

Mid Cycle Meeting
STN 125582//0
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

Meeting Summary

Application type: Original BLA

Tracking number: STN 125582/0

Product name: Coagulation Factor IX (Recombinant), Albumin Fusion Protein

Proposed Indication: To treat patients with hemophilia B (congenital Factor IX deficiency) for

- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- Control and prevention of bleeding episodes
- Control and prevention of bleeding in the perioperative setting

Applicant: CSL Behring Recombinant Facility Ag

Committee Chair: Dr. Mikhail Ovanesov

RPM: Mr. Edward Thompson

Meeting date & time: May 12, 2015, 3 p.m. to 5:00 p.m.

Attendees:

Meeting chair:

Paul D. Mintz, MD, Director, Division of Hematology Clinical Review (DHCR), OBRR

Review Team:

Chairperson: Dr. Mikhail Ovanesov, Laboratory of Hemostasis (LH), Division of Hematology Research and Review (DHRR), OBRR

CMC/Product Reviewer: Dr. Alexey Khrenov, OBRR/DHRR/LH

CMC/Product Reviewer: Dr. Ze Peng, OBRR/DHRR/LH

CMC/Product Reviewer: Dr. Wayne Hicks, OBRR/DHRR/LBVB

CMC/Product Reviewer: Dr. Yideng Liang, OBRR/DHRR/LH

CMC/Product Reviewer: Dr. Andrey Sarafanov, OBRR/DHRR/LH

Clinical Reviewer: Dr. Peter Waldron, OBRR/DHCR/CRB

Clinical Reviewer: Dr. Lisa Faulcon, OBRR/DHCR/CRB

Clinical Pharmacology Reviewer: Dr. Iftekhar Mahmood, OBRR/DHCR/HPRB

Toxicology Reviewer: Dr. Yolanda Branch, OBRR/DHCR/HPRB

Mid Cycle Meeting
STN 125582//0
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

Postmarketing Safety Epidemiological Reviewer: Dr. Laura Polakowski, OBE/DE/AEB

Statistical Reviewer: Dr. Chunrong Cheng, OBE/DB/TEB

Labeling Reviewer: Dr. Loan Nguyen, OCBQ/DCM/APLB

CMC/Facility Reviewer: Mr. Donald Ertel, OCBQ/DMPQ/BI

BIMO Reviewer: Ms. Christine Drabick, OCBQ/DIS/BMB

QC test Representative: Ms. Josephine Resnick (not present), OCBQ/DBSQC

QC test Representative: Ms. Karen Campbell, OCBQ/DBSQC/QAB

QC test Reviewer: Dr. Lokesh Bhattacharyya, OCBQ/DBSQC/LACBRP

QC test Reviewer: Ms. Simleen Kaur, OCBQ/DBSQC/LMIVTS

Regulatory Project Manager: Mr. Edward Thompson, OBRR/RPMS

Other meeting participants:

Mahmood Farshid, PhD, Deputy Director for CMC Policy and Review, OBRR/DHRR

John Eltermann, Director, Division of Manufacturing and Product Quality, OCBQ

Mark J. Weinstein, PhD, Associate Deputy Director, OBRR

Tim Lee, PhD, Acting Chief, OBRR/DHRR/LH

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

Lisa Stockbridge, PhD, Chief, Advertising and Promotional Labeling Branch,
OCBQ/DCM

Hua Wei, MD, OBE/DE/AEB

Renee Rees, PhD, Mathematical Statistician, OBE/DB

Iliana Valencia, MS, RPM Staff Chief, OBRR/IO

Deborah Trout, Team Leader, OCBQ/DMPQ/BI

Discussion Summary

The mid-cycle meeting addressed the status of the BLA review. Each discipline reviewer briefly presented his or her review focus and findings. There were no issues identified at this time that would prevent approval; however, the review is ongoing. There were a number of issues, most of them pertaining to CMC, which need to be addressed by the applicant. A mid-cycle information request listing the items will be conveyed to the applicant. Presentation of the BLA at an advisory committee meeting is not planned, and a waiver memo will be prepared to justify that referral to an advisory committee is not needed.

The following items were discussed at the mid-cycle meeting in accordance with the guidelines of the PDUFA V program:

Mid Cycle Meeting
STN 125582//0
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

1. Summary of discipline reviews from mid-cycle reports:

CMC - Process Validation and Potency Assignment

The company used a Quality by Design (QbD) approach to developing and validating the manufacturing processes for the Bulk Drug Substance (BDS) and Final Drug Product (FDP). However, the release specifications and in-process controls are as extensive as those found in manufacturing processes validated using a traditional approach. The applicant did not claim any design spaces for either the process or any unit operations.

The potency of the product is assigned by an APTT-based clotting assay using a product-specific reference standard calibrated against the current WHO ^{(b) (4)} International Standard (IS) for Coagulation Factor IX (FIX) Concentrate. However, there is a 20 % difference in the potency values derived from the assay methodology used in early clinical trial and that used in late clinical trial. This discrepancy was resolved through calibration of the in-house product-specific reference standard in units of the old assay. This approach maintains the unitage and dosing regimen throughout all stages of clinical development as long as the product-specific reference standard is used in the assay. At the same time, an overestimation of product potency will result if the product is tested by the current potency assay against the current IS for FIX concentrate.

CMC - Analytical Procedures

The manufacturer employs a large number of analytical methods. While the review is still ongoing, a number of issues were identified regarding the validation of several methods. The performance of the methods has to be verified at this point so the issues may not be considered critical for BLA approval. The reviewer will try to resolve the issues or get clarifications during the pre-license inspection. For other unresolved issues, information requests (IR) will be sent.

CMC - Albumin Moiety

(b) (4) was used to assess the (b) (4) structure of rFIX-FP. The assay was not properly validated. The (b) (4) of pilot-scale lots that were used for the initial characterization studies are different from those of manufacturing scale lots in the albumin moiety. This observation suggests differences in the (b) (4) stability of the albumin moiety in rFIX-FP.

Potential impact

The information provided does not indicate that CSL has a validated assay in place that can show consistency in the manufacture of the rFIX-FP, specifically regarding the integrity of the albumin moiety.

Plan for addressing the issue

Mid Cycle Meeting

STN 125582//0

Coagulation Factor IX (Recombinant), Albumin Fusion Protein

An IR will be submitted to inquire about (b) (4) assay validation and the differences in results between the pilot and manufacturing lots.

CMC - Stability

Stability data from (b) (4) pilot-scale BDS batches (b) (4) commercial scale BDS batches (b) (4) are submitted in the BLA. All specifications are met and to date support the storage of BDS at (b) (4)

Real-time stability data from (b) (4) pilot-scale FDP batches up to 24-36 months and (b) (4) commercial scale FDP batches up to 18-36 months are available. Additional stability data obtained after the initial submission will be provided until early August 2015. All data indicate that all rFIX-FP FDP batches are stable for at least 18 months at +5°C.

CMC - Viral Safety

CSL Behring only provided clearance data on (b) (4), which may be insufficient to support the safety profile for non-enveloped viruses. Murine minute virus (MVM) is a relevant non-enveloped virus to CHO cells used for the production of rFIX-FP. After consulted with Dr. Mahmood Farshid, we all agree to ask CSL to expand the validation studies to include MVM in viral clearance studies on the (b) (4).

CMC - Facility/Equipment/Container Closure – no issues at this time.

Clinical

The pivotal trial (3001) achieved the agreed upon primary efficacy endpoint of greater than 50% reduction in the annual spontaneous bleeding rate (AsBR) among subjects managed with an on demand regimen, when switched to a routine prophylaxis (RP) regimen (mean reduction = 93.49% (SD = 8.03); median = 95.86%; minimum = 75.2%). The primary safety endpoint of inhibitor development occurred in none of the subjects enrolled in this trial, and in none of the 111 subjects exposed to the study drug in all trials. The adverse reactions (adverse events related to study drug exposure) that did occur were uncommon, they were not rated severe, and they did not meet the regulatory definition of serious. The study demonstrated efficacy and safety for the indication, RP of bleeding episodes in previously treated patients (PTP) with congenital Factor IX (FIX) deficiency (hemophilia B). Previously untreated patients (PUP) are the subjects of an ongoing trial.

The indication, control and prevention of bleeding episodes, had a pre-specified success criterion: > 80% of mild or moderate bleeding events will be treated with two or fewer infusions. Across all studies, > 98% of bleeds were treated with 1 or 2 doses. There is a limitation in this evaluation since no major bleeds were reported.

Mid Cycle Meeting
STN 125582//0
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

The indication, control and prevention of bleeding episodes in the perioperative setting, did not have pre-specified endpoints. An agreement was reached that favorable safety and efficacy data from at least 5 subjects in 10 elective major surgical procedures would be sufficient to support the proposed surgical indication. The April 2015 update reported 7 subjects undergoing 9 major procedures across all trials. These subjects had favorable perioperative data.

Substantive issues

- Protein in urine (summarized in the consult to DCRP).
 - o This finding likely will have no association with direct harm to the patient, but it could result in additional testing that exposes the patient to some risk, as well consumption of the patient's resources.
 - o Labeling can address this concern effectively.

- Labeling for routine prophylaxis at an interval of more than 7 days.
 - o The applicant proposed labeling: 2.2 Routine Prophylaxis
For routine prophylaxis, appropriate FIX trough levels are required and are maintained by regular infusions. The recommended dose is 25-40 IU IDELVION per kg body weight every 7 days or 50-75 IU IDELVION per kg every 14 days. Adjust the dosing regimen based upon the individual patient's clinical condition and response.
 - o Due to the study design, the only claim that can be made is that a subset of subjects, selected based on PK and bleeding history, had annual spontaneous bleeding rates, on 10 and 14 day routine prophylaxis schedules, that were non-inferior to the rates observed in the general population on a 7 day routine prophylaxis schedule.

Clinical Pharmacology – No review issues found at this time.

Nonclinical Pharmacology/Toxicology – No review issues found at this time.

Epidemiology

Issues associated with the Risk Management Plan for hypersensitivity/ anaphylactic reactions, development of inhibitors to FIX, development of antibodies to product (rIX-FP), development of antibodies to CHO host cell proteins, and development of dosing errors based on variability in the assays used during treatment monitoring of FIX levels will have no impact on product approval; the issue would need to be followed post-approval using pharmacovigilance methods described in the Risk Management Plan.

Mid Cycle Meeting
STN 125582//0
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

The Risk Management Plan (Module 1.16) notes that there is Important Missing Information regarding experience in patients with a history of thrombosis, experience of inhibitor formation in PUPs, experience in pregnancy and lactation, including labor and delivery, experience in elderly patients (65 years and above) will have no impact on product approval; the issue would need to be followed post-approval using pharmacovigilance methods described in the Risk Management Plan.

Statistics

Regarding pivotal study 3001

1. The reviewer verified the analyses of primary and secondary efficacy endpoints provided by the applicant.
2. The study met the acceptance criteria for the primary efficacy endpoint (AsBR) and primary safety endpoint (inhibitor rate). Prophylaxis treatment significantly reduced the AsBR compared to the on-demand treatment regimen based on paired analysis. The result was robust to sensitivity analyses.
3. For the primary efficacy endpoint, all subgroups by race and region had similar efficacy.
4. The applicant compared the AsBR of different prophylaxis regimens among 26 subjects in the prophylaxis arm (Arm 1) who switched from weekly prophylaxis to an extended treatment interval (10-day or 14-day). It should be noted that compared to the other 12 subjects in Arm 1 who did not switch to any extended prophylaxis treatment regimen, these 26 subjects did have less frequent bleeding during weekly prophylaxis. Therefore, the data of the extended treatment interval should be interpreted with caution, and the efficacy may not be as good as observed if those 12 subjects switched as well.
5. The ABR was higher in the on-demand arm (Arm 2) compared to in the prophylaxis arm (Arm 1) during weekly prophylaxis (mean ABR 2.87 vs. 1.24).

This was mainly due to one extreme value observed from Arm 2: subject (b) (6) with an ABR of 21.07 during 260 days of prophylaxis treatment. With this subject excluded, the mean ABR from Arm 2 was reduced from 2.87 to 1.79. This subject experienced 15 (12 traumatic and 3 spontaneous) and 14 (2 traumatic and 12 spontaneous) bleeding episodes during the 260 days of weekly prophylaxis treatment and 111 days of on-demand treatment respectively. Most of them were joint bleeds requiring treatment.

6. The applicant claimed that subjects had less consumption of FIX products during routine prophylaxis in this study compared to prior treatment. This

Mid Cycle Meeting
STN 125582//0
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

claim cannot be made for three reasons: 1) it is not based on paired analysis; 2) it is not pre-specified; and 3) it is not based on formal hypothesis testing.

Bioresearch Monitoring (BIMO) Inspections

The BIMO inspections at Site # 250002 and Site # 3800023 are complete. No Form FDA 483 was issued at either site. The inspection at Site # 3760001 is scheduled to begin the week of May 10, 2015.

Site Number	Number of Subjects	Study Site	Location	Form FDA 483 Issued	Final Classification or Status
2500002	4	Centre Hospitalier Régional Universitaire	Brest Cedex, France	No	EIR Pending
3760001	11	The National Hemophilia Center	Tel Hashomer, Israel	Inspection Pending	Inspection Pending
3800023	4	Dipartimento di Medicina e delle Specialita Mediche	Milan, Italy	No	EIR Pending

Quality Control for the Lot Release Protocol and Testing Plan

- No lot release protocol is needed for this product as it is exempt.
- A draft product testing plan has been created and will be circulated to reviewers in the next few weeks.
- In-support testing of samples is currently being carried out for endotoxin, potency, purity, appearance, residual water, (b) (4) and (b) (4) FIX activity; as agreed to during the DBSQC/DHRR meeting.

No review issues noted at this time.

Quality Control for Lot Release Tests and Drug Product and Validation

The method validations for the four abovementioned tests are deficient. Additionally, it is not clear how the applicant ensured that (b) (4)

Also, it is not clear what reference standard was used during method validation of the FIX potency assay, and if the same standard will be used for routine lot release testing. DBSQC reviewers do not have any concern with the procedures of other lot release test methods that they are reviewing.

Potential impact

It is unlikely that the issue with the (b) (4) assay will prevent approval. Whether or not the issue with the potency assay will impact approval and review timeline will depend on the response we receive from the applicant.

Mid Cycle Meeting
STN 125582//0
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

Plan for addressing issues

Collaborate with DHRR reviewers and applicant to resolve the issues in a timely manner by (1) submitting IRs, (2) evaluating the test methods in LACBRP, and (3) sharing results with DHRR reviewers and applicant.

Quality Control for Drug Product- Endotoxin and Sterility

Drug - Sterility testing: is being proposed to be performed on (b) (4) Sterility method validation was performed using (b) (4) as well and since half the amount of product was validated, it does not ensure that the product does not have any bacteriostatic and fungistatic properties and will not inhibit the growth of microorganisms. In the IR dated April 17, 2015, CSL Behring was requested to repeat the sterility test validation.

2. Will Discipline Review Letters be issued (for PDUFA V Program submissions)?

The review team and chair confirmed that Discipline Review Letters will not be issued.

3. If the application will be discussed at an Advisory Committee, potential issues for presentation.

This application will not be discussed at an Advisory Committee.

4. Determine whether Postmarketing Commitments (PMCs), Postmarketing Requirements (PMRs) or a Risk Evaluation Mitigation Strategy (REMS) are needed.

The review committee did not identify a need for PMCs, PMRs or REMS at this time.

5. National Drug Code (NDC) assignments to product/packaging.

This action is being performed by the RPM.

6. Proper naming convention.

The committee chair accepts the current naming convention for this product as follows:
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

7. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval.

The following facility is scheduled for a pre-license inspection on 28 May 2015 to 5 June 2015:

CSL Behring GmbH, FEI: 3003098680, DUNS: 326530474

Mid Cycle Meeting
STN 125582//0
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

Emil-von-Behring-Str. 76, D-35041 Marburg, Germany

The pre-license inspection of (b) (4) [REDACTED] has been waived.

The BIMO inspections at Site # 250002 and Site # 3800023 are complete. No Form FDA 483 was issued at either site. The inspection at Site # 3760001 is scheduled to begin the week of May 10, 2015.

- 8. Components Information Table was obtained and notification to the Data Abstraction Team (DAT) if discrepancies were found per SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements.**

The task will be completed by July 15, 2015 by the CMC reviewer and Chairperson.

- 9. New facility information is included in the application, requiring implementation of regulatory job aid JA 910.01: Facility Data Entry. If not complete, indicate date it will be completed.**

Cmdr Ertel will complete this task and send the request to Mr. McGuire.

- 10. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan.**

A draft product testing plan has been created and will be circulated to reviewers in the next few weeks.

- 11. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid JA 900.01: Unique Ingredient Identifier (UNII) Code for additional information.**

This task will be completed by the RPM.

- 12. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision.**

PeRC presentation is not needed because this product has orphan designation.

- 13. Reach agreement on information to be included in the Mid-cycle communication with the applicant (see section below).**

Mid Cycle Meeting
STN 125582//0
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

The communication document has been drafted and the tentative attendees from the review team are Dr. Ovanesov and Mr. Thompson.

14. Major target and milestone dates from RMS/BLA. *The RPM will populate the target and milestones from RMS-BLA.*

External Late-Cycle Meeting	Aug 18, 2015
Circulate draft press release	Nov 5, 2015
Complete PMC Study, Labeling Review, Review Addenda	Nov 5, 2015
Complete Supervisory Review	Nov 5, 2015
Request Compliance Check, Lot Release Clearance	Nov 20, 2015
Send Press Release to OCTMA	Nov 20, 2015
T-minus date	Nov 20, 2015
Send FDA Action Letter	Dec 4, 2015

15. The status of the review for each discipline, inspection, EIR. If any primary reviews have not met the target date, provide the date the review will be completed. Include any consult disciplines. *Note: Individual reviewer requesting consult is responsible for reporting on status if the consultant is not present*

No delays in completing review were presented in the meeting or the reviewer reports. Target dates were noted.

16. Discuss pending dates of targets and milestones (e.g. late-cycle meeting, Advisory Committee, labeling discussion).

No issues with pending target dates or milestones were presented by any participants of this meeting,

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

A tentative labeling review meeting was proposed for September 4, 2015 for revisions of the package insert.

Mid Cycle Meeting
STN 125582//0
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

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Document Type: Mid-Cycle Meeting Summary

History:	Drafted:	Edward Thompson/ May 13, 2015
	Revised:	Mikhail Ovanosov/ May 18 and June 17, 2015
	Revised	Alexey Khrenov/ May 19, 2015
	Revised:	Ze Peng/ May 19, 2015
	Revised	Tim Lee/ July 15, 2015