

Bioresearch Monitoring Summary Memo, July 17, 2012 - Hyqvia

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, HFM-664

Division of Inspections and Surveillance

Office of Compliance and Biologics Quality

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

TO Dorothy Scott, HFM-345

Scientific Lead /Chair, BLA Licensing Committee

Jennifer Reed, HFM-345

Co-Chair, BLA Licensing Committee

SUBJECT Bioresearch Monitoring Summary Memo

SPONSOR: Baxter Healthcare Corporation

PRODUCT: Immune Globulin Infusion (Human), 10% with rHuPH20

BLA: STN 125402/0

Summary

The bioresearch monitoring inspections of one clinical investigator did not reveal significant problems that impact the data submitted in the Biologics Licensing Application (BLA). At another site the subject diaries for 36% of the subjects documenting the adverse events and concomitant medications use were unavailable for BLA data verification. A third site was inspected based on a complaint prior to the study closure and BLA data submission, and significant deficiencies were documented and were acknowledged by the sponsor for this study. We defer to the committee to decide whether to include the study data from the third clinical site.

Background

Two clinical sites 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 about the clinical study entitled *Efficacy, Tolerability and Pharmacokinetic Comparison of Immune Globulin Intravenous (Human), 10% (GAMMAGARD LIQUID/KIOVIG) Administered Intravenously or Subcutaneously Following Administration of Recombinant Human Hyaluronidase (rHuPH20) in Subjects with Primary Immunodeficiency Diseases*. A third clinical site was inspected as a result of a sponsor complaint that was submitted to CBER. To investigate the complaint the

FDA investigator selected this study for inspection so no BLA data verification was performed.

The inspections conducted at two clinical sites for data verification represented 28% of the total subjects enrolled in the study. Inspection of two clinical sites was based on the submitted data in the BLA by the sponsor. The data audit portion of the inspection focused on the verification of the study data on safety and efficacy endpoints submitted by the sponsor in the BLA for all subjects at one site and for 50% of the subjects from the second site. The inspection of the third site was limited in scope and did not verify data submitted in the BLA. The following table identifies the inspection results regarding this BLA.

Inspection of clinical sites and outcome				
Study site / Site #	Location	Number of subjects enrolled	Form FDA 483 issued	Final classification
Dallas Allergy Immunology Research/01	Dallas, TX	19	Yes	VAI
Emory Children's Center /05	Atlanta, GA	5	Yes	VAI
Children's Hospital Los Angeles /11 <i>**data verification not performed</i>	Los Angeles, CA	6	Yes	VAI

VAI- Voluntary 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 has 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 two sites, #01 and #05, for the investigators and sub-investigators; this information was not reviewed for site #11 since it was an inspection based on a complaint.

Inspectional findings:

Investigator responsibilities:

1. Protocol adherence:

Our inspections verified the protocol deviations submitted by the sponsor in Table 16.2-1 of the study report. These deviations include errors in study drug administration' such as dosage calculations and infusion rate; pharmacokinetic sample collection; administration of concomitant medications and non-drug therapies; measurement of vital signs; study visits; and physical examination for the subjects enrolled in the study at study sites 01 and 05.

2. Subject diaries:

The protocol instructed that subject diaries will serve as source documentation that was required to include information such as occurrence of adverse events (AEs) including infections, infusion rate and rate changes, concomitant medications use,

and non-study required out-patient visits. The entries in the subject diaries were to be transcribed onto the appropriate case report forms (CRFs). The investigator failed to retain diaries at site #01 as illustrated in the following example. Subject diaries for 7 of 19 subjects enrolled in the study were not available during the inspection. Subjects included: -----(b)(6)-----
----- During the inspection the sponsor communicated with the clinical investigator reminding him of the expectation that subject diaries would serve as the source data for collecting and reporting the subject reported events, in addition to laboratory reports, medical records, and other source documentation. Without adequate source documentation for the collected data we cannot verify the data reported on the CRF during our inspection.

3. Adequate and accurate record keeping:

Our inspections noted data discrepancies and corrections in subject case histories as described below.

Site #01: As noted below the two adverse events (AEs) for subject- (b)(6)- and the three sub-cutaneous treatments with immunoglobulin for subject -(b)(6)- were not reported in the BLA listing.

A. Our inspection noted that AEs captured in the study documents were not reported in the sponsor's BLA listing. For example, for subject # -(b)(6)-, at least two AEs of Sinusitis (one with an onset date of 3/4/10 and the other with an unknown date) were crossed out and changed without explanation. The subject was administered antibiotics as noted by the concomitant medication list, also crossed out without explanation. We further note that the list of AEs and the concomitant medications contained out of order entries.

We further note that the AE CRFs had crossed out data entries and data changes that appear to have been made at a later time after the investigator reviewed and signed the records without explanation for such changes.

B. For subject- (b)(6)-, the Screening/Baseline documents indicate the subject was "subcutaneous (SC) naïve". However during the inspection the study personnel provided a printed list of all concomitant medications and past treatments to which the subject was exposed. The list included at least three sub-cutaneous treatments of an immunoglobulin medication between 5/28/07 and 6/12/07. The investigator acknowledged that the subject was administered SC treatments as part of another sponsored study in 2007 and that indicating the subject as SC naïve on the eligibility checklist was an error on the part of study personnel.

Bimo follow-up:

We issued letters to two clinical investigators and plan to issue a letter to the third clinical investigator.

Should you have any questions or comments about the contents of this memo or any aspect of Bioresearch Monitoring, please contact me at 301-827-6188.

Bhanu Kannan

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