



Our STN: BL 125671/0

**LATE-CYCLE  
MEETING MEMORANDUM**  
December 6, 2018

Novo Nordisk, Inc.  
Attention: Ms. Barbara Davies  
P.O. Box 846  
Plainsboro, NJ 08536

Dear Ms. Davies:

Attached is a copy of the memorandum summarizing your November 29, 2018, Late-Cycle 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 in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact Ms. Jean Dehdashti at (240) 402-9146.

Sincerely,

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

### **Late-Cycle Meeting Summary**

**Meeting Date and Time:** Thursday, November 29, 2018, 3:00 – 4:00 PM ET

**Meeting Format:** Teleconference

**Application Number:** BLA 125671/0

**Product Name:** Antihemophilic Factor (Recombinant),  
GlycoPEGylated-exei

**Proposed Indication:** For use in adults and children with hemophilia A for:  
on-demand treatment and control of bleeding  
episodes; perioperative management; and routine  
prophylaxis

**Applicant Name:** Novo Nordisk, Inc.

**Meeting Chair:** Andrey Sarafanov, PhD

**Meeting Recorder:** Jean Dehdashti, MSc, RAC

#### **FDA ATTENDEES**

Ohenewa Ahima, MD, CBER/OBE/DE  
Ekaterina Allen, PhD, CBER/OCBQ/DMPQ  
Natalya Ananyeva, PhD, CBER/OTAT/DPPT  
Kim Benton, PhD, CBER/OTAT  
Najat Bouchkouj, MD, CBER/OTAT/DCEPT  
Wislon W Bryan, MD, CBER/OTAT  
Hector Carrero, CBER/OCBQ/DMPQ  
Suzanne Carter, PhD, CBER/OCBQ/DBSQC  
Dennis Cato, CBER/OCBQ/DIS  
Wambui Chege, MD, CBER/OBE/DE  
Jean Dehdashti, MSc, RAC, CBER/OTAT/DRPM  
Parmesh Dutt, PhD, CBER/OCBQ/DBSQC  
Karla Garcia, MS, CBER/OCBQ/DBSQC  
Bindu George, MD, CBER/OTAT/DCEPT  
Basil Golding, MD, PhD, CBER/OTAT/DPPT  
Anthony Hawkins, MS, CBER/OCBQ/DIS  
Cheryl Hulme, CBER/OCBQ/DMPQ  
Carla Jordan, CBER/OCBQ/DIS  
Alexey Khrenov, PhD, CBER/OTAT/DPPT  
Kristine Khuc, PharmD, CBER/OCBQ/DCM  
Tim Lee, PhD, CBER/OTAT/DPPT  
Yideng Liang, PhD, CBER/OTAT/DPPT  
Jing Lin, PhD, CBER/OCBQ/DBSQC  
Tony Lorenzo, CBER/OCBQ/DMPQ

Iftekhhar Mahmood, PhD, CBER/OTAT/DCEPT  
Mikhail Ovanesov, PhD, CBER/OTAT/DPPT  
Tao Pan, PhD, CBER/OCBQ/DBSQC  
Ze Peng, PhD, CBER/OTAT/DPPT  
Andrey Sarafanov, PhD, CBER/OTAT/DPPT  
Ramani Sista, PhD, CBER/OTAT/DRPM  
Mark Verdecia, PhD, CBER/OTAT/DPPT  
Charlene Wang, PhD, CBER/OCBQ/DBSQC

**APPLICANT ATTENDEES**

Tina Meinertz Andersen, PhD, Regulatory Affairs  
Frank Bringstrup, MD, Regulatory Affairs  
Wan Hui Clausen, PhD, Biostatistics  
Barbara Davies, MBA, Regulatory Affairs  
Silke Ehrenforth, MD, Medical  
Jonna Eskildsen, Quality  
Robert Fischer, MS, Regulatory Affairs  
Helene Jacobsen, PhD, Non-Clinical  
Andrea Landorph, MD, Medical  
Claus Rix Melchiorson, PhD, Manufacturing  
Jesper Nellemann, PhD, Project Management  
Bjarne Nielsen, PhD, Quality  
Hiral Palkhiwala, MS, Regulatory Affairs  
Jane Pedersen, PhD, Regulatory Affairs  
Michelle Thompson, PhD, Regulatory Affairs  
Jørli Ringsted, MS, Regulatory Affairs  
Sanne Valentin, PhD, Quality

**BACKGROUND**

BLA 125671/0 was submitted on February 27, 2018, for Antihemophilic Factor (Recombinant), GlycoPEGylated-exei.

Proposed indications: For use in adults and children with hemophilia A for: on-demand treatment and control of bleeding episodes; perioperative management; and routine prophylaxis

PDUFA goal date: February 27, 2019

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on November 14, 2018.

## **DISCUSSION**

### **1. Discussion of Substantive Review Issues**

To date, there are no pending substantive review issues identified by the review team.

### **2. Status of Information Requests**

FDA and applicant discussed the status of all information requests (IRs) listed below, where dates of applicant responses, or outstanding dates for the respective IRs are stated accordingly. All responses that have been received from the applicant are currently under review.

- a. Applicant communicated on November 1, 2018, that there will be a delay in response to OCBQ/DBSQC IR, issued September 7, 2018, with respect to (b) (4) method validation, (b) (4), because the commercially-obtained (b) (4) reference did not perform as expected and was found to be degraded. This delay will further affect applicant's response to the FDA OTAT/DPPT IR issued October 12, 2018, regarding Drug Substance (DS) and Drug Product (DP) specifications, where applicant anticipates altering the acceptance criteria for the DS specification parameter (b) (4) assessed by the (b) (4) method (b) (4). For these reasons, applicant plans to provide a single submission no later than December 19, 2018, discussing the (b) (4) method validation and procedure, and addressing the OCBQ/DBSQC and OTAT/DPPT IRs referenced above.
- b. Two OCBQ/DBSQC IRs regarding validation of the one-stage clotting and chromogenic assays (the accuracy study), issued September 20, 2018, and October 16, 2018, have not been completely addressed. Applicant agreed to include (b) (4) lots of (b) (4) and (b) (4) lots (different than reference standard) of DP, in addition to the reference standard, in both the one-stage clotting and chromogenic assays for the accuracy study. FDA confirmed that applicant submitted a full response on November 21, 2018.
- c. IR issued November 1, 2018, by OCBQ/DBSQC, requesting that the applicant provides details of how the data were obtained for the potency of Secondary Reference Standard (b) (4) by the chromogenic and one-stage clotting assays, including how many independent sample preparations, analysts, instruments, and laboratories were involved in this study. FDA confirmed that applicant provided a response on November 15, 2018.
- d. IR issued November 5, 2018, by OTAT/DCEPT clinical review team regarding applicant proposed dosing. FDA confirmed that applicant provided a response on November 13, 2018.

- e. IR issued November 14, 2018, by OTAT/DCEPT clinical review team regarding applicant proposed dosing. FDA confirmed that applicant provided a response on November 19, 2018.
  - f. FDA confirmed that updated stability data for DP were submitted by the applicant on November 16, 2018.
  - g. An IR regarding the use of the WHO international standard for factor VIII activity in the Primary Reference Standard stability study protocol will be submitted by FDA OTAT/DPPT. FDA confirmed that the IR is in preparation and will be issued soon.
  - h. IR issued by OTAT/DPPT on November 23, 2018, regarding the Quality Control lab at the (b) (4) facility. Post-Late Cycle Meeting teleconference, FDA confirms that the applicant provided a response on November 30, 2018.
  - i. IR issued by OTAT/DPPT on November 26, 2018, regarding DS and DP specifications, where applicant has agreed to respond by the target date of December 10, 2018.
3. **Current assessment of risk management activities (e.g., REMS)**  
The review team has not identified any issues related to risk management. We do not believe that a risk management action (e.g., REMS) is needed at this time. The applicant has proposed a non-interventional post-authorization safety study (PASS), based on EU regulatory requirement that has been reviewed.
4. **Postmarketing Requirements/Postmarketing Commitments**  
Currently, no post marketing commitments or post marketing requirements have been identified. The review for this application is ongoing and development of any post marketing commitments or requirements will be communicated to the applicant by January 25, 2019.
5. **Major Labeling Issues**
- a. The labeling review is ongoing, and modifications and recommendations for the text of Prescribing Information and labels for the vial and carton will be communicated to the applicant via IRs in late December 2018 – early January 2019.
  - b. FDA confirmed that applicant submitted revised labeling to include the proper name, Antihemophilic Factor (Recombinant), glycoPEGylated-exei, and the trade name, ESPEROCT, on November 12, 2018.
6. **Review Plans**  
Discipline reviews are ongoing. Reviews of responses to outstanding issued IRs are pending.

**7. Applicant Questions**

There were no questions presented by the applicant during the Late Cycle External teleconference.

**8. Wrap-up and Action Items**

No additional action items were taken from either FDA or applicant, outside of the listed pending IR's under section 2 of this Meeting Summary.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.

**Concurrence Page**

Application Type and Number: BLA 125671/0

Communication Type: Late-Cycle Meeting Summary (Teleconference)

History: Drafted by Jean Dehdashti / November 30, 2018  
Reviewed by Erica Giordano / December 3, 2018  
Revised by Andrey Sarafanov / November 30, 2018  
Revised by Natalya Ananyeva / December 3, 2018

Concurrence:

<b>Office/Division</b>	<b>Name</b>	<b>Date</b>
<b>OTAT/DRPM</b>	<b>Jean Dehdashti</b>	
<b>OTAT/DPPT</b>	<b>Andrey Sarafanov</b>	
<b>OTAT/DPPT</b>	<b>Basil Golding</b>	