Late-Cycle Internal Meeting Summary

Application number: BL 125661/0
Product name: JIVI (Recombinant B-domain deleted human coagulation factor VIII conjugated with polyethylene glycol (PEG) (BAY 94-9027))
Proposed Indication: For use in previously treated adults and adolescents (12 years of age and older) with hemophilia A (congenital Factor VIII deficiency) for on-demand treatment and control of bleeding episodes; perioperative management of bleeding; and routine prophylaxis to reduce the frequency of bleeding episodes
Applicant: Bayer Healthcare, LLC
Meeting date & time: May 8, 2018 [12:00pm – 1:00pm]
Committee Chair: Zuben Sauna
RPM: Olukayode Owosela
Candace Jarvis

Attendees:

Discipline	Name [with credentials (not title)]	Attended meeting?
Regulatory Project Manager (RPM)	Candace Jarvis Olukayode Owosela	Yes Yes
Chair/ CMC Inspector	Zuben Sauna	Yes
Clinical Reviewer	Najat Bouchkouj	Yes
CMC Reviewer	Ze Peng Daniel Lagasse	Yes Yes
Clinical Pharmacology Reviewer	Iftekhar Mahmood	No
Toxicology Reviewer	Sandhya Sanduja	Yes
OCBQ/DMPQ RPM	Ekaterina Allen	Yes
OCBQ/DMPQ Reviewer	Lori Peters	Yes
OCBQ/DMPQ/PRB Reviewer	Cheryl Hulme	No
Statistical Reviewer of clinical data	Lin Huo	Yes
Post marketing Safety Epidemiological Reviewer	Graca Dores	Yes
OCBQ/APLB Reviewer	Kristine Khuc	No
OCBQ/BIMO Reviewer	Bhanu Kannan	No
OCBQ/DBSQC RPM	Varsha Garnepudi	Yes
OCBQ/DBSQC or OVRR/LIB Reviewer	Hyesuk Kong Parmesh Dutt Ritu Agarwal	Yes Yes No

Discipline	Name [with credentials (not title)]	Attended meeting?
	Hsiaoling Wang Lokesh Bhattacharyya (Supervisor)	Yes Yes
OCBQ/DMPQ/Lead Inspector	Lori Peters	Yes
Labeling Reviewer	Oluchi Elekwachi	No
Other Attendees	Ramani Sista Kimberly Benton Rachael Anatol Wilson Bryan Timothy Lee Basil Golding Farshid Mahmood Patrick Riggins Carolyn Renshaw John Eltermann Lisa Stockbridge Mercedes Serabian Iwen Wu Deborah Trout Ilan Irony Tejashri Purohit-Sheth Bindu George Renee Rees Larissa Lapteva	Yes No No Yes Yes Yes No No No Yes No Yes No No No Yes Yes Yes No

Late–cycle internal meeting agenda:

1. **Short summary of the submission. [Z. Sauna, D. Lagasse, Z. Peng]**

   Jivi is Recombinant B-domain deleted human coagulation factor VIII conjugated with polyethylene glycol (PEG) (BAY 94-9027) for use in previously treated adults and adolescents (12 years and older) with hemophilia A (congenital Factor VIII deficiency) for:

   - On-demand treatment and control of bleeding episodes
   - Perioperative management of bleeding
   - Routine prophylaxis to reduce the frequency of bleeding

   The drug product is Supplied as lyophilized powder in a stoppered glass vial with aluminum over-seal:

   - Sterile water for injection in a prefilled syringe and vial adapter for reconstitution
   - Intravenous administration

The mode of action temporarily replaces coagulation Factor VIII needed for effective hemostasis in Hemophilia A patients. PEGylation at A3 domain reduces clearance and extends terminal half-life ($t_{1/2}$) compared to unmodified rFVIII product KOGENATE (Bayer), while maintaining normal FVIII function:

- [13.4 vs. 8.8 hours (hemophilia A mice); 17.1 ± 2.7 vs. 3.35 ± 0.64 hrs. (hemophilia A dogs)]

2. Substantive issues raised during review.

a. Z. Sauna, D. Lagasse, Z, Peng - CMC

i. Substantive issues to report

1. *There are no substantial issues which could prevent approval of this submission.*

ii. Review Update:

1. IR (02 February 2018) regarding DS release specification for (b) (4). Bayer response (16 February 2018) is acceptable

iii. Discipline Review Completion:

1. Primary discipline review memorandum should be ready for branch chief review by end of May 2018 (tentative).

b. H. Kong, P. Dutt, R. Agarwal, V. Garnepudi, H. Wang - DBSQC

i. Substantive issues to report

1. *There are no substantial issues which could prevent approval of this submission.* **(Kong)**
2. One outstanding IR, not substantial enough to prevent approval of the submission. **(Wang)**
3. One outstanding IR, not substantial enough to prevent approval of the submission. The sponsor has submitted data on 5/15/2018 to address the IR which is being reviewed. **(Dutt)**

ii. Review Update:

1. Review of primary material and information (amendment: 125661/0.14) received from the information request for the sterility and bacterial endotoxin test (BET) method qualification are in process. – (**Kong)**
2. BET licensing support testing result memo uploaded on 14 February, 2018. (**Kong)**
3. Review is ongoing: method validation issue. The sponsor has proposed a PMC (amendment 34) to reassess (b) (4) when accuracy and precision data are available. **(Wang)**
4. Sponsor has agreed to provide additional data for the accuracy of the method and update the method validation report by May 20, 2018. New update will need review. The sponsor has submitted data on 5/15/2018 to address the IR which is being reviewed. **(Dutt)**

iii. Discipline Review Completion:

1. Review memo will be completed end of May, 2018, tentative. **(Kong)**
2. PDR Memo is ongoing, will be completed by end of May, 2018. **(Dutt)**

c. Lori Peters – DMPQ

i. Substantive issues to report

1. *There are no substantial issues which could prevent approval of this submission.*

ii. Review Update:

1. The review of the original BLA is complete and IRs have been made for clarification and for equipment qualification/cleaning that were not provided in BLA.
2. Amendment #26 and #31 are currently under review.
3. Information request was sent to Bayer on April 20, 2018 and a response (via Amendment to BLA) is expected May 4, 2018.

iii. Discipline Review Completion:

1. The primary discipline review memo is complete as all pertinent DMPQ information in the BLA has been reviewed; the outstanding review items only include the review of the Amendments noted above.

d. Bhanu Kannan – BIMO

i. Substantive issues to report

1. *There are no substantial issues which could prevent approval of this submission.*

ii. Review Update:

1. *BIMO* inspections in all four sites have completed and classified. Refer to item D below.

iii. Inspectional Findings:

Site #	Number of subjects	Location	Final inspection classification
14002	10	Penn State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania	NAI
14013	3	SUNY Upstate Medical University Syracuse, New York	NAI
14024	3	University of California -Davis Sacramento, California	NAI
68001	6	Singapore General Hospital, Singapore	NAI

iv. Discipline Riiv. Discipline Review Completion:

1. The final primary discipline review will be completed by May 15, 2018.

e. Sandhya Sanduja – Pharmacology/Toxicology

i. Substantive issues to report

1. See below.

ii. Review Update:

1. The applicant submitted an audited interim report (Study No. 20127291) titled: A 13- and 26-Week Intravenous Toxicity Study of BAY 94-9027 in the Nude Rat (b) (4) nude rats, (b) (4)) followed by a 26-Week Recovery Period, on 04/25/2018. The male rats received twice weekly intravenous injections of BAY 94-9027 at dose levels of 40, 400, or 1200 U/kg/administration for 26 consecutive weeks. Groups of animals were sacrificed at Weeks 13 and 26. The recovery animals will be sacrificed at Week 52. The report contains all in-life data from all study animals through 26 weeks and the post-mortem data (including histopathology on a complete panel of tissues) from the rats sacrificed at Week 13. Submitted post-mortem data for all rats sacrificed at Week 26 include macroscopic pathology for all animals and histopathology assessment on select tissues for all animals. Review of these data is ongoing. No substantive issues have been identified from a preliminary review of the interim report. An IR was sent on 5/16/2018 for pathologist comments on the ocular and cardiac findings observed in some of the dosed animals sacrificed at 13 weeks.

iii. Discipline Review Completion:

1. P/T draft review memo will be completed by June 30, 2018.

f. Megha Kaushal – Clinical

i. Substantive issues to report

1. No substantial issues.
2. No safety issues.

ii. Review Update:

1. Post meeting update (IR sent on 5/14/18).

iii. Discipline Review Completion:

1. End of May depending if additional analysis is needed.

g. Iftekhar Mahmood – Clinical Pharmacology

i. Substantive issues to report

1. *There are no substantial issues which could prevent approval of this submission.*

ii. Review Update:

1. Now complete.

iii. Discipline Review Completion:

1. Complete April 2018.

h. Lin Huo – Biostatistics

i. Substantive issues to report

1. *There are no substantial issues which could prevent approval of this submission.*

ii. Review Update:

1. Review is completed.

iii. Discipline Review Completion:

1. Ready for supervisory concurrence in May.

i. Graca Dores – Epidemiology

i. Substantive issues to report

1. Complete results of the 26-week long-term preclinical toxicity study in nude rats have not been submitted, and therefore the pharmacovigilance plan (PVP) cannot be finalized.

ii. Review Update:

1. Review of available data is complete. There may be additional IRs related to questionannaires submitted as part of PVP. Depending on the long-term preclinical study results, there may be additional IRs for additional questionnaire(s) or other PVP acitivities.

iii. Discipline Review Completion:

1. Pending submission of complete preclinical study results (week 26) and input from Pharm/Tox.

3. Review of upcoming timeline/deadlines. **[Chair]**

Late-Cycle Meeting Internal	08-May-2018
Late-Cycle Meeting with Sponsor	29-May-2018
PMC Study Target	31-Jul-2018
Advisory Committee	TBD
Safety Working Group	TBD
SBRA	July 9, 2018
Division Review Memo (Branch Level)	July 16, 2018
**Letter Draft Circulation	August 1, 2018
Divison Review Memo (Divison Level)	August 2, 2018
Divison Review Memo (Offfice Level)	August 9, 2018
Labeling Target	31-Jul-2018
OTAT Target Date	16-Aug-2018
Action Date	30-Aug-2018

*****Please note that we are now using the new approval letter process where all edits and concurrences have to be in the Word version of the document.***

4. Assess status of the review including plans for completing outstanding discipline reviews and any remaining outstanding issues. **[Chair]**

There ar no substantive issues thus far that would prevent approval. The final outstanding reviews are pending the review of the pharmacology data.

5. Reach agreement on Late-Cycle Meeting Materials that will be sent to the Applicant. **[Chair, Review Committee Members]**

a. Any outstanding IRs if any will be conveyed to the sponsor during the late cycle communication with the sponsor.

6. Come to agreement on the issues to be included on the agenda for the LCM with the Applicant. The timeframes for each agenda item should also be agreed to. **[Chair, Review Committee Members, Management]**

a. Advisory Committee (AC) information:

i. Advisory committee meeting dependent on P/T review but at this point is highly unlikely

7. Concurrence: RPM, Chair, Division Director of the product office

Late-Cycle Meeting Agenda to Applicant

If there is no discussion planned for a topic listed below, indicate in the Agenda that discussion isn't planned and the reason, *for example, there is no anticipation for a REMS. There may be instances where information may still be sent in the Late-Cycle Meeting Materials even though a discussion might not be planned.*

1. Introductory Comments – **5 minutes (RPM/Chair)**

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – **10 minutes** *(INCLUDE IF APPLICABLE)* Each issue will be introduced by FDA and followed by a discussion.

   None to date pending P/T review

3. Discussion of Minor Review Issues – **5 minutes**

   No minor review items to discuss

4. Additional Applicant Data – **5 minutes** None to date pending P/T review

5. Information Requests – **5 minutes**

   Dependent on P/T review

6. Discussion of Upcoming Advisory Committee Meeting – **2 minutes**

   Dependent on P/T review

7. Current assessment of risk management activities, e.g, REMS **– 2 minutes**

   Non-applicable at the moment

8. Postmarketing Requirements/Postmarketing Commitments – **2 minutes**

   - Dependent on findings from P/T review
   - The current PVP includes assessments related to the PROTECT KIDs study (individuals <12 years of age). These PVP elements are included in the sections on "important identified risks" (development of FVIII inhibitors, hypersensitivity, lack of drug effect) and "missing information" (potential long-term PEG-related adverse reactions). Please remove "PROTECT KIDs" elements from the PVP since this study is being conducted in individuals outside the age range for which product approval is being sought. The PROTECT KIDs study will need to be monitored through another mechanism (i.e., IND) Please note that currently planned questionnaires may become unnecessary or may need to be added pending P/T review.
   - Bayer proposed PMC (b) (4)

9. Major labeling issues – **5 minutes**

   None at this time

10. Review Plans **– 5 minutes**

Review for P/T is ongoing

11. Applicant Questions –**10 minutes**
12. Wrap-up and Action Items – **2 minutes**