Our STN: BL 125661/0

MID-CYCLE COMMUNICATION SUMMARY
March 16, 2018

Bayer Healthcare, Inc.
Attention: Michelle Meng, PhD
100 Bayer Boulevard
Whippany, NJ 07981

Dear Dr. Meng:

Attached is a copy of the summary of your February 26, 2018, Mid-Cycle Communication Teleconference with CBER. This memorandum constitutes the official record of the Teleconference. If your understanding of the Teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to STN BL 125661/0 in your future submissions related to the subject product.

If you have any questions, please contact Candace Jarvis at (240) 402-8315 or Kay Owosela at (240) 402-2667.

Sincerely,

Basil Golding, MD
Director
Division of Plasma Protein Therapeutics
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Mid-Cycle Communication Teleconference Summary

Application type and number:	BLA 125661/0
Product name:	JIVI (Recombinant B-domain deleted human coagulation factor VIII conjugated with polyethylene glycol (PEG) (BAY 94-9027))
Proposed Indication:	Control and prevention of bleeding episodes and for surgical & long-term prophylaxis in patients with hemophilia A
Applicant:	Bayer Healthcare, LLC
Meeting date & time:	February 26, 2018, 1:00PM – 2:00PM
Committee Chair:	Zuben Sauna, PhD
RPM:	Candace Jarvis Kay Owosela

FDA Participants:
Ritu Agarwal, PhD, OCBQ/DBSQC/LACBRP
Graca Dores, MD, OBE/DE/AEB
Basil Golding, MD, OTAT/DPPT
Lin Huo, PhD, OBE/DB/TEB
Ilan Irony, MD, OTAT/DCEPT
Candace Jarvis, OTAT/DRPM/BR2
Megha Kaushal, MD, OTAT/DCEPT/CHB
Daniel Lagasse, PhD, OTAT/DPPT
Kay Owosela, MSc, OTAT/DRPM/BR1
Dutt Parmesh, PhD, OCBQ/DBSQC/LACBRP
Tejashri Purohit-Sheth, MD, OTAT/DCEPT
Sandhya Sanduja, PhD, OTAT/DCEPT/PTB2
Zuben Sauna, PhD, OTAT/DPPT/HB
Mercedes Serabian, MS, DABT, OTAT/DCEPT/PTB2
Ramani Sista, PhD, OTAT/DRPM
Hsiaoling Wang, PhD, OCBQ/DBSQC/LACBRP

Bayer Healthcare, Inc Participants
Anita Shah Clinical Pharmacology
Chi Li, Regulatory
Inge Ivens, Toxicology
Joel Krasnow, Pharmacovigilance
John Teare, CMC
Kapil Saxena, Clinical
Lisa Michaels, Clinical
Lisa Regan, CMC
Megan Ward, CMC Regulatory
Monika Maas Enriquez, Clinical
Silvana Schumacher-Goethel, Regulatory
Thomas Schwarz, DMPK
Yvonne Katterle, Bioanalytics

Todd Paporello Regulatory
Michelle Meng, Regulatory

Discussion Summary:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.

    a. Quality Control
        i. The method validation for the following assays is incomplete. A response to a previous IR #9 was received February 28. The remaining deficiencies will be communicated through second IR that will be sent out later.

        (b) (4) Drug Product

        - Purity by (b) (4)
        - Quantitation of Histidine and Glycine by (b) (4)
        - Determination of Polysorbate 80 by (b) (4)
        - Quantitation of Sodium and Calcium by (b) (4)
        - Determination of Particulate Matter
        - Moisture determination: incorrect calculation formula in the method
        - Chromatography assay for (b) (4) : Insufficient validation.

        FDA met with applicant on March 8, 2018 to discuss (b) (4) testing issues (slides were provided to aide in the discussion); send follow-up IR

    b. Pharmacology/Toxicology
        i. Ongoing Issue - A 26-week IV toxicity study in immune-deficient (b) (4) nude male rats, with a 26-week recovery interval, is ongoing. This study was requested by FDA in the May 31, 2017 Type B pre-BLA meeting. The applicant plans to submit an audited interim report containing all in-life data from all study animals and post-mortem data (including histopathology) from the animals sacrificed at the weeks 13 and 26 time points, in an amendment to the BLA by April 30, 2018, and a final audited report (to also include the 26-week recovery data) in the first quarter of 2019. The contents of the study report and possibly the date that the amendment is submitted will determine if it will constitute a Major Amendment to the BLA.
            1. Applicant Update
                a. Treatment finished end of February, most animals survived necropsies,
                b. Applicant suggests that they are on track with interim report due on April 30th.

c. Epidemiology:
    i. We await the results of the ongoing, long-term (26 week) preclinical toxicity study in immune deficient male rats. This information will be required to enable full assessment of the submitted pharmacovigilance plan.

2. Information regarding major safety concerns.
    a. No major safety concerns have been identified at this time. The review is ongoing.

3. Preliminary Review Committee thinking regarding risk management.
    a. No comments at this time.

4. Any information requests sent and responses not received.

    Information request #17 sent February 21, 2018- Epidemiology.

5. Any new information requests to be communicated.
    a. The following disciplines will be sending out information requests after this meeting
        i. Clinical and Statistical-Information Request #18 sent February 27, 2018
        ii. Facilities-Information Request #19 sent on March 1, 2018

6. Proposed date(s) for the Late-Cycle meeting (LCM).
    a. The LCM is currently scheduled for May 29, 2018 from 1:00 PM to 2:00 PM ET.
        i. We intend to send the LCM meeting materials approximately 5 business days in advance of the LCM.
        ii. If these timelines change, we will communicate updates to the applicant during the course of the review.

7. Updates regarding plans for the AC meeting.
    a. Need for AC meeting is contingent upon the Pharmacology/Toxicology study Report results expected at the end of April 2018

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

Late-Cycle Meeting with Applicant	29-May-2018
PMC Study Target	31-Jul-2018
Labeling Target	31-Jul-2018