



Internal Late-Cycle Meeting Summary
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Application:	STN 125577
Product:	von Willebrand Factor (Recombinant)
Proposed Indication:	The proposed indication for rVWF is prevention and treatment of bleeding episodes in adults (age 18 years and older) diagnosed with von Willebrand disease.
Meeting Date and Time	July 30, 2015 at 10:00 am
Applicant:	Baxter Healthcare Corporation
Committee Chair:	Chava Kimchi-Sarfaty, PhD
RPM:	Cherie Ward-Peralta

Attendees:

Chair Person/CMC Product Reviewer: Dr. Chava Kimchi-Sarfaty
CMC Product Reviewer: Dr. Zuben Sauna – Not Present
Clinical Reviewer: Dr. Victor Baum
Clinical Pharmacology: Dr. Iftekhar Mahmood
Toxicology Reviewer: Dr. Anne Pilaro
Postmarketing Safety Epidemiological Reviewer: Dr. Meghna Alimchandani
Statistical Reviewer: Dr. Shuya (Joshua) Lu
APLB Reviewer: Dr. Loan Nguyen
DMPQ CMC & Facility Reviewer: Jie He
OCBQ/BIMO Reviewer: Colonious King
OCBQ DBSQC Representative: Hyesuk Kong
OCBQ DBSQC Representative: Marie Anderson and Karen Campbell
OCBQ/DBSQC Reviewer: Dr. Lokesh Bhattacharyya
Regulatory Project Manager: Cherie Ward-Peralta

Additional Attendees:

Qiao Bobo, Team Lead, OCBQ/DMPQ/BII
Howard Chazin, MD, MBA, Deputy Director, DHCR, OBRR
John Eltermann, Director, DMPQ, OCBQ
Mitchell Frost, MD, Acting Branch Chief, DHCR, OBRR
Basil Golding, MD, Director, DHRR, OBRR
Tim Lee, PhD, Acting Chief, Laboratory of Hemostasis (LH), DHRR, OBRR
Ginette Y. Michaud, MD, Deputy Director, OBRR
Paul D. Mintz, MD, Director, DHCR, OBRR
Renee Rees, PhD, Lead Mathematical Statistician, Division of Biostatistics, OBE
Lisa Stockbridge, PhD, Chief, Advertising and Promotional Labeling Branch, OCBQ/DCM
Emily Storch, MD, Medical Officer, DHCR, OBRR
Iliana Valencia, MS, RPM Staff Chief, OBRR
Mark J. Weinstein, PhD, Associate Deputy Director, OBRR
Jane Woo, MD, Medical Officer, Pharmacovigilance Branch, Division of Epidemiology, OBE

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Please note the following agenda items for our internal late-cycle meeting for STN 125577/0. The goal of the internal late-cycle meeting is to have a comprehensive reading on the state of the review and pending actions for this original BLA subject to PDUFA V Program guidelines:

1. Substantive issues raised during review [**Reviewer Report**].

Chair Person/CMC Product Reviewer:

Baxter Healthcare Corporation has developed VONVENDI, a recombinant human VWF (rVWF) protein. The rVWF is manufactured and formulated in the absence of animal or human plasma proteins. rVWF protein is expressed in Chinese Hamster Ovary (CHO) cells that also express the licensed rFVIII product ADVATE. (b) (4)

. The potency of the product is measured by Ristocetin Co-Factor (VWF:RCo activity).

The following Chemistry, Manufacturing and Controls product issues were discussed and resolved with Baxter during the review:

1. Establish similar kinetics of ADAMTS13 degradation to plasma-derived VWF (pVWF).
2. Establishment of test to detect (b) (4).
3. Implementation of (b) (4) in the manufacturing process of recombinant furin.
4. Establishment of genetic stability of cell line (b) (4).
5. Establishment of (b) (4) and test method for drug product appearance. Baxter added the Mix2Vial (b) (4), which is included in the rVWF clinical kit.
6. Establishment of (b) (4) (b) (4) step to meet the specifications of the level of (b) (4) in the FDP.

Clinical Reviewer:

Two phase 1 and one phase 3 clinical studies, including 84 subjects, were submitted. The first phase 1 study evaluated PK profiles with increasing doses of VONVENDI and included a crossover trial with a comparator. PK profiles were similar and there was normal in vivo proteolytic degradation of VONVENDI, similar to native von Willebrand factor. The second phase 1 trial showed that co-administration with Factor VIII (ADVATE) did not decrease, and slightly sustained, Factor VIII. In the phase 3 trial of 37 subjects (predominantly type 3 disease but also types 1 and 2), 192 of 192 bleeding episodes were treated successfully. 82% of bleeding episodes required only a single dose of VONVENDI. Overall hemostatic efficacy was rated as excellent in 96.9% of bleeding episodes. There were no safety signals and no common adverse event profile. There were a total of 10 serious adverse events. Only two, chest discomfort and tachycardia in a single subject, were assessed as possibly related to VONVENDI. This subject had already received VONVENDI in the pharmacokinetic arm of the phase 3 trial and had received VONVENDI twice to treat ankle bleeds, two and 12 days previously. Treatment of a third ankle bleed was stopped for these symptoms after 6 mL. Spontaneous recovery began by 10 minutes and was complete by three hours without sequelae. There were no reports of immunogenicity or thrombosis. Orphan drug designation has been granted so PREA is not triggered. Studies have not been done in pregnant or lactating women or adults over

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60. The wording of the desired indication will need to be reworded to comply with recent changes in nomenclature.

In general, the review team did not have any substantive issues with the submission.

Mr. He reported of an information request to be sent regarding the acceptance criteria for testing the (b) (4) and to establish a time limit. He is awaiting a response to items originally listed on the 483 to be submitted in August 2015.

Dr. Alimchandani reported that at this time, there is no safety concern that would require either a Risk Evaluation and Mitigation Strategy (REMS), a safety postmarketing commitment (PMC) or a required postmarketing (PMR) study. There are two planned postmarketing efficacy studies proposed by Baxter (submitted under IND 13657) for (b) (4) in severe von Willebrand Disease.

Dr. Bhattacharyya reported of a couple of information request that need to be sent out for his review team to complete their reviews. The items being requested do not affect the approval of the submission, but may initiate discussion of requesting a PMC. Further internal discussions will take place shortly.

2. Review of upcoming timeline/deadlines [**Chair**]

Complete Discipline Reviews (Primary)	Jul 24, 2015
Internal Late-Cycle Review Meeting	July 30, 2015
Complete Discipline Reviews (Secondary Review)	Aug 7, 2015
Send Late Cycle / Advisory Comm briefing package	Aug 21, 2015
Labeling Review Meeting	Sep 1, 2015
External Late-Cycle Meeting	Sep 3, 2015
SBRA and Draft PI to Division Management	Sep 17, 2015
Complete inspection reports & PMR/PMC Requests	Sep 19, 2015
SBRA +PI + Approval Letter to OBRR Management	Oct 2, 2015
SBRA + PI + Approval Letter to Review Committee	Oct 30, 2015
Complete Approval Package	Nov 6, 2015
Route for Approval Package for Signature	Nov 9, 2015
Target ADD	Nov 17, 2015
Send FDA Action Letter	Dec 18, 2015
Post-Action Debrief Meeting	Jan 11, 2016

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3. Assess status of the review including plans for completing outstanding discipline reviews and any remaining outstanding issues [**Chair**]

Most reviewers suggested that their memos would be complete by mid-August. The review committee agreed upon meeting the revised action due dates especially since there are no substantive issues with the submission.

4. Outstanding Information Requests

- a. We are waiting for a response to IR due on July 30, 2015
- b. Some review members will have a couple of possible IRs to be sent the applicant following this meeting.

5. REMS or other risk management actions

Review committee informed that there will not be a REMS required for this submission.

6. PMRs/PMCs

At this time, there are no Safety PMRs or PMCs or CMC PMCs to be requested. If PMRs/PMCs arise, the review committee needs to begin requesting these in the next month or so for Baxter to submit their letter of commitment. The target date to finalize PMR/PMC is September 19, 2015

7. Major labeling issues

- a. At this time, the review committee did not raise any major labeling issues to be discussed at the External Late-cycle Meeting
- b. Labeling Meeting has been scheduled for September 1, 2015 to discuss and finalize revisions to the PI to be sent to Baxter following this meeting. Review committee needs to ensure that the label meets all the PLLR requirements.

8. Reach agreement on Late-Cycle meeting materials that will be sent to the applicant. [**Chair, Review Committee Members**]

A Draft Agenda for the Late-Cycle Meeting is available in SharePoint to begin editing for the review team. We should look to finalize this agenda by August 10, 2015 to provide time for Management to review and finalize before sending to Baxter.

The final agenda needs to be sent out on August 21, 2015.

Note: A template is also attached below for your reference.

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9. Come to agreement on the issues to be included on the agenda for the LCM with the applicant. The timeframes for each agenda item should also be agreed to. [**Chair, Review Committee Members, Management**]

The review committee did not have any items to be included in the agenda.

10. Establish a labeling review plan and agree on future labeling meeting activities.

Labeling review meeting is scheduled for Sept 1, 2015

Action items:

1. Review team to begin drafting and finalizing the External Late Cycle Meeting Agenda
2. Review team to finalize on the review memos by Mid-August to meet the revised target action due date.
3. Product office to begin drafting and informing the appropriate offices on issuing a Press Release
4. Review team to prepare for the labeling review meeting to be held on September 1, 2015. Also, to ensure the review of the PI is according to the PLLR labeling format.