

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125422Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125422

Supplement Number: _____

NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Transplant and Ophthalmology Products

PDUFA Goal Date: October 17, 2012

Stamp Date: April 17, 2012

Proprietary Name: Jetrea

Established/Generic Name: ocriplasmin

Dosage Form: intravitreal Injection, 2.5 mg/mL

Applicant/Sponsor: ThromboGenics, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of Symptomatic Vitreomacular Adhesion including Macular Hole

Q1: Is this application in response to a PREA PMR? Yes Continue

No Please proceed to Question 2.

If Yes, NDA/BLA#: _____

Supplement #: _____

PMR #: _____

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): <u>October 31, 2012</u>							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

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pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

 Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)
- Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

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drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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
09/25/2012

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.

On April 17, 2012, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. Please respond to our proposals as soon as possible.

If you have any questions, call me at 301-796-1002.

Sincerely,
Jacquelyn Smith, MA
Senior Regulatory Project Manager
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:

Content of Labeling
Carton and Container Labeling

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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
10/11/2012

Smith, Jacquelyn

From: Rusty Johnson [rusty.johnson@thrombogenics.com]
Sent: Tuesday, October 09, 2012 9:28 AM
To: Smith, Jacquelyn
Cc: Fang Li
Subject: RE: CMC PMCs for Ocriplasmin (BLA STN 125422)

Hi Jackie,

ThromboGenics concurs with the revisions to the language for the PMC's that the FDA has listed below.

For clarity, we have re-stated the commitment dates that have been previously provided in the text below for PMC 1 and PMC 4. No date was committed previously for PMC 8, and so one is now provided.

Best regards,
Rusty

From: Smith, Jacquelyn [mailto:Jacquelyn.Smith@fda.hhs.gov]
Sent: Tuesday, October 09, 2012 7:08 AM
To: Fang Li
Cc: Rusty Johnson
Subject: CMC PMCs for Ocriplasmin (BLA STN 125422)

Hi Fang,

Based on recent ThromboGenics responses, the CMC group revised the PMC language a bit for PMCs #1, #4, and #8. Here is the current version. Please respond and let me know if ThromboGenics concurs with these revisions.

CMC PMC#1: To 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."

ThromboGenics commits to providing the revised information by December 2012

CMC PMC#4: To revise the system suitability criteria for RP-HPLC drug substance and drug product release and stability method to ensure adequate column performance.

ThromboGenics commits to providing the revised information by March 2013

CMC PMC#8: To develop release and stability method(s) to detect all types of aggregates observed [REDACTED] (b)(4) in your drug product.

ThromboGenics commits to providing the revised information by August 2013

Please let me know if you have any questions.

Thanks,
Jackie

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/s/

JACQUELYN E SMITH
10/09/2012

Smith, Jacquelyn

From: Fang Li [fang.li@thrombogenics.com]
Sent: Friday, October 05, 2012 11:57 AM
To: Smith, Jacquelyn
Cc: Rusty Johnson
Subject: RE: BLA 125422 Information Request

Dear Jackie:

ThromboGenics concurs with the modified language in this PMC.

We will update the BLA to reflect the modification in the next amendment.

Best regards,

Fang

From: Smith, Jacquelyn [mailto:Jacquelyn.Smith@fda.hhs.gov]
Sent: Friday, October 05, 2012 11:16 AM
To: Fang Li
Subject: FW: BLA 125422 Information Request

Hi Fang,

After discussion with CMC micro regarding your below email, the PMC was modified. Please send to your CMC group and let me know if they concur with the PMC modification.

Thanks,
Jackie

PMC:

Validate the efficacy of the [REDACTED] (b) (4) and submit a protocol with pre-established acceptance criteria as a CBE-0 by the end of 3/2013. Fulfillment of acceptance criteria at the [REDACTED] (b) (4) should be filed in subsequent Annual Reports.

From: Fang Li [mailto:fang.li@thrombogenics.com]
Sent: Wednesday, October 03, 2012 10:20 AM
To: Smith, Jacquelyn
Cc: Rusty Johnson
Subject: FW: BLA 125422 Information Request

Jackie:

Our CMC folks has new information regarding the PMC regarding the date of fulfillment.

Could you pass it to the CMC reviewers to see whether it is OK to perform the study in step-wise?

Fang

From: Mukesh Sehdev
Sent: Wednesday, October 03, 2012 9:54 AM

To: Fang Li; Rusty Johnson
Cc: Phil Challis; Filip Borgions; Jean-Luc Jonniaux; Ove Pedersen; Lene Rose Arfelt
Subject: FW: BLA 125422 Information Request

Dear Fang,

Upon review of PMC 4, see attachment. We feel we need to clarify/amend this PMC with the FDA ASAP.

On 9th July we informed the FDA that the (b) (4) was currently unavailable, and consequently studies will be performed on samples of the (b) (4) at this time, in order to obtain data on the (b) (4) efficacy, albeit not at the (b) (4) and will be reported by the end of 3/2013. More recently the FDA have communicated the study on samples of the (b) (4) is not necessary.

Once (b) (4) the validation studies will be performed. The results of this additional studies will be provided and are presented in the Table 1 below. In addition, we could propose at the validation of (b) (4) (b) (4) (b) (4), as presented in Table 1.

We will therefore have to inform the FDA that validation of the efficacy of the (b) (4) and submit much later than 3/2013 and as presented in Table 1.

(b) (4)

Please advise?

Regards,

Mukesh

From: Fang Li
Sent: Tuesday, September 18, 2012 15:25
To: TG CMC
Cc: TG RA; David Pearson; Andy De Deene; Patrik De Haes
Subject: FW: BLA 125422 Information Request

Dear CMC:

FDA requests TG's concurrence for post marketing commitments. Please let me know whether we can keep this commitments. Once agreed upon, we have to meet the commitments otherwise risking the biologics license.

The deadline is **Sept. 20, 2012**.

Fang

From: Smith, Jacquelyn [<mailto:Jacquelyn.Smith@fda.hhs.gov>]
Sent: Tuesday, September 18, 2012 9:20 AM
To: Fang Li
Cc: Rusty Johnson
Subject: BLA 125422 Information Request

Hi Fang,

Please respond to the attached PMC concurrence request no later than September 20, 2012, if possible. It is so important that we receive the official submission(s) in response to PMC concurrence requests that we have sent to you so far as soon as possible. There may be other PMCs and some PMRs forthcoming. The PMC/PMR review process by our safety staff can be quite lengthy, so I'm providing the requests as I get them.

Regards,
Jackie

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/s/

JACQUELYN E SMITH
10/05/2012

Smith, Jacquelyn

From: Fang Li [fang.li@thrombogenics.com]
Sent: Thursday, October 04, 2012 3:32 PM
To: Smith, Jacquelyn
Cc: Rusty Johnson
Subject: RE: Ocriplasmin BLA 125422-- CMC PMR changed to PMC

Jackie:

We agree with the change. Please make note in your record.

Best regards,

Fang

From: Smith, Jacquelyn [mailto:Jacquelyn.Smith@fda.hhs.gov]
Sent: Thursday, October 04, 2012 3:07 PM
To: Fang Li
Cc: Rusty Johnson
Subject: Ocriplasmin BLA 125422-- CMC PMR changed to PMC

Hi Fang,

Please note that the below has been changed from a postmarketing requirement (PMR) to a postmarketing commitment (PMC).

(b) (4)

It will now read as follows:

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.

Please respond and let me know if you are in agreement with this change. If you have any questions or need clarification, please contact me.

Kind Regards,
Jackie

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/s/

JACQUELYN E SMITH
10/05/2012

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Thursday, October 04, 2012 10:27 AM
To: 'Fang Li'
Cc: 'Rusty Johnson'
Subject: Jetrea, BLA 125422

Hi Fang,

After further review, we need this information. Please submit as soon as possible via email and follow with an official submission.

- 1) Please provide a table which includes patient number, treatment group, adverse event, visual acuity at each visit for all patients who had ≥ 2 lines of vision loss at month 6 for the phase 3 trials and who also had a reported adverse event of macular edema, retina edema or iritis.
- 2) Please provide a table which includes patient number, and treatment group, for patients who had ≥ 2 lines of vision loss at month 6 for the phase 3 trials by baseline macular hole status (and include size of hole at baseline). Also, include the size of macular hole if present at month 6.

Thanks,

Jackie

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/s/

JACQUELYN E SMITH
10/04/2012



Michael Tolentino, M.D.
Center for Retina and Macular Disease
250 Avenue K SW, Suite 200
Winter Haven, FL 33880

Dear Dr. Tolentino:

Between July 9 and 25, 2012, Ms. Jana Caylor, representing the FDA, met with you and your staff to review your conduct of a clinical investigation (Study TG-MV-006, entitled "A Randomized, Placebo Controlled, Double Masked, Multicenter Trial of Microplasmin Intravitreal Injection for Non Surgical Treatment of Focal Vitreomacular Adhesion") of the investigational drug ocriplasmin (JETREA™), performed for ThromboGenics Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Ms. Caylor presented and discussed with you Form FDA 483, Inspectional Observations. We have reviewed the Form FDA 483, the establishment inspection report, and the documents submitted with the report. We acknowledge your August 7, 2012 written response to the inspection findings and note that you have implemented corrective actions to prevent the recurrence of the inspection findings.

We appreciate the cooperation shown to Investigator Caylor during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{ See appended electronic signature page }

Susan Thompson, M.D
Acting Branch Chief
Good Clinical Practices Assessment Branch
Division of Good Clinical Practice Compliance
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg 51, Rm 5350
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

KASSA AYALEW
10/04/2012

SUSAN LEIBENHAUT
10/04/2012

SUSAN D THOMPSON
10/04/2012



Matthew S. Benz, MD
Retina Consultants of Houston
6560 Fannin Street, Ste 750
Houston, TX 77030

Dear Dr. Benz:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected. Between June 25 and 28, 2012, Ms. Amanda J. White, representing the FDA, met with you and your staff to review your conduct of a clinical investigation (Study TG-MV-006, entitled "A Randomized, Placebo Controlled, Double Masked, Multicenter Trial of Microplasmin Intravitreal Injection for Non Surgical Treatment of Focal Vitreomacular Adhesion") of the investigational drug ocriplasmin (JETREA™), performed for ThromboGenics Inc.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to Investigator White, during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Susan Leibenhaut, M.D
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5366
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

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/s/

KASSA AYALEW
10/03/2012

SUSAN LEIBENHAUT
10/03/2012



Carl Baker, MD
Paducah Retinal Center
1900 Broadway, Ste. 2
Paducah, KY 42001

Dear Dr. Baker:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected. Between July, 16 and 18, 2012, Ms. Karen Cooper, representing the FDA, met with you and your staff to review your conduct of a clinical investigation (Study TG-MV-007, entitled "Randomized, Placebo Controlled, Double Masked, Multicenter Trial of Microplasmin Intravitreal Injection for Non Surgical Treatment of Focal Vitreomacular Adhesion") of the investigational drug ocriplasmin (JETREA™), performed for ThromboGenics Inc.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to Investigator Cooper, during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Susan Leibenhaut, M.D
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5366
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

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/s/

KASSA AYALEW
10/03/2012

SUSAN LEIBENHAUT
10/03/2012



J. Michael Jumper, MD
West Coast Retina Group, Inc
185 Berry Street, Suite 130
San Francisco, CA 94107

Dear Dr. Jumper:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected. Between June, 25 and July, 09, 2012, Mr. Ashar P. Parikh, representing the FDA, met with you and your staff to review your conduct of a clinical investigation (Study TG-MV-007, entitled "Randomized, Placebo Controlled, Double Masked, Multicenter Trial of Microplasmin Intravitreal Injection for Non Surgical Treatment of Focal Vitreomacular Adhesion") of the investigational drug ocriplasmin (JETREA™), performed for ThromboGenics Inc.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to Investigator Parikh, during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Susan Leibenhaut, M.D
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5366
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

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/s/

KASSA AYALEW
10/03/2012

SUSAN LEIBENHAUT
10/03/2012

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Monday, October 01, 2012 1:58 PM
To: 'Fang Li'
Cc: 'Rusty Johnson'

Hi Fang,

Please address the below information request and respond expeditiously both via email and officially through the gateway. We need to get agreement and dates from ThromboGenics as soon as possible.

Thanks,

Jackie

CMC PMCs and PMR

(b) (4)

1. To perform a feasibility study to adjust the drug product final fill volume or concentration to reduce the likelihood that (b) (4) 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 final study report will be submitted in xxxxxx.

PMC

1. To 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 SDS-PAGE "No new bands greater than the limit of quantitation."

The updated specifications will be submitted in December 2013.

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

The final study report and, if required, revised specification will be submitted in xxxxxx.

3. To evaluate and revise, as needed, the acceptance criteria for all the drug substance and drug product release specifications based on data from at least thirty lots of each.

The final study report and, if required, revised specification will be submitted in xxxxxx.

4. To revise the system suitability criteria for (b) (4) RP-HPLC, and (b) (4) drug substance and drug product release and stability methods to ensure adequate column performance.

The updated system suitability criteria will be submitted in [REDACTED].

5. To 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 [REDACTED] (b) (4)

The updated system suitability criteria will be submitted in March 2013.

6. To establish the limit of quantitation for the RP-HPLC and SDS-PAGE methods.
The validation reports will be submitted in December 2013.
7. To provide data to support alternative sampling methodology for sub-visible particles testing using USP <789> monograph.

The final study report will be submitted in October 2013.

[REDACTED] (b) (4)

The final study report will be submitted in [REDACTED].

9. To 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 final study report will be submitted in [REDACTED].

10. To determine the approximate percentage of [REDACTED] (b) (4) by 2D SDS-PAGE or a similarly sensitive and discriminating assay.

The final study report will be submitted in June 2013.

11. To 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 new protocol will be submitted in March 2013.

12. To 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 final study report will be submitted in [REDACTED].

13. To 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 final study report will be submitted in [REDACTED].

14. To 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 [REDACTED].

the quality, safety and efficacy of ocriplasmin and propose an appropriate control strategy.

The final study report will be submitted in xxxxxx.

15. To 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 final study report will by submitted in xxxxxx.

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/s/

JACQUELYN E SMITH
10/01/2012

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.

After review of your application, we are requesting your concurrence to the below post-marketing commitments (PMCs). Please respond by September 20, 2012.

1. Submit new limits for bioburden (action limit (b)(4) and endotoxin (action limit (b)(4); alert limit (b)(4)) in (b)(4) as a CBE-0 by the end of 3/2013.
2. Qualify bioburden and endotoxin methods for (b)(4) and (b)(4) and establish bioburden and endotoxin specifications based on an assessment of risk to ocriplasmin product quality. The outcome of the risk assessment and the bioburden and endotoxin specifications will be submitted as a CBE-0 by the end of 3/2013.
3. Investigate the use of (b)(4) for endotoxin measurements of in-process samples (b)(4) and revise the endotoxin methods accordingly. Any changes to the in-process endotoxin methods will be submitted as a CBE-0 by the end of 3/2013.
4. Validate the efficacy of the (b)(4) and submit a report as a CBE-0 by the end of 3/2013.
5. Evaluate the effects of freezing on endotoxin recovery from ocriplasmin drug substance. These studies will include (b)(4) as appropriate. Any changes to the in-process endotoxin methods will be submitted as a CBE-0 by the end of 3/2013.
6. Qualify the bioburden method for (b)(4) and submit a report as a CBE-0 by the end of 3/2013.

If you have any questions regarding the contents of this transmission, please contact me at 301-796-1002. Thank you.

Jacquelyn Smith, M.A.
Senior Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JACQUELYN E SMITH
09/18/2012

Smith, Jacquelyn

From: Rusty Johnson [rusty.johnson@thrombogenics.com]
Sent: Monday, September 10, 2012 4:37 PM
To: Smith, Jacquelyn
Cc: Fang Li
Subject: BLA 125422 Information Request
Attachments: BLA 125422 CMC IR_September 6 2012.pdf

Hi Jackie,

In response to the request from the FDA of September 6th (attached), we commit to providing data from our (b) (4) by March 29, 2013.

Best regards,
Rusty

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/s/

JACQUELYN E SMITH
09/12/2012

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 are providing the below information request. Please respond by September 12, 2012.

Information Request

FDA comments to the response to Information Request (August 13, 2012)

1. Description of the manufacturing process (3.2.P.3.3)

(b) (4) (b) (4) *manufacturing process description (3.2.P.3.3.7) section. Please (b) (4) the manufacturing process description and update Sections 3.2.P.2.3 and 3.2.P.3.5 as per your response.*

2. Process validation (3.2.P.3.5)

The validation strategy and data summaries for the (b) (4) (b) (4) are included in APPENDIX III. Please move the relevant information and data to Section 3.2.P.3.5.

3. Analytical procedures (3.2.P.5)

a. *Your response to question 4a (bioburden testing) does not include the following details: (b) (4) Please provide this information.*

b. *USP <61> Bioburden method suitability recommends TSA plates for the isolation of bacteria with an incubation period of ≤ 3 days at 30-35°C and SDA plates for mold and yeast incubated for ≤ 5 days at 30-35°C. For bioburden testing, TSA plates should be incubated for a minimum of 3 days and SDA for a minimum of 5 days. Please validate the method suitability testing of yeast and mold recovery in TSA plates and demonstrate the comparability to the traditional compendial method or requalify the method suitability testing using SDA plates for mold & yeast incubated at 30-35°C for ≤ 5 days as per USP<61> with 3 lots of in process samples. Please provide the information and data of the validation / requalification as a PMC. Please confirm and indicate when the results will be submitted to the Agency.*

BLA 125422/0

If you have any questions regarding the contents of this transmission, please contact me at 301-796-1002. Thank you.

Jacquelyn Smith, M.A.
Senior Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JACQUELYN E SMITH
09/10/2012

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 are providing the below information and information request.

Information Request

Comment to response to initial FDA Information Request 11 from May 31, 2012: Your commitment in Amendment 0010 to perform an (b) (4) study as a Post-marketing Commitment **and indicate when the results will be submitted to the Agency**. Another study in support of the efficacy of the solutions using the (b) (4) is not required.

If you have any questions regarding the contents of this transmission, please contact me at 301-796-1002. Thank you.

Jacquelyn Smith, M.A.
Senior Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JACQUELYN E SMITH
09/06/2012

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 are providing the below information requests and requesting that you address these items by September 10, 2012.

Information Requests

1. In the August 31, 2012 IR letter, we requested that you change the system suitability acceptance criterion for the reference standard for no new peaks to be “no new peaks above the LOQ” for the three HPLC assays, SE-, CEX-, and RP-HPLC (IR comments 14 and 15). In addition, please add to your release and stability specifications for the low pH SE-HPLC, low pH CEX-HPLC, and RP-HPLC methods an acceptance criterion for the test samples that states “no new peaks above the LOQ.”
2. Please provide your sampling plans for Drug Substance and Drug Product lot release. In addition, please describe and justify any hold times allowed prior to release testing the samples taken from a lot.
3. The release specifications for the critical raw material,  (b) (4)

 (b) (4)

If you have any questions regarding the contents of this transmission, please contact me at 301-796-1002. Thank you.

Jacquelyn Smith, M.A.
Senior Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JACQUELYN E SMITH
09/05/2012

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 are providing the below information requests and requesting that you address these items by September 10, 2012. Please note that if you do not have the data to support or meet these requests, the items may become post marketing commitments (PMCs).

Information Requests



2 Pages have been
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(CCI/TS) immediately
following this page

If you have any questions regarding the contents of this transmission, please contact me at 301-796-1002. Thank you.

Jacquelyn Smith, M.A.
Senior Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JACQUELYN E SMITH
08/31/2012

The following information request was sent to ThromboGenics' representative, Fang Li, on August 16, 2012. ThromboGenics was asked to provide the below information or provide the location where the below information can be found, if previously submitted to FDA.

- 1) All patients who had a decrease in vision of 2 lines or greater. According to Thrombogenics' briefing package, page 89 of 158, for the two studies together, there were 11 (5.9%) placebo and 36 (7.8%) ocriplasmin patients who had a 2 line or greater worsening of vision. The patient numbers and the OCT images for all of these patients should be provided. In addition, Thrombogenics should provide a summary table and/or graph by treatment arm showing when the vision decreased, how much it decreased and an interpretation of what OCT anatomic changes were associated with the visual decrease, e.g., increased traction, progression of disease, macular edema, etc.
- 2) If data were collected for visual worsening of 1 line of vision, those patients should also be reported, including patient ID numbers, how many patients on each arm, and the associated OCT findings.
- 3) All patients who had VMA resolution during trial: provide patient ID numbers for each ocriplasmin arm and placebo arm patient (this may already be available since these patients had a successful outcome for the primary endpoint), and their OCT images should be provided. For each patient, provide whether their visual acuity after VMA resolution got better, stayed the same, or got worse. For any patient (ocriplasmin or placebo) for whom vision worsened after VMA resolution, provide information on visual changes and worsening and an anatomic description of OCT findings.

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/s/

JACQUELYN E SMITH
08/29/2012

The below information request for BLA STN 125422/0 was emailed to ThromboGenics' representative, Fang Li, on August 22, 2012.

IR for BLA STN 125422/0 Jetrea® (ocriplasmin)- ThromboGenics Inc.

Please provide us with the SAS program codes for analyzing the primary and key secondary endpoints using multiple imputation methods.

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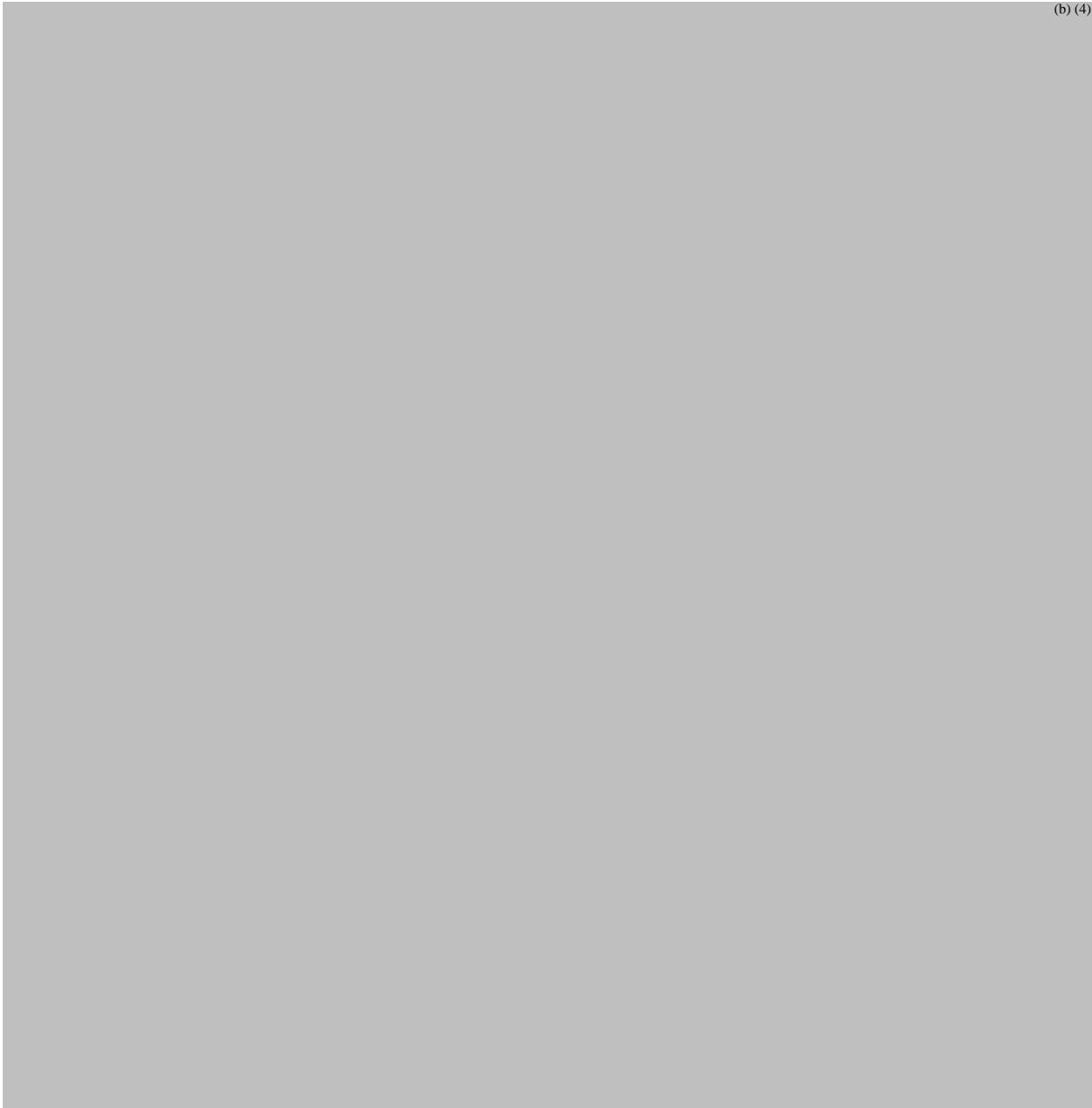
/s/

JACQUELYN E SMITH
08/28/2012

The below information request for BLA STN 125422/0 was emailed to ThromboGenics' representative, Fang Li, on August 22, 2012.

IR6 for BLA STN 125422/0 Jetrea® (ocriplasmin)- ThromboGenics Inc.

FDA's clarification on ThromoGenics questions:



FDA Comments and Information Request to STN 124422/0

Reviewer comments to ThromboGenics responses in amendment 0010 received 6-August-2012.

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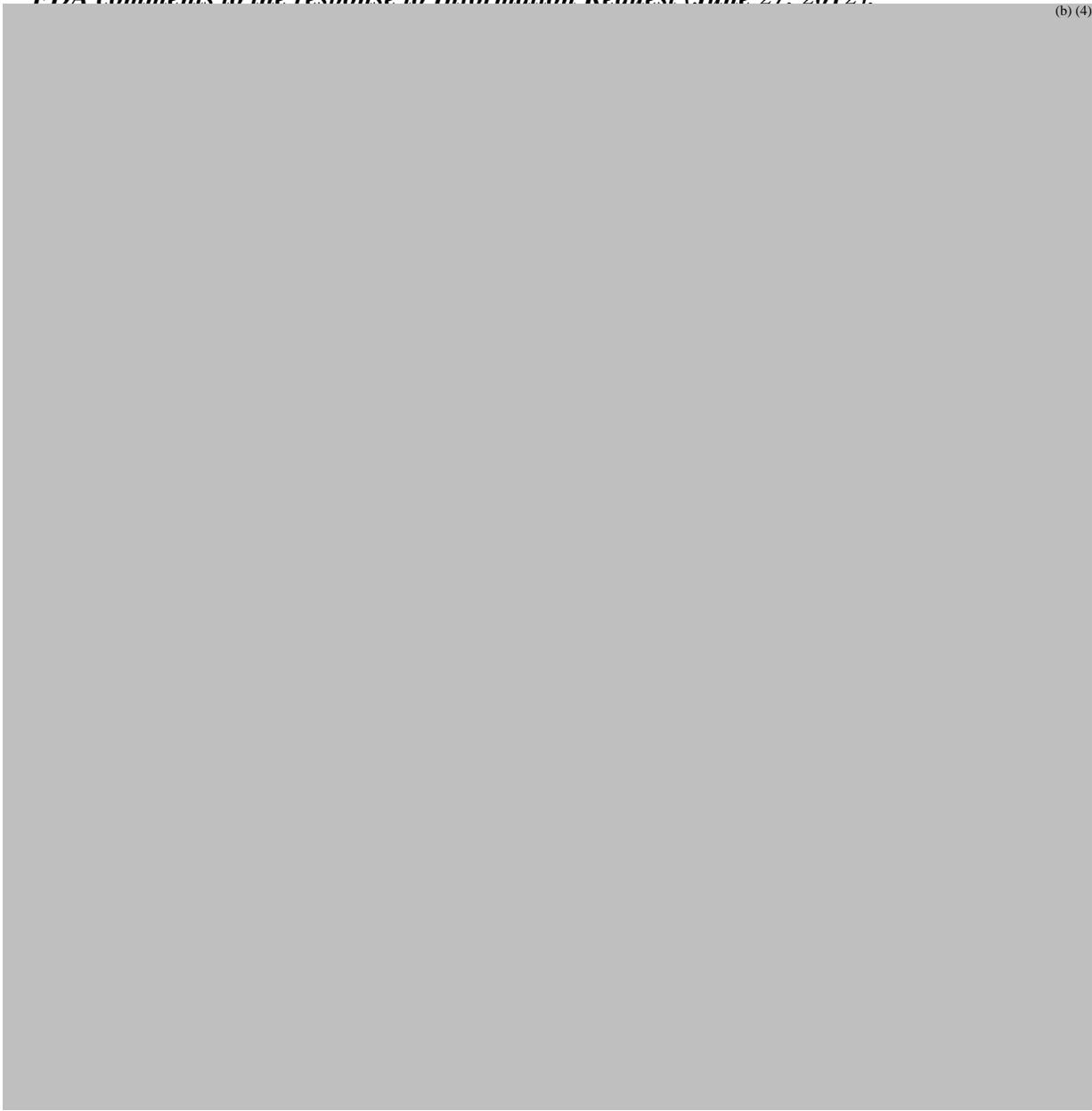
JACQUELYN E SMITH
08/22/2012

The below information request for BLA STN 125422/0 was emailed to ThromboGenics' representative, Fang Li, on August 17, 2012 with FDA request to respond by August 23, 2012.

IR for BLA STN 125422/0 Jetrea® (ocriplasmin)- ThromboGenics Inc.

FDA comments to the response to Information Request (June 27, 2012):

(b) (4)



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/s/

JACQUELYN E SMITH
08/17/2012

The below information request was emailed to ThromboGenics' representative, Fang Li, on August 15, 2012 with a request for a response by August 21, 2012.

IR for BLA STN 125422/0 Jetrea® (ocriplasmin)- ThromboGenics Inc.

(b) (4)



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/s/

JACQUELYN E SMITH
08/16/2012

The below information request was emailed to ThromboGenics' representative, Fang Li, on 8/13/12.

IR 4 for BLA STN 125422/0 Jetrea® (ocriplasmin) - ThromboGenics Inc.

Please provide the current list of licensed products manufactured at the (b) (4)

(b) (4)

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/s/

JACQUELYN E SMITH
08/13/2012

The below information request was emailed to Fang Li on 8/13/12.

IR 3 for BLA STN 125422/0 Jetrea® (ocriplasmin)- ThromboGenics Inc.

(b) (4)



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/s/

JACQUELYN E SMITH
08/13/2012



IND 100370
BLA 125422

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

ThromboGenics Inc.
101 Wood Avenue South, 6th Floor
Iselin, NJ 08830

ATTENTION: Fang Li, PhD, RAC
Head of Regulatory Affairs, US

Dear Dr. Li:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act and your original Biologics License Application (BLA) dated and received April 17, 2012, submitted under section 351 of the Public Health Service Act for Ocriplasmin.

We also refer to:

- your February 2, 2012, correspondence received February 3, 2012, requesting review of your proposed proprietary name, Jetrea, under the IND; and
- your April 26, 2012, correspondence, received April 26, 2012, requesting review of your proposed proprietary name, Jetrea under the BLA

We have completed our review of the proposed proprietary name, Jetrea and have concluded that it is acceptable. The proposed proprietary name, Jetrea, will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you. Additionally, if **any** of the proposed product characteristics as stated in your April 26, 2012, submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Jacqueline Smith at (301) 796-1002.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/25/2012

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Thursday, July 19, 2012 4:03 PM
To: 'Fang Li'
Cc: Rusty Johnson
Subject: FW: IR2 for STN 125422/0

Hi Fang,

Please address the below information request.

IR for BLA STN 125422/0 Jetrea® (ocriplasmin)- ThromboGenics Inc.

In response to question 5.2a and 5.2c from our information request (dated June 27, 2012) it is stated that results will be submitted to the Agency by September 28, 2012. Due to stringent internal review deadlines, the proposed timeframe is not acceptable. We expect that you submit the results by August 15, 2012.

Regards,
Jacquelyn

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Food and Drug Administration
Division of Transplant and Ophthalmology Products
10903 New Hampshire Avenue
White Oak, Bldg. 22, Room 6141
Silver Spring, Maryland 20993
Telephone: 301-796-1002
Fax: 301-796--9881
Email: jacquelyn.smith@fda.hhs.gov

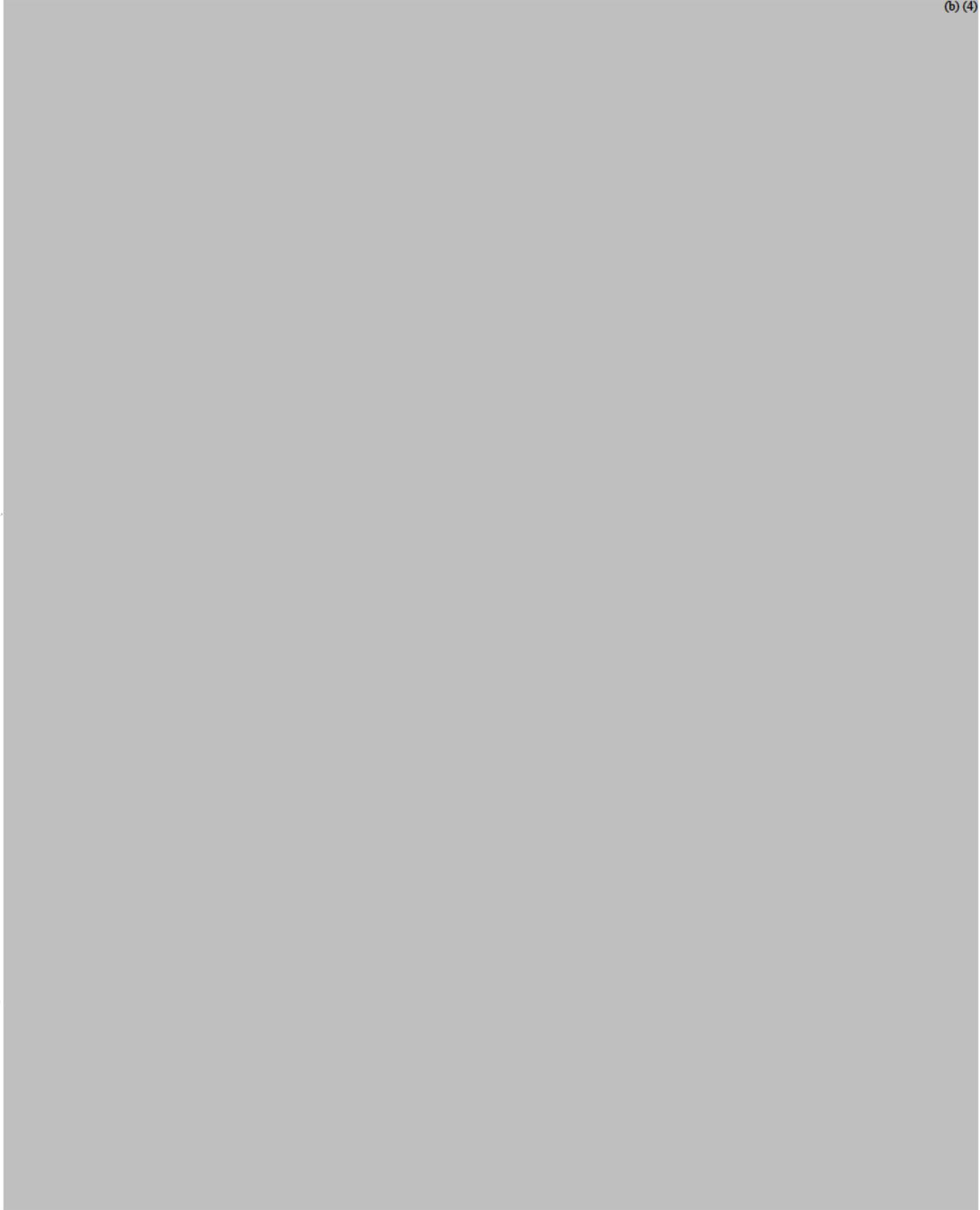
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/s/

JACQUELYN E SMITH
07/24/2012

The information request below was emailed to Thrombogenics' representative, Fang Li, on July 9, 2012.

Please find below reviewer comments to ThromboGenics responses in amendment 0003 submitted June 15, 2012. Please provide responses by July 31, 2012.



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/s/

JACQUELYN E SMITH
07/10/2012

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Tuesday, July 03, 2012 12:13 PM
To: 'Rusty Johnson'
Cc: 'Fang Li'
Subject: BLA 125422--Ocriplasmin Information Request

Hi Rusty,

Please respond to the below information request as soon as possible.

There is a substantial difference in the placebo response rate for the primary efficacy endpoint for the two pivotal trials. Some possible reasons for this given in the BLA submission are the differences in patients with ERM, MH and > 1500 micron VMA at baseline. Please conduct an analysis of baseline demographic and ocular characteristics of patients who responded in both the placebo and drug groups for both clinical trials. Please summarize the analysis results in two tables (one for responders and one for non-responders) in a similar manner as in Table 4 presented in your document "summary-clin-efficacy-vma.pdf".

Sincerely,
Jacquelyn

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Food and Drug Administration
Division of Transplant and Ophthalmology Products
10903 New Hampshire Avenue
White Oak, Bldg. 22, Room 6141
Silver Spring, Maryland 20993
Telephone: 301-796-1002
Fax: 301-796--9881
Email: jacquelyn.smith@fda.hhs.gov

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/s/

JACQUELYN E SMITH
07/03/2012



BLA 125422/0

REVIEW ISSUES

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.

During our filing review of your application, we identified the following potential review issues:

Microbiology



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We request that you respond to all of the above deficiencies by July 10, 2012.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. Depending on when you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

Labeling

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. There should not be periods following the Section numbers and Subsection numbers. The periods currently present in the package insert should be deleted.
2. The abbreviation for “micro” should be presented as “mc” instead of “μ” in order to avoid misinterpretation.
3. White space must be present before each major heading in the Highlights.
4. A horizontal line must separate the Table of Contents from the Full Prescribing Information.

We request that you resubmit labeling (Microsoft Word format) that addresses these issues by July 10, 2012. The resubmitted labeling will be used for further labeling discussions.

Pediatric Studies

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 acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you of our decision.

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

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.

Director

Division of Transplant and Ophthalmology Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

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/s/

RENATA ALBRECHT
06/27/2012



BLA 125422/0

REVIEW ISSUES

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.

In reviewing the correspondence previously sent on June 27, 2012 regarding “REVIEW ISSUES” for this BLA, we note that the following information was inadvertently omitted:

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any post-marketing commitment requests by September 26, 2012.

We apologize for any inconvenience this may have caused. The effective date of the action will remain June 27, 2012, the date of the original letter.

During our filing review of your application, we identified the following potential review issues:

Microbiology

1. CCI testing of Drug product (3.2.P.2.5)

Regarding CCI testing of ocriplasmin drug product:

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We request that you respond to all of the above deficiencies by July 10, 2012.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. Depending on when you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

Labeling

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. There should not be periods following the Section numbers and Subsection numbers. The periods currently present in the package insert should be deleted.
2. The abbreviation for “micro” should be presented as “mc” instead of “μ” in order to avoid misinterpretation.
3. White space must be present before each major heading in the Highlights.
4. A horizontal line must separate the Table of Contents from the Full Prescribing Information.

We request that you resubmit labeling (Microsoft Word format) that addresses these issues by July 10, 2012. The resubmitted labeling will be used for further labeling discussions.

Pediatric Studies

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 acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you of our decision.

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

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

RENATA ALBRECHT
06/27/2012

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Thursday, June 21, 2012 8:18 AM
To: 'Fang Li'
Cc: Smith, Jacquelyn
Subject: BLA 125-422 Information Request

Hi Fang,

Please respond to the below information request as soon as possible. Sorry for the short turnaround, but an expeditious response is important.

Please provide two tables and two forest plots for the subgroup analysis results (one for Day 28 and one for Month 6) of the proportion of patients with non-surgical resolution of focal VMA. The mock-up table is provided below for your consideration. The forest plots should be for the treatment difference with a 95% confidence.

Proportion of Patients with VMA Resolution in the Study Eye at Day 28 without Creation of an Anatomical Defect (TG-MV-006, TG-MV-007 and Integrated Studies (Full Analysis Set)

Characteristic	TG-MV-006			TG-MV-007			Integrated Studies		
	Placebo (N=107)	Ocriplasmin (N=219)	Difference	Placebo (N=81)	Ocriplasmin	Difference	Placebo (N=188)	Ocriplasmin (N=464)	Difference
All	14 (13.1)	61 (27.9)	14.8 (6, 23.5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
Gender									
Male	14 (13.1)	61 (27.9)	14.8 (6, 23.5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
Female	14 (13.1)	61 (27.9)	14.8 (6, 23.5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
Age (yrs)									
<65	14 (13.1)	61 (27.9)	14.8 (6, 23.5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
≥65	14 (13.1)	61 (27.9)	14.8 (6, 23.5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
Race, n (%)									
White	14 (13.1)	61 (27.9)	14.8 (6, 23.5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
Non-White	14 (13.1)	61 (27.9)	14.8 (6, 23.5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
FTMH									
Yes	14 (13.1)	61 (27.9)	14.8 (6, 23.5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
No	14 (13.1)	61 (27.9)	14.8 (6, 23.5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
ERM									
Yes	14 (13.1)	61 (27.9)	14.8 (6, 23.5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
No	14 (13.1)	61 (27.9)	14.8 (6, 23.5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
Phakic									
Yes	14 (13.1)	61 (27.9)	14.8 (6, 23.5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
No	14 (13.1)	61 (27.9)	14.8 (6, 23.5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
DR									

Yes	14 (13.1)	61 (27.9)	14.8 (6, 23,5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
No	14 (13.1)	61 (27.9)	14.8 (6, 23,5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
Type (Diameter) of Focal VMA									
> 1500µm	14 (13.1)	61 (27.9)	14.8 (6, 23,5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
≤ 1500µm	14 (13.1)	61 (27.9)	14.8 (6, 23,5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
Expected Need for Vitrectomy									
Yes	14 (13.1)	61 (27.9)	14.8 (6, 23,5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
No	14 (13.1)	61 (27.9)	14.8 (6, 23,5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
BCVA (letter score)									
<65	14 (13.1)	61 (27.9)	14.8 (6, 23,5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)
≥65	14 (13.1)	61 (27.9)	14.8 (6, 23,5)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)

Regards,
Jacquelyn

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Food and Drug Administration
Division of Transplant and Ophthalmology Products
10903 New Hampshire Avenue
White Oak, Bldg. 22, Room 6141
Silver Spring, Maryland 20993
Telephone: 301-796-1002
Fax: 301-796--9881
Email: jacquelyn.smith@fda.hhs.gov

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/s/

JACQUELYN E SMITH
06/21/2012

The information request below was emailed to Thrombogenics' representative, Fang Li, on June 19, 2012.

Information Request:

Please provide an Adverse Event table that lists all of the adverse events reported for at least 1% of the patients in either treatment group for the Pivotal placebo-controlled trials and for all studies combined. Please format it the same as the one provided in section 2.7.4 Summary of Clinical Safety, Table 12 on page 39. Please submit by Monday, June 25, 2012.

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/s/

JACQUELYN E SMITH
06/19/2012

The information request below was emailed to Thrombogenics' representative Fang Li, on June 11, 2012.

Information Request:

For studies 006 and 007, please analyze the primary efficacy endpoint, and the key secondary endpoint for each study by imputing missing data using multiple imputation methods.

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/s/

JACQUELYN E SMITH
06/11/2012

The information request below was emailed to Thrombogenics' representative Fang Li, on June 8, 2012.

Information Request:

We note that, as indicated in your BLA submission (BLA STN 125,422), you performed (b) (4) analyses on genetic stability using a (b) (4). We recommend that you perform your (b) (4) testing using samples taken from the commercial-scale (b) (4) production run. Please be sure to utilize appropriate procedures and methods (*i.e.* sample numbers, volume, and storage conditions) to ensure that the new (b) (4) data support its intended purpose. Please note that the battery of tests you included for (b) (4) testing in the original BLA appears appropriate and should be performed on the new (b) (4) samples. For details on test methods, please see Table 11 below (Ref; 3.2.S.2./3.2.8.).



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/s/

MICHAEL J PUGLISI
06/11/2012

Smith, Jacquelyn

From: Smith, Jacquelyn
Sent: Monday, June 04, 2012 3:28 PM
To: 'Fang Li'
Subject: FW: BLA 125422/ocriplasmin timelines

Hi Fang:

Please respond to this information request as soon as possible. It is very important to receive this information expeditiously. We are in the process of inspecting the sites in reference to BLA 125422, JETREA™ (ocriplasmin) Intravitreal Injection, 2.5 mg/mL for treatment of patients with symptomatic vitreomacular adhesion including macular holes.

For the following clinical investigators listed below, we would like you to provide Subject Level Data Listings by Site (as described below). Please submit subject level data listings for the listed CI's below as fast as possible.

Matthew Benz, MD/ Study TG-MV-006

Vitreoretinal Consultants
6560 Fannin Street, Ste 750
Houston, TX 77030

Michael Tolentino, MD/ Study TG-MV-006

Center for Retina and Macular
Disease
250 Avenue K SW, Suite 200
Winter Haven, FL 33880

Carl Baker, MD/ Study TG-MV-007

Paducah Retinal Center
1900 Broadway Street, Ste. 2
Paducah, KY 42001, USA

J. Michael Jumper, MD/ Study TG-MV-007

West Coast Retina Group, Inc
185 Berry Street Suite 130
San Francisco, CA 94107, USA

We are asking you:

To provide site-specific individual subject data ("line") listings for each investigator listed above. The data listings should contain:

- Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
- Subject listing for treatment assignment (randomization)
- Subject listing of drop-outs and subjects that discontinued with date and reason
- Evaluable subjects/ non-evaluable subjects and reason not evaluable
- By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
- By subject listing, of AEs, SAEs, deaths and dates
- By subject listing of protocol violations and/or deviations reported in the BLA, description of the deviation/violation
- By subject listing of the primary efficacy parameters. For derived or calculated endpoints, provide the raw data

listings used to generate the derived/calculated endpoint.

- By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
- By subject listing, of laboratory tests performed for safety monitoring

Thank you,

Jackie

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/s/

JACQUELYN E SMITH
06/06/2012

BL STN 125422/0

Dear Dr. Li:

Please refer to your Biologics License Application (BLA) submitted April 16, 2012, received April 17, 2012, under section 351 of the Public Health Service Act (PHS Act) for JETREA (ocriplasmin) Intravitreal Injection, 2.5 mg/mL. After initial review of your BLA, we have the following information request.

FDA Information Request

(b) (4)



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BL STN 125422/0

(b) (4)

Please submit your response by June 15, 2012.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
05/31/2012



BLA 125422/0

BLA ACKNOWLEDGEMENT

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:

We have received your Biologics License Application (BLA) submitted under section 351 of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product:	JETREA (ocriplasmin) Intravitreal Injection, 2.5 mg/mL
Date of Application:	April 16, 2012
Date of Receipt:	April 17, 2012
Our Submission Tracking Number (STN):	BLA # 125422/0
Proposed Use:	Treatment of Symptomatic Vitreomacular Adhesion including Macular Hole

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology Products

5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at 301-796-1600.

Sincerely,

{See appended electronic signature page}

Jacquelyn Smith, M.A.
Senior Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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
04/24/2012

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	List of investigators attached and provided in table 1	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Chris Buysc	TITLE Chief Financial Officer
FIRM/ORGANIZATION ThromboGenics	
SIGNATURE 	DATE (mm/dd/yyyy) 11/14/2011

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

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in Full as b4 (CCI/TS)
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