DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125422/0 **BLA APPROVAL**

ThromboGenics, Inc.
Attention: Fang Li, Ph.D., RAC
Head of Regulatory Affairs, US
101 Wood Avenue South, 6th Floor
Iselin, NJ 08830

Dear Dr. Li:

Please refer to your Biologics License Application (BLA) dated April 16, 2012, received April 17, 2012, submitted under section 351 of the Public Health Service Act for Jetrea (ocriplasmin) Intravitreal Injection, 2.5 mg/mL.

We acknowledge receipt of your amendments dated:

April 26, 2012	July 20, 2012	September 28, 2012
June 11, 2012	July 31, 2012	October 2, 2012
June 15, 2012	August 15, 2012 (2)	October 5, 2012
June 21, 2012	August 16, 2012	October 7, 2012
June 22, 2012	August 22, 2012	October 16, 2012
June 25, 2012	August 31, 2012	October 17, 2012
June 27, 2012	September 5, 2012	
July 10, 2012	September 14, 2012	

LICENSING

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

MANUFACTURING LOCATIONS

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

DATING PERIOD

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

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

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

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

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below.

1. There are periods following the section numbers, some of the subsection numbers in the Table of Contents and in the Full Prescribing Information. These should be deleted in the final printed labeling when submitted.

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are

printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125422/0**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENT

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric study until December 31, 2012, because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

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

   The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

   Final Report Submission: 12/12

Reports of this required pediatric postmarketing study must be submitted as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2. To perform a feasibility study to adjust the drug product final fill volume or concentration to reduce the likelihood that more than one patient could be dosed from the same single use vial due to excess reconstituted drug product remaining in the vial after the initial dosing.

   The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

   Final Report Submission: 03/13

3. Revise the acceptance criteria for the drug substance and drug product release and stability specifications for low pH CEX-HPLC, RP-HPLC, and low pH SEC-HPLC to include "No new peaks above the limit of quantitation" and for non-reduced SDS-PAGE "No new bands greater than the limit of quantitation."

   The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

   Interim Report Submission: 12/12
   Final Report Submission: 04/13

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

   The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

   Final Report Submission: 12/12

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

   The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

   Final Report Submission: 12/17

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

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 12/15

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

   The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

   Final Report Submission: 03/13

8. Revise the system suitability criteria for the SDS-PAGE the drug substance and drug product release and stability methods to establish an acceptance criterion for the (b) (4) .

   The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

   Final Report Submission: 03/13

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

   The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

   Final Report Submission: 03/13

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

    The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

    Final Report Submission: 10/12

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

    The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

    Final Report Submission: 08/13

12. Provide the results of the study conducted to evaluate the discrepancy in copy number results between the [redacted] (b) (4) assay and the [redacted] (b) (4) assay.

    The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

    Final Report Submission: 03/13

13. Determine the approximate percentage of [redacted] (b) (4) by 2D SDS-PAGE or a similarly sensitive and discriminating assay.
    The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

    Final Report Submission: 06/13

14. Submit a reference (standard) material qualification protocol for new primary and secondary reference materials which contains characterization testing and more stringent acceptance criteria for release assays performed as part of the qualification of the new reference materials.

    The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

    Final Report Submission: 03/13

15. Conduct an extractable study for the [redacted] (b) (4) rubber stoppers used for the drug product container closure [redacted] (b) (4) This information should be used in the risk assessment conducted for drug product final container closure system leachable study.

    The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

    Final Report Submission: 12/12

16. Conduct a quantitative (ppb and ppm) leachables study and risk assessment of leachates into the drug product in the final container closure system at the end shelf-life.

    The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

    Final Report Submission: 12/13

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

    The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

    Final Report Submission: 03/13

18. Conduct a drug product stability study demonstrating that drug product stored at -70°C for 120 days followed by storage at -20°C up to the expiry (18 months) does not adversely impact product quality.

    The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

    Final Report Submission: 12/13

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

    The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

    Final Report Submission: 03/13

20. Validate yeast and mold recovery in TSA and demonstrate the comparability to the traditional compendial method or requalify the method suitability using SDA plates for mold & yeast incubated at 30-35ºC for ≤ 5 days as per USP<61> with 3 lots of in process samples.

    The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

    Final Report Submission: 03/13

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

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

22. Qualify bioburden and endotoxin methods for [redacted] (b) (4) and [redacted] (b) (4) and establish bioburden and endotoxin specifications based on an assessment of risk to ocriplasmin product quality. We request that you submit the outcome of the risk assessment and the bioburden and endotoxin specifications as a CBE-0.

    The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

    Final Report Submission: 03/13

23. Investigate the use of [redacted] (b) (4) for endotoxin measurements of in-process samples [redacted] (b) (4) and revise the endotoxin methods accordingly. We request that you submit any changes to the in-process endotoxin methods CBE-0.

    The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

    Final Report Submission: 03/13

24. Validate the efficacy of the [redacted] (b) (4) and submit a protocol with pre-established acceptance criteria. We request that you submit the protocol as a CBE-0. Fulfillment of acceptance criteria at the [redacted] (b) (4) should be filed in subsequent Annual Reports.

    The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

    Final Report Submission: 03/13

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

    The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

    Final Report Submission: 03/13

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

The timetable you submitted on October 2, 2012 states that you will conduct this study according to the following schedule:

Final Report Submission: 03/13

Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations sent by courier or overnight mail should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Jacquelyn Smith, M.A., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Edward Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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

/s/

EDWARD M COX
10/17/2012