

Mid-Cycle Meeting
STN 125566/0
Antihemophilic Factor (Recombinant), PEGylated

May 7, 2015
10 a.m. to 12 p.m.
White Oak Building 71
Room 1208/1210

Mid-Cycle Meeting Agenda:

Review Team

Chairperson: Ze Peng, PhD

Clinical Reviewer: Stephanie Omokaro, MD

CMC Product Reviewer: Alexey Khrenov, PhD

Clinical Pharmacology: Carl-Michael Staschen, MD/PhD

Toxicology Reviewer: La’Nissa Brown, PhD

Chief Toxicology Reviewer: Anne Pilaro, PhD

Postmarketing Safety Epidemiological Reviewer: Jane Baumblatt, MD

Statistical Reviewer: Judy Li, PhD

APLB Reviewer: Loan Nguyen, PharmD

DMPQ CMC & Facility Reviewer: Cmdr Jeremy Wally, PhD

DMPQ CMC & Facility Reviewer: Anthony Lorenzo

DBSQC Representative: Karen Campbell

BIMO Reviewer: Dennis Cato

DBSQC Reviewer: Lokesh Bhattacharyya, PhD

DBSQC Reviewer: Hyesuk Kong, PhD

Regulatory Project Manager: Yu Do, MS

Regulatory Project Manager: Edward Thompson

Additional Attendees:

Ginette Michaud, MD, Deputy Director, OBRR

Basil Golding, MD, Division Director, OBRR/DHRR

Paul D. Mintz, MD, Division Director, OBRR/DHCR

Mahmood Farshid, PhD, Deputy Division Director, OBRR/DHRR

Howard Chazin, MD, Deputy Division Director, OBRR/DHCR

Mark Weinstein, PhD, Associate Deputy Director, OBRR/IO

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

Joseph Quander III, Chief, OCBQ/DMPQ/PRB

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Please note the following agenda items for our mid-cycle meeting for STN 125566/0. The goal of the Mid-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. Reviewer Reports

CMC – Primary reviewer

There are no substantive issues which could prevent approval of this submission from the product perspective. However, the following minor issues should be conveyed to Baxter:

- The submission did not include the test results of Free PEG, Total PEG and Degree of PEGylation on the conformance lots of Antihemophilic Factor (Recombinant), PEGylated (i.e., PEG-rFVIII or BAX855) final drug product (FDP). To support the shelf life of BAX855 FDP, we will ask Baxter to take these parameters into account in the ongoing stability studies of the conformance lots of BAX855 FDP, and include the test results of these parameters when Baxter submits updated stability data.
- Baxter provided an assessment for most of impurities including host cell proteins in the manufacture of BAX855, except for murine IgG from the (b) (4) step. Although the profile of murine IgG is the same in ADVATE (b) (4) as for BAX855 (b) (4), an assessment of the levels of murine IgG/PEGylated murine IgG in BAX855 (b) (4) is still needed.

CMC – Analytical Procedures

There are no substantive issues about analytical procedures which could prevent approval of this submission. Updated validation reports were submitted recently in response to an Information Request (IR) from DBSQC and are still under review. However, it is unlikely that major issues will arise.

Clinical

Key findings and substantive issues with the application are as follows:

- Data provided may support an indication in adolescents at this time. Pediatric study is deferred. Twenty-five subjects aged 12-17 were included in the pivotal study.
- 85.5% of all bleeding episodes (N=518) were controlled with a single injection and 95.9% with 1 or 2 injections.
- Median dose per injection to control a bleeding episode was 29 IU/kg.
- The primary efficacy endpoint was evaluated and demonstrated a significant reduction with between prophylaxis (ABR = 1.9) and on-demand regimens (ABR = 41.5).
- In terms of safety, there were no inhibitors, allergic reactions including anaphylaxis and no evidence of vascular thrombosis. There were transient binding antibodies to FVIII and PEG that were below the frequency of that observed in healthy subjects.
- Adverse events of concern was headache but low in frequency and severity (<3%).

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Clinical Pharmacology

There are no hold issues identified with this submission. The Clinical Pharmacology of BAX 855 has been assessed in two clinical studies (No. 261101 and No. 261201). These studies were designed to evaluate the PK characteristics of BAX 855 and to compare BAX 855 to ADVATE with respect to PK in previously treated patients (PTPs), aged 12 to 65 years, with severe hemophilia A (FVIII levels <1%).

The following preliminary Clinical Pharmacology conclusions can be drawn from the studies submitted to this BLA:

- In comparison with ADVATE, BAX 855 showed a 1.4-fold increase in elimination half-life (HL). The overall mean HL was calculated to be 15.1 h for BAX 855 and 10.5 h for ADVATE. The overall incremental recovery of BAX 855 was 2.62 IU/dL per IU/kg and comparable to ADVATE (2.46 IU/dL per IU/kg). The PK parameters after repeated dosing with BAX 855 for 6 months were consistent with the initial parameter estimates.
- PK parameters derived from the chromogenic assay data were generally higher, but overall consistent with those generated from the one-stage clotting assay data (primary assay).
Overall, the study designs for the pharmacokinetic evaluations were adequate and the general conclusions drawn by the sponsor based on the PK assessments in the PK studies are acceptable.

Pharmacology/Toxicology

There are no outstanding or substantive nonclinical issues at the present time that would preclude approval of BLA STN 125566/0 for Baxter's Original Biological License Application (BLA) for PEGylated Antihemophilic Factor (Recombinant) (codename PEG-rFVIII) indicated for the treatment for hemophilia A in adolescent (12 to less than 18 years) and adult (greater than or equal to 18 years) patients and for the control and prevention of bleeding episodes (also during and after surgery) in adults and children with hemophilia A. Additionally, there are no Pharmacology/Toxicology post-marketing commitments or requirements that have been identified. From the pharmacology/toxicology reviewer's perspective, the submitted nonclinical data appear to be sufficient to continue the ongoing review of the BLA STN 125566/0 for PEGylated Antihemophilic Factor (Recombinant).

PEGylated Antihemophilic Factor (Recombinant) was determined to be safe for its intended use as treatment for the control and prevention of bleeding episodes, including during and after surgery, in adults and children with hemophilia A. This decision is based on nonclinical data demonstrating reasonable safety of PEG-rFVIII from Good Laboratory Practices (GLP)-compliant and non-GLP studies and on its clinical use both within and outside the United States. The completed nonclinical program consisted of a series of studies to demonstrate the safety and effectiveness of PEG-rFVIII in animals including hemophilic mice, and wild-type FVIII-expressing (b) (4) monkeys, rats, and rabbits. Previous experience with similar recombinant and plasma-derived FVIII

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products has demonstrated that the toxicities of exogenously administered FVIII are extensions of its pharmacologic activity, i.e., hypercoagulability of blood, thrombosis and thromboembolus formation in treated animals and patients. Additional expected nonclinical findings are development of neutralizing and non-neutralizing antibodies directed against the human FVIII protein (i.e., immunogenicity), with the potential to cross-react and neutralize endogenous FVIII in wild-type animals and potential increase in inhibitor antibody titers.

There are no special labeling concerns from the nonclinical discipline; however, revisions to Section 8.1 (Pregnancy), 8.3 (Nursing Mothers), 13 (Nonclinical Toxicology), and 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) will be recommended and conveyed to the Applicant at a later date. Nonclinical labeling recommendations will be addressed in a separate labeling review memorandum.

Biostatistics

The analysis of the primary efficacy endpoint of the pivotal study has been verified. There are no substantive issues from statistical point of view so far.

Analytical Epidemiology

Safety data from the studies 261101, 261201, 261202 Pediatric, 261204 Surgery, and 261302 Continuation will be thoroughly reviewed for the memo. On initial review, there were no safety concerns. Study 261201 will be reviewed as the pivotal study.

Safety Summary

- Pooled safety data from 2 completed and 3 ongoing studies had 169 subjects (adolescent and adult PTPs) treated with BAX 855 for prophylaxis, bleeding episodes, perioperative management, or received a single-dose for a PK evaluation.
- 117 adolescent and adult subjects were treated long-term with BAX 855 (treatment initiated in the pivotal study and continued in the continuation study).
- No AEs of allergic or hypersensitivity reactions were observed in any of the studies.
- None of the subjects developed inhibitory antibodies to rFVIII of ≥ 0.6 BU/mL.
- No persistent binding antibodies to rFVIII, PEG-rFVIII, or PEG developed.
- A total of 16 SAEs in 11 subjects were observed, none of which were considered related to BAX 855 as assessed by the investigator and the sponsor.

SAEs list: Neuroendocrine tumor, humerus fracture, osteoarthritis, herpes zoster infection, muscle hemorrhage, abdominal pain, diabetic gastroparesis, vomiting, splenic hematoma, post op abscess, splenic rupture, pancreatitis x2, and pneumonia.

Possibly related AEs (temporal): hypertension post infusion, nausea and diarrhea, headache, and flushing

Analytical Method for Lot Release Tests

The method validations for four of the lot release tests are deficient. An IR was sent on 01 May 2015 on the following assays:

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- Determination of PEG-rFVIII Potency by a (b) (4)
- Determination of Total Protein Concentration by (b) (4)
- Residual Moisture Content by the (b) (4)
- Determination of Polysorbate 80 by (b) (4)

The IR was sent because Baxter did not provide a complete response to the previous IRs or the response was not acceptable. The methods themselves do not appear to have issues. Only the method validation is not acceptable by the current standard. Of these tests, FVIII potency and residual moisture are really critical. No issue with other test methods that are used for lot release.

We will work with the CMC Reviewers to guide Baxter to have the methods adequately validated in a timely manner. We will also replicate the methods at the DBSQC laboratory to evaluate the methods and their performance characteristics.

Quality Control (Bioburden, Sterility, and Endotoxin)

No substantive issues need to be resolved. One IR for endotoxin specification will be sent at a later date.

Quality Control (Development of the Testing Plan and In-Support Testing in DBSQC)

Currently, there are no issues. The draft Product Testing Plan will be sent for review during the week of May 4. The request of samples, reagents, and documentation for in-support testing will be sent during the week of May 4 as well.

Facilities and Equipment

No pre-approval inspection is currently planned for this BLA, and no major facilities- and equipment-related issues have been identified to date. Comments for an IR are being drafted and will be sent to Baxter when finalized.

Bioresearch Monitoring

Currently, no issues need to be addressed. BIMO clinical investigator inspection assignments were issued for one foreign and two domestic clinical investigators for BAX855. All three inspections are pending schedules for completion. The primary discipline review will depend upon receipt, review, and classification of the EIRs. BIMO will complete the discipline review after the EIRs for all inspections are received. The review committee will be updated as new information becomes available.

2. The review committee confirmed that no Discipline Review Letters will be issued.
3. The current thinking of the review committee is that this BLA will not be presented at the Blood Products Advisory Committee.

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4. The review committee identified no need for Postmarketing Commitments (PMCs), Postmarketing Requirements (PMRs) or a Risk Evaluation Mitigation Strategy (REMS) at this time.
5. RPM or APLB review of National Drug Code (NDC) assignments to product/packaging is pending.
6. The recommended proper name of this product is Antihemophilic Factor (Recombinant), PEGylated.
7. The status of GMP and BIMO inspections has been updated under Item #1 (see the BIMO and DMPQ reviewers' comments).
8. The review of Components Information Table is in progress per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. It should be finished in June 2015.
9. Cmdr Wally will follow the regulatory job aid *JA 910.01* to upload new facility information from the application to RMSBLA.
10. The lot release testing will be waived because this is a recombinant product. Ms. Karen Campbell stated that the draft Product Testing Plan will be sent for review during the week of May 4. The request of samples, reagents, and documentation for in-support testing will be sent during the week of May 4 as well.
11. Unique ingredient identifier (UNII) code process has been initiated. RPM action is pending to submit the request and complete this task.
12. PeRC presentation date is set for September 23, 2015, and the clinical reviewer will address the deferral for pediatric subjects and assessment for adolescent subjects. PeRC forms will be submitted on September 9, 2015 in advance of the scheduled PeRC meeting.
13. No substantial issues need to be discussed with Baxter for the scheduled Mid-cycle Communication. The tentative attendees from the review committee are Ze Peng, Yu Do, and Edward Thompson.
14. Pending dates for major targets and mile stones from RMS/BLA are listed as follows:

Mid-Cycle Communication with Applicant	05/19/2015
Internal Late-Cycle Meeting	07/07/2015
Send Late Cycle briefing package	07/21/2015

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External Late-Cycle Meeting	08/06/2015
Complete Supervisory Review	10/26/2015
T-minus date	11/11/2015
Send FDA Action Letter	11/25/2015
Post-Action Debrief Meeting	12/11/2015

15. Please see Item #1 for details on the status of the review for each discipline, inspection, and EIR.

16. A tentative labeling review meeting for BAX855 is proposed on or after 27 August 2015.

End

Drafted/Revised: Yu Do / May 12 & June 15, 2015
Revised: Edward Thompson/ May 13, 2015
Reviewed/Revised: Stephanie Omokaro/ May 29, 2015
Revised: Ze Peng/ June 16, 2015
Reviewed/Revised: Mark Weinstein/ June 12, 2015