



Our STN: BL 125611/0

January 5, 2017

Novo Nordisk Inc.
Attention: Ms. Patricia D. Wilson
PO Box 846
Plainsboro, NJ 08536

Dear Ms. Wilson:

Attached is a copy of the summary of our December 8, 2016, Mid-Cycle Communication Teleconference Summary.

This Summary 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 125611/0 in your future submissions related to the subject product.

If you have any questions, please contact Edward Thompson at (240) 402-8443.

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 number: STN BL 125611/0
Applicant: Novo Nordisk Inc.
Product name: Coagulation Factor IX (Recombinant), GlycoPEGylated
Proposed Indication: Indicated for use in adults and children with hemophilia B for:

- Control and prevention of bleeding episodes
- Perioperative management
- Routine prophylaxis

Meeting date & time: December 8, 2016, 12:00 PM to 1:00 PM
Committee Chair: Chava Kimchi-Sarfaty
RPM: Edward Thompson

FDA Attendees:

Chava Kimchi-Sarfaty, Chairperson, CBER/OTAT/DPPT/HB
Edward Thompson, RPM, CBER/OTAT/DRPM/BII
Megha Kaushal, Clinical Reviewer, CBER/OTAT/DCEPT/CHB
Maura O'Leary, Team Leader, CBER/OTAT/DCEPT/CHB
La'Nissa Brown-Baker, Pharmacology/Toxicology Reviewer,
CBER/OTAT/DCEPT/PTB2
Becky Robinson, Team Leader, CBER/OTAT/DCEPT/PTB2

Other Attendee:

Christopher Sese, Independent Assessor, Eastern Research Group

Novo Nordisk Participants:

Lars Wichmann Madsen, CVP Nonclinical Development
Helene Jacobsen, Senior Non-clinical Project Manager
Inga Bjørnsdottir, Principal Scientist, Development ADME
Judi Møss, Senior Clinical Pharmacology Advisor
Silke Ehrenforth, International Medical Vice President
Karin Knobe, VP Medical & Science Biopharm
Stephanie Seremetis, CVP, Chief Medical Officer Biopharm
Wan Hui Ong Clausen, Principal Statistician
Mette Duelund Simonsen, Safety Surveillance Principal Specialist
Jesper Nellemann, Project Vice President
Henning Stennicke, CVP Biopharm
Hanne Henriksen, Senior Global Regulatory Lead
Maria Jose Arce Tomas, CVP, Regulatory Biopharm
Nina Hagen, Regulatory Professional
David Cooper, Senior Director, Medical Affairs
Patty Wilson, Assoc. Director, Regulatory Affairs
Lewis Pollack, Senior Director, Regulatory Affairs
Shawn Hoskin, Senior Director, Regulatory Affairs
Payal Mehta, Senior Associate, Regulatory Affairs

Discussion Summary:

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

FDA has concerns regarding the accumulation of the 40-kDa PEG in the choroid plexus observed in several animal species. The significance of this observation is currently under internal discussion (please also see item #2 below).

Additional discussion:
See discussion in item #2.

2. Information regarding major safety concerns.

Based on the results of the animal studies, we are concerned that intravenous administration of your product might result in vacuole formation in the choroid plexus in humans. This safety concern is a review issue that could impact the approval of your BLA.

Additional discussion:
Novo Nordisk clarified that the PEG accumulation and vacuole formation in the brain were evident in the PEG-only studies, and no such findings were observed in the studies evaluating administration of 40-kDa PEG-rFIX (the proposed clinical product).

FDA requested that Novo Nordisk submit in writing their comprehensive assessment of any observations of PEG accumulation and vacuole formation in the animals.

3. Preliminary review committee thinking regarding risk management.

FDA is analyzing the risk management plan, and is considering the possible utility of additional studies to evaluate potential safety issues from vacuole formation in the choroid plexus.

Additional discussion:
Novo Nordisk reiterated that in studies evaluating administration of 40K PEG-rFIX (the proposed clinical product) no PEG accumulation or vacuole formation was observed in any organs of the animals.

FDA requested that Novo Nordisk submit a comprehensive discussion to support their claims regarding the lack of PEG accumulation and vacuole formation in the animals that received 40-kDa PEG-rFIX in an amendment to the application.

4. Any information requests sent and responses not received.
 - a. Request for pediatric assessment sent on November 29, 2016.

- b. Request for column lifetimes studies, drug substance data, container closure data, QC testing data, combination product data, the microbial environmental data, and data on Building (b) (4) sent on November 23, 2016.
- c. Request for data on potency by One-Stage Clotting Assay and (b) (4) Content by (b) (4) Assay sent on November 22, 2016.
- d. Request for data on Study NN7999-3639 and Study NN7999-3774 on December 4, 2016.
 - a. Request for benefit-risk analysis, data on PEG exposure in human versus animals, potential risk-mitigation strategies, and data for the Risk Management Plan sent on December 5, 2016.

No further discussion in the teleconference.

- 5. Any new information requests to be communicated.

Clinical:

- a. Please provide the maximum duration (in years) of exposure to REBINYN for the subjects receiving the study drug from each trial.
- b. Please clarify if any baseline or subsequent detailed neurologic exams were performed in the trial subjects.
- c. In the Pediatric Study-3774, please provide the dose subjects received throughout this pediatric study in tabulated form with justifications for increases in dosing regimen.
- d. Please also provide a separate list of subjects with their subject ID who received the following median and mean doses: 40-50 IU/kg; 50-60 IU/kg; 60-70IU/kg; 70-80 IU/kg; and >80IU/kg. Please provide a detailed report including the Annualized Bleeding Rate (ABR) for each of the subjects who received a mean or median dose of >80 IU/kg.

Additional discussion:

Novo Nordisk provided additional clarification on the dosage and stated they will submit this information as an amendment to the application. In response to 5b, Novo Nordisk stated that exams were done at baseline and at visit intervals and were included in the CRF. They stated they will provide the location of this data in the response to the IR. In response to 5d, Novo Nordisk stated that there was no change in dose escalation or frequency, except one subject who received 80 IU/kg every 2 weeks. FDA requested that all of the requested information will be sent as an amendment to the BLA.

6. Tentative date for the late-cycle meeting is Tuesday, February 14, 2017. The meeting package will be delivered on or before February 2, 2017.

Not discussed in the teleconference.

7. Updates regarding plans for the AC meeting – internal discussion is on-going for a decision to present your application.

Additional discussion:

FDA stated that the application is still being evaluated for presentation to an advisory committee meeting.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates. The action due date for your application is June 3, 2017.

Additional discussion:

FDA stated that internal discussion is on-going with the Office of Orphan Product and an update will be provided to Novo Nordisk during the review of the application.

End