

# Mid Cycle Meeting Minutes, August 27, 2013 - Eloctate

**Application type and number:** BLA 125487/0

**Product name:** Antihemophilic Factor (Recombinant), Fc Fusion Protein

**Proposed Indication:**

- Control and prevention of bleeding episodes in adults and children;
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children;
- Perioperative management (surgical prophylaxis) in adults and children

**Applicant:** Biogen Idec Inc.

**Meeting date & time:** 27-Aug-13 13:30-15:00 WOC I Room 583

**Committee Chair:** Nancy Kirschbaum

**RPM:** Leigh Pracht

**ADD:** March 7, 2014

**Review Committee:**

<b>RPM</b>	Leigh Pracht, OBRR/DBA/RPMB >	301 827-6116 >
<b>Chairperson &gt;</b>	Nancy Kirschbaum, PhD, OBRR/DH/LH >	301-827-3893 >
<b>Clinical &gt;</b>	Lisa Faulcon MD, OBRR/DH/CRB Nisha Jain, MD, OBRR/DH/CRB >	301-827-9769 / 6110 >
<b>Statistics &gt;</b>	Judy Li, PhD, OBE/DB/TEB >	301-827-3596 >
<b>Clinical Pharm. &gt;</b>	Carl-Michael Staschen, MD, PhD, OBRR/DH >	301-827-6148 >
<b>Pharm/Tox &gt;</b>	Keith Wyatt PhD, OBRR/DH >	301-827-9258 >
<b>APLB &gt;</b>	Loan Nguyen PharmD, OCBQ/DCM/APLB, >	301-827-6333 >

<b>CMC &gt;</b>	Andrey Sarafanov, PhD, OBRR/DH/LH >	301-827-4025 >
<b>CMC &gt;</b>	Ze Peng, PhD, OBRR/DH/LH >	301-827-9219 >
<b>BIMO &gt;</b>	Christine Drabick, OCBQ/DIS/BMB >	301-827-6323 >
<b>Lot Release &gt; DBSQC &gt;</b>	Cheryl Hulme, OCBQ/DMPQ/PRB > Karen Campbell, OCBQ/DBSQC Lokesh Bhattacharyya, PhD, OCBQ/DBSQC James Kenney, D.Sc., OCBQ/DBSQC/LACBRP >	301-827-0863 > 301-594-6255 301-594-6242 301-594-6243 >
<b>DMPQ &gt;</b>	Jie He, OCBQ/DMPQ/BII Ellen Huang OCBQ/DMPQ/BII >	301-827-0183 / 7199 >
<b>Epidemiology &gt; Human Factors review &gt;</b>	Wambui Chege, MD, OBE/DE/AEB Quynh Nhu Nguyen, LCDR, CDRH/ODE/DAGID >	301-827-6086 > 301-796-6273 >

**Additional Attendees:**

John A. Eltermann, Jr., RPh, M.S., OCBQ/DMPQ  
Mahmood Farshid, PhD, OBRR/DH  
Basil Golding, MD, OBRR/DH  
Chris Joneckis, PhD, OD/RMS  
Timothy Lee, PhD, OBRR/DH/LH  
Paul Mintz, MD, OBRR/DH  
Anne Pilaro, PhD, OBRR/DH  
Joseph Quander, OCBQ/DMPQ/PRB  
Destry Sullivan, M.S., OCBQ/DMPQ/BII  
Boguang Zhen, PhD, OBE/DB/TEB

**Discussion Summary:**

**Dr. Lisa Faulcon (Clinical)**

Dr. Faulcon advised that no post-marketing studies have been proposed and there will not be extension studies post-marketing. No issues have been identified that could significantly impact the review timeline or prevent approval.  
Two post-approval commitment studies are recommended to be discussed with the applicant:

1. Safety and Efficacy in Prevention and Treatment of Bleeds in Pediatric previously Untreated Patients and Safety and
2. Safety and Efficacy during Long-Term Treatment

An information request will be forthcoming as well as comments for the mid-cycle communication.

**Judy Li, PhD (Biostatistics)**

No major statistical issues have been identified; the statistical endpoint has been verified.

**Dr. Carl-Michael Staschen (Pharmacology)**

No major issues have been identified. An increase of 50% of the mean half-life (12 to 18 hours) compared to Advate.

**Keith Wyatt, PhD (Pharmacology/Toxicology)**

No major issues have been identified.

**Loan Nguyen, PharmD (APLB)**

The proprietary name (ELOCTATE®) will be re-evaluated in September. Vial labels may be missing from the submission; another check on their status to be performed.

**Christine Drabick (BIMO)**

No major issues have been identified. Four inspections have been completed; three have been NAI. One report is pending; an FDA Form 483 was issued.

**Karen Campbell (DBSQC)**

Testing is ongoing; a lot release protocol will not be required.

**Dr. Wambui Chege (OBE)**

Agrees with Clinical reviewer and plans on requesting an IR. At this time OBE agrees with routine pharmacovigilance activities as listed in the PVP. OBE recommends that the two postmarketing studies listed in the PVP be considered clinical PMCs requiring submission to FDA of interim reports at pre-specified intervals and a final study report for each of the two studies. Pending review of outstanding Information Requests, OBE may provide additional recommendations.

**Dr. Quynh Nhu Nguyen (CDRH Human Factors)**

No major issues found – the human factors study report is acceptable.

**Nancy Kirschbaum, PhD (CMC)**

- Process validation lots: FDA requested three lots of 3000 IU and three lots of 250 IU and one lot of the remaining strengths
- Data from eleven conformance lots would qualify as a major amendment
- A *retrospective* validation of 500-2000 IU doses was submitted to the BLA

- Biogen should manufacture conformance lots for all dosage strengths under a *prospective validation protocol*. Drug product conformance lots should be manufactured exclusively from drug substance conformance batches. All conformance batches and lots should be monitored for stability.
- Process validation should be repeated (product manufacture and stability)
- The DH Division Director inquired as to whether any of the dose configurations were acceptable; NK replied, "One." This had been communicated at the pre-BLA meeting.
- Commercial manufacture cannot be simulated

**Jie He, MS (DMPQ)**

- IR will be sent after the mid-cycle meeting.
- The validation report for sterilization and –b(4)----- for the drug product and diluent was not provided.
- The validation for the lyophilization process was not provided
- There is insufficient data to support –b(4)-----  
----- suites in the BLA. There are --b(4)-----  
----- suites labeled as Purification Suite b(4) at the Biogen Idec Cambridge site. –b(4)----- conformance lots were manufactured in –b(4)-----, respectively. –b(4)----- were not used for cell culture for the conformance lots. The associated areas for –b(4)----- were used for storage and glass washing. There are limited data to support manufacturing on cell culture –b(4)----. Only one DS conformance lot (--b(4)----- was manufactured on –b(4)---. One purification suite was used for the conformance batches, but not clear which of the –b(4)--was used. (module 2.3.S Page 39)
- For the DP conformance lots, some of the DS lots used were not from DS conformance batches. The DS batches were --b(4)-----  
-----  
----- It is not clear which -b(4)- these batches were manufactured on. Furthermore, it is not clear if these batches were manufactured under the process validation master plan.
- Regarding the –b(4)----- test for container closure integrity testing (CCIT),
  - The validation report for the drug product and diluent was not provided.
  - The positive control was –b(4)- which is–b(4)-. Typically positive controls should be about –b(4)--
  - The acceptance criterion is, --b(4)-----  
----- It is not clear if the firm qualified the operators to be able to detect –b(4)-----  
-----.
  - It is unclear if CCIT was done for b(4)- vial vendors for the DP and for which vial sizes.
- The firm stated that they use –b(4)----- for the DP and diluent manufacturing process, such as post-compounding to the product. It is not clear if the –b(4)----- the DP and diluent in its final configuration (vial and

syringe, respectively). Also, it is not clear if the product is stoppered –b(4)-----  
----- . If so, --b(4)----- test may not be appropriate for CCIT.

- It is not clear if any part of the container closure system that is product contact contains latex.
- Regarding hold time limits for the drug product, two lots (--b(4)-----) were studied (2.3.P. Table 23). As shown in the table below, claimed maximum hold times far exceed times validated by conformance lot manufacture.

Solution description >	Hold time start description >	Hold time finish description >	Storage conditions >	Max. Hold time >	Sample # >	-b(4)--- result >	--b(4)--- result >
--b(4)--- ----- ----- >	--b(4)--- ----- ----- >	--b(4)--- ----- ----- ----- >	--b(4)--- >	-b(4)- >	--b(4)--- >	--b(4)--- >	--b(4)--- >
Formulated Drug Product >	--b(4)--- ----- >	--b(4)--- ----- ----- >	2 – 8 °C --b(4)--- ----- ----- >	b(4)-- >	--b(4)--- >	--b(4)--- >	--b(4)--- >
Lyophilized Drug Product >	--b(4)--- ----- ----- >	--b(4)--- ----- ----- >	--b(4)--- >	b(4)-- >	--b(4)--- >	--b(4)--- >	--b(4)--- >
Lyophilized Drug Product >	--b(4)--- ----- ----- >	--b(4)--- ----- ----- >	--b(4)--- >	b(4)-- >	--b(4)--- >	--b(4)--- >	--b(4)--- >

- The drug product dosage strengths are 250 IU, 500 IU, 750IU, 1000 IU, 1500 IU, 2000 IU, and 3000 IU. It is not clear what the fill volume is for each dosage strength.
- The firm states that equivalent equipment may be used at the –b(4)----- facilities for DP (3.2.A.1). Additional information is needed.

- The firm stated DP filled final vials are 100% visually inspected, but no information on how the inspection is conducted. (module 3.2.P.3.3.1). Additionally, no information regarding the qualification of the visual inspection process was provided.

## Report and Discuss:

1. Reviewer Reports.
2. Discipline Review Letters will not be issued.
3. A waiver from presentation at the BPAC has been submitted to upper management
4. Postmarketing Commitments (PMCs), Postmarketing Requirements (PMRs) or a Risk Evaluation Mitigation Strategy (REMS) are under discussion.
5. National Drug Code (NDC) assignments to product/packaging were submitted on July 3, 2013:

**250 IU >** 64406-801-01 >

**500 IU >** 64406-802-01 >

**750 IU >** 64406-803-01 >

**1000 IU >** 64406-804-01 >

**1500 IU >** 64406-805-01 >

**2000 IU >** 64406-806-01 >

**3000 IU >** 64406-807-01 >

6. Proper naming convention. Antihemophilic Factor (Recombinant), Fc Fusion Protein
7. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval. DMPQ: Waiver - signed on July 16, 2013; BIMO: The Establishment Inspection Report (EIR) is pending receipt and review for –b(5)-----  
-----.

## Confirm

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*. If not complete, indicate date it will be completed.  
Yes No
9. New facility information is complete to this point.
10. Antihemophilic Factor (Recombinant), Fc Fusion Protein is exempt from lot release.
11. The UNII Codes have been assigned by CBER SRS and were conveyed to the Applicant on February 21, 2013.

## **Review**

12. Major target and milestone dates from RMS/BLA.

Mid-cycle communication with the Applicant 10-Sept-13: 1:00-2:00 p.m.

Late Cycle Meeting with the Applicant¶ 14-Nov-13: 1:00-2:30 p.m.

Labeling Target§ 6-Feb-14

PMC Study Target§ 6-Feb-14

**Action Due Date§ 8-Mar-14**

¶The Late Cycle meeting was postponed to April 3, 2014, 1:30 – 3:00 p.m. to allow for submission of outstanding process validation data

§The Action Due Date was reset to June, 7, 2014 upon receipt of amendment 27 on November, 15 2013 and its designation as a major amendment on November 25, 2013.

Labeling and PMC Study target dates were likewise reset forward by 3 months.

## **Mid-cycle Communication Summary:**

## **Discussion Summary**

1. Any significant issues identified by the review committee members to date:

Process validation submitted to BL STN 125487/0 was inadequate in that designated process validation lots for 500 IU, 750 IU, 1000 IU, 1500 IU and 2000 IU were analyzed under a retrospective validation protocol. Retrospective validation is only applicable to legacy products with a long history of commercial manufacture. Please manufacture the following lots under a prospective validation protocol:

- 500 IU dosage, small –b(4)-- vial) lot size
- 1,000 IU dosage
- 2,000 IU dosage, large –b(4)--- vial) lot size

Please ensure that drug product conformance lots are manufactured from drug substance lots manufactured under a prospective validation protocol. Please ensure that all drug substance conformance batches and drug product conformance lots are monitored according to the approved, commercial stability program.

2. Pharmacovigilance and Post-marketing Studies:

Your current Pharmacovigilance Plan (PVP) is insufficient to evaluate the long-term safety and efficacy of rAHFFc, and the safety and efficacy in previously untreated patients (PUPS). Please classify the following ongoing studies as Post-marketing Commitment Studies (PMCs) and submit appropriate timelines for completion of each study and submission of final study reports:

- a. "An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor VIII Fusion Protein (rFVIII Fc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia, an extension to the Phase 3 study 997HA301."
- b. "An Open-Label, Multicenter Evaluation of Safety, Pharmacokinetics, and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein, BLIB031, in the Prevention and Treatment of Bleeding Episodes in Pediatric Subjects With Hemophilia A"
3. Any information requests sent and not received:

There are no outstanding information requests.

4. Any new information requests to be communicated:

A multi-discipline information request will be conveyed to Biogen by 13 September 2013. FDA updated its requested response time to 01 March 2014, to accommodate completion of process validation studies..

5. Proposed date for the Late-cycle meeting:

The Late Cycle meeting is tentatively scheduled to occur on Thursday, November 14, 2013 from 1:00 – 2:30 p.m. The Late Cycle was rescheduled form April 3, 2014.

6. Updates regarding plans for an Advisory Committee:

BL STN 125487/0 will not be presented to the Blood Products Advisory Committee.

7. Other projected milestones:

**Milestone >**

**Date >**

Second PNR review and action letter >

7-December-2013  
>

Complete Label Review >

6-February-2014 >

**Milestone >****Date >**

Post-marketing commitments (PMC) and post-marketing requirements (PMR) finalized >

6-February-2014 >

Action due date and press release >

8-March-2014 >

The Action Due Date, Labeling Review and PMC Study target dates were reset forward by 3 months upon receipt of amendment 27 on November, 15 2013 and its designation as a major amendment on November 25, 2013.