to be inactivated in human eyes in a similar manner to the inactivation rate observed in an in vitro study, which suggests that ocriclasmin is inactivated mostly via α 2-antiplasmin, and the systemic absorption of ocriclasmin following a single dose of 125 μ g IVT ocriclasmin injection will be minimal. No drug related systemic adverse events were observed.

3.3 BLA Filing and Review Form

| Office of Clinical Pharmacology <i>NEW DRUG APPLICATION FILING AND REVIEW FORM</i> | | | | |
|---|--------------------------------------|-----------------------------|----------------------------|--|
| General Information About the Submission | | | | |
| | Information | | Information | |
| NDA/BLA Number | 125,422 | | Brand Name | Jetrea |
| OCP Division (I, II, III, IV, V) | IV | | Generic Name | Ocriplasmin |
| Medical Division | DTOP | | Drug Class | Poteolytic |
| OCP Reviewer | Yoriko Harigaya, Pharm.D. | | Indication(s) | Treatment of symptomatic vitreomacular adhesion including macular hole |
| OCP Team Leader | Philip M. Colangelo, Pharm.D., Ph.D. | | Dosage Form | Solution for injection |
| Pharmacometrics Reviewer | N/A | | Dosing Regimen | Single dose |
| Date of Submission | April 16, 2012 | | Route of Administration | Intravitreal injection |
| Estimated Due Date of OCP Review | October 16, 2012 | | Sponsor | ThromboGenics |
| Medical Division Due Date | N/A | | Priority Classification | Priority |
| PDUFA Due Date | N/A | | | |
| <i>Clin. Pharm. and Biopharm. Information</i> | | | | |
| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
| STUDY TYPE | | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | | | | |
| Tabular Listing of All Human Studies | | | | |
| HPK Summary | | | | |
| Labeling | | | | |
| Reference Bioanalytical and Analytical Methods | | | | |
| I. Clinical Pharmacology | | | | |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | | | | |
| Healthy Volunteers- | | | | |
| single dose: | | | | |
| multiple dose: | X | 1 | | |
| Patients- | | | | |
| single dose: | X | 1 | | |
| multiple dose: | | | | |
| Dose proportionality - | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| Drug-drug interaction studies - | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| Subpopulation studies - | | | | |

| | | | | |
|---|--|----------|--|--|
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| PD - | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| PK/PD - | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| Population Analyses - | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| II. Biopharmaceutics | | | | |
| Absolute bioavailability | | | | |
| Relative bioavailability - | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| Bioequivalence studies - | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| Food-drug interaction studies | | | | |
| Bio-waiver request based on BCS | | | | |
| BCS class | | | | |
| Dissolution study to evaluate alcohol induced dose-dumping | | | | |
| III. Other CPB Studies | | | | |
| Genotype/phenotype studies | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | | 2 | | |
| | | | | |

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

/s/

YORIKO HARIGAYA
09/26/2012

PHILIP M COLANGELO
09/26/2012

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

| <i>General Information About the Submission</i> | | | |
|---|--------------------------------------|-------------------------|--|
| | Information | | Information |
| NDA/BLA Number | 125,422 | Brand Name | Jetrea |
| OCP Division (I, II, III, IV, V) | IV | Generic Name | Ocriplasmin |
| Medical Division | DTOP | Drug Class | Poteolytic |
| OCP Reviewer | Yoriko Harigaya, Pharm.D. | Indication(s) | Treatment of symptomatic vitreomacular adhesion including macular hole |
| OCP Team Leader | Philip M. Colangelo, Pharm.D., Ph.D. | Dosage Form | Solution for injection |
| Pharmacometrics Reviewer | N/A | Dosing Regimen | Single dose |
| Date of Submission | April 16, 2012 | Route of Administration | Intravitreal injection |
| Estimated Due Date of OCP Review | October 16, 2012 | Sponsor | ThromboGenics |
| Medical Division Due Date | N/A | Priority Classification | Priority |
| PDUFA Due Date | N/A | | |

Clin. Pharm. and Biopharm. Information

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|--|---------------------------|-----------------------------|----------------------------|--------------------------|
| STUDY TYPE | | | | |
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| Tabular Listing of All Human Studies | | | | |
| HPK Summary | | | | |
| Labeling | | | | |
| Reference Bioanalytical and Analytical Methods | | | | |
| I. Clinical Pharmacology | | | | |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | | | | |
| Healthy Volunteers- | | | | |
| single dose: | | | | |
| multiple dose: | X | 1 | | |
| Patients- | | | | |
| single dose: | X | 1 | | |
| multiple dose: | | | | |
| Dose proportionality - | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| Drug-drug interaction studies - | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| Subpopulation studies - | | | | |

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | | | | |
|---|--|---|--|--|
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| PD - | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| PK/PD - | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| Population Analyses - | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| II. Biopharmaceutics | | | | |
| Absolute bioavailability | | | | |
| Relative bioavailability - | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| Bioequivalence studies - | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| Food-drug interaction studies | | | | |
| Bio-waiver request based on BCS | | | | |
| BCS class | | | | |
| Dissolution study to evaluate alcohol induced dose-dumping | | | | |
| III. Other CPB Studies | | | | |
| Genotype/phenotype studies | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | | 2 | | |

On initial review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|-----|----|-----|---------|
| Criteria for Refusal to File (RTF) | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | | | X | |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | | | X | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | | | X | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | | | X | |
| 5 | Has a rationale for dose selection been submitted? | X | | | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | X | | | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | | | X | |
| 8 | Is the electronic submission searchable, does it have appropriate | X | | | |

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | | | | | |
|---|--|---|---|---|--|
| | hyperlinks and do the hyperlinks work? | | | | |
| Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) | | | | | |
| Data | | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | X | | | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | X | |
| Studies and Analyses | | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | X | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | | | X | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | | | X | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | | X | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | X | |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | X | |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | | | X | |
| General | | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | X | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | X | | |

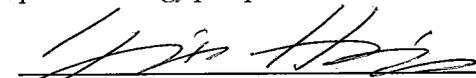
IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
There are no potential review issues to be forwarded to the applicant for the 74 day letter from a clinical pharmacology perspective.



Reviewing Clinical Pharmacologist

5/24/2012

Date



Team Leader/Supervisor

5/24/2012

Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for
NDA_BLA or Supplement 090808

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

/s/

JACQUELYN E SMITH
06/20/2012