

MEMORANDUM

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

DATE

FROM Bhanu Kannan, Bioresearch Monitoring Branch
Division of Inspections and Surveillance
Office of Compliance and Biologics Quality

THROUGH Patricia Holobaugh, Chief, Bioresearch Monitoring Branch

THROUGH Gilliam Conley, Director, Division of Inspections and Surveillance

TO Natalya Ananyeva, Chair, BLA Licensing Committee

SUBJECT *Bioresearch Monitoring Summary Memo*
Status of the Bioresearch Monitoring (BIMO) Inspections
APPLICANT: Bayer HealthCare Pharmaceuticals Inc.
Application type and number: original BLA, STN 125574/0
PRODUCT: Antihemophilic Factor (Recombinant)

Summary Statement:

Bioresearch Monitoring inspections of three clinical investigators were conducted in support of this Biologics Licensing Application (BLA). Two of the clinical investigator inspections did not reveal significant problems in the study conduct. The inspection of the third clinical investigator noted significant problems that impact the data, and we recommend that data from this site be excluded from final analyses. In addition, based on our review of the European Medicines Agency (EMA) inspection reports we recommend that the data for all eight subjects at Site #54005 and subject (b) (6) be excluded from final analyses.

Background

Three clinical investigators were inspected in support of the BLA and the inspections 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 about the clinical studies entitled:

Leopold I-- A two-part, randomized, cross-over, open-label trial to evaluate the pharmacokinetics, efficacy, and safety profile of plasma protein- free recombinant FVIII formulated with sucrose (BAY 81-8973) in previously treated subjects with severe hemophilia A under prophylaxis therapy (hereafter referred to as Study 1), and

Leopold II -- A phase II/III, randomized, cross-over, open-label trial to demonstrate superiority of prophylaxis over on-demand therapy in previously treated subjects with severe hemophilia A treated with plasma protein-free recombinant FVIII formulated with sucrose (BAY 81-8973) (hereafter referred to as Study 2).

Study 1 was conducted at 26 study centers in 12 countries enrolling 84 subjects. Study 2 was conducted at 30 study centers in 11 countries randomizing 80 subjects. The inspections conducted at the three clinical sites represented 2% and 15% of the enrolled subjects in Studies 1 and 2, respectively. The data audit portion of the inspection focused on the verification of the safety and efficacy data submitted in the BLA by the sponsor for all the subjects enrolled at the respective study sites. The following table identifies the results of the FDA inspections regarding this BLA:

Inspection of the clinical sites and outcome

Site / Site # / Study	Location	Number of subjects enrolled	Form FDA 483 issued	Final classification
Iosif Nemoianu No, 2 Spitalul Clinic de Urgenta pentru Copii /#82001/Study 2	Timisoara Timis, Romania	4	No	NAI
SANADOR SRL H Hematologie 26-28 Dimitrie Sergiu Street, Sector 1/#82002/Study 2	Bucharest, Romania	8	No	NAI
University of California - Davis Hemophilia Treatment Center 4625, 2nd Avenue, /#14006/Study 1	Sacramento, California	2	Yes	OAI

NAI-No Action Indicated

OAI-Official Action Indicated

Financial disclosure: The Clinical Investigator Compliance Program directs the FDA investigator to ask the clinical investigator if and when he/she disclosed information about his/her financial interests to the sponsor and/or interests of any sub-investigators, spouse(s) and dependent children, and if and when the information was updated. Further, the inspection assignment had specific request for the FDA investigator to verify the financial disclosure information submitted by the sponsor in the BLA. The information submitted to the BLA was verified at the inspected sites, for the investigator and sub-investigators.

Inspectional findings:

The inspections at two clinical sites (#82201 and 82202) verified the data for the subjects submitted in the BLA, including, but not limited to, the protocol deviations, comments, adverse events, and efficacy end points reported in data listings and datasets.

The inspection at site #14006 noted additional unreported adverse events and bleeds, incorrect study drug administration, protocol deviations, inadequate record keeping by the clinical investigator, and deficiencies in reporting research activities to the Institutional Review Board (IRB) by the clinical investigator as described below.

1. The clinical investigator dispensed incorrect study drugs for subjects (b) (6) and (b) (6) in Part A of the study. Listing 16.2.2 in the BLA included data for the planned and actual arm of the study drugs assigned and dispensed to the study subjects. The table below shows the discrepancies in study drug administration based on the documents found at the site. The following table illustrates the actual drugs dispensed to the study subjects at the site.

Study drug assignment and administration in Part A

Subject	Planned arm (ARM) in data listing 16.2.2	Actual arm (ACTARM) in data listing 16.2.2	Planned randomization number	Actual randomization number	Actual drug dispensed
(b) (6)	KogFS followed by IP	IP followed by KogFS	(b) (6): IP followed by KogFS	(b) (6): KogFS followed by IP	KogFS followed by KogFS
(b) (6)	IP followed by KogFS	“Unplanned treatment”	(b) (6): KogFS followed by IP	(b) (6): IP followed by KogFS	IP followed by KogFS

IP: Investigational product KogFS: Kogenate FS, reference drug

2. Both subjects enrolled in the study had one measurement of the inhibitor antibody and not two as required by the study protocol.
3. The clinical investigator treated subjects’ bleeds that were not reported in the BLA. For example, Subject (b) (6) had a bleed at right leg groin and right side ribs treated with IP on 2/9/12, and bleed at left shoulder treated with IP on 2/16/12 that are not listed in the BLA.
4. Subjects’ case histories were incomplete or inaccurate. Examples include but are not limited to:
 - a. The original signed informed consent forms were missing Part B for both subjects enrolled in the study; the clinical investigator re-consented the subjects at a later study visit.
 - b. The case histories were incomplete about adverse experiences, including pain over olecranon, olecranon bursitis, and ear infection for subject (b) (6); and intermittent epistaxis for subject (b) (6)
5. The clinical investigator did not report changes in research activity to the IRB, including but not limited to, administration of incorrect study drug and drawing of pharmacokinetic samples outside protocol limits.

In addition, we reviewed the reports submitted by the sponsor that included the inspection results and the sponsor's response for the EMA inspections of Chinese clinical sites #54005 and #54001 for Study 2. The EMA findings and the sponsor's response to the EMA raised concerns for CBER with regard to study conduct at these sites. CBER requested that the sponsor submit their monitoring reports for selected clinical sites from Studies 1 and 2 to independently assess the monitors' findings of the EMA-inspected sites and other sites that were not inspected by the FDA. BIMO found no additional questions during our review of the monitoring reports and discussed our review with members of the BLA review team.

Due to substantial deviations from the study protocol and inadequacies in overall study conduct by the clinical investigators we recommend that the data for all eight subjects at site #54005 and subject (b) (6), at site #54001 be excluded from final analyses.

BIMO follow-up:

We sent informational letters to the inspected clinical investigators.

Should you have any questions or comments about the contents of this memo or any aspect of Bioresearch Monitoring, please contact me at 240-402-8979.

Bhanu Kannan

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History

Kannan draft: 01-10-16

Reviewed:Holobaugh: 11-Jan 2016