Food and Drug Administration
Center for Biologics Evaluation and Review

SUMMARY MINUTES
115th Meeting of the BLOOD PRODUCTS ADVISORY COMMITTEE

April 4, 2017
Thomas Douglas Conference Center
10000 New Hampshire Avenue, Silver Spring, MD 20903

Committee Members
Sridhar V. Basavaraju, M.D., FACEP
Meera B. Chitlur, M.D.
Michael DeVan, M.D., F.C.A.P., CDR MC USN
Miguel Escobar, M.D. #
John B. Holcomb, M.D., F.A.C.S. #
Susan F. Leitman, M.D.
Norma B. Lerner, M.D., M.P.H.
Thomas Ortel, M.D., Ph.D.
Margaret V. Ragni, M.D., M.P.H.
Robert J. Rees, MHA, MT (ASCP)
Sonja Sandberg, SB., Ph.D.
Christopher Stowell, M.D., Ph.D. (Chair)
Kathleen Sullivan, M.D., Ph.D. #

Temporary Voting Members
Steven T. DeKosky, M.D., FACP, FANA, FAAN +
Michael Dobbs, M.D., MHCM
Susan Elmore, MS, DVM, DACVP, DABT
Robert H. Garman, DVM
Maria Lehtinen, Ph.D. (Non-Voting member)
Laura Manuelidis, M.D.
Chiadikaobi U. Onyike, M.D., MHS
Roger J. Packer, M.D.
Kevin Shapiro, M.D., Ph.D.

Designated Federal Official
LCDR Bryan Emery, B.S.N. USPHS

FDA Participants
Wilson Bryan, M.D.
Chava Kimchi-Sarfaty, Ph.D.
Becky Robinson-Zeigler, Ph.D.
Megha Kaushal, M.D.
Jennifer Scharpf, M.P.H.

Guest Speaker
Maria Lehtinen, Ph.D.

Acting Industry Representative
Roger Dodd, M.D.

Acting Consumer Representative
Judith Baker, DrPH., MHSA

Patient Representative
Christopher Templin

Committee Management Specialists
Joanne Lipkind
Rosanna Harvey

Did not attend
+ Attended by phone

These summary minutes for the April 4, 2017 meeting of the Blood Products Advisory Committee were approved on 10/12/2017.

I certify that I participated in the April 4, 2017, meeting of the Blood Products Advisory Committee and that these minutes accurately reflect what transpired.

/Signed/
Bryan Emery, LCDR
Designated Federal Official

/Signed/
Christopher P. Stowell., M.D., Ph.D.,
Chair

The Chair, Dr. Christopher Stowell, called the 115th meeting of the Blood Products Advisory Committee (BPAC) to order at 8:30 a.m. EST on April 4, 2017. The meeting was held in an open session. The Chair invited the members, temporary members, and participants seated at the table to introduce themselves. The Designated Federal Official (DFO) LCDR Bryan Emery made administrative remarks and read into the official record the Conflicts of Interest Statement pertaining to the meeting participants. There were no waivers issued for the conflicts of interest for this meeting. After the Conflicts of Interest Statement was read for the public record by the DFO, the FDA and non-FDA speaker presentations began.

QUICK SUMMARY

Topic I: Recombinant Human Coagulation Factor IX, GlycoPEGylated

FDA sought the advice of the Blood Products Advisory Committee on Recombinant Human Coagulation Factor IX GlycoPEGylated, specifically regarding the observation that following repeated doses of N9-GP, PEG accumulation was found in the choroid plexus of animals in the nonclinical studies.

Dr. Wilson Bryan from the Food and Drug Administration (FDA) first introduced the topic and provided the committee with the Biologics License Application (BLA) overview of Coagulation Factor IX (Recombinant), GlycoPEGylated [N9-GP] STN 125611/0 and the discussion questions to the committee, emphasizing to focus on Factor IX GlycoPEGylated and not to discuss other licensed products that carry PEG. This was followed by presentations introducing the bleeding disorder Hemophilia B, caused by a deficiency of the blood clotting Factor IX, clinical efficacy of the drug, clinical safety data, benefit-risk of N9-GP by Shawn Hoskin, Dr. Stephanie Seremetis, Lars Wichmann Madsen and Dr. Guy Young of Novo Nordisk. Dr. Chava Kimchi-Sarfaty from the Food and Drug Administration (FDA) gave a brief introduction of the product and its manufacturing process. Dr. Becky Robinson-Zeigler of the FDA spoke on the non-clinical issues and reviewed the non-clinical data from the N9-GP (BLA) and PEG-only toxicity studies. Next, Dr. Megha Kaushal of the (FDA) provided a clinical overview for N9-GP.

After a break, the committee reconvened in open session and asked clarifying questions concerning the FDA and NOVO NORDISK presentations.

Questions for Novo Nordisk and FDA:

1. Two Committee members asked if there are drugs that are similar to this N9-GP that also accumulate in the choroid plexus and if so, if there is any known

implication of that, and if there is any study assessing whether PEG or PEGylated products increase secretion of protein into the CSF.

2. Another Committee member asked NOVO NORDISK what the monitoring would be for neurologic and neurocognitive issues in pediatric patients moving forward. He was also concerned with achieving the appropriate level of post-marketing follow-up for children.

3. Several questions were asked about specific ages of patients, how the follow-up would be performed, whether the monitoring will be formalized, and whether pediatric patients should be restricted to receiving treatment with N9-GP within hemophilia treatment centers.

4. Several questions were asked about how the applicant intends to define and monitor for developmental delays, specifically regarding what components of the neurological examination in the findings would be most relevant and sensitive. The issue that potential neurocognitive deficits may be subtle and difficult to detect was raised, which highlights the need to incorporate standardized clinical testing instruments and further supports the potential rationale of carrying out follow-up at hemophilia treatment centers.

5. An additional question regarding the age of the pediatric patients was raised, specifically about the reason for treating children who are less than 4 years old and especially less than 2 years old, given the fact (per the Committee member) that the PEGylation does not keep the half-life of the factor IX intact.

6. Several Committee members asked about the tissues that were examined and had specific technical questions about the pre-clinical studies, including: where in the brain the PEG accumulation was seen and how extensively the brain was sampled (e.g., number of sections, which neuroanatomic regions were tested, and whether the immunostains for PEG were performed on every brain section or just selectively for the choroid plexus). A specific question referred to staining in the blood: was PEG detectable within monocytes in the blood? Moreover, Committee members asked whether it was technically feasible to distinguish free PEG from PEG-FIX conjugate protein. Moreover, were the eyes of animals examined in any way? Was the pituitary tested for the presence of PEG? Was there any quantification of PEG? Did the rodents or primates have a reduction in brain weight?

7. A Committee member inquired about the reason the animal experiments were a few weeks, and not several years, in duration, and whether the duration was related to neutralizing antibodies.

8. A Committee member inquired about the proposed indication for the drug and the anticipated number of patients that will be treated with this drug.

When the questions from the committee concluded, Dr. Maria Lehtinen, an FDA-invited speaker from Boston's Children's Hospital provided a presentation on the development and biologic functions of the choroid plexus-cerebrospinal fluid system and relevant ongoing research.

Following the questions for the speaker, the Chair read the Open Public Hearing statement at the beginning of the Open Public Hearing. Three oral presentations were made during the Open Public Hearing. Mark Skinner, a private citizen, was first to speak about how he lived with severe hemophilia. Wayne Cook, president of the Coalition for Hemophilia B, spoke about his perspective of what is going on in the Hemophilia B community. Ben Shuldiner, another private citizen, spoke last about being a little older in age and having to live with severe factor IX hemophilia.

After the Open Public Hearing presentations, the committee broke for lunch.

After the lunch break, Novo Nordisk displayed several additional slides to further answer the questions raised during the morning session. The committee discussion began in open session and the Committee considered the following discussion questions. A summary of the key responses and considerations are as follows:

1. **Please discuss the clinical significance, if any, of the preclinical findings.**
    - The comments from the first discussant are based on peer reviews of 5-6 PEGylated compounds. Each compound studied had greater amounts of PEG in the choroid plexus than the compound being discussed today. She also commented that to assess if PEG is present in the choroid plexus epithelial cells, one simply can't just look for vacuoles; one really needs to determine the presence of PEG by immunohistochemistry and electron microscopy (EM). She also stated that a sole point of concern is the accumulation of PEG within these epithelial cells, and there is no insight from the literature as to what that means from a safety point. She suggested to use the Society of Toxicologic Pathology which is a group that would be more familiar with these type of studies, using a standardized grading scheme which might allow for these studies to be compared more accurately.
    - The second discussant added that more can be done in terms of the following issues: First, PEG accumulation in the choroid plexus is a concern even though at present there are no obvious toxic effects. The discussant highlighted that PEG also accumulates in the eye, which should be further examined. The second issue was regarding the ultrastructural studies: more needs to be studied concerning the impacts of chronic PEG exposure in the older brain, using an older animal. This committee member also suggested performing proteomic studies specifically to examine if the composition of CSF is altered in the setting of chronic intravenous PEG administration. He mentioned that one may consider the choroid plexus as being the seventh CVO (circumventricular organ). It was noted that various reasons can give rise to vacuoles, and one cannot definitively determine their cause. Finally the committee member noted that the animal studies should include a greater number of sections throughout the brain to gain a comprehensive understanding of anatomical predilections of PEG accumulation.
    - Two members of the Committee commented that the existing preclinical studies are relatively short duration and have not completely addressed all the relevant questions.
    - A member of the Committee focused on concerns about the alteration of CSF fluid dynamics, perhaps by transcytosis of PEG, and noted that the accumulation of PEG may affect the concentrations of various CSF components and lead to changes to CSF pressure. His major concern was for

patients in the 0-6 month age range, in addition to some unease about patients 6 months to 2 years in age and the elderly, expecting that the impact of choroid plexus dysfunction or accumulation of foreign material in the CSF would be most impactful/clinically apparent in these age groups. He suggested long-term monitoring plans that focus on periodic assessment of executive function and global aspects of neurocognitive development.

- An additional member of the Committee expressed concern about the use of N9-GP in young children and older adults because the choroid plexus function changes during development. Retained PEG in the choroid plexus cells and CSF could hypothetically vary during different stages of life. The applicant's sample size to assess the neurologic and development effects of choroid plexus PEG accumulation is too small, particularly in the two populations of young children and elderly. He added that the neurologic and developmental evaluations to date appear to have been broadly defined and not very sensitive to subtle changes.
- Another concern focused on the removal of PEG and the half-life of retained PEG that may be studied by PET signal to the PEG, MR spectroscopy. This Committee member opposed the use of lumbar puncture to obtain spinal fluid.

2. **Please discuss the nature and level of your concerns, if any, regarding the safety of the product in different age populations: e.g., from birth to < 6 years, 6 years to < 12 years, 12 years to 17 years, adults, and older adults.**
    - The Chair made a comment suggesting that the FDA would like to get an opinion from the committee, if these finding are alarming, not concerning, or some place in between, and if the level of these concerns depend upon the age group that is being discussed.
    - The discussant reiterated that we should learn from other PEG compounds.
    - Another Committee member summarized the Committee opinions suggesting that there are safety concerns only in the particularly vulnerable populations, but no specific concerns for 2 years and higher, up to 65 years; an informed consent was suggested to accompany the administration of the drug. Another Committee member supported giving the drug for some length of time, rather than being limited by a mandated age cutoff.
    - Extensive pre-clinical studies, rather than invasive tests, were suggested as a "postmarketing mechanism."

3. **Considering the findings from the toxicology and clinical studies, please discuss whether the data provide sufficient evidence of the safety of the product for: (1) Intermittent use (i.e., for perioperative management and control of bleeding episodes); (2) Chronic, and possibly life-long, use (i.e., routine prophylaxis).**
    - The first discussant for this question noted the absence of any indication that taking the drug chronically or intermittently poses any increased danger, and therefore opposed using age cutoffs, especially if those arbitrary cutoffs will prevent people who need the medication from obtaining it. He expressed that it is very important to have a robust post-marketing surveillance program.
    - The second discussant preferred the idea of a very systematic user assessment approach. The discussant recommended that there be one approach for the chronic users of the product, and a different approach for intermittent users.

- Several Committee members indicated that they do not need further evidence of the safety of intermittent use.

4. **Please discuss any clinical or laboratory assessments (including, but not limited to, assessments of neurologic function), either short-term or long-term, that you would recommend to help ensure the safety of patients (or study subjects) who receive the product.**
    - A discussant expressed concern regarding the small size of the trial.
    - One member suggested that a neuropsychologist create post-marketing questionnaires in order to best keep track of patient data, including data from vulnerable populations.
    - A Committee member suggested investigating further the CSF from animals and specifically to perform proteomics studies. On the other hand, another committee member had concerns about the comparison between the animal models and human.

5. **Please discuss your recommendations, if any, for additional preclinical or clinical studies, either pre-marketing or post-marketing, to support the safety of the product. For example, please discuss the clinical examinations and laboratory studies, the duration of follow-up, the inclusion or exclusion of specific age groups, and safety endpoints that you would recommend for any subsequent clinical trials or post-marketing studies.**
    - One member commented that safety data from the same molecular weight PEG products should also be studied.
    - One member also asked if the product or similar product has been given to pregnant women and another asked if PEG crosses the placenta, since the developing brain is anticipated to be most vulnerable.
    - Another member suggested following cognitive outcomes in the post-marketing data, probably requiring more neurocognitive data in pediatrics with some validated standardized tests.
    - A discussant suggested that if there is clinical necessity for other reasons to test the CSF or perform MRI, then the treatment center should focus also on the effect of PEG accumulation.

After the discussion questions were completed, the committee took a 15-minute break.

Committee Updates:

The committee reconvened in open session to listen to a committee update presentation. Jennifer Scharpf of the FDA presented a summary of responses to the FDA docket, FDA-2016-N-1502 titled,: "Blood Donor Deferral Policy for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products."

An Open Public Hearing was announced after the Committee update presentation. Two oral presentations were made during the Open Public Hearing. Sharon Carayiannis, the Director of Regulatory Affairs at the AABB gave a combined statement for AABB, America's Blood Centers and the American Red Cross. Dr. David Hardy, Senior Director of Evidence Based Practice at Whitman Walker Health concluded with a statement about a possible 4 point plan to test the adequacy of an improved individual risk-based donor questionnaire. No other presentations were made during the Open Public Hearing

When the Open Public Hearing was completed, the Chair, Dr. Christopher Stowell, adjourned the meeting at approximately 3.45 p.m.

Additional information and details may be obtained from the transcript and the recording of the webcast of the meeting that may be viewed at:

https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm554807.htm