

Bioresearch Monitoring Inspection Results - RECOTHROM

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE August 17, 2007

FROM

Janet White, Bioresearch Monitoring, HFM-664 Division of Inspections and Surveillance
Office of Compliance and Biologics Quality

THROUGH Patricia Holobaugh, Bioresearch Monitoring Branch Chief, HFM-664

TO Roman Drews, HFM-392, Chair, BLA Committee

SUBJECT

Bioresearch Monitoring Inspection Results

BLA/STN 125248/0

Product: Recombinant Human Thrombin (rhThrombin)

Sponsor: ZymoGenetics, Inc.

SUMMARY STATEMENT

The bioresearch monitoring inspections of three clinical sites did not reveal problems that significantly impact the data submitted in the application.

BACKGROUND

Inspections of three clinical investigators were performed in support of this Biologics License Application (BLA). Information from the BLA was compared to source documents during the inspections. The inspections focused on specific questions concerning the study.

STUDY TITLE

Protocol 499E01: A Phase 3, Randomized, Double-Blind, Controlled, Comparative Efficacy and Safety Study of Topical Recombinant Human Thrombin (rhThrombin) and Thrombin-JMI (Bovine Thrombin) in Surgical Hemostasis

STUDY DATES

25 October 2005 - 30 June 2006

SUBJECTS ENROLLED

Protocol 499E01: 411 subjects

CLINICAL INVESTIGATORS	SUBJECTS	483	FDA INSPECTION CLASSIFICATION
Yuri S. Genyk, M.D. USC Healthcare Consultation Center Los Angeles, California	33	No	NAI
James W. McNeil, M.D. Vascular Surgery Associates Baton Rouge, Louisiana	31	No	NAI

CLINICAL INVESTIGATORS **SUBJECTS** **483** **FDA INSPECTION**
CLASSIFICATION

Kenneth L. Renkens Jr., M.D Indiana Spine Group Indianapolis, Indiana	28 Yes VAI
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INSPECTIONAL FINDINGS

1. Failure to ensure that the investigation was conducted according to the investigational plan, the signed agreement, and applicable FDA regulations. [21 CFR § 312.60].
 - A. Some physical exams required by the protocol were not performed or were incomplete. (McNeil, Genyk)
 - B. Documentation of the assessment of childbearing potential (inclusion/exclusion criteria) was sometimes not recorded until after the subject completed the study. (McNeil)

2. Failure to prepare, maintain, and retain accurate and complete records of each subject's case history, including observations, data pertinent to the investigation, and informed consent forms. [21 CFR § 312.62(b)].
 - A. In the following subjects' records the surgeon listed in the case report form and the surgeon performing the procedure are not the same people. According to the investigational plan for Site 640, only Dr. McNeil and Dr. ----- could apply the investigational product and make the time to hemostasis (TTH) evaluation. Therefore, the TTH source document should have been signed by one of these doctors instead of the study coordinator. In addition, the surgeon dictating the operative report should have named any doctor performing administration of the investigational product and any evaluations related to that administration. (McNeil)
 - i. Subject 6119: Although the surgeon listed on the *Investigational Product Movement Form* is Dr. ----- is listed on both the operating room nurses' notes and the anesthesia records as the surgeon for the procedure. In addition, ----- dictated the Procedure Report that has no mention of-----.
 - ii. Subject 6120: Although the surgeon listed on the *Investigational Product Movement Form* is ----- is listed on the anesthesia records as the surgeon for the procedure. In addition, ----- dictated the Procedure Report that has no mention of -----.
 - iii. Subject 6168: Although the surgeon listed on the *Investigational Product Movement Form* is ----- is listed on both the operating room nurses' notes and the anesthesia records as the surgeon for the procedure. In addition, ----- dictated the Procedure Report that has no mention of -----.
 On the TTH source document,-----noted "applied study drug on 1/16/06." However, his note was dated 5/4/06, more than three months after the administration of the investigational product.
 - iv. Subject 6203: Although the surgeon listed on the *Investigational Product Movement Form* is ----- is listed on both the operating room nurses' notes and the anesthesia records as the surgeon for the procedure. In addition, ----- dictated the Procedure Report that has no mention of -----
 --. In addition, ----- dictated the Operative Report that has no mention

----- or Dr. McNeil. Dr. McNeil signed the TTH source documents on 5/5/06 noting "performed 1/31/06," more than three months after the administration of the investigational product.

- B. The following baseline conditions, adverse events, and concomitant medications are listed in the source documents, but are not recorded on the subjects' case report forms. (Renkens)

SUBJECT #	BASELINE CONDITION	ADVERSE EVENT	CONCOMITANT MEDICATIONS
631-S-6178	R-Leg (Ongoing) and Back Pain	Muscle Spasms Nausea/Vomiting	Biscodyl, Flexiril, Marcaine and Epinephrine
631-S-6194	Leg and Back Pain (Ongoing)		KCL, Senokot, Milk of Magnesium, Diovan, Vicodin, Bisacodyl
631-S-6199	L-Arm Pain, Numbness and Weakness	Neck Pain	Marcaine and Epinephrine, Flexamin, Occuvite, KCL
631-S-6205	Low Back and L-Leg Pain		Norco , Dilaudid, KCL, Maxzide, Marcaine and Epinephrine, Cepacol Lozenges
631-S-6218	Lower Back and Leg Pain-(Ongoing)		Cefazolin, Dilaudid, Demerol, Marcaine, Synthroid, Fexofenadine
631-S-6222	R-Leg Pain-(Resolved Visit 4)		Glycolax, Marcaine and Epinephrine
631-S-6236	Lower Back, Posterior Legs, and Buttocks Pain-(Ongoing)		Cleocin, Hydroxyzine, Talwin, Carisoprodol, Clonazepam
631-S-6237	Moderate Lower Back and Leg Pain-(Resolved Visit 4), Allergy to Keflex	Nausea and Vomiting	Valium, Lisinopril, Acetaminophen, Neurontin, KCL
631-S-6263			Phenergan
631-S-6272	Headaches, Back, Neck, R-Buttocks and Leg Pain		Senokot
631-S-6278	Low Back Pain		Biscodyl, Atarax
631-S-6285	Leg (Resolved at Visit 4) and Back		Lorazepam, Prozac

SUBJECT #	BASELINE CONDITION	ADVERSE EVENT	CONCOMITANT MEDICATIONS
	Pain (decreased at Visit 4), Sleep Apnea, Diarrhea, Fainting Spells		
631-S-6304	L-Buttocks and Hip-(Resolved Visit 4), Back Pain-(Ongoing)	Muscle Spasms	
631-S-6313	Low Back (Ongoing) and Leg Pain (Resolved at Visit 4)		
631-S-6325	Low Back Pain-(Ongoing)	L-Foot Pain and Bilateral Leg Swelling	Sinvastatin, Tegaserod, Fluticasone Nasal Spray, Montelukast, Morphine, Zofran, Acetaminophen, Vicodin, Cefazolin
631-S-6341			Alprazolam
631-S-6347	Back and Leg Pain-(Ongoing)		Bisacodyl, Protonix, Wellbutrin
631-S-6385			Valium
631-S-6386	R-Leg Pain, Shortness of Breath, Constipation, Gastric Distention and Reflux, Urgency, and Frequency		
631-S-6437			Thorazine
631-S-6438			Marcaine and Epinephrine, Caltrate, Hydroxyzine, ASA, MVI, Polymixin and Bacitracin, KCL
631-S-6442			Cefzol, Lisinopril, Glucosamine and Chondroitin
All Subjects			Epinephrine

C. Subject 6070: Information was not recorded in the source documents regarding the subject's hyperglycemia; however, the subject did receive Novulin-R insulin while in

the hospital. Hyperglycemia was also documented on the case report form. Also, there were no labs drawn on 12/16/05, which would have been Day 2 (Visit 3) (Genyk)

D. Subject 6078: The subject had numbness in their feet on 12/02/05 as recorded on the source documents; however this information was not recorded on the CRF. (Genyk)

E. Subjects 6250 and 6472: the source documents were not signed or dated.

3. Failure to retain records for the required period of time. [21 CFR § 312.62(c)].

Subjects 6035 and 6486 withdrew from the study and their consent forms were not available for review during the inspection. (Genyk)

SPONSOR FINDINGS

The following discrepancies were noted between the BLA submission data from the sponsor and the source documents:

1. Listed above in Item 2B are numerous baseline conditions, adverse events, and concomitant medications that are recorded in the source documents, but are not included in study data reported to the FDA by the Sponsor. (Renkens)
2. Subject 6068: Blood was drawn for laboratory analysis on 1/30/05, but the sponsor data provided in the BLA submission lists the specimen draw date as 12/01/05. (Genyk)
3. Subject 6070: The TTH value recorded on the source documents was 78 seconds, but the sponsor data provided in the BLA submission lists the TTH as 79 seconds. Information was not recorded in the source documents regarding the subject's hyperglycemia; however, the subject did receive Novulin-R insulin while in the hospital. Hyperglycemia was also documented on the case report form. There were no labs drawn on 12/16/05 which would have been day (Genyk)
4. Subject 6174: The information on the source documents at the time of surgery listed this individual as a 20 year old male Hispanic, but the sponsor data provided in the BLA submission listed him as a 22 year old male Hispanic.

BIMO ADMINISTRATIVE FOLLOW-UP

Close out letters were issued to Drs. Genyk, McNeil, and Renkens. Should you have any questions or comments about this memorandum or any aspect of Bioresearch Monitoring, please contact me at (301) 827-6336.

/Janet K. White/

Janet K. White

Consumer Safety Officer