



Our STN: BL 125671/0

**MID-CYCLE COMMUNICATION
SUMMARY**

AUGUST 10, 2018

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

Dear Ms. Davies:

Attached is a copy of the summary of your August 08, 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 125671 in your future submissions related to Antihemophilic Factor (Recombinant), GlycoPEGylated-exei.

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

Mid-Cycle Communication Teleconference Summary

Application type and 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: Novo Nordisk, Inc.
Meeting date & time: August 08, 2018; 3:00 – 4:00 PM ET
Committee Chair: Andrey Sarafanov, PhD
RPM: Jean Dehdashti, MSc, RAC

FDA Attendees:

Najat Bouchkouj, MD, CBER/OTAT/DCEPT
Jean Dehdashti, MSc, RAC, CBER/OTAT/DRPM
Jing Lin, PhD, CBER/OCBQ/DBSQC
Mikhail Ovanesov, PhD, CBER/OTAT/DPPT
Ze Peng, PhD, CBER/OTAT/DPPT
Andrey Sarafanov, PhD, CBER/OTAT/DPPT
Mark Verdecia, PhD, CBER/OTAT/DPPT

Novo Nordisk Attendees:

Frank Bringstrup, MD, Senior Global Lead, Regulatory Affairs
Wan Hui Ong Clausen, PhD, Principal Statistician, Biostatistics
Barbara Davies, MBA, Senior Manager, Regulatory Affairs
Silke Ehrenforth, MD, International Medical Vice President, Medical & Science
Mirella Ezban, PhD, Scientific Vice President, Haemophilia Research
Helene Jacobsen, PhD, Project Director, Nonclinical Development
Andrea Landorph, MD, International Medical Director, Biopharm
Claus Rix Melchiorsen, PhD, Project Director, Biopharm Project Office
Jesper Nellemann, PhD, Vice President, Project Management
Bjarne Rønfeldt Nielsen, PhD, CMC Project Director, CMC Biopharm
Hiral Palkhiwala, MS, Specialist, Regulatory Affairs
Lisbeth Palm, PhD, Senior Project Manager, CMC API Analytical Project Office
Jørli W. Ringsted, MS, Senior Regulatory Professional, Regulatory Affairs
Michelle Thompson, PhD, Senior Director, Regulatory Affairs
Barbara Hee Schmidt, MS, CMC Specialist, Regulatory Affairs
Sanne Slot Valentin, PhD, Vice President, CMC Biopharm

Discussion Summary:

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

FDA clarified that they are in the process of drafting detailed information requests (IRs) that will provide the background and specifics on their concerns regarding the deficiencies outlined below, and that FDA expects to issue these IRs in the next couple of week. The deficiencies identified by FDA were as follows:

- Regarding process capability and product stability analyses to support proposed release specification limits, FDA noted that the (b) (4) increased almost (b) (4) during the room temperature storage of drug product, almost reaching the upper specification limit for this parameter. Because Novo Nordisk has proposed to use identical specification limits for the release and the stability, FDA is concerned that a batch, released with a slightly elevated level of (b) (4), may fail in stability studies at room temperature.
- FDA noted that Novo Nordisk used several historical primary potency standards, and asked Novo Nordisk to provide data to bridge the potencies of these standards.
- FDA noted that Novo Nordisk has not provided results of investigations into unexpected and adverse stability trends, for example, unexpected increase in potency of (b) (4) increase in (b) (4) species and (b) (4) in drug product stored at room temperature.
- FDA noted that the description of the proposed room temperature storage condition is not sufficiently justified with the stability data provided. For example, stability studies were not conducted for the product kept for 12 month at room temperature before it was placed in refrigerator for another 18 months.

Novo Nordisk clarified that they intend to provide a stability update by end of November 2018 for ongoing stability studies, as per agreements reached with FDA in the IND 14410 Pre-BLA Meeting (CRMTS #10950), dated, December 15, 2017.

2. Information regarding major safety concerns.
 - FDA clarified that no major safety concerns have been identified thus far by the review committee.
3. Preliminary Review Committee thinking regarding risk management.

- FDA clarified that review committee has not identified the need for risk management thus far.
4. Any information requests sent and responses not received.
 - Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT) IR, issued on July 31, 2018, with a response due date of August 13, 2018, regarding detailed information on subjects who were randomized to receive the Q3-4 D versus Q7D dosing.
 - DBSQC IR, issued on August 01, 2018, with a response due date of August 15, 2018, requesting the Standard Operating Procedure (SOP) for Turoctocog alfa pegol (b) (4) [REDACTED], and a detailed description of how HCP in the Turoctocog alfa (b) (4) [REDACTED] method.
 - DCEPT IR, issued on August 06, 2018, with a response due date of August 15, 2018, requesting additional Pharmacology/Toxicology study reports.
 5. Any new information requests to be communicated.
 - IRs regarding release specifications, potency standards and stability studies will be submitted approximately two weeks following the August 8, 2018, Mid-Cycle Communication teleconference.
 6. Scheduled date for the Late-Cycle meeting (LCM).
 - The LCM between Novo Nordisk and FDA Review Committee is scheduled for November 29, 2018, from 3:00 – 4:00 PM ET.
 - FDA stated that they intend to send the LCM materials to Novo Nordisk approximately 5 business days in advance of the LCM, November 22, 2018. However, because November 22, 2018, falls in the week of Thanksgiving holiday, FDA stated that their goal is to provide the LCM materials to Novo Nordisk by Friday, November 16, 2018.
 - If this timeline changes, FDA will communicate updates to Novo Nordisk.
 7. Update regarding plans for an Advisory Committee (AC) meeting.
 - FDA confirmed that BLA 125671/0 will not be discussed at an AC meeting.
 8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.
 - Post-Marketing Commitment (PMC) study target date of January 28, 2019.
 - Labeling target date of January 28, 2019.

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