

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

Iftekhar Mahmood, PhD, CBER/OTAT/DCEPT
Mikhail Ovanosov, 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 Nellesmann, 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:

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