

BIMO Summary Memo, August 1, 2013 - Novoeight

Memorandum
Health and Human Services

Department of

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research

DATE August 1, 2013

FROM Bhanu Kannan, Bioresearch Monitoring Branch, HFM-664
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THROUGH Patricia Holobaugh, Chief, Bioresearch Monitoring Branch, HFM-664

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

TO Natalya Ananyeva, HFM-345
Chair, BLA Licensing Committee

SUBJECT *Bioresearch Monitoring Discipline Review*
Summary of Bioresearch Monitoring (BIMO) Inspections

SPONSOR: Novo Nordisk Inc.

PRODUCT: Anti-Hemophilic Factor (Recombinant)

BLA: STN 125466/0

Review summary:

The bioresearch monitoring inspections of four clinical investigators did not reveal significant problems that impact the data submitted in the Biologics Licensing Application (BLA).

Background

Four 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 about the clinical study entitled *A Multi-Centre, Open-Label, Non-Controlled Trial on Efficacy and Safety of N8 in Prevention and On-demand Treatment of Bleeding Episodes in Previously Treated Subjects with Haemophilia A*.
Sub-Trial: Efficacy and Safety of N8 in Prevention and Treatment of Bleeding during Surgical Procedures in Subjects with Haemophilia .

The completed inspections conducted at four clinical sites for data verification represented 22% of the total subjects enrolled in the study. Inspection of four 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 100% of the enrollees at each of the inspected US sites, and at least 67% at each of the inspected Brazil sites. The following table identifies the status and results of the assigned inspections regarding this BLA.

Inspection of clinical sites and outcome

| Study site / Site # | Location | Number of subjects enrolled | Form FDA 483 issued | Final classification |
|---------------------------------------------------------------|------------------------|------------------------------------|----------------------------|-----------------------------|
| Oregon Health and Science University/861 | Portland, OR | 6 | Yes | VAI |
| University of Iowa Hospitals and Clinics /868 | Iowa City, IA | 6 | Yes | VAI |
| Instituto Estadual Arthur de Siqueira Cavalcanti, HEMORIO/351 | Rio de Janeiro, Brazil | 6 | Yes | VAI |
| Universidade Estadual de Campinas/352 | Campinas,SP, Brazil | 10 | 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 inspected sites for the investigators and sub-investigators.

Inspectional findings: Protocol adherence

Our inspections verified the protocol deviations reported in the line listings 1.43.9 and 1.45.9, (Important Protocol Deviations) and the deviations reported in Appendix 16.2.2 such as eligibility criteria, protocol procedures, endpoint assessment, treatment compliance, collection and testing of laboratory samples, and study drug storage temperatures. In addition our inspections noted the following deviations from the study conduct that were not reported in the BLA.

1. The protocol section 8.3.5 required the ECG to be performed prior to the study drug dosing to the study subjects. At sites #861 and #868 ECGs were performed after the study drug dosing as described:

- a) At site #868, for 4 subjects for a total of 6 visits, the ECGs were performed between 5 and 19 minutes after the study drug dosing.
- b) At site #861, for 5 subjects for total of 12 visits, the ECGs were performed between 5 and 37 minutes after the study drug dosing.

2. Site #861: At least for 5 of the 6 subjects enrolled in the study for a total of 14 visits, the clinical investigator used the body weight from the previous visit to calculate the study drug dose for administration. For three subjects the actual body weights during a visit were higher by more than 3 kg from the previous visit body weights that were used for dosing.

3. We further note that the listing 1.43.9 (Important Protocol Deviations) for site #861 is incomplete in that the entries are cut off mid-word and mid-sentence. This table also does not include data for subjects -----(b)(6)-----.

Data discrepancies:

Subject case histories at the inspected sites contained discrepant study data as described below. Source documents found at the study sites were discrepant from the data reported on the BLA line listings and/or the electronic case report forms (eCRFs) found at the study sites.

4. We note that the study coordinator revised a CRF data entry on 8/11/11 for the FVIII recovery for subject --(b)(6)-- to 0.01 IU/ml entered on 8/25/10 in response to a query from the sponsor. However, the source document at the site indicated the value as 1.02 IU/ml.

5. For subject --(b)(6)--, the BLA line listings and the eCRF collected from the study site indicate that the subject received 30 IU/kg of the study drug and corresponded to 4.8ml of an injection volume of the study drug. However, the source document was discrepant and indicated that the subject was administered 7.8 ml of the study drug.

6. One of the secondary efficacy endpoints is the actual total amount of the drug administered to each subject ("consumption") of the study drug through this time period. The BLA did not accurately report this information. For example, source documents indicate that Subjects --(b)(6)-- and --(b)(6)-- received study drug during Part C, C1 days 8 through 12, Recovery Period of the study, but the BLA line listings,

Appendix 16.2.5, and the eCRFs located at the study site do not report administration of study drug to the subjects on the specific dates.

| Subject # | C2 surgery recovery days (5 days) | Study drug dosage administered |
|--------------|-----------------------------------|--------------------------------|
| ---(b)(6)--- | 04/21/10 through 04/25/10 | 50 lu/kg (11.4 ml) |
| ---(b)(6)--- | 06/16/10 through 06/20/10 | 50 IU/kg (8.4 ml) |

7. Source data such as adverse events (AE) or bleeding episodes or study visits collected at the study site #861 were not reported by the sponsor in the BLA as described in the examples below:

| Subject | Source data located at the study site | BLA data listing or study report |
|--------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| ---(b)(6)--- | AE of left forearm bleed from 2/14/10 to 2/15/10 Bleeding episode-2/14/10 to 2/15/10 | No data in AE listing 1.43.6 No data in "Bleeding episodes" 1.43.11 |
| ---(b)(6)--- | AE of right foot laceration | No data in AE listing 1.43.6 ; data reported as a 'Bleeding episode' in 1.43.11 |
| ---(b)(6)--- | Visit on 5/12/10 and infusion | No data in the BLA 16.2.4 or 1.43.11 |

8. Data were prematurely entered and electronic case report forms were completed for subjects' eligibility prior to the receipt of laboratory results and study visits for at least three subjects at site #868, all six subjects at site #351, and ten subjects at site #352.

BIMO follow-up:

Letters were issued to two clinical investigators for the US sites and we plan to issue letters to the inspected clinical investigators for the Brazil sites.

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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