

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE January 09, 2015

FROM Colonious King, Bioresearch Monitoring Branch
Division of Inspections and Surveillance
Office of Compliance and Biologics Quality
Telephone: 240-402-8759 Fax: 301-595-1304

THROUGH Patricia Holobaugh, Chief, Bioresearch Monitoring Branch

THROUGH Gilliam Conley, Director, Division of Inspections and Surveillance

TO Andrew Sarafanov Chair, Review Committee
Jiahua Qian RPM
Lisa Faulcon Clinical Reviewer

SUBJECT Bioresearch Monitoring Discipline Review Memo
BLA/STN: 125555/0
IND: 13722
Sponsor: Octapharma AG
Product: Antihemophilic Factor (Recombinant) BDD-rVIII / Nuwiq

REVIEW SUMMARY

Bioresearch Monitoring (BIMO) inspections for three foreign clinical investigator study sites did not reveal problems that impact the data submitted in this Biologics Licensing Application (BLA).

BACKGROUND

Three clinical investigators were inspected in support of the BLA and were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The inspection assignment included specific questions related to the study protocols and verification of the study data on safety and efficacy endpoints submitted by the sponsor in the BLA. The completed inspections conducted at three clinical sites for data verification represented 34% of all the subjects studied for this new BLA application. The data audit portion of the inspections focused on the verification of the study data on safety and efficacy endpoints submitted by the sponsor in the BLA for 100% of the enrollees in study GENA-03 at site 43 and study GENA-08 site 14. Twelve out of the seventeen subjects enrolled data was verified with the submission from the sponsor at site 03-41.

PROTOCOLS AUDITED

*Prospective clinical study in children with severe haemophilia A to investigate clinical efficacy, immunogenicity, pharmacokinetics, and safety of Human-cl rhFVIII. (Protocol **GENA-03**)*

*Clinical study to investigate the efficacy, safety, and immunogenicity of human-cl rhFVIII in previously treated patients with severe haemophilia A (Protocol **GENA-08**)*

The table below summarizes the inspection results:

Site Number	Study Site	Location	Enrolled Subjects	483 Issued	Classification
03-41 Gena03	University Medical School in Warsaw	Warsaw, Poland	17	Yes	VAI
03-43 Gena03	Medical University of Silesia (GENA-03)	Zabrze, Poland	6	Yes	VAI
08-14 Gena08	Royal Hallamshire Hospital (GENA-08)	Sheffield, United Kingdom	5	NO	NAI

VAI= Voluntary Action Indicated; NAI = No 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. The inspected study site had a copy of the financial disclosure forms on hand for the clinical investigator and sub-investigators.

INSPECTIONAL FINDINGS

Sponsor/Monitor Issues

Thirteen subjects from two Poland sites were supposed to take part in an extension study (GENA-13). With delays in the approval process for the extension study, the sponsor decided to keep the subjects on the GENA-03 study, and no subject waiver was issued by the sponsor or by the lead medical monitor for the GENA-03 study. This lead to the subjects having significant delays for their 6 month study visits.

Clinical Investigator (CI) Study Site Issues

Study Site 03-41: The FDA investigator noted a few minor problems during the inspection. A review was conducted of testing records, regulatory binders, study specific standard operating procedures, and general study conduct. The six month visit was not followed according to the protocol for nine subjects. One subject had a Port-a-cath insertion and the trough level was not determined in accordance with the protocol. The dispensing requirement was not followed resulting in one subject from study GENA-03

receiving the study drug that was assigned to a different but related study (GENA 13). A Form FDA 483 was issued at close of this inspection and the inspection was classified as VAI.

Study Site 03-43: The FDA investigator noted a few minor problems during the inspection. A review was conducted of testing records, regulatory binders, study specific standard operating procedures, and general study conduct. The six month visit was not followed according to the protocol for four subjects. A Form FDA 483 was issued at close of this inspection and the inspection was classified as VAI.

Study Site 08-14: 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. No discrepancy was found between source documents at the site and the data submitted by the sponsor in the application. No Form FDA 483 was issued at close of this inspection and the inspection was classified as NAI.

BIMO ADMINISTRATIVE FOLLOW-UP

An information letter was issued for the study sites inspected. Please contact me should you have any questions about this memo or any aspect of Bioresearch Monitoring.

Colonious King
Consumer Safety Officer

Distribution

Electronic Copy

EDR STN 125555/0

Gilliam Conley

Lillian Ortega

Andrew Sarafanov Chair

Jiahua Qian RPM

Lisa Faulcon Clinical Reviewer

Marcelo Mangalindan, FDA Investigator

cberbimonotification@fda.hhs.gov

Draft: King: 01/07/2015

Reviewed: McDowell 1/08/2015