

## Mid-cycle meeting summary

**Application type and number:** BLA 125591/0  
**Product name:** Antihemophilic Factor (Recombinant), Single Chain  
**Proposed Indication:** Treatment and prophylaxis of patients with hemophilia A (Congenital Factor VIII deficiency) in adults and children for:

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

**Applicant:** CSL Behring Recombinant Facility AG  
**Meeting date & time:** November 12, 2015, 11:30 am – 1 pm, EST  
**Committee Chair:** Alexey Khrenov, PhD  
**RPM:** LT Thomas J. Maruna, MSc, MLS(ASCP), CPH

### Attendees:

Meghna Alimchandani	Epidemiology, OBE/DE/PB
Natalya Ananyeva, PhD	CMC/Product, OBRR/DHRR/LH
Victor Baum, MD	Clinical, OBRR/DHCR/CRB
Yolanda Branch, PhD	Toxicology, OBRR/DHCR/TRS
Karen Campbell, MS	Testing Plan, OBRR/DBSQC
Haecin Chun, MS	BIMO, OCBQ/DIS/BMB
Christine Drabick, MS	BIMO, OCBQ/DIS/BMB
Jay Epstein, MD	Director, OBRR
LCDR Donald Ertel, MT(ASCP)	CMC/Facility, OBRR/DMPQ
Mahmood Farshid, PhD	Deputy Director, OBRR/DHRR
Mitchell Frost, MD	Chief, OBRR/DHCR/HPRB
Basil Golding, MD	Director, OBRR/DHRR
Ms. Patricia Holobaugh	Chief, BIMO, OCBQ/DIS/BMB
Jiang (Jessica) Hu, PhD	Statistics, OBE/DB/TEB
Alexey Khrenov, PhD	Chair/CMC/Product, OBRR/DHRR/LH
Nancy Kirschbaum, PhD	Chemist, OBRR/DHRR/LH
Timothy Lee, PhD	Acting Chief, OBRR/DHRR/LH
Iftekhar Mahmood	Clinical Pharmacology, OBRR/DHCR/CRB
LT Thomas J. Maruna, MSc, MLS(ASCP)	Regulatory Management, OBRR/IO/RPMS
LCDR Adamma Mba-Jonas, MD	Epidemiology, OBE/DE/PB
Paul D. Mintz, MD	Director, OBRR/DHCR
LCDR Loan Nguyen	Promotional Labeling, OCBQ/DCM/APLB
Ze Peng, PhD	CMC/Product, OBRR/DHRR/LH
Anne M. Pilaro, PhD	Toxicology Supervisor, OBRR/DHCR/TRS
Renee Rees, PhD	Stat Team Lead, OBE/DB/TEB
Ms. Carolyn Renshaw	Chief, OCBQ/DMPQ/BI
Iliana Valencia, MS	Chief, OBRR/IO/RPMS

**Discussion Summary:**

**1. Reviewer Reports**

a. CMC (DHRR)

The active ingredient in this product (termed CSL627) is a recombinant Factor VIII (rFVIII), based on the human amino acid sequence and produced in Chinese hamster ovary (CHO) cells. The unique feature of the molecule is that it is secreted as a single-chain (sc) polypeptide, in contrast to plasma-derived FVIII (pd-FVIII), which circulates as a heterodimer composed of heavy and light chains (HCh and LCh) generated by a site-specific cleavage of the sc-polypeptide precursor. A modification of the CSL627 molecule involves deletion of most of the B-domain (b) (4) (HCh), and 4 amino acids in the adjacent region of the LCh. It results in the removal of the (b) (4) introduction of a new N-glycosylation site at this junction.

The underlying concept for sc-FVIII is to (b) (4)

Upon activation by thrombin, CSL627 molecule forms a structure identical to that of pd-FVIIIa (A1/A2/A1-C1-C2 heterotrimer) and is functionally active in the coagulation cascade.

i. **Key findings and substantive issues with the information and data in the application:**

The potency discrepancy between chromogenic and one-stage assays is significant (b) (4) times). CSL proposes potency assignment based on chromogenic assay. The drug product (b) (4) specifications are not sufficiently justified. Acceptance criteria for some parameters are not suitable for intended purpose. Additional validation of analytical procedures may be required for revised acceptance criteria. Testing instructions for (b) (4) appear to be different from the validated method. Post-approval stability protocols are not properly described in the BLA

Potency assignment issues will require significant time to resolve, including the input from outside experts. CSL Behring is aware of specification and some of the validation issues as similar issues were encountered during the BLA for rFIX-FP (STN 125582/0). CSL is already working on the updated specifications; thus, these issues may be resolved expeditiously. Supplemental method validations can be performed in the time remaining in the review cycle.

The potency assignment issue will be presented to OBRR management at a meeting scheduled for December 9, 2015. The input from SGEs is being sought on this issue. SGE candidates are being currently vetted by OBRR.

The information request addressing specifications and analytical procedures is being prepared currently and will be sent within 2 weeks.

Generation of the cell substrate for (b) (4)



According to summary information, MCB, WCB (b) (4) adequately characterized according to ICH Q5A(R1), Q5B, and Q5D guidelines. (b) (4) cell banks were tested for sterility, mycoplasma, viability, (b) (4) identity (b) (4) ), and absence of viruses (*in vitro* and *in vivo* assays; tests for (b) (4) -specific adventitious viral contaminants). The stability of the (b) (4) was confirmed by (b) (4) genetic analyses of (b) (4)

Analytical characterization of product manufactured in the (b) (4) confirmed consistency of product quality. The original reports are under review.

The BLA, however, does not appear to contain protocols to monitor stability of cell banks over time, and this information is requested.

No substantive issues with the characterization of cell banks have been identified at this time.

No substantive issues with bioburden, sterility and endotoxin qualification reports have been identified at this time.

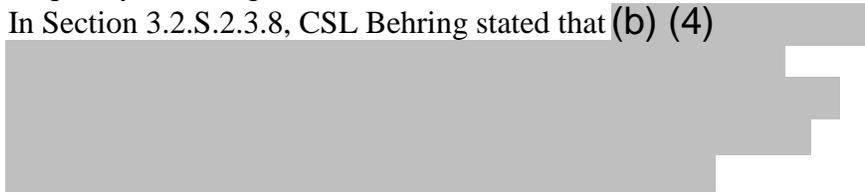
- ii. Assigned areas *not* completely reviewed to-date:**
- 3.2.P.5.3 Validation of Analytical Procedures
  - 3.2.P.8 Stability

- 3.2.S.2.3.4 Original Reports for Cell Substrate and Cell Banks
- Section 3.2.A.2 Adventitious Agents Safety Evaluation
- IR response (bioburden, sterility and endotoxin qualification reports) was received on 10-29-2015 and is under review.

iii. **Outstanding Information Requests:**

Information request (in preparation):

- Questions to address justification of drug substance and drug product specifications and validation of analytical procedures are under preparation.
- Please submit Stability Protocols for Master Cell Bank and Working Cell Bank, and specify tests to be performed and frequency of testing.
- In Section 3.2.S.2.3.8, CSL Behring stated that (b) (4)



b. CMC/Facilities (DMPQ)

i. **Key findings and substantive issues with the information and data in the application:**

No substantive issues identified at this point.

ii. **Assigned areas *not* completely reviewed to-date:**

- Section 3.2.A 1 Facilities and Equipment not finished
- Section 3.2.P.7 Container Closure System not finished

iii. **Outstanding Information Requests:**

- November 5, 2015 – requested verification of shared equipment and utilities; responses expected on or before 11/19/15

c. Clinical

i. **Key findings and substantive issues with the information and data in the application:**

Indication: Treatment and control of bleeding episodes

Treatment of bleeding episodes (BE) was rated as excellent or good in 92.3% of treated episodes.

Indication: Routine prophylaxis

Routine prophylaxis resulted in 1.14 total BE per year and 0 spontaneous BE per year. Forty three percent (43%) of those on routine prophylaxis had no BE. The annualized rate of spontaneous BE decreased 92% from

subjects' prior rates with on-demand treatment with other FVIII products. The lower limit of the 95% CI of 88.9% for the annualized spontaneous bleeding rate complied with the pre-specified success criterion of >70%. These rates did not differ with twice weekly or thrice weekly dosing.

**Indication: Perioperative Management**

Efficacy was evaluated in 16 surgical procedures. Results were assessed as excellent in 94% of surgical prophylaxis cases and good in 6% (a single case). The recommended doses are in line with the recommendations for frequency of dosing and duration of therapy in the European Medicines Agency (EMA) Core Summary of Product Characteristics (SPC) for human plasma-derived FVIII and recombinant FVIII products, which are applicable to Afstyla.

**Use in Children:**

The pediatric trial (3002) is ongoing. An interim Pharmacokinetic (PK) and Safety Report on 39 pediatric subjects was submitted on September 24 and those results have been included in the clinical review. These data fulfill the commitment in CRMTS #9559, November 20, 2014 that PK data only from this trial would suffice for a pediatric indication and preliminary efficacy data from this trial are not considered at this time. PK values differed in the pediatric population than the adult population in an expected way (shorter  $t_{1/2}$  and greater clearance). The ratio of clearance was 1.96:1 (ages 0 to <6:adult) and 1.82 (ages >6 to <12:adult). The draft label has a pediatric indication.

The matter of which assay (chromogenic or one stage) to use/require has been discussed with the applicant throughout the application process and remains undefined. It is not expected that this will impact the review timeline. The issue of the appropriate assay to use (chromogenic or one stage) will be the topic of a meeting scheduled for December 9, 2015.

**ii. Assigned areas *not* completely reviewed to-date:**

- Response to IR sent November 5, 2015 requesting clarification data including HIV data on subjects; these data were:
  - Discrepancy in number of subjects
  - Missing HIV records
  - Numerous “Not Done” HIV tests
  - Missing CD4 counts on several subjects

**iii. Outstanding Information Requests:**

- There are no outstanding information requests

d. Epidemiology

**i. Key findings and substantive issues with the information and data in the application:**

No substantive issues which could prevent approval and impact the review timeline have been identified at this time.

Adverse events related to hypersensitivity, inhibitor development, non-inhibitory anti-drug antibodies, and development of antibodies to Chinese hamster ovary proteins in previously treated patients were infrequently reported.

Thrombosis was not reported as a safety concern. No treatment-related thrombotic events were reported in the safety population, and available literature reviewed thus far does not suggest that patients treated with exogenous Factor VIII are at increased risk of such events.

**ii. Assigned areas *not* completely reviewed to-date:**

- All assigned areas have been reviewed.

**iii. Outstanding Information Requests:**

- No outstanding information is being requested.

e. Clinical Pharmacology

**i. Key findings and substantive issues with the information and data in the application:**

- There are no substantial issues at this time.

**ii. Assigned areas *not* completely reviewed to-date:**

- The review of the Pediatric pharmacokinetic study is not complete

**iii. Outstanding Information Requests:**

- There are no outstanding information requests related to clinical pharmacology.

f. Pharmacology/Toxicology

**i. Key findings and substantive issues with the information and data in the application:**

- At the present time, there are no outstanding or substantive nonclinical issues that would prevent approval of BLA 125591/0 for Afstyla, a recombinant Factor VIII product. Additionally, there are no Pharmacology/Toxicology post-marketing commitments or requirements that have been identified.

**ii. Assigned areas *not* completely reviewed to-date:**

- The following studies have not been reviewed to date: (b) (4)0016, (b) (4)0018, (b) (4)0020, (b) (4) 0/11, (b) (4) 14-03, (b) (4) 14-10, (b) (4) 12-18 AND, (b) (4) 12-23

**iii. Outstanding Information Requests:**

- There are no outstanding information requests related to this nonclinical program.

g. Quality Control

**i. Key findings and substantive issues with the information and data in the application:**

The testing plan is not complete; there is a draft. Since this is recombinant and exempt from lot release, there is no lot release protocol to review. In-support testing samples have been requested; they are expected in mid-December

**ii. Assigned areas *not* completely reviewed to-date:**

- None

**iii. Outstanding Information Requests:**

- None

h. Statistics

**i. Key findings and substantive issues with the information and data in the application:**

The efficacy endpoints of CSL627\_1001 met the following pre-specified criteria for subjects:

- For the hemostatic efficacy endpoint, the proportion of success [92.3% with 95% CI (88.9%, 94.8%)] is higher than 70%;
- The annualized spontaneous bleeding rate (AsBR) of the prophylaxis group is statistically significantly (with p-value <0.0001) lower than the AsBR of the on-demand group, (AsBR: 1.6% vs. 19.5%);
- For the hemostatic efficacy endpoint of surgical subjects, the proportion of success is also higher than 70%. The IMP achieves 100% success for 16 subjects.

**ii. Assigned areas *not* completely reviewed to-date:**

- Verification of some secondary efficacy endpoints in study CSL627\_1001
- Verification of safety analysis for study CSL627\_1001

**iii. Outstanding Information Requests:**

- None

**i. Bioresearch Monitoring (BIMO)**

**i. Key findings and substantive issues with the information and data in the application:**

There are no substantive BIMO issues to date.

Several HIV data related discrepancies and missing HIV data were observed during the BIMO review. An IR letter was issued to the applicant on November 05, 2015, regarding these observations.

The BIMO inspections at Site # 6080001, Site # 6160014 and Site # 7100001 are complete. No Form FDA 483 was issued for two out of three clinical study sites (Site # 6080001 and Site # 7100001). However, a Form FDA 483 was issued to Site # 6160014 in Wroclaw, Poland. The EIR and a Form FDA 483 response letter from the clinical investigator from Site # 6160014 are under review.

The following table summarizes the status of BIMO inspections:

Site Number	Number of Subjects	Study Site	Location	Form FDA 483 Issued	Final Classification or Status*
6080001	12	Perpetual Succour Hospital	Cebu, Philippines	No	NAI
6160014	12	Klinika Hematologii Nowotworow Krwi i Transplantacji Szpiku Samodzielny Publiczny Kliniczny	Wroclaw, Poland	Yes	EIR pending review
7100001	16	Charlotte Maxeke Johannesburg Academic Hospital	Johannesburg, South Africa	No	NAI

\*NAI = No Action Indicated

**ii. Assigned areas *not* completely reviewed to-date:**

- BIMO is in the process of reviewing the EIR and a 483 response letter from the clinical investigator at Site 6160014 in Wroclaw, Poland.
- An information request (IR) was issued to the applicant on November 05, 2015, to explain HIV data discrepancies and provide HIV related missing information. The IR response is under review.

**iii. Outstanding Information Requests:**

- None

2. Discipline Review Letters will not be issued for this application.
3. This application will not be presented to the Blood Products Advisory Committee.
4. This application is due to be reviewed by the Pediatric Review Committee (PeRC) on February 3, 2016.
  - a. PeRC forms have to be submitted two weeks in advance of scheduled PeRC meeting.
5. The National Drug Code (NDC) assignments to product/packaging are currently under review, and are anticipated to be completed by January 1, 2016.
6. Proper naming convention confirmed: Antihemophilic Factor (Recombinant), Single Chain
7. Unique ingredient identifier (UNII) code process has been completed. The appropriate UNII is VQ723R7O8R.
8. Review committee chair will provide an agenda for the mid-cycle communication scheduled with the applicant on November 19, 2015. The agenda should be sent to the applicant by November 17, 2015.
9. This product is exempt from lot release testing.
10. Major target and milestone dates:
  - Complete Discipline Reviews (Primary) Jan. 01, 2016
  - Complete Discipline Reviews (Secondary Review) Jan. 15, 2016
  - Internal Late Cycle Meeting Jan. 13, 2016
  - Send Late Cycle briefing package Jan. 29, 2016
  - PeRC Meeting Feb. 03, 2016
  - External Late Cycle Meeting Feb. 15, 2016
  - Complete inspection reports Mar. 28, 2016
  - Send **Final** PI to sponsor May 12, 2016
  - T-minus date May 13, 2016
  - Target ADD May 27, 2016

**Action items:**

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

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

1. No major issues in the BLA have been identified by the review committee to date.
2. The review of the clinical data to date did not raise any major safety concerns. The response to the IR regarding HIV related data discrepancies is still under review.
3. A number of CMC issues with regard to specifications, analytical methods validations and post-approval stability commitments were identified. The information request is being prepared and will be sent shortly.
4. The method to be used for potency assignment and labeling (one-stage vs. chromogenic) is still under discussion. The decision hasn't been made yet.
5. The change of language for on-demand indication is requested in the labeling. New recommended language is, "On demand treatment and control" (not "control and prevention"). The comprehensive discussion of labeling will occur after potency issue is resolved.
6. The current thinking of the review committee is that this BLA will not be presented at the Blood Products Advisory Committee meeting. However the external experts will be involved to help resolve the potency issue.
7. The late-cycle meeting will be scheduled for February 15, 2016. The format of the meeting (i.e., a face-to-face meeting or a teleconference) will be determined in the course of the next two months.

**END**