



**FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH**

Memorandum

Date: October 25, 2007
From: Hon-Sum Ko, CBER/OBRR/DH, HFM-392 *H. S. K.*
To: DBA File: BLA 125251/0
Subject: Telecon with Octapharma on BLA STN 125251/0 (Wilate)

APPROVED
By KoH at 8:00 am, Oct 30, 2007

Meeting Date: October 25, 2007

Time: 9:00- 10:00 am

Location: Room 300N

Type of Meeting: Teleconference

Octapharma Participants:

Wolfgang Frenzel, Martina Jansen and Bruce Schwartz from clinical department
Olaf Walter, Int. Business Management
Tor-Einar Svae, R&D
Stan Ammons, Barbara Rangetiner and Xenia Serro from Regulatory department

CBER Participants:

Dr. B. Golding
Dr. I. Mahmood
Dr. H. Ko
Dr. J. Kim
Dr. T. Lee
Mr. F. Stephenson

Meeting Objective:

- To discuss the pharmacokinetics data in BLA STN 125251
- To have clarification on information for (b)(4) subjects in Wilate clinical studies
- To convey FDA's plan for reviewing data on hemostatic efficacy for bleeding episodes (b)(4)
- To clarify discrepancies between proposed labeling and clinical database

Discussion:

- FDA noted that Octapharma's PK data on VWF:RCoF have been based on a manual assay with serial dilution with serious flaws that make the information obtained very difficult to interpret. This would result in inaccurate information to physicians and dosing guidelines. FDA recommended Octapharma to use an automated assay to restudy PK in VWD patients. Octapharma stated that the automated assay uses a machine specific for Humate-P, which may erroneously give low values for VWF:RCoF for other products. Octapharma will provide this publication to FDA for review.
- Octapharma clarified information on (b)(4) subjects as follows:

(b)(4)

- FDA conveyed to Octapharma the plan to be used for reviewing data on hemostatic efficacy for bleeding episodes (b)(4) by the Agency (see Appendix). Octapharma asked FDA to send this to them via email. FDA agreed.

Action Items:

- OBRR will send the review plan for bleeding episodes (b)(4) to Octapharma.
- Octapharma should send the publication on automated assay for VWF:RCof problems to FDA.
- Octapharma stated that they will reply any outstanding issues to FDA via email (discrepancies between proposed label and database).

Appendix. Review Plan on Wilate Bleeding Episodes (b)(4)

For both bleeding episodes (b)(4) only a success/failure rating will be used in the evaluation of hemostatic efficacy.

1. Bleeding Episodes¹

A. Success/Failure

In addition to the 4-point subjective verbal rating scale (VRS) scale used in the studies by the Investigator or patient to determine clinical efficacy, an arbitrary but more objective success/failure determination is to be based on additional factors. As a conservative approach, moderate and none scores in the 4-point scale will be regarded as failures, and excellent and good scores will be subjected to more objective criteria as follows:

a) use of other products that contain VWF* (failure)

*not including whole blood

b) inadequate hemostasis as shown by requiring unexplained blood transfusions (failure)

c) Increase in dose without adequate justification or unexplained doses above that recommended in the protocol and proposed labeling (failure).

d) number of infusions used -

- o Minor bleeds > 2 treatments (failure)
- o Moderate bleeds > 3 treatments (failure)
- o Severe bleeds > 4 treatments (failure)**

**For severe bleeding, the site of bleeding will be taken into consideration, and each deviation from the 4-treatment cutoff must be justified.

Previously unrated episodes under the subjective 4-point scale will also be assigned success/failure rating based on the above objective criteria.

B. Dosing

The final recommended dosing should be based on that used by the successful cases in the studies for each type of bleeding.

(b)(4)

¹ Counting of "Episode". When bleeding episodes are separated by 3 or more days (i.e., ≥ 2 calendar days), they can be counted as separate. If it is fewer than 3 days, they should be counted as within one episode.

(b)(4)

(b)(4)

- a) use of other products that contain VWF* (failure)
*not including whole blood

(b)(4)

- c) increase in dose or unexplained doses above that recommended in the protocol and proposed labeling, in the absence of adequate justification with plasma (FVIII or VWF) levels (failure).

(b)(4)

(b)(4)

D. Dosing.

The final recommended dosing should be based on that used by the successful cases in the studies.

3. Overall Success Criteria for the Study of Hemostatic Efficacy

A. Bleeding Episodes

- We would apply a lower bound 95% C.I. of 70% for hemostasis success rate for treatment of bleeding episodes in an integrated analysis of the data from all four studies.
- As a more objective secondary analysis, we would evaluate the number of infusions required for a bleeding episode. An artificial cutoff for the proportion of bleeding episodes requiring 2 or fewer infusions would be tested against a hypothesis that the lower bound 95% C.I. for this proportion be at least 0.8.

(b)(4)