

MEMORANDUM

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

DATE December 7, 2011

FROM Carla Jordan, 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, Chair, BLA Committee, HFM-392

SUBJECT Bioresearch Monitoring Final Review Memo
STN: 125398/0
Product: Recombinant Human Factor XIII subunit A (NovoThirteen ®)
Sponsor: Novo Nordisk, Inc.

STUDY TITLE

A Multi-Centre, Open-Label, Single-Arm and Multiple Dosing Trial on the Efficacy and Safety of Monthly Replacement Therapy with Recombinant Factor XIII (rFXIII) in Subjects with Congenital Factor XIII Deficiency (F13CD-1725)

SUMMARY STATEMENT

CBER BIMO issued five high-priority inspection assignments covering four clinical investigators and one contract laboratory. The inspections did not reveal problems that impact the data submitted in the BLA.

BACKGROUND

Four clinical investigator inspections and one laboratory inspection were performed in support of this BLA. Study subject enrollment and previous inspection history related to this product were among the factors used to select the inspected sites. The inspections focused on specific questions concerning the study protocol and the comparison of information from the BLA to source documents. The contract laboratory was inspected, at the request of the committee, to review the raw data used to produce the final (b) (4) results for the anti-FXIII antibodies.

INSPECTION SITES

Location	Site #	# of Subjects	FDA 483
Petah-Tikva, Israel	201 IL_025	7	No
Toronto, Canada	120	3	Yes
Bonn, Germany	180 DE_546	3	No
Boston, Massachusetts	304	2	No
Indianapolis, Indiana	Central laboratory	629 samples (31 subjects)	No

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 also the interests of any subinvestigators, spouse(s) and dependent children, and if and when the information was updated. The four clinical investigators provided copies of the financial disclosure forms to the FDA investigators. The information submitted to the BLA was verified for each investigator.

SPONSOR ISSUES

The FDA investigator observed several discrepancies between source documents, case report forms (CRFs), and the sponsor's data listings at the Petah-Tikva site. The information in the CRFs and the laboratory reports (source documents) was the same for Subject #s (b) (6) . However the data listings submitted to FDA by the sponsor in the BLA contained different information.

Subject	Visit	Laboratory Test	Source Document/Case Report Form	BLA Data Listing
(b) (6)	6	Pre-dose rFXIII Ammonia Activity	0.110	0.127
	13	Post-dose rFXIII A2 subunit	17.04	3.60
	2	Pre-dose rFXIII Ammonia Activity	0.154	0.184
	5	Pre-dose rFXIII Ammonia Activity	0.109	0.107
	1	rFXIII Ammonia Activity	0.169	0.159
	4	Pre-dose rFXIII Ammonia Activity	0.191	0.158
	8	Post-dose rFXIII B Subunit	0.23	1.79
	2	Hematocrit	40.9	40.0
	2	Neutrophils	2.90	2.70
	12	Monocytes	0.29	0.79

INSPECTIONAL FINDINGS

There were a few minor problems noted.

Laboratory Testing - (b) (4) did not report results from all samples with coefficients of variation greater than 20% between duplicates in the Final Report used to determine adequate validation of (b) (4) used to test subject samples.

Serious Adverse Event (SAE) Reporting - Subject #(b) (6) reported having a sprained ankle at Study Visit #14, week 44; however, this AE was not reported to the Sponsor. (Site 120)

BIMO ADMINISTRATIVE FOLLOW-UP

Informational letters have been issued to all of the inspected parties. Please contact me at (301) 827-6348 if you have any questions about this memo or any aspect of bioresearch monitoring.

Carla V. Jordan
Consumer Safety Officer

Anthony D. Hawkins
Consumer Safety Officer

Cc:

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EDR STN 125398/0
HFM-650 Gilliam Conley
HFM-392 Roman Drews
HFM-380 Debbie Cordaro
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HFR-NE2530 Steve Souza
ORA HQ DFFI IOB BIMO
HFC-180 Yvette Arline
HFC-130 Oumou Barry

History

Draft: Jordan: 12/6/11
Reviewed: Hawkins: 12/7/11
Reviewed: Holobaugh: 12/7/11