

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Biologics Evaluation and Research

DATE May 07, 2014

FROM Dennis T. Cato, Bioresearch Monitoring Branch, HFM-664

Division of Inspections and Surveillance

Office of Compliance and Biologics Quality

Telephone: 301-827-2588 Fax: 301-827-6748

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

THROUGH Gilliam Conley, Director, Division of Inspections and Surveillance, HFM-650

TO

HFM-392 Natalya Ananyeva Chair, Review Committee

HFM-380 Thomas Maruna RPM

HFM-392 Lisa Faulcon Clinical Reviewer

SUBJECT Bioresearch Monitoring Discipline Review Memo

BLA/STN: 125512/0

IND: 10695

Sponsor: Baxter Healthcare Corporation

Product: Recombinant Porcine Factor VIII, B-Domain Deleted

(OBI-1)

REVIEW SUMMARY

Bioresearch Monitoring (BIMO) inspections of three domestic clinical investigator study sites did not reveal significant problems that impact the data submitted in this biologics licensing application (BLA).

BACKGROUND

Clinical Investigator Inspection Assignments were issued for three clinical study sites in support of this BLA. Two US and one foreign sites were inspected in support of this BLA. The 3 selected sites represent 60 percent of all the clinical study sites that enrolled subjects. The number of subjects selected for data verification and enrolled at the selected sites represents 80 percent of subjects enrolled in the study.

The inspections were conducted in accordance with the FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The inspection assignments included specific questions related to the study protocol, and verification of the study data on efficacy endpoints submitted by the sponsor in the BLA.

PROTOCOL AUDITED

Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (OBI-1) in the Treatment of Acquired Hemophilia A Due to Factor VIII inhibitory Auto-antibodies. (OBI-1-301)

The table below summarizes the inspection results:

Site Number	Study Site	Location	Enrolled Subjects	483 Issued	Classification
-------------	------------	----------	-------------------	------------	----------------

Site Number	Study Site	Location	Enrolled Subjects	483 Issued	Classification
01	Tulane University	New Orleans, Louisiana	4	No	NAI
02	Indiana Hemophilia and Thrombosis Center	Indianapolis, Indiana	4	Yes	VAI
40	Maisonnette-Rosemont Hospital	Montreal, QC, Canada	4	No	NAI

NAI = No Action Indicated VAI = Voluntary Action Indicated

FINANCIAL DISCLOSURE

The Clinical Investigator Compliance Program directs the FDA investigator to ask the clinical investigator if and when s/he disclosed information about her/his financial interests to the sponsor and/or interests of any sub-investigators, spouse(s) and dependent children including if and when the information was updated. Each inspected study site had a copy of the financial disclosure forms on hand for the clinical investigators and sub-investigators.

INSPECTIONAL FINDINGS

Sponsor/Monitor Issues

There were no sponsor/monitor issued identified at any of the study sites audited.

Clinical Investigator (CI) Study Site Issues

A review was conducted of testing records, regulatory binders, study specific standard operating procedures, and general study conduct. In addition, source documents were reviewed and the information contained was compared to the data tables submitted by the sponsor in the application. Individual site observations are listed below:

Study Site 01: A Form FDA 483 was not issued at close of this inspection and the inspection was classified as NAI.

Study Site 02: A 3-part Form FDA 483 was issued at the end of this inspection. The inspection was classified as VAI and an Untitled Letter was issued to the clinical investigator. The findings included:

- Eligibility inclusion criteria were not met for two subjects who participated in the OBI-1 study. Specifically:
 - There is no documentation that Prothrombin Time (PT) was performed for one subject at screening. PT is required for the protocol as a criterion for inclusion into the study.
 - The platelet count at screening for another subject was not within the normal range specified by the protocol.
- There are more than 7 (seven) instances where study procedures were not conducted in accordance with the OBI-1 protocol and/or were not documented in the deviation log or the electronic case report form (eCRF) as deviations. These include incorrect infusion

rates for the test product, missed or missing lab tests, activities performed not consistent with protocol time frames, and discrepancies in various recorded times.

- There are at least 10 (ten) instances of discrepancies and omissions involving source documents (SD) and eCRFs. The discrepancies include incomplete documentation of medical and surgical histories, discrepancies between information in SD and eCRFs, and missing laboratory assessments at screening.
- One subject participated in the OBI-1 study after signing an outdated informed consent form. The subject signed protocol version dated 7/14/10 amendment 1.0, which was approved by the Institutional Review Board (IRB) on 9/8/11, instead of protocol version dated 2/10/12 amendment 3.0, which was approved by the IRB on 5/23/12.
- Eighteen protocol deviations were not reported to the IRB at the time of continuing review as per IRB procedures, in that protocol deviations from 2011 and 2012 for two subjects were not reported to the IRB until 2/21/14.

Study Site 40: A form FDA 483 was not issued at close of this inspection, and the inspection was classified as NAI.

BIMO ADMINISTRATIVE FOLLOW-UP

Information and untitled letters were issued for respective clinical sites inspected.

Please contact me should you have any questions about this memo or any aspect of Bioresearch Monitoring.

Dennis T. Cato

Consumer Safety Officer

CC:

HFM-664 Access/Chron

EDR STN 125512/0

Draft: Cato: 5/7/2014

Reviewed: Holobaugh:

Reviewed Conley: