



Our Reference: STN BL 125574/0

Bayer HealthCare LLC  
Attention: Ms. Vicki Chen  
100 Bayer Boulevard  
PO Box 915  
Whippany, NJ 07981-09115

Dear Ms. Chen:

Attached is a copy of the memorandum summarizing your October 8, 2015 Late-Cycle Meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to STN BL 125574/0 in your future submissions related to the subject product.

If you have any questions, please contact the Regulatory Project Manager, Pratibha Rana, at [pratibha.rana@fda.hhs.gov](mailto:pratibha.rana@fda.hhs.gov) or (240) 402-8433.

Sincerely,

Iliana Valencia, MS  
Chief, Regulatory Project Management Staff  
Office of Blood Research and Review  
Center for Biologics Evaluation and Research



## Meeting Summary

**Application Type and Number:** BLA, STN BL 125574/0

**Product Name:** Antihemophilic Factor (Recombinant)  
[KOVALTRY]

**Proposed Indication:** For use in adults and children with hemophilia A for: (i) routine prophylaxis to prevent or reduce the frequency of bleeding episodes, (ii) on-demand treatment and control of bleeding episodes, and (iii) peri-operative management of bleeding.

**Applicant:** Bayer HealthCare LLC

**Meeting Category:** Late-Cycle Meeting

**Meeting Date & Time:** October 8, 2015, 12:30 pm-2:00pm

**Meeting Format:** Face-to-Face

**Meeting Chair:** Natalya Ananyeva, PhD

**Meeting Recorder:** Pratibha Rana, MS

**Preliminary Responses sent** September 25, 2015

### FDA Participants:

Fatima Abbasi, MPh, Regulatory Project Manager (Detail), RPMS/OBRR

Natalya Ananyeva, PhD, Senior Staff Fellow, Division of Hematology Research and Review (DHRR), OBRR

Deepa Arya, MD, Acting Chief, Analytic Epidemiology Branch, Division of Epidemiology (DE), OBE

Marthe Bryant, MD, Reviewer, DE, OBE

Gilliam Conley, Director, Division of Inspections and Surveillance (DIS), OCBQ

Yu Do, MS, Regulatory Project Manager, RPMS/OBRR

Jay Epstein, MD, Director, Office of Blood Research and Review

Mahmood Farshid, PhD, Deputy Director, DHRR, OBRR

Bindu George, MD, Acting Chief, Clinical Review Branch, Division of Hematology Clinical Review (DHCR), OBRR

Cherry Geronimo, Regulatory Project Manager (Detail), RPMS/OBRR

Basil Golding, MD, Director, DHRR, OBRR

Patricia Holobaugh, Chief, Bioresearch Monitoring Branch, DIS, OCBQ

Lin Huo, PhD, Visiting Scientist, Division of Biostatistics (DB), OBE

Bhanu Kannan, Consumer Safety Officer, DIS, OCBQ

Megha Kaushal, MD, Medical Officer, DHCR, OBRR

Nancy Kirschbaum, PhD, Chemist/Acting Team Leader, DHRR, OBRR  
Tim Lee, PhD, Acting Chief, Laboratory of Hemostasis, DHRR, OBRR  
David Martin, MD, Director, Division of Epidemiology, OBE  
Ginette Michaud, MD, Deputy Director, OBRR  
Paul D. Mintz, MD, Director, DHCR, OBRR  
Loan Nguyen, PharmD, APLB, Division of Case Management, OCBQ  
Lori Peters, Consumer Safety Officer, Division of Manufacturing and Product Quality, Office of Compliance and Biologics Quality (OCBQ)  
Pratibha Rana, MS, Regulatory Project Manager, RPMS/OBRR  
Renee Rees, PhD, Lead Mathematical Statistician, DB, OBE

**Eastern Research Group Attendee**

Christopher Sese, Independent Assessor

**Bayer Attendees:**

Horst Beckmann, PhD, Principal Statistician, Medical Expert in Clinical Statistics, Global Clinical Statistics  
Vicki Chen, MS, Associate Director, Global Regulatory Affairs - Hematology  
Steve Garger, BA, Director, Isolation and Purification, Global Biological Development  
Mark Goldman, MS, Deputy Director, Global Regulatory Affairs - CMC  
Andy Hargreaves, BS, Head of Global Quality Strategy, Global R&D Quality  
Chi Li, PhD, MBA, Senior Director, Head of Hematology Group, Global Regulatory Affairs  
Monika Maas Enriquez, MD, Global Clinical Leader, Global Clinical Development  
Lisa Michaels, MD, Vice President, Head of Hematology, Global Clinical Development  
Bettina Müller, MD, MSc, Head of Specialized Therapeutics, Global Pharmacovigilance - Risk Management  
Todd Paporello, PharmD, MBA, Vice President, Head of US Regulatory Affairs, Global Regulatory Affairs  
Lisa Regan, PhD, Vice President, Analytical Development, Global Biological Development  
Gerhard Schlueter, PhD, Vice President, Head of Specialty Medicine, Global Regulatory Affairs  
Joseph Scheeren, PharmD, Senior Vice President, Head of Global Regulatory Affairs

**BACKGROUND AND OBJECTIVES:**

The purpose of the meeting is to discuss substantive review issues that FDA has identified to date, and to develop further objectives for the review of Biologics License Application (BLA), STN BL 125574/0, for Antihemophilic Factor (Recombinant), proprietary name Kovaltry. The BLA was submitted by Bayer HealthCare LLC to FDA on December 16, 2014, under the PDUFA V Program and is on a standard review schedule with the original action due date on December 16, 2015.

In the preparation for this meeting, FDA sent the Late-Cycle Meeting (LCM) Briefing Package to Bayer HealthCare LLC on September 25, 2015.

**LATE-CYCLE MEETING SUMMARY**

After introduction and opening comments from OBRR management and the Chair, the discussion was held by review discipline according to the Agenda agreed upon between FDA and the Applicant:

- Discussion of CMC Review Issues
- Discussion of Substantive Review Issues/Clinical, Statistical, BIMO, Epidemiology
- Status of Information Requests and Pending Reviews

The Applicant presented their slides to facilitate the discussion.

**CHEMISTRY, MANUFACTURING AND CONTROLS**

1. We acknowledge receipt of amendment 19 on July 31, 2015, containing the updated report, “Chromogenic Substrate Assay for Release of BAY 81-8973,” and receipt of amendment 24 on August 17, 2015, containing Field Study Report, “KINE 140146.” The choice of potency assay for labeling Kovaltry (One-Stage Clotting or Chromogenic Substrate) remains under FDA internal discussion.
2. Submitted data in support of (b) (4) at the (b) (4) step were deemed insufficient. Prospective process validation of the (b) (4) step will be required to provide a high degree of assurance of no negative impact to product quality. Process validation should include complete manufacture of three conformance lots through the (b) (4) step with extended characterization after appropriate phases of manufacture and stability monitoring of final drug product lots.
3. We note that the currently used assay for quantitation of host cell proteins (HCP) has been validated using an antibody generated from a mock transfected BHK cell line that does not express HSP70. The comparative data in section 3.2.S.3.2 Impurities demonstrated differences in the HCP profiles of the antigens derived from HSP70-non-expressing and HSP70-expressing cells. This may potentially result in differences in the level of detection and coverage for these two antibodies. Please validate a (b) (4) assay for Kovaltry as a post-marketing commitment.

4. Remaining concerns related to control strategy will be communicated through future information requests (IR). There is one outstanding IR, which was sent to Bayer on September 15, 2015.

### **Additional discussion**

1. Bayer presented their justifications for the use of the Chromogenic Substrate (CS) assay for potency assignment of Kovaltry:
  - a. Over the course of development, the ratio of the CS to the One-Stage Clotting (OS) assays has improved from the original ratio of (b) (4) to the current ratio of (b) (4) as a result of changes in the standard used and how the standard was assigned a value. Bayer also noted more consistent results from the CS assay over time.
  - b. In the clinical program, dosing patients based on the CS assay was as effective during prophylaxis or on-demand treatment as dosing with approximately (b) (4) more Kovaltry (based on the original CS/OS ratio of (b) (4)).
  - c. The field study indicated comparable performance of the CS and OS assays in measuring the recovery of Kovaltry in plasma samples compared to nominal target values.

FDA stated that the choice of potency assay for labeling Kovaltry remains under FDA internal discussion. FDA noted that the licensed predecessor product, Kogenate FS, contains the same formulated, full length recombinant Factor VIII and is labeled using the OS assay. Therefore, FDA expressed concern regarding continuity of protein fill when transitioning from Kogenate FS to Kovaltry; specifically, a predicted (b) (4) less Factor VIII protein filled per vial. FDA further cited results from comparative protein content submitted to the BLA. Protein values for Kogenate FS final container vials were consistently (b) (4) higher than Kovaltry values labeled with the same nominal potency.

Bayer stated Kovaltry is viewed as a new product. Bayer will summarize their justification and address the filling aspect in their response to the LCM Package.

2. Bayer stated that the cautionary (b) (4) at the (b) (4) step is justified by the results of (b) (4) runs, and by the production of (b) (4) conformance batch of drug substance manufactured as part of the prospective process validation plan. The small-scale studies did not reveal differences in rFVIII before and after (b) (4) as judged by *Specific Activity*, (b) (4). The full-scale conformance batch of (b) (4) drug substance was manufactured further into (b) (4) lots of drug product. All conformance lots met all acceptance criteria for release testing and extended characterization, and have remained stable.

FDA requested that Bayer describe the conditions under which the (b) (4) full-scale drug substance conformance batch was produced (nominal or worst-case in terms of processing time), and explain how small-scale studies are representative of the full-scale production process. Bayer agreed to provide this information in their responses to the LCM Package.

3. Bayer committed to validate a (b) (4) assay by June 30, 2016.

FDA stated that the wording for this postmarketing commitment (PMC) needs to be finalized, and the reporting category for this PMC may be a CBE-30 supplement assuming no changes to the release specification are made.

#### **NON-CLINICAL PHARMACOLOGY / TOXICOLOGY**

There are no substantive review issues at this time.

#### **CLINICAL PHARMACOLOGY**

There are no substantive review issues at this time.

#### **CLINICAL AND BIOSTATISTICS**

The following substantive review issues/major deficiencies have been identified, to date:

1. Please provide your efficacy analysis comparing the low-dose prophylaxis regimen versus the high-dose prophylaxis regimen in the Leopold II studies, where we noted differences. Please also provide the justification for the low-dose regimen to support your plans to include this dose in the label.
2. Please provide sensitivity analyses for the primary efficacy results in the Leopold I and II studies, and also the combined data for Leopold I and II excluding:
  - a. Two subjects from Site 14006 in the Leopold I study based on the findings of the FDA Bioresearch Monitoring (BIMO) inspection of this site.
  - b. Nine subjects from Sites 54005 and 54001 in the Leopold II study. The findings from the European Medicines Agency (EMA) inspections raised substantial concerns for the Agency with regard to study conduct at these sites. Therefore, we recommend exclusion of these subjects from this analysis.
3. We note that the Factor VIII inhibitor rate in previously untreated patients (PUPs) in the ongoing Leopold Kids study is 6 of 14 patients (43 %) based on the information in amendments 27 and 29 (sequence 0026 and 0028), received August 31, and September 2, 2015, respectively. This is a safety concern. Please propose a plan to address this immunogenicity concern. Please provide projections for enrollment from now until December 2015, including the number of subjects and number of exposure days with

Factor VIII doses, as well as any updated data. Also, please provide the timeline projections for enrollment of all (25) subjects specified in the study protocol and for completion of the study.

4. In the Leopold II study (study 14319), please perform a sensitivity analysis by using Poisson regression (instead of ANOVA) for the primary and secondary comparisons of Annualized Bleeding Rates (ABR).
5. In the Leopold II study (study 14319), please perform a subgroup analysis by race on ABR.

### **Additional discussion**

1. Bayer stated that in the Leopold II study, the median ABR was higher in the low-dose subgroup during the first 6-month period of treatment, but it improved in the second 6-month period (mean dose, 28.7 IU/kg) and was comparable to the high-dose subgroup (mean dose, 36.5 IU/kg). In the Leopold II study, superiority of prophylaxis versus on-demand treatment was demonstrated for both low-dose and high-dose regimens. In the Leopold I study (prophylaxis), where dose selection was based on individual patient characteristics, the median ABRs were similar for the low-dose and high-dose subgroups. Bayer stated that efficacy of low-dose prophylaxis regimen justifies inclusion of the low-dose regimen in the label.

FDA requested that a detailed response be submitted as an amendment.

2. Bayer presented the results of the sensitivity analyses for primary efficacy in the Leopold I study (excluding 2 subjects), Leopold II study (excluding 9 subjects), and for the combined data from the Leopold I and II studies. FDA stated that the results were presented in the Power Point format and requested that Bayer submit the formal results in written and tabular format as an amendment. FDA explained that for the sensitivity analysis for the primary efficacy of the combined data, 9 instead of 7 subjects should be excluded (2 subjects from the Leopold I Site 14006 and 7 subjects from the prophylaxis arm in the Leopold II study).
3. Bayer presented the inhibitor data in PUPs, reporting that the low titer inhibitors were transient and the last measured inhibitor was negative. Bayer stated that the high titer inhibitor patients have at least one identified risk factor. FDA commented that although this is an ongoing study, these preliminary results warrant discussion on final labeling. Bayer stated that they continue to expect 2-3 additional subjects enrolled by December 2015. FDA requested that Bayer submit complete inhibitor data in PUPs and projections for the study progress and completion in their response to the LCM Package.

### **BIORESEARCH MONITORING**

1. The BIMO inspection of Site 14006 for the Leopold I study identified failure to conduct required testing for inhibitors and under-reporting of bleeding episodes and adverse

events for the two subjects, and we recommend excluding them from analyses of safety and efficacy.

2. The findings of the EMA inspections of Sites 54005 and 54001 for the Leopold II study identified substantial deviations from the study protocol and inadequate documentation of medical history. These findings raised concern for the Agency with regard to study conduct at these sites, and we recommend the exclusion of all eight subjects at Site 54005 and subject (b) (6) at Site 54001 from analyses.
3. Monitoring reports from all other sites for the Leopold I and II studies were requested (please refer to IR dated September 11, 2015).

### **Additional discussion**

FDA stated that additional information for the 9 subjects from Sites 54001 and 54005 in the Leopold II study will be helpful. FDA also requested analysis minus the two sites. Bayer agreed to provide, as an amendment, the summarized information for these 9 subjects (dose, treatment duration and bleeding rate) to support their eligibility.

FDA also stated that the monitoring reports from the requested sites for the Leopold I and II studies have been received and are currently under review.

### **PHARMACOVIGILANCE**

Final protocols and milestone schedules for the planned and ongoing postmarketing commitment studies listed in the pharmacovigilance plan should be submitted:

- Ongoing clinical trial Leopold Kids Part B and Extension
- Clinical trial Leopold IV (Study 16817), *“Investigation of Safety and Efficacy of Kovaltry in Children from China”*
- Study 14149, *“Evaluation of AEs of Special Interest in EUHASS Registry”*
- Study 15689, *“Epidemiological Study Evaluation of AEs of Special Interest in the PedNet Registry”*

### **Additional discussion**

Bayer agreed to submit the final protocols and reporting mode for the planned studies upon Investigator’s consent, and to provide milestone schedules for the ongoing clinical studies listed in the pharmacovigilance plan.

### **CDRH REVIEW OF RECONSTITUTION DEVICES**

We acknowledge your amendment 31 received on September 11, 2015. A review of this amendment is ongoing, and a final decision on the device constituent part issues addressed within this response is pending.



**LABELING**

Recommendations to the *Prescribing Information* and the vial and carton labels will be provided as part of the labeling review.

**ADVISORY COMMITTEE MEETING**

Presentation of the BLA at the *Blood Products Advisory Committee* is not planned.

**REMS OR OTHER RISK MANAGEMENT ACTIONS**

We have not identified any issues related to risk management. We do not believe that a risk management action (REMS) is needed at this time.

**STATUS OF INFORMATION REQUESTS AND PENDING REVIEWS**

FDA stated that responses to all information requests (IR) stated in the briefing package were received and are currently under review. The need for additional IRs will be determined based on the outcome of these reviews. Two IRs are in preparation: (1) for additional CMC information and (2) for recommendations to the Prescribing Information and other labeling components.

**ACTION ITEMS**

1. To address the CMC issues, Bayer will submit:

- a. summary information in support of the (b) (4) ;
- b. summary justification for the use of the Chromogenic Substrate assay for potency assignment of Kovaltry; and
- c. a postmarketing commitment regarding validation of (b) (4) assay after the final wording is agreed upon with FDA via email.

2. To address the clinical issues, Bayer will submit:

- a. additional data for 9 patients from Sites 54001 and 54005 in the Leopold II study with dose, treatment duration, and bleeding rate;
- b. the justification for the low-dose regimen to support its inclusion in the label;
- c. sensitivity analyses in written and tabular format for the primary efficacy in the Leopold II study (excluding 9 subjects), and for the pooled population (excluding 2 subjects in the Leopold I study and 7 subjects from the prophylaxis arm in the Leopold II study);

- d. a sensitivity analysis for the primary and secondary comparisons of ABR in the Leopold II study by using Poisson regression (instead of ANOVA);
  - e. a subgroup analysis by race on ABR in the Leopold II study;
  - f. complete inhibitor titer data of 6 PUPs positive for inhibitors, including association with risk factors, projections of study completion, and Bayer's plan to address the immunogenicity concern;
  - g. and final protocols and milestone schedules for the planned and ongoing clinical studies listed in the pharmacovigilance plan.
- 3. Bayer will submit the above information as an amendment(s) to the BLA and will include the slide deck presented at the LCM.
  - 4. FDA will send Bayer a CMC Information Request within 2 weeks after the LCM.
  - 5. FDA will send Bayer recommendations to the Prescribing Information after receiving an amendment with Bayer's responses to the LCM requests.

#### **POST-MEETING COMMENTS**

Amendment 33 dated September 25, 2015, containing monitoring reports from selected clinical sites was classified as a Major Amendment extending the review clock to March 16, 2016. A *Major Amendment Acknowledgement Letter* was sent to Bayer on October 16, 2015.

**END**