UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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115TH MEETING OF THE BLOOD PRODUCTS ADVISORY COMMITTEE

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April 4, 2017
8:30 a.m.

Tommy Douglas Conference Center
10000 New Hampshire Avenue
Silver Spring, MD 20993

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MEETING

(8:31 a.m.)

DR. STOWELL: Good morning, everyone. Welcome to the 115th meeting of BPAC. We have an interesting couple days in store for us, so thanks to all the regular members of the Committee who have come, as well as the various invited members, experts, and so forth who have come to contribute to this meeting.

I'd like to begin by just introducing ourselves, go around the table here, and I'll start with myself. I'm, as I said, Christopher Stowell. I'm the Director of the Blood Transfusion Service at Mass General.

And maybe we'll start down with you, Dr. Chitlur, and then just come around the table. Yeah, press the red button to speak in.

DR. CHITLUR: Sorry. I'm Meera Chitlur from Children's Hospital of Michigan in Detroit. I'm a pediatric hematologist and the Director of the Hemophilia Treatment Center there.

DR. ORTEL: Hi, Tom Ortel from Duke. I'm Chief of Hematology there.

DR. BASAVARAJU: Sridhar Basavaraju, CDC Office of Blood, Organ and Other Tissue Safety.

DR. DeVAN: Hi, I'm Mike DeVan. I'm at Walter Reed, and I'm the Director of Transfusion Services.

DR. BAKER: Judith Baker with the Center for Inherited

Blood Disorders in Orange County, California, and the University of California, Los Angeles.

DR. LERNER: Norma Lerner, pediatric hematologist at the Blood Division of NHLBI/NIH.

DR. ELMORE: Susan Elmore, National Toxicology Program, NIEHS, a veterinarian toxicologic pathologist.

LCDR EMERY: I'm Bryan Emery. I'm the DFO for this meeting, and next will be Dr. Shapiro.

DR. SHAPIRO: I'm Kevin Shapiro. I'm a child neurologist at the University of California, San Francisco.

MR. TEMPLIN: Christopher Templin, a person with hemophilia B, a father of a daughter with hemophilia B.

DR. PACKER: Roger Packer. I'm a child neurologist. I'm Senior Vice President of Neuroscience and Behavioral Medicine at the Children's National Health Systems in Washington, D.C.

DR. GARMAN: Hi, I'm Bob Garman. I'm a veterinary pathologist specializing in neuropathology.

MR. REES: Good morning, I'm Robert Rees. I'm the manager of the New Jersey Department of Health Blood Bank Regulatory Program.

DR. DODD: I'm Roger Dodd. I'm the Industry Rep replacing for today Toby Simon. I was head of research and development for the American Red Cross, now retired but still doing some work for the Red Cross.

DR. LEHTINEN: Hi, I'm Maria Lehtinen. I'm an assistant

professor at Harvard Medical School and my research lab. I'm a developmental neurobiologist at Boston Children's Hospital.

DR. STOWELL: And I believe we have one member who will be calling in. I don't know if he's done so, so far, but that would be Dr. DeKosky.

(Off microphone comment.)

DR. STOWELL: Okay, all right. The other thing that I'd like to point out to you folks today at the beginning of the meeting is that these things do not work if your face is like 6 inches away from them. The microphone has really got to be less than 6 inches from your face; otherwise, it looks great, but it doesn't amplify.

LCDR EMERY: Good morning. I'm Bryan Emery, the Designated Federal Official for today's meeting of the Blood Products Advisory Committee.

Mrs. Joanne Lipkind, Mrs. Denise Royster, and Mrs. Rosanna Harvey are the Committee Management Specialists, and they can assist you with any needs at the tables in the back.

I would like to welcome all of you to the 115th meeting of the Advisory Committee held in the Thomas Douglas Conference Center. Dr. Christopher Stowell is the Blood Products Advisory Committee chair. The CBER press/media contact is Lyndsay Meyer, and Tom Bowman will be the transcriber.

I would like to request that everyone please check your cell phones and pagers to make sure they're turned off or in

silent mode.

Please also remember to speak directly into the microphone at all times and please identify yourself; it is helpful for the public, people attending by webcast and for the transcriber, for the members around the table and the audience.

Coffee, drinks, and snacks are in the cafeteria for the public, the general public, and that's out the door and off into the right direction. For the Committee Panel members, the lunches will be delivered to a break-off room which is right through this door, Room 9225, and the coffee and your refreshments are in there.

All committee topic and update discussion needs to be done in a public forum and not in groups during breaks. The FDA and public needs your advice and expertise.

The public and industry must stay behind the stanchions and in the audience area. Please do not enter into the FDA or BPAC committee table area. Please wait until the Open Public Hearing designated time to make any remarks using the center aisle microphone.

Now I'd like to read into the record the Conflict of Interest Statement for this meeting.

Good morning. I welcome you to the Blood Products Advisory Committee meeting. The Food and Drug Administration is convening today, April 4th, 2017, for the 115th meeting of the Blood Products Advisory Committee under the authority of

the Federal Advisory Committee Act of 1972.

On April 5th, in open session, the Committee will hear overview presentations on the research programs in the Laboratory of Emerging Pathogens in the Division of Emerging Transfusion-Transmitted Diseases, Office of Blood Research and Review, Center for Biologics Evaluation and Research

At the conclusion of the open session, the meeting will be closed to permit discussion where disclosure would constitute an unwarranted invasion of personal privacy in accordance with 5 U.S.C. During the closed session, the Committee will discuss the research progress made by staff involved in the intramural research programs and make recommendations regarding their personnel actions and staffing decisions.

The following information on the status of the Advisory Committee's compliance with Federal ethics and conflict of interest laws including, but not limited to, 18 U.S. Code 208 is being provided to participants at this meeting and to the public. This conflict of interest statement will be available for review at the registration table.

With the exception of the Industry Representative, all participants of the Committee are special Government employees or regular Federal employees from other agencies and are subject to federal conflict of interest laws and regulations. Related to the discussions at this meeting for Topic I, members and consultants of this Committee have been screened for

potential financial conflict of interest of their own, as well as imputed to them, including those of their spouse and minor children and, for the purposes of 18 U.S. Code 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents/royalties; and primary employment.

FDA has determined that all members of the Advisory Committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S. Code 208, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

However, based on today's agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued under 18 U.S. Code 208.

Dr. Roger Dodd is currently serving as the Acting Industry Representative to this Committee. Dr. Dodd is employed by the American Red Cross, and representatives act on behalf of all related industry and bring general industry perspective to the Committee. Industry representatives are not special government employees and do not vote and do not participate in the closed sessions.

Dr. Judith Baker is serving as a temporary Consumer Representative to this Committee at this meeting. She is appointed as a special Government employee and a Temporary Voting Member who will bring consumer perspective to the Committee. Consumer representatives are screened for their financial conflicts of interest and cleared prior to their participation.

At this meeting there will be regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer or with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals are not screened by the FDA for conflicts of interest.

FDA encourages all other participants to advise the Committee of any financial relationships that you may have with any firms, its products, and if known, its direct competitors.

We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

This concludes my reading of the Conflict of Interest

statement for the public record.

DR. STOWELL: Thank you, Bryan.

The first topic for consideration, which will take us through this afternoon, has to do with a PEGylated recombinant factor IX, which has been developed by Novo Nordisk, and to introduce this topic will be, from the FDA, Dr. Wilson Bryan. So Dr. Bryan.

DR. BRYAN: Good morning. I'm Wilson Bryan. I'm Director of the Office of Tissues and Advanced Therapies in the FDA Center for Biologics Evaluation and Research.

Novo Nordisk has submitted this Biologics License Application, or BLA, to bring a new therapy available for patients with hemophilia B. This therapy is Coagulation Factor IX (Recombinant), glycoPEGylated, which we will refer to as N9-GP.

The Office of Tissues and Advanced Therapies, or OTAT, appreciates that hemophilia B is a serious disease, and we need new and improved therapies to benefit patients. We also appreciate that this is a rare disease which limits the availability of data to address issues of safety and effectiveness.

OTAT is bringing this particular BLA to this Committee because of a safety concern that we think warrants public discussion. Particularly, we are concerned about a finding in preclinical studies related to the accumulation of polyethylene

glycol, or PEG, in the choroid plexus of animals exposed to N9-GP.

I should mention that among the FDA review team there are a variety of levels of concern about this issue. Some of us are extremely concerned, some of us not so concerned, and a variety of intermediate levels of concern. In this situation, we think that it's very important to have a public discussion and to get perspectives from the individuals on this Committee who have a variety of relevant expertise.

As will be obvious from the questions that we're posing, we are particularly concerned about the potential for neurologic or cognitive risks associated with this product.

The first question that we're asking the Committee is to discuss the clinical significance, if any, of the preclinical findings.

Then we ask the Committee to discuss the nature and level of their concerns. And here, we're particularly interested in some populations, particularly children, who have developing brains, and the elderly, who may be neurologically vulnerable.

Next, we ask the Committee to consider the risks associated with intermittent administration of the product versus chronic administration of the product, even lifelong administration of the product.

The last two questions: The next one focuses on whether there are any clinical or laboratory assessments that might be

useful to protect the safety of the study subjects or the safety of patients who receive this product. And then the last question, whether there are additional studies, and those could be preclinical studies or clinical studies, either premarketing or postmarket, are there any additional studies that would help us to consider this safety issue.

Now, I should point out that we're not asking this Committee to consider all aspects of the BLA; particularly, we have not asked for a discussion of the effectiveness of the product, we don't have a voting question to get the overall benefits versus overall risks of the product, and we're not asking the Committee to particularly focus on safety issues other than this particular safety issue regarding PEG accumulation in the choroid plexus.

We also recognize that there are many marketed products that are glycoPEGylated. Because of differences between those products and among these glycoPEGylated products, including the molecular weight of the PEG, the pharmacokinetics, the route of administration, the duration of administration, because of these variety of differences, the relevance of the preclinical and clinical and postmarketing experience of these other products to the Novo Nordisk product is unclear, and we don't think that we can have a fair and balanced discussion of all of these other PEGylated products in the context of this Committee. So we're asking the Committee to focus really on

one issue, which is the safety issue related to PEG accumulation in the choroid plexus.

I want to thank Dr. Lehtinen, who has kindly agreed to give a presentation on the function of the choroid plexus. I want to thank all the members of the Committee for taking their time to consider this issue and help us out in thinking about this BLA. I particularly want to thank, also, the members of the FDA review team and the Advisory Committee staff who have worked tirelessly to prepare for this meeting.

OTAT appreciates the folks who will be participating in the Open Public Hearing today. We think it's very important that we hear from patients and patient advocates regarding these issues.

We also recognize that there are some folks who are very interested, patients and physicians who are very interested in this product who were not able to be here today and have sent comments to the docket, and we look at those very carefully.

And last but certainly not least, I want to recognize that developing a new therapy for the benefit of patients is a challenging enterprise that requires courage and dedication, and we very much appreciate the efforts of Novo Nordisk in bringing this product this far in development.

So I'll stop there and turn it back over to Dr. Stowell.

DR. STOWELL: Thank you, Dr. Bryan.

The next set of presentations will be from Novo Nordisk,

and the first of the presenters will be Shawn Hoskin.

MR. HOSKIN: Good morning, Mr. Chairman, members of the Committee, FDA colleagues, ladies and gentlemen. My name is Shawn Hoskin, and I am the Senior Director of Regulatory Affairs for Novo Nordisk.

Novo Nordisk is pleased to be here today to review our coagulation factor IX glycoPEGylated hemophilia medicine, also referred to as nonacog beta pegol or N9-GP, for short.

Hemophilia B is a bleeding disorder caused by a deficiency in factor IX, a protein that regulates clotting. It is an ultra-rare disorder. In the U.S. there are approximately 1,000 patients diagnosed with severe hemophilia B.

The likelihood and severity of bleeding episodes are generally inversely related to the amount of factor IX, with low factor levels having the highest risk. Therefore, treatment of hemophilia B is focused on replacing factor IX historically at levels above 1% factor IX activity.

N9-GP is a new biological treatment that is specifically designed to provide higher levels of factor IX for patients. With N9-GP, it is possible for adults and adolescents to maintain factor IX activity levels in the non-hemophilia range for most of the dosing cycle with a once-weekly injection.

For children, all hemophilia products have more rapid clearance. Nevertheless, N9-GP is able to sustain factor IX levels substantially above what can be achieved with current

products with the same simple once-weekly dosing regimen.

Our proposed indication is for use in adults and children with hemophilia B for control and prevention of bleeding episodes, perioperative management, and routine prophylaxis.

Taking a closer look at the molecule, N9-GP is a recombinant factor IX that uses PEGylation to extend the half-life of the molecule. PEGylation is a well-established technology with an accepted safety profile that has been used to prolong the half-life of many marketed chronic use products. Today, you're being asked to consider the clinical significance, if any, of nonclinical findings related to PEG accumulation in clearance from tissues, including the choroid plexus.

Novo Nordisk has conducted a range of acute and chronic animal studies, which we will elaborate on later in the presentation. These studies will provide data to address the questions raised by FDA.

In summary, no adverse findings were observed at doses up to 42 times the human clinical dose, and specifically, no adverse effects related to PEG were reported in nonclinical studies. However, since N9-GP is a novel therapy, Novo Nordisk will continue to monitor its long-term safety, including potential risks associated with chronic exposure to a PEGylated product.

To briefly outline our clinical development program, we

conducted five clinical trials with N9-GP, including Phase III trials for prophylaxis and episodic treatment in children and adults, treatment in surgery, and extensions to collect additional safety data.

Our trials demonstrate that the higher factor IX levels achieved with N9-GP lead to better outcomes for patients, including a reduced annualized bleeding rate, or ABR, a reduction in the number of spontaneous bleeds, and resolution of target joints. Target joints remain the most important consequence of inadequate treatment of hemophilia.

The overall safety profile of N9-GP is consistent with that of current hemophilia B treatments. And the once-weekly dosing reduces the number of infusions and the overall administration burden on patients.

I'll now review our agenda and presenters for this morning. Dr. Guy Young will discuss the unmet public health need for sustained factor IX activity levels in the normal or non-hemophilia range. Dr. Stephanie Seremetis will review clinical efficacy. Dr. Lars Madsen will address long-term PEG safety. And Dr. Seremetis will present the clinical safety data. Lastly, Dr. Young will share his perspective on the benefit-risk of N9-GP.

We are also joined by additional experts. They or their institutions have been compensated for their time and travel expenses.

I'll now invite Dr. Young to the podium.

DR. YOUNG: Good morning. My name is Guy Young. I'm the Director of the Hemostasis and Thrombosis Center at Children's Hospital Los Angeles and a Professor of Pediatrics at the University of Southern California Keck School of Medicine. It is my pleasure to be here with you to discuss the unmet needs in patients with hemophilia B.

Hemophilia B is a serious and potentially life-threatening bleeding disorder. The most common manifestation of the disorder is bleeding into the joints. Bleeding begins at a very early age and can reoccur throughout a patient's life. When inadequately treated, hemophilia B can lead to recurrent bleeds and eventually permanent joint damage and reduced quality of life.

The severity of bleeding in hemophilia generally correlates with factor IX activity levels. Patients with severe hemophilia experience bleeds, often without a cause, also referred to as spontaneous bleeds. Patients with mild and moderate hemophilia can also experience spontaneous bleeds but more often bleed as a result of surgery or trauma.

A single bleed can initiate a cycle of recurrent joint bleeds. A joint which experiences repeated bleeding is referred to as a target joint, and symptoms of target joint formation include chronic pain and reduced range of motion, typically become evident in adolescence and progress through

adulthood, as repeated bleeding episodes prevent healing. Ultimately, this can lead to irreversible joint damage, and this risk prompts the use of prophylaxis therapy to prevent or delay damage.

Historically, patients on prophylaxis have been treated to target a trough of 1% factor activity. But increasing evidence suggests that achieving this level does not eliminate bleeding. In addition, asymptomatic bleeds may occur and go untreated. This means patients are still at risk for joint damage even with troughs around 1%.

For example, two studies that followed children treated to troughs around 1% with prophylaxis showed soft tissue changes in and around their joints by MRI even though they were unaware of any joint bleeding. These changes have been seen in ankles, knees, and elbows as early as age 6. Knowing this, patients and families often limit their normal activities to avoid both silent and overt bleeds. But if targeting to greater than 1% with prophylaxis isn't effective, then what is the right target?

In a U.S. study, the CDC evaluated the association between joint bleeds and factor IX levels in mild and moderate hemophilia B patients receiving on-demand treatment. Here are regression models of the data by age group. Overall, the models predict about one joint bleed every 2 years in patients with factor levels at 15%. While current data do not identify

the precise factor level above 1% of target during prophylaxis, the hemophilia community is discussing new treatment goals surrounding higher levels. But treatment burden cannot be forgotten. Frequent intravenous injections are needed to provide therapy, and these can be burdensome. Standard products require two to three injections per week to maintain levels to 1%.

In addition to time, treatment also requires venous access. In some patients, like children, just hitting a vein may be difficult, and frequent needle sticks can cause pain and anxiety. Thus, there is an unmet medical need for a therapy which reduces treatment burden while achieving higher factor levels. By sustaining higher factor levels, it may be possible to reduce the risk for bleeding, prevent the development of target joints or the progression of joint disease in patients with preexisting target joints.

So what might having normal factor IX levels mean to a patient? It could mean living without a constant fear of bleeding. It could mean being active instead of avoiding normal activities. It could mean being able to go to work or participate in sports or, for children, just to go out and play. It could mean living a normal life.

To summarize, what we need in hemophilia B are safe and efficacious products that also reduce the burden of treatment and disease. This means having products that maintain higher

factor levels with fewer injections.

Thank you for your attention, and I will now turn the presentation over to Dr. Stephanie Seremetis.

DR. SEREMETIS: Thank you, Dr. Young.

My name is Stephanie Seremetis, and I am the Chief Medical Officer for Biopharmaceuticals at Novo Nordisk and responsible for the N9-GP clinical program.

Prior to joining Novo Nordisk, I was director of one of the largest hemophilia centers in the U.S. and treated patients with hemophilia for more than 20 years. Our clinical program was designed to test the hypothesis that maintaining higher factor IX levels may help to reduce bleeding and resolve target joints. The program followed published guidelines for hemophilia B from EMA as well as FDA precedent and feedback. Once weekly 40 international units per kilogram dose was selected to achieve higher levels than current products for children, adolescents, and adults. This dose should achieve factor IX levels in the non-hemophilia range of about 40% for more than a week.

For comparison purposes, the 10 international unit per kilogram dose was expected to provide factor IX levels analogous to those achievable with current factor IX products. We conducted five clinical trials in patients with hemophilia B. We will focus on three of them: adults/adolescents, children, and surgery.

Let's review the common endpoints. The primary endpoint was inhibitory antibody formation expressed as a limit of one inhibitor in 50 previously treated patients. We had none. Furthermore, we met the predefined hierarchical endpoints that allowed us to complete the planned statistical analysis. Hemostatic efficacy was 92.2%, the annualized bleed rate was 2.51 bleeds per year, below the pre-specified threshold for the 40 IU per kilogram dose.

I will now discuss key points from the trial in adolescent and adult patients. For the prophylactic part of this trial, patients were blinded and randomized to one of two dosing regimens: either 40 international units per kilogram or 10 international units per kilogram once weekly. The 40 IU per kilogram dose allows us to test the hypothesis that keeping patients in the normal non-hemophilia range is beneficial. In comparison, the 10 IU per kilogram dose acts as an active control, keeping patients in the moderate or low-mild range with trough levels of 4 to 8% factor activity.

The data we'll present support our hypothesis that keeping factor IX levels in a non-hemophilia range translates into improvements across all efficacy measures.

Moving now to the results, looking first at the PK data, we see that the 40 IU per kilogram dose, as predicted, keeps most adult patients in the non-hemophilia range above 40% for most of the week. In comparison, the 10 IU per kilogram dose

provides fourfold lower factor IX levels, similar to today's treatment standards. Importantly, these are head-to-head randomized data.

On average, all of the 40 IU per kilogram dose patients were above 31% for the entire treatment week and are further maintained in the non-hemophilia range for almost five ½ days each week. These PK results predict the efficacy results that we will now show you. You will see that today's standard treatment, based on low factor IX troughs, are no longer sufficient when now we have the opportunity to sustain normal levels with N9-GP.

Let's look at how higher factor levels impact the rate of bleeding.

In the blinded randomized trial, 40 international units per kilogram once weekly in adult and adolescent patients resulted in an estimated mean annualized bleeding rate of 2.51, which was superior to the 10 IU per kilogram control arm with a p-value of 0.03. This result is reinforced by the median ABR of 1.04 with 40 international units per kilogram.

Now, let's move on to target joints, the most important complication of inadequate treatment of hemophilia.

Here we are looking at patients who entered the trial with preexisting target joints. As defined by the International Society of Thrombosis and Hemostasis, target joints are very damaged joints that bleed three or more times in a 6-month

period. Forty IU per kilogram was better than 10 IU per kilogram for target joints. At the end of the trial, 67% of the 15 patients with preexisting target joints receiving 40 IU per kilogram reported no target joint bleeding requiring treatment. In comparison, only 8%, that is 1 of 13 patients, treated to lower factor IX levels, were free of target joint bleeds.

Importantly, when looking at each joint in the group randomized to receive 40 IU per kilogram, 90% of the 20 baseline target joints were no longer considered a target joint compared to only 58% in the 10 IU arm. These data show that in most patients we can prevent target joint bleeds with higher factor IX levels.

How do these results translate to quality of life? Using the EQ-5D VAS scale, which measures patients' overall health today, we see that only 40 IU per kilogram results in an improvement in patients' quality of life from baseline to the end of the trial. In comparison, we see no change in the 10 IU per kilogram arm.

Turning to our pediatric study, this trial was an open-label confirmatory trial evaluating safety, efficacy, and pharmacokinetics of N9-GP in prophylaxis therapy in previously treated hemophilia B children up to 12 years of age. The main trial lasted 52 weeks with the option to continue N9-GP in the extension phase. Overall N9-GP dose at 40 IU per kilogram once

weekly maintains higher factor IX levels than typical factor IX therapy can. N9-GP is able to keep these children above levels of 15% for those ages 0 to 6, and 19% for those ages 7 to 12 for the entire week. The pediatric patients had lower factor IX levels than the adults, since younger patients have more rapid clearance of factor IX.

Let's look at the clinical outcomes. As predicted by the high activity level, we saw a low annualized bleed rate in children regardless of age. Using a Poisson regression model, the estimated ABR was 1.44 bleeds per patient per year for the entire patient population.

By age, patients between the age of 0 and 6 had 0.87 bleeds per patient per year, and patients aged 7 to 12 had 1.88 bleeds per patient per year. These rates are lower than published for other factor IX products, supporting the hypothesis that higher factor IX levels can reduce the risk for bleeding.

Turning now to the surgery study, this was an open-label trial to assess efficacy and safety during major surgical procedures in patients greater than 12 years of age with hemophilia B. Thirteen patients were enrolled ranging in age from 15 to 56 years. On the day of surgery, all patients received a single 80 IU per kilogram dose administered 15 minutes to 4 hours prior to surgery. During the postoperative period, patients could receive up to two doses of 40 IU per

kilogram N9-GP. From Day 7 to 14, additional doses could be given.

All surgeries performed were elective and non-emergency. Nine of the 13 were for orthopedic surgery to address musculoskeletal deterioration, including knee, hip, ankle, and Achilles tendon repair. These highlight the importance of preventing overt joint bleeds and micro-bleeds that can lead to joint deterioration. The other four surgeries were for molar extractions and rectal surgery.

Let's look now at the results. The hemostatic effect of N9-GP was confirmed with a success rate of 100% in 13 surgeries. No patients required additional dosing during surgery. We also examined the post-surgical use of N9-GP.

The mean number of injections was two in the post-surgery 0 to 6-day period, and 1.5 in the post-surgery 7 to 13-day period. The mean accumulative dose of N9-GP injections was 3.8 in the post-surgery period to the end of the trial. This is an important consideration for treating physicians because unmodified factor IX therapies would require approximately 17 injections over 2 weeks to maintain World Federation of Hemophilia recommended factor levels during surgery.

To conclude our efficacy presentation, the N9-GP clinical program demonstrates the value of higher factor IX levels and the value of treating patients to the normal non-hemophilia range.

Across all endpoints, we see that the 40 IU per kilogram dose performs statistically and clinically better than the 10 IU per kilogram dose. The 10 IU dose represents factor IX levels and efficacy reported with today's available standard and extended half-life products.

Our trial has shown that these target levels are inadequate. With higher levels we see an improvement in both ABR and in target joints.

Forty IU per kilogram N9-GP is the only long-acting product that achieves sustained factor IX levels in the normal range without excessive and untested dosing.

I'll now turn the presentation over to Dr. Lars Madsen to present our PEG-related safety data.

DR. MADSEN: Thank you. I'm Lars Madsen, head of nonclinical development at Novo Nordisk. I'll now review our nonclinical study data focusing on the key questions related to long-term exposure to PEG. This includes PEG accumulation and clearance from tissues, including the choroid plexus. It also includes the significance of PEG presence.

We observed vacuoles microscopically in some tissues, both in animals dosed with N9-GP and in controls. And it is relevant to consider whether PEG may contribute to vacuole formation. Further, I'll provide context to assess the clinical significance of our nonclinical data. Let me begin by giving you some brief background on PEG, vacuoles, and the

choroid plexus.

PEG is used widely and supported by substantial nonclinical and clinical data. Multiple peer-reviewed publications conclude that PEG is inert and not associated with toxicity. However, vacuolations of cells is a finding observed in some animal studies using very high doses. This has been described as an adaptive response. When observed with 40-kDa PEG, the size used in N9-GP, vacuolation was often seen in macrophages and the choroid plexus. Yet, vacuoles have not been associated with cellular damage.

This published illustration shows the proposed mechanism for how a PEGylated protein is taken up and removed from a cell. First, the protein is taken up by fluid-phase pinocytosis and transported into the endosome and lysosome represented by numbers 1 and 2. Then the protein is metabolized, as shown by Step 3. Metabolic products, including PEG, are excreted from the cell back into the bloodstream, which is shown as 4. At high PEG concentrations, lysosomal vesicles may increase in size and become less visible as vacuoles.

So what are vacuoles, and how do we identify them in tissues? Vacuoles are normal cellular structures involved in endocytosis and exocytosis, which are physiological processes. Vacuoles can be observed using standard light microscopy. They are often found in excretory tissues and phagocytic cells, for

example, in lymph node, macrophages, as shown here from a control animal.

Vacuolation is defined as an increase in the number of size of vacuoles. Importantly, there are no data to suggest that vacuolation in itself is adverse.

In relation to vacuoles in 40-kDa PEG, the choroid plexus is of particular interest. It is a highly vascularized tissue situated in the ventricles of the brain. The choroid plexus is formed prior to birth and maintains production of the cerebral spinal fluid. It also acts as a filtration system as part of the blood-CSF barrier.

With this background information in mind, let's review the nonclinical data for N9-GP.

Novo Nordisk conducted six nonclinical toxicity studies. There were no PEG-related histopathological changes in any tissue after dosing with N9-GP in rats and monkeys. Also, we saw no vacuolation related to treatment with N9-GP.

Using additional sensitive techniques, PEG was detectable in vascularized tissues, including the choroid plexus. However, PEG was not detected in the brain tissue and does not cross the blood-brain barrier.

Further, our data show that PEG is eliminated from both plasma and tissues. These data indicate that steady state was reached, after which no further accumulation occurred.

Overall, we found no PEG-related safety concerns using

high multiples of the clinical dose of N9-GP. Our studies included clinical observations, hematology, clinical chemistry, as well as histopathological examination of more than 40 tissues from every animal. There were no adverse findings in the longest study, a 26-week study in rats. In monkeys dosed with 3,750 international unit per kilogram, that is more than 90-fold the clinical dose of N9-GP, transient tremors were observed at one or two occasions initially in the study. These reactions were considered infusion related as they were only seen following the first few doses.

The only adverse pathology finding was the expected development of acquired hemophilia due to formation of cross-reacting antibodies. This is a well-known phenomenon when using human correlation factors to animals.

Looking now at the question around vacuoles in more detail, we saw no signs that PEG caused vacuolation in any tissue in rats dosed chronically for 26 weeks. This is shown by the similarity of incidents between the vehicle control in black and N9-GP in gray.

As you can see, there were comparable incidences of minimal to slight vacuoles in the different tissues. Vacuoles were only observed in 9 out of more than 40 tissues examined and in 68 out of 3,200 tissue slides examined. There was no consistent pattern or differences that would indicate an association with PEG. We further examined vacuoles for the

presence of PEG, and it was not detected.

This study was assessed by two external board-certified pathologists. Their conclusion was that these sporadic vacuoles were background findings.

The same conclusion was reached in monkeys dosed for 4 and 13 weeks. Here, vacuoles were only observed in one tissue, the liver, and they were only observed in two animals, one vehicle control and one animal dosed with N9-GP; that is, two out of more than 1,800 tissues.

So in all of our animal studies, there was no indication that N9-GP causes vacuolation. Yet, to better understand PEG safety, we expanded our studies with more extensive analysis. These studies also showed the choroid plexus was not affected by the presence of PEG.

We examined PEG presence, localizations, and effects by sensitive techniques beyond those typically applied in toxicity studies. Applying a specific immunohistochemical staining, we found that PEG was distributed via the blood to connective tissue and epithelial cells of the choroid plexus. PEG was not detected in brain tissue.

Applying electron microscopy in the rat study, we observed lysosomes with PEG. This was consistent with the filtration function of the choroid plexus as well as with what is known about PEG.

The data also confirmed that there were no

ultra-structural signs of toxicity inflammation degeneration or necrosis; thus, the presence of PEG was not associated with any signs of cellular damage.

We next investigated the kinetics of PEG accumulation, which required a quantitative approach. These data demonstrated that PEG is eliminated from plasma and tissues and excreted via the kidney and liver.

We conducted a single-dose rat tissue distribution study and were able to quantitate PEG using N9-GP with a radiolabeled PEG moiety. As shown here for plasma, kidney, liver, and choroid plexus, the PEG concentration decreases over time from 1 hour to 12 weeks with elimination from plasma and tissues. There was no evidence that PEG is stored in any tissue.

These data were then used to determine elimination rates in key tissues. As shown by the green lines, linear regression was used to determine the terminal half-life of PEG. The terminal half-life of N9-GP PEG ranged from 15 to 49 days in these rat tissues.

We then estimated human half-lifes using allometric scaling. These data could be used to estimate time to steady state, that is, the time it takes to reach stable PEG concentrations. The results show that during the 26-week rat study, steady state was achieved in both plasma and tissues.

In humans, time to steady state was within 2 years for both plasma and all tissues, including the choroid plexus.

This is important since we already have patients who have been treated with N9-GP for 2 to 4 years in a clinical program.

We further used the PEG distribution data to build a plasma tissue model, since tissue PEG concentrations are determined by plasma levels. Based on the relationship between PEG plasma and tissue levels in rats, we used this model to predict for humans. Thus, combining modeling and allometric scaling, PEG concentrations were predicted for human plasma and tissues.

In this figure, the area between the dashed lines represents the predicted human plasma concentrations over time for children and adolescents. In this population, we were able to generate PEG plasma concentration data. Let's look at the data.

These symbols represent actual PEG concentrations in plasma samples taken over time from children and adolescents participating in the ongoing pediatric trial with N9-GP. These are PEG data for up to 4.5 years of dosing.

Plasma levels measured were within the predicted steady state range with low variability. This validated the model prediction.

The only outlier was one patient at one time point. This patient, the top red diamond, had a period of heavy N9-GP treatment resulting in higher levels. He returned to steady state PEG levels after resuming his normal weekly prophylactic

dose. This pattern was also predicted by the model. Based on these data, we conclude that steady state has been reached in human plasma.

Steady state is equilibrium between the rate of input and the rate of output. Here, no further accumulation occurs. Measuring PEG steady state concentrations in human tissue, such as the choroid plexus, is not feasible; therefore, we used established pharmacokinetic principles to predict these based on animal data. Thus, the rat data were again scaled allometrically to predict for human tissues.

Now, on similar algorithmic scales, we see the actual plasma PEG levels in humans shown on the left in symbols and the predicted choroid plexus concentration shown on the right. The predicted steady state PEG levels from a 26-week rat study are represented by dash lines. For both plasma and tissues, PEG steady state levels were significantly lower in humans than in rats.

To summarize, our nonclinical data support long-term PEG safety with N9-GP. We observed no adverse findings related to PEG in animal studies using high multiples of the clinical dose. Also, there was no evidence that N9-GP caused vacuolation in any tissue, including the choroid plexus.

Our data are consistent with literature supporting that PEG is inert and does not cause tissue damage. Clinical data also support the long-term PEG safety.

Steady state levels of PEG were reached in our clinical program, and based on our comprehensive nonclinical investigations and literature, we conclude that it is highly unlikely that PEG levels resulting from N9-GP dosing will have any clinical effect.

However, acknowledging the residual uncertainty, Novo Nordisk plans to continue surveillance related to PEG safety. This will be described later.

Dr. Seremetis will now present our clinical safety data.

DR. SEREMETIS: Thank you, Dr. Madsen.

One hundred and fifteen patients were exposed to N9-GP in the completed clinical trials. In total, we have 226 patient-years of treatment. The overall safety profile across all age groups is similar to those reported with other factor IX products. Eighty-five percent of patients experienced an AE with 9% classified as severe; 10% of patients had a serious adverse event.

This slide shows the AEs from the pooled trial that align with events reported in other published hemophilia B trials using factor IX replacement. As you can see, many could be signs and symptoms related to the underlying condition of hemophilia. Other events, like infections, contusions, GI events, and headaches are events that are expected to occur occasionally in the general population as well as in hemophilia patients.

Moving now to SAEs, in the completed trials, a total of 12 serious adverse events were reported. Other than one case of hypersensitivity in the single-dose PK trial, no events were considered related to N9-GP by the investigator.

Novo Nordisk actively investigated potential safety risks. Across all age groups, N9-GP has a safety profile similar to that of other factor IX therapies.

There were no AEs suggestive of thromboembolic events. There was no indication of increased hypersensitivity compared to other factor IX products. There was only one event of hypersensitivity observed in 8,801 injections in previously treated patients, and none of the previously treated patients developed factor IX inhibitors.

We also investigated for possible neurologic signals. Overall, no safety concerns were identified based on neurological assessments. These included prospective assessments of the nervous and musculoskeletal systems as part of the physical exams in all clinical trials.

The protocols specified general evaluations of the central and peripheral nervous systems, musculoskeletal function, and general appearance assessment of the patient.

To more comprehensively address the theoretical safety concern, we also performed a thorough retrospective analysis of neurologic, psychosocial, and developmental adverse events.

Acknowledging the possible uncertainty around long-term

PEG safety, we propose a robust multifactorial post-approval monitoring plan. We will continue to collect data from our ongoing pediatric trials. We are developing a post-approval safety study, including monitoring of renal, hepatic, and neurologic function. We are expanding our existing collaborations with registries, both national and international. And specific questions have been designed to collect additional details related to renal, hepatic, and neurologic function for any events reported.

Let's review each of these elements. We will continue to collect data from our pediatric patients in our ongoing clinical trials. This includes 19 previously treated patients still active in the extension trial. For previously untreated patients, we already have 17 patients in treatment and plan to enroll a total of 40. This represents a large prospective cohort, given the rarity of hemophilia B.

Periodic clinical evaluations will support the surveillance of neurologic, psychosocial, and developmental status. We will continue to assay for renal and hepatic biomarkers and collect plasma PEG levels moving forward. We are also developing a post-approval safety study to assess overall safety with a focus on monitoring neurologic, renal, and hepatic systems growth and development. The planned study will also include an exploratory measurement of PEG plasma levels.

We anticipate enrolling at least 50 patients with 5 years of follow-up. We have ongoing collaborations with international and national hemophilia registries, including a pediatric registry known as PedNet and the European Haemophilia Safety Surveillance Network, or EUHASS. We will closely work with them to identify and collect all potential AEs, in particular, those relating to renal, hepatic, and neurologic signs or symptoms. And we have also undertaken initial discussions regarding a collaboration in the U.S. with the American Thrombosis and Hemostasis Network, or ATHN, which collects data from all U.S. hemophilia treatment centers.

In addition, Novo Nordisk will follow up with specific questions for all events potentially indicative of or related to impaired renal, hepatic, or neurologic function. This includes follow-up of neurologic symptoms such as seizures, non-resolving or repetitive headaches, or developmental delays. These additional surveillance measures will help us to detect new signals and ensure patient safety.

Dr. Young will now provide his clinical perspective and review of the benefit-risk of N9-GP.

DR. YOUNG: Thank you, Dr. Seremetis.

I'll now present the benefit-risk of 40 IU per kilogram once weekly N9-GP. First, here are the benefits of N9-GP across all age groups. N9-GP maintains higher factor IX levels than current standard and extended half-life products with a

simple once-weekly dose.

There were significant and clinically meaningful outcomes in hemophilia patients treated with N9-GP. These included low annualized bleeding rates, and importantly, most patients with preexisting target joints did not have target joint bleeding during the study. These improvements led to enhanced quality of life. So let's look at the data supporting these benefits.

Shown here are simulated factor IX levels in adolescents and adults for the two currently approved extended half-life products, Idelvion and Alprolix. For most of the week, patients do not maintain high factor levels with these products. Little time is spent above 40% with once-weekly injections. In contrast, here's N9-GP where factor levels are sustained above 40% for most of the week.

Patients on 40 IU per kilogram N9-GP, including children, adolescents, and adults, had a median annualized bleeding rate between 0 and 2 and an annualized spontaneous bleeding rate of 0. Patients on 10 IU per kilogram did not achieve the same level of protection against bleeds.

To put these results into context, the 10 IU per kilogram dose achieves factor IX levels similar to currently available products.

From a clinician's perspective, I wanted to know the potential impact of N9-GP on the three most important concerns for patients: spontaneous bleeding, target joints, and

mobility. Regarding spontaneous bleeding, I found that considering only the ABR really understates the benefits of N9-GP. To appreciate the whole story, it's important to also look at the number of patients on 40 IU per kilo who had no spontaneous bleeds. In fact, 83% of younger children and 69% of older children had no spontaneous bleeding during 1 year of treatment. And 69% of adolescents and adults experienced no spontaneous bleeds over the same treatment duration. This is impressive considering that many of these patients had preexisting target joints or arthritis.

I really want to emphasize that the formation of target joints is the most important complication of inadequate hemophilia treatment. Here I'm showing data that you saw earlier, just to underline the benefit of 40 IU per kilogram N9-GP in the treatment of target joints.

Two-thirds of the patients who entered the trial with target joints did not have any target joint bleeds on the 40 IU per kilogram dose; in comparison, the 10 IU per kilogram dose, which is comparable to other therapies, does not alleviate target joint bleeding.

Although not shown on this slide, all patients on 40 IU per kilogram who continued in the extension trial had target joint resolution.

So how did the N9-GP treatment impact mobility? We see improvement in mobility with the 40 IU per kilogram dose

supporting that higher factor levels lead to meaningful outcomes for patients. This is shown by looking at the mobility dimension contained in the EQ-5D. About half of the patients randomized to the 40 IU per kilogram dose reported problems walking at baseline, but within just 1 year of treatment with N9-GP, almost 80% had no problems walking. This is very important to my patients since being able to walk affects every aspect of their life.

Of course, we, as treaters, need to consider the potential risks. Long-term safety data of N9-GP in all age groups revealed a safety profile similar to the other factor IX products with no unexpected risks. Importantly, safety in children age 0 to 12 is supported by more than 4 years of active treatment data. And these data, along with the nonclinical data shown earlier, support PEG safety.

In addition, I really want to emphasize that PEG is not new. As a pediatric hematologist/oncologist, I and my colleagues have been treating children with PEGylated products for years.

To summarize, I believe N9-GP has a favorable benefit-risk across all age groups. High factor levels drive a reduction in ABR, the resolution of target joints, and improvements in quality of life. These treatment outcomes are meaningful to my patients.

Ultimately, by sustaining higher factor levels, N9-GP

achieves better outcomes with less treatment burden.

In addition, N9-GP effectively treats bleeds and provides coverage during and after surgery.

Lastly, the long-term safety of N9-GP has been demonstrated with more than 4 years of data in children and a safety profile similar to that of other factor IX products.

Thank you very much for your attention.

DR. STOWELL: Thank you to the presenters for Novo Nordisk. We will hold questions. There will be a period for questioning later on, both of the presenters from Novo Nordisk as well as the FDA.

And so we'll move along, then, to the FDA presentation, and I think the first speaker will be Dr. Kimchi-Sarfaty.

(Pause.)

DR. STOWELL: Also, I just want to introduce -- Dr. DeKosky was able to join us by telephone. Can you speak up, let us know you're here?

DR. DeKOSKY: Sorry, I'm here. Thank you, everyone.

DR. STOWELL: Okay. And also, we have a couple people, members of the Committee who came in late, if you could just introduce yourselves, starting --

DR. LEITMAN: Susan Leitman, Director of the Medical Research Scholars Program at the NIH and formerly Deputy Chief of the Department of Transfusion at NIH for about 30 years.

DR. STOWELL: Dr. Dobbs.

DR. DOBBS: Thanks. Dr. Michael Dobbs, Professor of Neurology at the University of Kentucky and Director of the Stroke Care Network also there.

DR. STOWELL: Dr. Sarfaty. Oh.

DR. ONYIKE: Sorry, one more introduction. Dr. Chiadi Onyike, Associate Professor of Psychiatry and Behavioral Sciences at Johns Hopkins and Director of the Young-Onset Dementias Program.

DR. MANUELIDIS: Dr. Manuelidis. I'm head of neuropathology in the surgery department at Yale, and basically, I've seen lots of neurodegenerative diseases and ultrastructure. I'm a pathologist, a neuropathologist by training.

DR. KIMCHI-SARFATY: Good morning, my name is Chava Kimchi-Sarfaty, and I'm the chairperson of the review committee for this application. I am also one of the product reviewers evaluating the chemistry, manufacturing, and controls information for this product.

Since the questions addressed to the Advisory Committee are mainly related to nonclinical and clinical issues, and some of the information has already been covered in the applicant's presentation, the following few slides will serve as a brief introduction for the product and its manufacturing process.

As mentioned earlier, the drug of our discussion is a recombinant analog of human coagulation factor IX that is

covalently linked to a 40-kDa polyethylene glycol molecule via its carbohydrate moiety on the protein. In this presentation, the polyethylene glycol molecule will be referred to as PEG, and the drug product as N9-GP.

As previously described by Dr. Bryan, the purpose of this Advisory Committee meeting is to open a discussion based on the findings of the accumulation of PEG in the choroid plexus of animals that were infused repeated doses of N9-GP. The FDA is seeking the opinion of the Committee regarding the significance of these findings and how they may inform us about the safety of the product, and that includes:

- The risks in hemophilia B population, with special attention to pediatric and elderly individuals in setting of lifelong administration.
- And whether monitoring, particularly of neurologic function, should be provided for the safety of patients or study subjects.

I will now provide a brief overview on factor IX, hemophilia B, the currently available treatment options for hemophilia B, and the N9-GP product.

As has already been described, hemophilia B is a congenital bleeding disorder. Bleeding episodes are treated or controlled by intravenous infusion of factor IX-containing products, and the most serious complication in management of hemophilia B is the development of neutralizing antibody

against factor IX.

As indicated earlier, factor IX is synthesized as a single polypeptide with extensive co-translational and post-translational modifications. The zymogen is activated by proteolytic cleavage to activated factor IX. Activated factor IX then contributes to the conversion of factor X to its active form, Xa.

The manufacturing process has been well described in the applicant's briefing document. In brief, the applicant's recombinant factor IX is expressed in Chinese hamster ovary cell line. The protein is purified using traditional manufacturing methods. A 40-kDa PEG moiety is enzymatically attached to recombinant factor IX. This PEG-protein complex is further processed into the final drug product.

This table summarizes the products that are currently available to treat hemophilia B. In particular, please note the two licensed long-acting factor IX fusion protein products which allow people with hemophilia B to be infused once a week or less often. This is comparable to the applicant's proposed dosing regimen for N9-GP.

This concludes my brief introduction. Thank you. And Dr. Robinson-Zeigler will now give an overview of the nonclinical issues.

DR. ROBINSON-ZEIGLER: Thank you, Dr. Kimchi-Sarfaty.

Good morning, my name is Becky Robinson-Zeigler. I am the

Chief of the Pharmacology/Toxicology Branch II. Our branch was responsible for review of the nonclinical data in this BLA. I will provide a more detailed overview of the nonclinical program for the product N9-GP.

The nonclinical program for N9-GP consisted of multiple activity and safety studies. Safety pharmacology studies were conducted in mouse and dog models of hemophilia and in healthy monkeys. Pharmacokinetic studies included general PK and ADME studies. Autoradiography studies were conducted to determine the distribution of N9-GP and the 40-kDa PEG moiety. Local tolerance studies were also conducted in healthy rabbits.

For their definitive nonclinical safety studies, the applicant conducted single and repeat-dose toxicity studies in healthy rats and monkeys and in immune-deficient nude rats. These definitive nonclinical safety studies evaluated the proposed prophylactic clinical dose level of 40 international units, IU, per kilogram and dose levels ranging from 5-fold to almost 100-fold higher than the clinical dose. Finally, the applicant conducted a second set of studies evaluating the toxicity of 40-kDa PEG alone in healthy monkeys and rats.

All studies administered N9-GP using the intravenous route of administration, which is also the proposed clinical route of administration.

I will now focus on the toxicity studies, and specifically the findings of accumulation of PEG in animals administered

N9-GP. For clarity, we have defined accumulation of PEG as presence of PEG in tissue samples as determined by immunohistochemistry staining and described as such in the pathology test reports included in the BLA.

The following tables summarize the general study design and findings for the N9-GP toxicity studies. These tables also summarize the findings related to accumulation of PEG, as determined by immunohistochemistry.

A single-dose toxicity study was conducted in healthy rats at dose levels ranging from 200 to 2,000 IU, which are 5- to 50-fold higher than the proposed clinical dose level of 40 IU. No systemic toxicities were observed in these animals, and accumulation of PEG was not evaluated.

In study number 2, healthy monkeys were administered dose levels of N9-GP ranging from 350 to 3,750 IU, which are approximately 9- to almost 100-fold higher than the proposed clinical dose level of 40 IU. This was a repeat-dose study in which animals were administered N9-GP weekly for up to 4 weeks, followed by a 5-week recovery period in which animals did not receive N9-GP.

The majority of animals in each dose group were sacrificed at the end of the 4-week administration period, the terminal sacrifice. Tissues from various organs in these animals were collected and histologically evaluated. Following the recovery period, animals from each dose group were sacrificed, and

tissues from various organs were histologically evaluated.

In animals sacrificed before the recovery period, at all dose levels accumulation of PEG was observed in the connective tissue and epithelial cells of the choroid plexus. PEG was also found in the blood in brain blood vessels and in skeletal muscle blood vessels. In animals sacrificed after the 5-week recovery period, accumulation of PEG was not observed.

An additional longer study, study number 3, was conducted in healthy monkeys. In this study, monkeys were administered 200 IU of N9-GP weekly for 13 weeks, followed by a 5-week recovery period. This dose level is fivefold higher than the proposed clinical dose level of 40 IU. Unlike study number 2, in healthy monkeys, accumulation of PEG was not observed in any animals.

Study number 4 was a short-term study in healthy rats. Animals were administered 25 IU or 250 IU weekly for 2 weeks. No systemic toxicities were observed in these animals. An accumulation of PEG was not evaluated.

Interpretation of the data in the previous studies conducted in healthy animals may have been confounded by the development of neutralizing antibodies to N9-GP. In addition, development of neutralizing antibodies to N9-GP limits the duration of the study. Therefore, in order to conduct longer-term studies in animals without the development of neutralizing antibodies, the applicant conducted two studies in

immune-deficient nude rats.

In study number 5, 40 IU and 1,200 IU of N9-GP was administered twice weekly for 6 weeks, followed by a 2-week recovery period. This study evaluated the proposed clinical dose level, 40 IU, as well as a dose level 30-fold higher. However, unlike the other studies, this dosing regimen was different from the proposed clinical dosing regimen of once weekly administration.

Following the recovery period, animals were sacrificed, and tissues from various organs were histologically evaluated. Accumulation of PEG was not observed in animals administered the lower dose of 40 IU. However, in animals that received 1,200 IU of N9-GP, accumulation of PEG was observed in the connective tissue and epithelial cells of the choroid plexus. PEG was also observed in the blood in brain blood vessels.

In the final toxicity study, study number 6, 40 IU to 1,200 IU of N9-GP was administered once weekly for 26 weeks, after which animals were sacrificed, and tissues from various organs were histologically evaluated. A separate group of animals were administered the high dose level of 1,200 IU once weekly for 26 weeks, followed by a 26-week recovery period. Following the recovery period, these animals were sacrificed, and tissues from various organs were histologically evaluated.

Accumulation of PEG in the connective tissue and epithelial cells of the choroid plexus was observed at all dose

levels in animals dosed for 26 weeks with no recovery period. These animals also had accumulation of PEG in the blood in brain blood vessels, mesenteric lymph nodes, and spleen. For the group administered 1,200 IU with a 26-week recovery period, PEG accumulation was only noted in the epithelial cells of the choroid plexus.

To summarize, the two major toxicity findings from the studies where N9-GP was administered to animals were vacuolation and PEG accumulation. Although not discussed in this presentation in detail, vacuolation was observed in various organs such as the liver, spleen, and mesenteric lymph nodes of control animals and animals administered N9-GP.

Based on the independent pathology reports provided in the submission, vacuolation did not appear to be dose or time dependent.

The most consistent toxicity findings in animals administered N9-GP was accumulation of PEG in the choroid plexus. Upon further histological examination, PEG was present in vesicles and vacuoles.

The studies discussed in the previous slides evaluated toxicity of the product N9-GP in animals. I will now discuss the studies evaluating the toxicity of the 40-kDa PEG moiety alone.

Two studies were conducted to evaluate the toxicity of repeat administration of high dose levels of 40-kDa PEG.

In the first study, healthy monkeys were administered 7 or 45 mg/kg/week of PEG for 2, 6, or 13 weeks. The amount of PEG administered to these animals would be equivalent to approximately 1,300 IU and 8,400 IU, respectively, of N9-GP. These represent approximately 32 times to 210 times the proposed clinical dose of 40 IU.

Vacuolation and PEG accumulation were not noted in animals administered the lower dose of 7 mg; however, both vacuolation and PEG accumulation were noted in the ependymal cells of the choroid plexus in animals administered 45 mg/kg/week for 6 weeks. However, no systemic toxicities were reported in the animals in either group.

In the final PEG-only toxicity study, healthy rats were administered 45 or 117 mg/kg/week of PEG for either 2 or 6 weeks. The amount of PEG administered to these animals would be equivalent to approximately 8,400 IU and 22,000 IU, respectively, of N9-GP. These represent approximately 200 to 550 times the proposed clinical dose level of 40 IU.

Vacuolation was noted in the brain, spleen, lymph nodes, and liver in animals administered these dose levels for 6 weeks, and based on statements in the final pathology report, accumulation was inferred to be also noted in the same tissues in animals administered these dose levels for 6 weeks.

Unlike the previous study in monkeys which showed no signs of clinical abnormalities, all animals in this study exhibited

a decrease in food consumption and body weight in a dose-dependent manner.

To conclude, accumulation of PEG in the choroid plexus following administration of N9-GP was the most consistent pathologic finding. Although these findings were present, no clinical abnormalities related to N9-GP were reported.

Since the nude rat studies were not designed to assess neurologic function, the significance of the absence of neurologic abnormalities is unclear. Furthermore, the mechanism by which PEG is cleared or removed from the choroid plexus remains unknown. One possibility is that PEG is excreted from the cells in the choroid plexus and into the cerebrospinal fluid, or CSF. CSF samples were collected from recovery animals in study number 6; however, these samples were not analyzed.

The findings of accumulation of PEG in the choroid plexus raises potential safety issues that cannot be addressed in animal studies for the following reasons:

- Studies can be conducted in monkeys; however, due to the development of cross-reacting, neutralizing antibodies to N9-GP, longer-term studies are not possible.
- As the data demonstrate, longer-term studies can be conducted in immune-deficient rodents; however, there is a limited ability to assess neurocognitive

function in these animals.

- Finally, there is no clinical biomarker to assess choroid plexus function.

Now Dr. Kaushal will provide an overview of the clinical data.

DR. KAUSHAL: Good morning. I am Megha Kaushal, the clinical reviewer for this BLA, and I will provide a clinical overview of this application.

The applicant submitted this original BLA seeking approval for the following indications for adults and children. First, the control and prevention of acute bleeding with a dose of 80 IU/kg for major bleeds and 40 IU/kg for minor bleeds with a maximum dose of 200 IU/kg per 24 hour period; (2) for perioperative management: 80 IU/kg for major surgery and 40 IU/kg for minor surgery with repeat dosing of 40 IU/kg to achieve factor IX levels of greater than 50%; and third, for routine prophylaxis: 40 IU/kg once weekly.

A description of each of the Phase III studies is presented here, which were conducted to support the indications previously stated. These studies included previously treated children, adolescents, and adults.

Trial 3747 was a single-blind randomized study which included both adolescents and adults. Subjects were randomized to either 10 IU/kg or 40 IU/kg doses for routine prophylaxis. The 15 subjects who received on-demand treatment were not part

of the randomization.

Trial 3774 was an open-label study which included pediatric subjects less than 12 years of age. Subjects were dosed with 40 IU/kg for routine prophylaxis.

Trial 3773 was an open-label study which included adolescents and adults undergoing surgery. Subjects were dosed with 80 IU/kg preoperatively. Postoperatively, the subjects were treated with injections of 40 IU/kg.

Trial 3775 was an open-label extension study. The majority of subjects were dosed with 10 IU/kg or 40 IU/kg, whereas two subjects were dosed with 80 IU/kg and five subjects with on-demand treatment.

Some subjects transitioned from Study 3747 to extension Study 3775. In addition, subjects who were in Study 3747 or the extension study were permitted to transfer to the surgery study. Once a subject completed the surgery study, the subject could then transition back to Study 3775. A total of 105 adult, adolescent, and pediatric subjects were treated with N9-GP in Studies 3773, 3774, 3775, and 3747.

Safety monitoring included clinical evaluations, such as vital signs, physical exams, adverse events, and laboratory assessments. Physical examinations were performed 2 to 8 weeks prior to Week 0, at Week 0, then at 28 weeks, 52 weeks, and at follow-up 4 weeks after the 52-week period. Adverse events were evaluated at each study visit, which occurred every 4

weeks up to Week 12 and then every 8 weeks until the end of study at 52 weeks. A final evaluation occurred at follow-up 4 weeks after the 52-week period. Laboratory assessments were evaluated on the same schedule as the adverse event assessments.

The initial study visit included a general physical exam of each organ system, including the neurologic system. However, there was no pre-specified structured exam that was to be performed by each investigator. The protocol and case report forms did not specify any detailed neurologic or neurocognitive evaluations. At this initial visit, laboratory evaluations were also performed, including labs to assess renal function.

At subsequent visits, the investigator was to identify and judge any new findings to be an undesirable adverse event. These did not include neurologic or cognitive evaluations.

Exposures for subjects by age group are listed here. As previously noted by the applicant, some subjects were exposed to N9-GP for more than 3 years with a maximum of 4 years in some cases. However, there were only 12 subjects less than 6 years of age and only two subjects over the of age 60.

The effectiveness of this product is not a primary issue for consideration of this Advisory Committee. However, the applicant has discussed trough levels of up to 40%, but we would like to highlight that despite 40% trough levels, acute

bleeding still occurred, as illustrated by the annualized bleeding rates, or ABRs, in each of the studies at the 40 IU/kg dose.

Thirteen surgeries were performed in 13 subjects. Control of bleeding was judged to be excellent or good in all 13 surgeries.

Moving on to the safety findings, there were no neutralizing antibodies reported in any subject. A total of 647 adverse events occurred in 98 subjects. The most common adverse events were related to upper respiratory symptoms and contusion and were not serious.

Due to the issues raised in the nonclinical findings, we focused on nervous system adverse events. There were 29 nervous system adverse events in 16 subjects. These neurologic events included headache, dizziness, sciatic neuralgia, tongue biting, and a speech disorder. All of these events were transient and not serious. As stated, neurocognitive assessments were not part of the pre-specified monitoring plan, and it is unclear whether subtle neurologic adverse events would have been detected.

In this slide, I will summarize the unresolved issues. The nonclinical studies found PEG accumulation in the choroid plexus following repeat dosing with N9-GP. The clinical trials did not find any safety signal that was clearly likely to be caused by PEG accumulation. However, it is unclear whether the

clinical monitoring of neurologic or cognitive function was adequate to detect all clinically important neurologic signs or symptoms.

In addition, it is unclear whether the size of the safety database, including the number of adult or pediatric subjects exposed to the product and the duration of follow-up of those subjects, is sufficient to assess the safety of the product.

The FDA seeks the opinions of this Advisory Committee regarding the preclinical findings of PEG accumulation in the choroid plexus. Of interest to the FDA is the Committee's assessment regarding safety in the intended population, particularly in the pediatric and elderly populations, and in the setting of chronic administration. FDA is also seeking the Committee and asking the Committee to consider whether monitoring, specifically of neurologic function, should be provided for the safety of patients or study subjects.

In addition, we are asking whether additional data are necessary regarding the issue of PEG accumulation in the choroid plexus.

Thank you.

DR. STOWELL: We are running uncharacteristically ahead of schedule, which is good. I wonder if what we should do at this point is to take our 15-minute break and then come back and resume the meeting. We'll be about 15 minutes ahead of ourselves at that point, but I think that's fine. And after

the break, at that point we'll entertain questions for the presenters from Novo Nordisk and also from the FDA. So 15 minutes from now will be just about 10:20.

(Off the record at 10:01 a.m.)

(On the record at 10:19 a.m.)

DR. STOWELL: Hello, again. I'd like to get started. So we have a bit of time now to pose questions to the presenters from Novo Nordisk and also to FDA. So if you have got questions, please speak up and raise your hand, and I'll recognize you, pose your question, and then the respondents will determine who's the best person to speak and show up. So it looks like Dr. Basavaraju.

DR. BASAVARAJU: Yes. So I had a question for FDA as to whether there's other drugs that are this PEG that also accumulate in the choroid plexus and, if so, if there's any known implications of that.

DR. STOWELL: And if the respondent from FDA would please come to the microphone, and also, if you would restate your name for the purpose of the transcriber.

DR. BRYAN: Yes, this is Wilson Bryan.

There are many other PEGylated products on the market, and these products differ in a variety of ways. They have different molecular weights, they have different pharmacokinetics, route of administration and duration of administration, and we really don't think that getting into a

discussion of these other PEGylated products which are of questionable relevance to the Novo Nordisk product would be useful for today's discussion. Some of this information that you're asking for may be proprietary to these other products and really couldn't be discussed today, so we don't think that we can have a fair and balanced discussion of that. I appreciate that folks are interested in it, and we will consider these things in the context of the BLA review, but I really don't want to go there for today's discussion.

DR. PACKER: Hello, Roger Packer.

For the company: I'm struck with only a little over 20 children, and about 10 less than 12 actually have been treated with the drug. Could you give me some idea of the specifics of if the drug is approved, what the monitoring would be for neurologic and neurocognitive issues in these patients moving forward? What exactly would you monitor, and how would that monitoring be supported financially?

DR. SEREMETIS: So just to clarify, there were 25 children between the ages of 0 and 12 enrolled in the study, and these were sequestered by age group 0 to 6 and 7 to 12, so there were 12 and 13 respectively in each age group. These children have been --

DR. PACKER: Let me clarify.

DR. SEREMETIS: Sure.

DR. PACKER: But there weren't that many that were

followed for greater than 2 to 3 years. I mean, some are still early in your follow-up period.

DR. SEREMETIS: In fact, all of them have been followed for more than 2½ years.

DR. PACKER: Okay.

DR. SEREMETIS: What we're describing is the tail of the earlier enrolled patients. There are eight patients who have now been followed up to 4½ years, so the follow-up continues and will continue. That's the plan. The monitoring, to date, has relied upon the monitoring that is central to the hemophilia treatment network, the comprehensive care that is delivered in the context of hemophilia care, and to describe the nature of monitoring in the context of hemophilia care, I'm going to ask Dr. Manny Carcao to come to the microphone.

DR. CARCAO: Thank you, my name is Manuel Carcao. I'm a pediatric hematologist -- thank you -- at the Hospital for Sick Children in Toronto, Canada, where I look after the hemophilia program there and have been doing so for 19 years. I look after 500 children with bleeding disorders, of which 180 have hemophilia but only actually 26 have hemophilia B. So hemophilia B is a rare disorder, and it does cause studies to have a relatively low number of patients.

As you heard, there have been 25 children treated on the study; 4 of those were in my institution. Those four children started receiving the product in June of 2012, so my children

have actually been on this product for the longest, and they're actually quite approaching 5 years. They've been monitored very closely, as all children are, through hemophilia comprehensive centers, so they see me every 3 months. They also see my nurse, they see my social worker, they see my physical therapist.

And in addition to us, they are also being monitored by their own pediatrician, who they see for routine pediatric care, and of course, these are all children who are going to school, and so they're also being monitored, to a certain extent, by their teachers.

And so during this time period, we've been able to assess their development and also look for neurological signs or symptoms, and we have found nothing. There's been no signal in any of these children, they are doing extremely well, so I'm very confident in this product.

DR. PACKER: I'm sorry, that wasn't the question. My question was what if this drug is approved, will the post-monitoring follow-up of these children be -- will it be formalized? Will it be individual for each center or each patient on it? That's what I was asking.

DR. SEREMETIS: So the follow-up will be as it has been in the context of the clinical development program, relying on the comprehensiveness of the overview of the patient within the hemophilia treatment center with no specifics dictated. Of

course, we are currently in discussion with the FDA with regard to the elements of a post-approval safety study, and those could inform any post-approval commitments.

DR. SHAPIRO: Yeah, I had a question about that breakdown of the ages of the children. So I believe the documents indicated that there were 12 in the 0 to 6 age range, but how many of those were 0 to 2, and how many were 2 to 6? I think that may help inform our discussion later about the potential safety issues in children who are very young.

DR. SEREMETIS: Could I have a breakdown of the ages? As you can imagine, I mean, there were 13 patients total to distribute over the years, and children qualify as previously treated patients once they have had 50 doses of drug, so there would be some time frame. So we're talking probably a year to two, but let's see. Do we have the data available? If we don't have it immediately available, I can provide it to you after the lunch break.

DR. SHAPIRO: Yeah, thank you. I guess a broader question is what are the indications for treatment in children less than 2 years old?

DR. SEREMETIS: So we found the data for you, sorry. So we have -- no. Okay, so we have one patient below the age of 6 months at enrollment and then -- no, I'm sorry. No, this is not what he's asking, so we're going to come back to you with this after the lunch break. And please ask your question, I'm

sorry. Indication for patients --

DR. SHAPIRO: Yeah, what would be the reason for a treatment in patients less than 2 years of age?

DR. SEREMETIS: As any child with hemophilia would be, it's important to prevent bleeding, so prophylaxis of bleeding would be an indication in these patients, also treatment of bleeding, also if there were any anticipated surgery. But to comment on the application of the drug in children, I'm going to ask Dr. Carcao to come to the microphone.

DR. CARCAO: Thank you. So Manuel Carcao, for the record.

So yes, children with severe hemophilia B will start to experience bleeds generally between 6 and 12 months of age, so there is a need for a drug that particularly lasts a long time, and these children can certainly receive it.

I will also add that you may have seen in the presentation that there are 17 what are called PUPs; these are previously untreated patients. They tend to be very young patients who are already receiving this product, and those children would, in general, be under 1 or 2 years of age. So there are quite a number of children already on this product who are less than 2 years of age, as per your question.

DR. STOWELL: I think Dr. Onyike had --

DR. ONYIKE: Yes. I wonder if you have any data on multiple cognitive milestones in the children and also whether you have any data on school performance.

DR. SEREMETIS: These would normally be recorded within the construct of the hemophilia treatment center. We would have reported any deviations from these in the case reporting and as part of the physical examination that is recorded regularly.

DR. ONYIKE: Sorry, I was specifically referring to whether you've had any -- whether you've analyzed the data.

DR. SEREMETIS: We have not analyzed in detail any milestone data, no.

DR. BAKER: Thank you. I was curious to see if you had any data you could show us on the number of U.S. hemophilia treatment centers that were involved in the studies, the cities in which they were located, the number of patients total in the U.S., and a breakdown of the race/ethnicity of those U.S. patients.

DR. SEREMETIS: So I don't have the data immediately available at the treatment center level, but we can certainly provide that for you after the lunch break.

With regard to the number of patients represented from the U.S. in the overall development program, it's summarized here. So a quarter of the patients between 0 and 6, about a half between 7 and 12, about a half of the adolescents and roughly a third of the patients -- or a quarter of the patients who are between the ages of 18 and 65 were enrolled from the U.S. With regard to the specifics of treatment centers in cities, we can

get that for you after the break.

DR. BAKER: And the race/ethnicity as well?

DR. SEREMETIS: Yes.

DR. BAKER: Thank you.

DR. DOBBS: Can you go to slide 74, please? Thank you. That was fast. Questions here about the neurological function or symptoms, I got a couple questions about it. One, is this what is being proposed as the monitoring for a pass, really?

DR. SEREMETIS: So just to clarify, this is one of four elements of our post-approval plan. The post-approval safety study is a separate and distinct entity that will have -- that we can detail for you, if you wish.

This is a summary of specific events in terms that will be followed up specifically with queries and particular questionnaires around the details of the presentation of seizure, severe non-resolving headaches. This will be applied universally to any reporting we receive in the context of any of the elements of our post-approval program.

DR. DOBBS: So then on the last two bullets, developmental delays and neurological examination findings, can you tell us more about how you're defining and monitoring for developmental delays and defining a neurological examination in the findings?

DR. SEREMETIS: So we can certainly go into, again, the detail of what is done in the hemophilia treatment centers to evaluate. These would be outputs of the evaluations done at

the centers. Perhaps Dr. Young can comment on this?

DR. YOUNG: Sure, this is Guy Young from Children's Hospital, Los Angeles.

So in our centers, our comprehensive care hemophilia treatment centers in Los Angeles, we take care of children and adults in my center, so we have a multidisciplinary team which includes physicians, nurse practitioners, physical therapists, social workers, and a psychologist, and all are specifically expert in hemophilia. In other words, all these people focus their work on hemophilia; they're not doing too many other things, or most of them are not doing any other things.

And so developmentally, our physical therapists are trained in doing the motor part, of course, of the developmental exam, and we do have them do those from time to time if we have any concerns whatsoever. We have social workers and psychologists that are attuned to cognitive issues. And of course, as physicians, I'm a pediatrician as well by training and a pediatric hematologist/oncologist, so of course, I'm aware of the motor milestones, cognitive milestones that we have to find in children, and we do evaluate children with severe hemophilia every 6 months in the clinic, which is just routine.

And I think with that multidisciplinary team, I think we have the tools to be able to pick up clearly any obvious finding, and I think we also have the tools to pick up subtle

findings. And if there are any subtle findings or any concerns, we have at our disposal, in our center and in most of the hemophilia treatment centers that take care of children, pediatric neurologists as well that we can consult with if necessary.

DR. SEREMETIS: Perhaps to give you a better flavor for what goes on in the hemophilia world, I'm going to ask Dr. Young to come back to the microphone and talk about the importance that maintaining normal quality of life has played in hemophilia monitoring over the years and the importance of maintaining the capacity to continue with school and work and that the community is extremely sensitive to this.

DR. YOUNG: Yes, certainly. I think that whenever I see a new patient with hemophilia, which we get about one a month in my center -- not hemophilia B, hemophilia overall. We get maybe one or two with hemophilia B because it's so rare. You know, parents always ask, you know, what's going to happen to my child, is my child going to be normal, and my reply to them is always -- we always have this discussion that our goal is for you to lead a normal life. They will need to receive factor infusions, but the goal is for them to lead a normal life, to go to school, to be able to participate in sports, to really be like any other kid other than receiving the factor infusion. So our aim is for normalcy and a normal full quality of life.

And, you know, one brief anecdote is -- you know, one mom sent me a picture of her son, who she was told when he was born that he could never do any kind of physical activity, and at the age of 7, she sent me a picture with him and his athletic coach showing me that he was the top athlete in his class, and she said, you know, I never thought I would see this happen. But with modern hemophilia treatment, that's what we want, is for him to be not just cognitively normal, developmentally normal, but to live a normal life and to be able to be the top athlete in his class. So quality of life is very, very important to us, and we strive for absolute normalcy.

DR. STOWELL: Mr. Templin.

MR. TEMPLIN: So I'm correctly hearing that the safety of this issue will be followed up through the HTC system; is that correct?

DR. SEREMETIS: That's correct.

MR. TEMPLIN: Well, I got some ground-shaking news. Not every patient with hemophilia goes to a hemophilia treatment center; not every hemophilia treatment center can be equally compared to another hemophilia treatment center, even in the same state.

I go to one hemophilia treatment center, my daughter goes to another hemophilia treatment center, and that was because they chose not to take care of my daughter the way the other hemophilia treatment center would.

So I almost think any kind of follow-up should go with the drug because the drug may be prescribed by a non-hemophilia treatment center physician, and all safety information should be sent along with the drug to that physician because I think there's an estimate, 30% of patients with hemophilia don't go to an HTC for various reasons: they're too far away, they don't trust the doctor, past history, grievances, or whatever. I think that's a big issue, and I'm sorry if I offended anybody, but that's just my opinion.

DR. STOWELL: Dr. Onyike.

DR. ONYIKE: Yes, this is for Dr. Young. You had spoken about function and normal life, but it's not clear how you measure that, and it's striking when you have a striking anecdote, but otherwise, as you know, in these things we have variation. So how do you measure this? That's one thing.

Now, the other thing is I'm thinking to myself about micro-hemorrhages and I'm thinking perhaps in the brain. Is it typical to monitor with MRI scans, for example? So two questions in one, sorry.

DR. YOUNG: Yeah. No, let me answer the second question because that's a simple answer. The answer is no, there are no routine MRI examinations done in children, or in adults for that matter with MRIs. That would require a clinical indication to be asked that.

I mean, as far as monitoring for, you know, normalcy or

normal quality of life, there are settings in which we do quality of life studies, but in many situations it's really sort of the gestalt of talking to the parents or talking to the patient and asking them the appropriate questions: Are you advancing in school? Our social workers are very attuned to their school performance. Are they advancing in school? Are they getting good grades? Is there any issue with them not advancing in school?

Now, of course, it may not be related to hemophilia, but any such thing that happens with our patients, we get immediately concerned. If somebody's school performance drops off, that probably would warrant an MRI, looking for microscopic hemorrhages and things like that.

So it's an overall sort of clinical gestalt, but with our multidisciplinary comprehensive care team, I think we're very attuned to picking up any kind of changes. So we ask, like I said, school performance, we have psychologists that literally see every single patient and make sure that they're psychologically doing okay. We have physical therapists who examine every patient. So it's the multidisciplinary care team and their overall gestalt that sort of tells us they're doing well.

DR. ONYIKE: So if I may just quickly follow up. I have here a stack of, you know, notes that are anecdotes from families, and one can imagine that people who are enthusiastic

about the treatment will write favorably.

But as Mr. Templin pointed out, you know, reactions to any treatment or any clinical interaction can vary, and you're not necessarily hearing from everyone, and the antidote to that really is systematic monitoring.

And I believe school performance, for example, can be monitored through school records. But what I'm suggesting is that these things can be quantified, and there should be consideration to doing so.

DR. STOWELL: Dr. Packer.

DR. PACKER: Yes, just as a follow-up, since I started this frenzy in some ways, the issue on following up patients, there are ways to systematically follow up patients. They don't have to be MRI scans. There are validated ways to follow development, validated ways to follow quality of life. And I do think that if there's been any experience gained from the past 30 to 40 years of watching these things, unless you systematically build those in, you can miss some very important data. And if this is a critical issue to the safety of the drug, it would be nice to have the, at least, reassurance that there's some thought being put in, except to keep saying that we follow them to the clinics, that we'll really be able to gather the data if this is going to be an issue.

It may not be an issue. The reason I ask it is what is the systematic plan for follow-up, rather than self-reporting

from a center, and especially since a majority of patients will be treated at different centers, that they be all across the world with different capabilities, and some will never see the center. That was the question.

DR. SEREMETIS: So as we've alluded to and introduced in our earlier presentation, we do plan an extensive post-approval program to follow up. We will continue actually monitoring patients who are already in our clinical trials. These are very closely monitored patients. And as was alluded to by Dr. Carcao, not only will we have the 19 patients we continue to follow who are in the pediatric age who were enrolled 3 to 4 years ago, but we have an additional cohort of patients being enrolled right now who are previously untreated patients. These are quite young, and we expect to follow them, to continue to follow them.

We will also develop a post-approval safety study. We can discuss the details that could be included in that, but -- and we can certainly review that. And we will also work with the hemophilia community in general, which casts a quite wide net with international and national registries to capture safety data with regard to the use of all products that are currently being used in hemophilia. And then we talked about the queries we will make of any spontaneous adverse reporting.

If you want more detail than that, I'm going to ask for our safety officer, Dr. Mette Simonsen, to come to the

microphone. Or are you okay with where we are with this?

DR. PACKER: I'd really love to hear the details.

DR. SIMONSEN: Mette Simonsen, clinical safety specialist.

So as mentioned -- well, we are discussing here a theoretical risk where we don't really know what the signs and symptoms would be. We've not seen anything in our clinical data. It was confirmed by a retrospective analysis where we actually looked into nervous system disorders and psychiatric disorders. This focus we will continue to have also in the postmarketing setting, so everything that is reported to us will focus on the nervous system and psychiatric disorders.

We'll get data from a number of different sources, as mentioned here, so we'll have the ongoing clinical trials, the tests, and the registries. And we will further substantiate this by when we get an event, for example, a seizure or a headache, we will have these specific follow-up questions where we'll collect as many details as possible that will support us then in the signal management process so that we will be able to detect a new signal.

DR. STOWELL: Dr. Manuelidis.

DR. MANUELIDIS: So I would like to follow up a little bit on this age question because you mentioned what is the -- well, what is the reason for treating children who, let's say -- I would say even less than 4 years old and especially less than 2 years old, given the fact that the PEGylation does not really

come anywhere close to keeping the half-life of the factor IX intact. So if I looked at the data, it seems to say it's about 2.3 or 2.5 days as opposed to 6 days in adult. So that immediately means that you have to give -- you have a gap of at least 3 to 4 days where the infant does not have the same kind of adequate level of factor IX.

So you have really a high risk also in the developing nervous system. Many things are happening in the first 4 years of life, especially the first two. I mean, you still have cerebellum isn't developed, you have the choroid plexus, which has something to do with T4, thyroxine excretion, and those are very important for things like migration of the external granule cells. There's still mitoses going on in the hippocampus. So can you justify treating children at a really early age?

DR. SEREMETIS: So, in general, it's extremely important to maintain as close as possible to normal levels in every patient with hemophilia. Given that it is possible to do so with an extended half-life product, N9-GP, and given that the levels you -- as you described, yes, we don't approximate the normal range with children because clearance is higher in children, but the factor levels that are obtained are considerably higher than those available in the context of treatment with any other product, including the other extended half-life product.

So this is a very vulnerable age group, as you described, in general. It's very vulnerable to bleeding and the consequences of bleeding as well, so it's important that those children be maintained as high as possible with regard to the factor IX levels. And to comment on the importance of that and the really relevance of treating the younger patient population, I'm going to ask Dr. Carcao to come to the microphone.

DR. CARCAO: Thank you. I'll also bring up the slide. So I would like to have the audience recognize that the patients who would benefit the most from this product are the youngest children. The reason is that this product, as you can see here, this is with once-a-week administration, so every 7 days, maintains these very young children with a factor IX of above 15% throughout the entire course of the week.

And in comparison to previously available products prior to this, those products would require dosing not once a week, but two or three times a week, and despite that would only maintain levels above 2 or 3%. So with this product, children are getting one injection per week, and every injection is painful, and every injection is anxiety provoking for them and for their parents. So this now allows them to do it only once a week rather than two or three times a week, maintaining much higher levels, and as you heard, they're not really bleeding.

And if I could have slide 81, please. I just wanted to

show here that in slide 81 you'll notice -- oh, sorry. You'll notice that 83% of the youngest children, over a course of 1 year, experience no bleeds with this regimen of once a week rather than previous products where they would get two or three needles per week.

Thank you.

DR. MANUELIDIS: I think I was asking about 0 to 2 or 0 to 3 years, and I think it's very difficult when you look at 0 to 6, that you may not have as good results in the really, really young children, 0 to 3.

DR. CARCAO: Well, I will comment that of the four children that I have enrolled onto this study, one of them was 1½ years of age when he went onto the study. He's had no bleeds the entire time that he's been on study, and he's been on study now for -- in November it will be 5 years this year. So they benefit actually, as I said, I think the most from this product.

DR. LEITMAN: I have a technical question in the FDA's presentation on the 40-kDa PEG-only toxicity study. I don't know. Oh, slide number 15 of that presentation. The presentation included data on monkeys and on rats, and it was only a very high dose in a rat that it was mentioned that PEG accumulation in the brain was seen. That's not mentioned in any other presentation this morning. Everything else focused on choroid plexus.

The word "brain" is just there. It doesn't say brain parenchyma, it doesn't say glial cells, it doesn't say what that was about. It was a very high dose, so maybe that's not clinically relevant. But I was wondering where in the brain the PEG was seen.

DR. ROBINSON-ZEIGLER: Hi, Becky Robinson-Zeigler, for the record.

Yes. So the pathology test report that was included with that complete study stated brain, but then further examination in the individual animal line listings did list choroid plexus. So it's brain in general, just based on general pathology, but choroid plexus when they look closer.

DR. SEREMETIS: Perhaps Dr. Madsen wants to comment.

DR. MADSEN: Yes. Lars Madsen, nonclinical.

Maybe I could just come back to the high doses used in this study. So if we could have slide PN6, please. So as you correctly described, this was not with N9-GP; this was actually data from using 40-kDa PEG alone to explore potential toxicities of that. And as you can see, the dose overarches here to the tune of 2 to 500 at the doses where there were actually vacuolations seen, whereas in the study at the bottom, a 13-week monkey study, there was no vacuolation seen.

DR. STOWELL: Dr. Shapiro.

DR. SHAPIRO: I guess I just wanted to clarify something. So it was mentioned in the FDA presentation that in one of the

nonclinical studies, CSF was sampled from animals that had been administered this product, but the CSF was not analyzed, so we don't know whether there was increased protein content or whether PEG was secreted into the CSF.

And I guess a question to either Novo Nordisk or to the FDA is whether there's any study assessing whether PEG or PEGylated products increase secretion of protein into the CSF.

DR. ROBINSON-ZEIGLER: Hi, Becky Robinson-Zeigler.

That particular test report stated that CSF was collected. We further probed the applicant in terms of what happened to those samples; those samples were not evaluated. But I think there's another challenge in terms of what to do with those samples, exactly what to look for, looking for PEG, developing a method for that.

And in terms of availability of looking for PEG in the CSF in the literature, we have not found any articles, you know, that have a method for that. But that is, you know, a question that we would like the Committee to think about in terms of, well, how could we assess those samples, you know, if they're still available?

Thank you.

DR. SEREMETIS: Dr. Madsen.

DR. MADSEN: Thank you, yeah. So maybe just to comment, what we did look for was the presence of PEG in brain tissue, and we did not detect PEG immunohistochemically in brain

tissue. So even though it's correct that those samples were not analyzed for PEG, and it would also be very unlikely that it would be detectable given at least the currently available methods and the level of quantification, however, we did confirm that there was no transport of PEG into the brain, which I believe is at least one important concern to lay at rest.

DR. STOWELL: I think Dr. Garman had his hand up beforehand.

DR. GARMAN: Yes, since we're discussing the pathology report, I would like to know at some point how extensively the brain was sampled, numbers of sections, what neuroanatomic regions. For example, were the circumventricular organs examined, and were the immunostains for PEG performed on every brain section or just selectively, say, for the choroid plexus?

DR. SEREMETIS: I'm going to ask Dr. Lars Madsen to elaborate on this.

DR. MADSEN: Lars Madsen.

Could we have PN-1 to 9? So excuses for the maybe not so appealing photograph, but this is a picture of where the sections from the brain were taken. So it's a total of five sections, including the circumventricular organs. They were all examined both by histopathology as well as also by immunohistochemistry, and this is on that basis that we concluded there was no PEG in the brain tissue and also that

there was no vacuolation or any other adverse effects for that matter related to PEG.

DR. GARMAN: How about on the monkey studies?

DR. MADSEN: So in the monkey studies, I will spare you for any pictures, as I don't have any, but there was also more samples examined. Do we have a slide showing exactly which? But we can come back to you. Okay, I do have it here. So this is the brain sections that were examined in monkeys in the two top rows, so two sections by standard H&E, and one section, including the choroid plexus, by immunohistochemistry.

DR. RAO: This is Deepa Rao.

DR. STOWELL: Speaker from the FDA.

DR. RAO: From the FDA.

So, in general, about three to five sections were reviewed. There was no PEGylation accumulation within the brain parenchyma. They were within the blood vessels, and the animals were dosed intravenously, so that makes sense. But the question is that we saw the accumulation within the choroid epithelial cells, also potentially within the macrophages in the choroid plexus and within the stroma and the connective tissue subepithelial. So as the applicant showed in one of their slides that there is pinocytosis of this material into the choroid epithelial cells, so the real question is where is it going after it is within the choroid epithelial cells? Is it getting into the CSF, and is it getting cleared?

DR. GARMAN: And just as a follow-up, when you see staining in the blood, are we talking about within monocytes in the blood? Are we talking about free PEG?

DR. RAO: So within the blood vessels, and this was immunohistochemistry, so the blood vessels just light up, so we're not seeing clear accumulation within the individual's blood cells. But there's no perivascular inflammation around the blood vessels either.

DR. GARMAN: Just one other follow-up about the animal studies. One question, I see that because of the neutralizing antibodies, that these animals were not -- especially the primate model was not carried out in long term; it was a relatively short-term look. Is there any way to analyze, in this model, long-term effects 1 to 2 years out in the primate model, or is it really true that the neutralizing antibodies don't allow that to happen?

DR. SEREMETIS: I'm going to ask Dr. Lars Madsen to walk you through this.

DR. MADSEN: So Lars Madsen.

No, unfortunately, with regards to monkeys, it's not possible to dose beyond -- between 2 and 4 weeks until the development of antibodies induce acquired hemophilia. However, for all the PEGylated products, there have been long-term chronicled sub-studies with very high doses also in monkeys. And the only finding beyond normal has been vacuolation;

there's been no toxicities observed.

DR. STOWELL: Dr. Onyike.

DR. ONYIKE: Sorry. Were there any changes in brain weight in the rodents or primates?

DR. SEREMETIS: Dr. Madsen.

DR. MADSEN: No. So in terms of the extensive literature on PEG, the overall and general conclusion from every review paper and original -- that there is no toxicity specifically associated with PEG. But to comment further on that, I would like to ask our PEG expert, Dr. Jennifer Sims, to the microphone.

DR. SIMS: Good morning. My name is Jennifer Sims. I'm an independent nonclinical expert with experience in PEG safety and disposition. I was also coauthor on a couple of recent peer-reviewed manuscripts on these aspects. And in one of these recent peer-reviewed manuscripts, we reviewed the safety of PEGylated protein, so the 11 approved PEGylated proteins and also, in addition, 17 PEGylated proteins that were currently in clinical development.

And in no case we did not see any evidence of any toxicity, any organ dysfunction. Even though there was vacuolation observed with some of the 30 and 40-kDa PEGylated proteins, it was not associated with any cellular damage or any toxicity or any organ dysfunction.

DR. STOWELL: Maybe start with Dr. Manuelidis.

DR. MANUELIDIS: A very fast question. Has anyone done any studies inoculating a monkey, a newborn, in the first few days with these substances? And two, has anybody done any studies intravenously infusing a very old monkey that has probably some senile changes?

DR. SEREMETIS: With regard to the first, the answer is no. With regard to the last question, Lars Madsen.

DR. MADSEN: No, not to our knowledge. You could say the age span that we have covered in the animal studies that we have conducted does not include very old monkeys. They're up to 3 years of old -- old.

DR. STOWELL: Dr. Lerner.

DR. LERNER: Couldn't you just look at the PEG molecule itself in the monkeys rather than have it with the factor IX?

DR. SEREMETIS: Dr. Madsen.

DR. LERNER: Because you would avoid the immunogenicity supposedly.

DR. MADSEN: Yes. So these were the studies that I actually referred to before, so maybe I can have PN-7 again. So the studies, and maybe it wasn't clear from what I said, but what you see in this table are the studies that were discussed in our core presentation, namely the studies that were conducted with N9-GP without finding any adverse events.

And then the studies at the bottom are studies that were conducted with PEG alone up to 13 weeks of dosing in monkeys up

to 200-fold of the clinical dose, again, without any adverse effects. But however, in these studies we were able to demonstrate vacuolation, which is a known phenomenon.

DR. LERNER: I think Dr. Packer was suggesting longer-term studies, and that's what I was really referring to.

DR. MADSEN: Yeah. And there I have to refer to literature. There is at least studies of 52 weeks duration at very high doses in monkeys without any adverse function consequences, as described by Dr. Sims.

DR. STOWELL: I think there was another hand out here. Yeah, Dr. Ortel.

DR. ORTEL: So a more practical question. You described having more follow-up of reported events, and it's been recommended that a more systematic approach be taken to that. But looking at the types of events that have been reported, they're fairly nonspecific, and I was just curious, what are you going to tell people to do if these events turn up, if a child has headaches or if somebody has something? What is going to be a recommendation or what should the provider do other than note it?

DR. SEREMETIS: We fully agree that these are quite nonspecific events. We have, in fact, in up to -- in fact, over 4 years of follow-up in some of the younger children, seen no signals suggestive of repetitive or severe headaches and so forth. So we will ask for reporting of events as in the

context of ongoing clinical care and, on a case-by-case basis, follow up in detail.

Do you want to comment on this, Mette, in terms of exactly how this will proceed?

DR. SIMONSEN: Yes, Mette Simonsen.

So as just mentioned, we have seen no clinical signs or symptoms related to this. We monitor the events that come in, and in case we evaluate that there could be a concern based on the events we evaluate, we'll make appropriate actions to ensure the patient's safety. So it would really depend on the situation. We evaluate the data. Currently, we have not seen that there is a causal relation between the events and N9-GP.

DR. STOWELL: Dr. Packer.

DR. PACKER: I don't want to belittle how exciting it is for these kids to be able to potentially live completely normal lives, and I think that's extremely important, but we still have to put this into some context. We're talking about 20, 25 children at this point. What is the number of children between 0 and 12 and also between 0 and 6 you believe would be candidates for this drug over the next 2 to 3 years? How many do you see treating if this drug is approved? As we talk about surveillance events.

DR. SEREMETIS: Okay, we can look at reported numbers in the U.S. for hemophilia B, and this is from the ongoing data collection by the CDC. So we're talking about severe patients

with hemophilia B. These are the numbers below the age of 10, and below the age of 2 is broken down. So a subset of these would be candidates for --

DR. PACKER: I'm a little confused. Only between those with severe hemophilia B, or will this drug be available for all patients with hemophilia?

DR. SEREMETIS: Within the clinical development program, we've only treated severe hemophilia B.

DR. PACKER: I'm asking what this would be used for, if approved.

DR. SEREMETIS: The indication would be broader. So should a treating physician choose to treat to higher factor levels than are the ambient factor levels in the mild or moderate hemophilia patient, the drug could be used in mild or moderate hemophilia.

DR. PACKER: So theoretically, you're looking at possibly about a thousand children who would be candidates under age 10, and if there are any side effects, and we hope there are not, if they're in the 5% or lower range, that's when you'd start seeing them. Right now, with 20 kids or 25, it's hit or miss. So with chronic use, I'm just looking at the numbers, what you're looking at. So, in theory, if I read your slide, there would a thousand patients less than 10 who would be potential candidates.

DR. SEREMETIS: That's a reasonable reading of the

numbers.

DR. PACKER: Okay, thank you.

DR. DOBBS: I think I'd like to clarify something that it seems that members of the Committee are stating, but I'm not sure it's really being understood.

When looking at the safety of something and at rare events, you kind of need to have standard work and standard operational definitions of really what you're looking for, and it just doesn't seem, like on slide 74, that we really have those operational definitions yet for what are severe, non-resolving, repetitive headaches, what's the threshold for calling it that? How are we defining developmental delays in the neurological examination findings? I didn't know what's done at the hemophilia treatment centers; it's really extraordinary. It's really extraordinary work. I didn't know about those. But I'm not sure that it's really standard enough to give useful definitions to those clinicians that are seeing these patients and identifying what we hope are rare events that really do need standard work around them. Will these definitions be clarified?

DR. SEREMETIS: It's certainly the intent to clarify the definitions with regard to what should be sought. But again, you've reflected these are rare and perhaps nonexistent events.

DR. DOBBS: Yes.

DR. SEREMETIS: We're talking about a theoretical risk

that has not yet been documented in this or any other development program using a 40-kDa PEG. So it's very difficult to finely describe precisely what we're looking for because -- and I leave it to you to describe what the potential complications of choroid plexus dysfunction might be, and in fact, we have shown no evidence of choroid plexus dysfunction in the nonclinical trials either. So we're left in a little bit of a conundrum. I think this is the best we can do.

We've thought very hard about this. We've consulted with a number of external neurologists, neurosurgical experts with regard to this question, and they're as puzzled as you are as to what could be asked. But we're pointing in a direction of looking for --

DR. DOBBS: I mean --

DR. SEREMETIS: -- events that we could define, yes. And we will plan to define those in the course of our discussions with the Agency.

DR. DOBBS: But there are good operational definitions for these things.

DR. SEREMETIS: Sure.

DR. DOBBS: I mean, you know, if you ask me, I could give you some in about an hour really. Don't ask me to do that.

DR. SEREMETIS: Okay.

(Laughter.)

DR. DOBBS: But I mean seriously, I think these could be

pretty well defined.

DR. SEREMETIS: Good. Okay, thank you.

DR. SHAPIRO: I think a related concern is that, you know, it seems that -- I also was not entirely aware of all the great work that's been done by hemophilia treatment centers, but it seems like they might vary in their resources and attention to subtleties of potential neurocognitive deficits, and also there's the fact that not all patients receive treatment through hemophilia treatment centers. So from what I understand, if the monitoring is through those centers, then any adverse effects experienced by those patients would fall through the cracks.

I guess another concern that's being expressed by the members of the Committee is that we may not want to only look for adverse events reported by patients, but to have some way of systematically detecting whether there might be emerging problems, especially in development, and it would seem like a monitoring plan for that could be produced that would involve, you know, standardized instruments that are not too burdensome.

So all these children, in order to receive this treatment, have to present to medical care fairly frequently. So it's a regular interval. It would be possible, at least in theory, to incorporate a standardized instrument measuring, for example, executive function or a standardized neurologic exam, of which there are several, several varieties, and so those could be

included as instruments as, you know, part of follow-up for receiving this treatment. I think that I agree, it seems like there is this theoretical -- but I wonder if that is something that is viewed as too burdensome to include in a follow-up monitoring plan.

DR. SEREMETIS: The Sponsor does not consider any measure too burdensome should it assure the safety of the patient, so it's certainly something we'll consider as we discuss further.

DR. STOWELL: Dr. Garman.

DR. GARMAN: I just wanted to jump back to my question about brain sampling to make sure I didn't misunderstand. The three sections of monkey brain that were shown, were those the three on which immunohistochemistry was performed, or were those the only sections of the monkey brain that were examined? And somewhere there was talk of 45 different tissues were examined. I'm sure the eyes were examined for evidence of PEG and maybe not immunohistochemically, and also the pituitary.

DR. SEREMETIS: Dr. Madsen, can you review these data?

DR. MADSEN: Yes. So the slide that I showed previously, just to share it once it again, so in the monkey studies there were two H&E sections performed, including the forebrain and the hindbrain, and immunohistochemistry was conducted on one of these. With regards to the tissues otherwise examined, you're correct that it's around 45 tissues. It included the standard OECD guideline tissue list, including, as you mentioned, the

pituitary and the eye and the optic nerve.

DR. GARMAN: But those two slides, H&E stained sections, that was the only part of the monkey brain you examined microscopically; is that correct?

DR. MADSEN: No, not -- every tissue was examined microscopically. It was only this brain section that was examined by immunohistochemistry, and you could say the reason why that was selected was due to the concern around potential accumulation of PEG in the choroid plexus, which has been listed by other 40-kDa PEGylated compound.

But whereas you could say that the tissue distribution and the quantification of PEG that we conducted, we used a quantitative method, which was using array overlay molecule, and there we were able to show the elimination of PEG from N9-GP in more than 30 tissues that were examined. All tissues that were examined, we could describe the elimination, and as you saw in my previous presentation, it was eliminated from all tissues also, thereby substantiating the fact that steady state was reached in both the clinical and the nonclinical studies.

DR. GARMAN: Thank you for clarifying. I'm just curious how many brain sections would be examined by H&E staining from a monkey. Not including immunohistochemistry, but just how extensive sampling was performed on these brains.

DR. MADSEN: So I'd like to come back to that question after the break. We will prepare a slide with details on this.

DR. STOWELL: I think we have time just for one more question.

DR. ONYIKE: Yeah.

DR. STOWELL: Dr. Onyike.

DR. ONYIKE: Thank you. I'm not quite sure I heard the answer to the question. Was there change in the brain weight of the rodents and the primates? Now, it's possible to stain for things and find nothing. There's a long history of that in neurodegenerative disease. So I really want to know, did the rodents or primates have a reduction in brain weight?

DR. STOWELL: And I think I --

DR. SEREMETIS: Dr. Madsen.

DR. STOWELL: -- missed Dr. Baker, if you have -- no? Okay.

DR. MADSEN: The answer is no. There was no change in brain weight.

DR. STOWELL: I think at this point we will have our invited speaker, Dr. Maria Lehtinen from Boston Children's.

DR. LEHTINEN: Well, thank you very much. I'm pleased to join you here for this meeting today, and I'm going to describe some of the development and functions of the choroid plexus-cerebrospinal fluid system and some of the ongoing research on that area.

And so cerebral spinal fluid is very well established in its passive roles for providing a fluid cushion for the

mammalian brain and its ability to maintain ionic balance for the nervous system, and also for its role in providing a sink for nervous system waste, and many of these waste products can then be sampled and used as biomarkers of many neurologic conditions.

More recent research in the field has begun to point to an active role that proteins in the cerebrospinal fluid, especially during brain development, have in instructing neural stem cells and the brain.

To summarize and give an overview of the mammalian brain and how the CSF flows, it's produced primarily by the choroid plexus tissues, which are highly vascularized tissues located in each ventricle in the brain. Certainly, other tissues that are adjacent to the ventricles can contribute to CSF composition, and there is mixing with the interstitial fluid in the brain.

The CSF flows, it's typically viewed that the CSF flows from the two lateral ventricles to the third ventricle to the fourth ventricle. Then it bases the spinal canal, and also, it can surround the brain in subarachnoid space from where it's then resorbed into the venous circulation by -- at the arachnoid granulations, for example, and as well as the lymphatics.

The image on the bottom right zooms in on sort of the structure, the basic structure, of the choroid plexus, which is

common to each ventricle in the brain, and here we can zoom into it in a little bit greater detail.

And so the epithelium consists of these choroid plexus epithelial cells that are joined by tight junctions, and these tight junctions and the epithelial cells form the blood CSF barrier. And so as I mentioned in the previous slide, the tissue is highly vascularized and it -- and which water from the blood is part of the water that then is found in the CSF. The vasculature in the choroid plexus is fenestrated, and so there is not the formal blood-brain barrier present in the choroid plexus that we see in other parts of the brain.

The cerebrospinal fluid is secreted primarily by these microvilli that extend into the cerebral ventricles.

In addition to the epithelial cells, we have many vascular cells. As I mentioned, there are these fenestrated capillaries, endothelial cells, and pericytes. In addition, the choroid plexus is home to many immune cells. We have choroid plexus macrophages, dendritic cells, Kolmer's epiplexus cells, which are thought to be sort of antigen presenting cells that reside on the internal side of the ventricles; and the choroid plexus is believed to be a port of immune cell entry into the CNS in various conditions.

It's estimated that healthy adults circulate about 150 mL of CSF at any given time and that the CSF turns over about three to four times on a daily basis, meaning that we're

producing upwards of 600 or 700 mL of CSF, which is about one pint of CSF over a 24-hour period. The CSF is secreted mostly by the microvilli, and as we age, the microvilli on the surface of the choroid plexus epithelial cells has been shown to decrease. And so along with that, there's the observation of reduced CSF production in the aging brain.

And on the bottom, these images, we have sort of EM images showing the surface of the choroid plexus epithelial cells as well as a cross-sectional image of an epithelial cell.

The epithelium is highly polarized, and this leads to the asymmetric localization of many channels, ion transporters, ATPases, which help establish gradients in ionic concentrations that then help drive water from the blood into the CSF. These epithelial cells then also produce a lot of proteins and various proteins, especially during development, that are secreted into the CSF along with the water from the blood that help constitute the cerebrospinal fluid.

We know from landmark studies carried out decades ago that the embryonic CSF is crucial for normal brain development, and these examples are from a developing chick carried out by Mary Desmond and Antone Jacobson. And what they found is that where the normal neural tissue expands and develops around these CSF-filled brain ventricles, if you intubate the brain during early stages of brain development and you prevent the accumulation of CSF in the brain ventricles, we have essentially a collapse of

the brain; we have very inappropriately dividing regions of the brain, and there's a lot of cell death.

In the converse condition, we have a condition called hydrocephalus, which is characterized by an excess accumulation of CSF inside the brain's ventricles, and this can really result from several different conditions. There can be a presence of excess production of CSF by the choroid plexus, such as in the condition of villous hypertrophy of the choroid plexus. Hydrocephalus can result from blockage of flow due to injury or disease or just developmental malformation of the brain, and there can also be an impaired resorption of CSF in the ventricular system.

In very young children, this can present itself with a rapid enlargement of the brain's ventricles. On MRI this can be monitored as an expansion of the ventricular space. On the right we have an MRI example of a normal individual, and an expanded hydrocephalic brain is shown on the left.

And so hydrocephalus can present an entire population from infants, very young infants, all the way to adults, and the clinical presentation can be slightly different. And so as I mentioned, in infants there could be a very rapid increase in brain size; that can be accompanied by vomiting, sleepiness, seizures, downward pointing of the eyes.

As a part of normal aging, there is a condition called normal pressure hydrocephalus, which is a gradual increase in

CSF volume in the adult brain that's thought to be attributed -- it's rooted to largely a decrease in the ability to reabsorb CSF into the venous circulation. And this is accompanied by increasing headaches, double vision, poor balance, urinary incontinence, personality changes, cognitive impairments, a diversity of clinical features that slowly characterize the onset of this disease.

Other pathologies of the choroid plexus can include choroid plexus cysts as an example of Aicardi syndrome. Choroid plexus cysts are common in the developing fetus with about 1 to 2% incidence. They can often resolve on their own. And they can occur with increased frequency in trisomies, for example, and occur in certain syndromes such as Aicardi syndrome.

We can have choroid plexus hemorrhages, for example, which tend to occur in infants at term rather than in premature infants, such as -- and so we're looking at infants greater than 35 weeks of gestation.

Choroid plexus hemorrhages are often associated with perinatal stress, hypoxia-ischemia, in addition to factors such as trauma, and anticoagulation therapy can trigger the onset of this condition. Vascular malformations can also contribute to choroid plexus hemorrhages.

Additional pathologies include choroid plexus tumors, which can present themselves in the form of benign -- more

benign papillomas and malignant carcinomas. They represent less than about 1% of brain tumors overall; however, in children it really represents -- they represent 10 to 20% of all tumors in the first year of life.

Choroid plexus carcinomas are regionalized, and they typically present in the lateral ventricles of children mostly between the ages of 2 and 4. In adults, these tumors are more often papillomas of the fourth ventricle. And this regionalization of tumor location and age of onset is very poorly understood.

In addition to these conditions, the CSF in the choroid plexus system is implicated in a number of other neurological conditions, and so I'd like to highlight just a few of these.

So the central nervous system really has only one major thyroid hormone carrier-distributor, and this is the choroid plexus derived transthyretin. CNS deficiencies in thyroid hormone are linked to abnormal brain development, dementia, depression, and other cognitive difficulties, and they can be due to systemic hypothyroidism or choroid plexus transthyretin defects.

The choroid plexus is also central to several different mechanisms that clear A-beta from the CSF in the brain, and A-beta is a compound which is implicated in the pathophysiology of Alzheimer's disease. And so we're looking at conditions, at steps in this process involving CSF-mediated A-beta clearance,

direct A-beta absorption, and A-beta chaperone and protease production, and these can be regulated in part by the choroid plexus.

Alzheimer's disease is also associated with accelerated atrophy of the choroid plexus, which may lead to decreased A-beta clearance via these three mechanisms.

And finally, I'd like to just point out that accelerated choroid plexus atrophy is also described in other neurologic conditions, including stroke, multiple sclerosis, schizophrenia, and other CNS diseases, really raising the possibility that accelerated choroid plexus atrophy can exacerbate and complicate multiple CNS disorders.

On this slide I'd like to summarize some recent findings on transcytosis of folate at the choroid plexus.

Folate is an essential vitamin B, and we acquire that from our diet. It's required for DNA and RNA synthesis, and the folate receptor alpha is actually highly expressed by these choroid plexus epithelial cells, and so there's a model in which folate transcytosis via the exosomes is a critical mechanism for transferring folate from the blood into the brain.

And here's an immunohistochemical section showing staining of the folate receptor alpha, and in this model we have a schematic showing how folate can be -- is internalized by choroid plexus epithelial cells at the basal membrane of these

cells and then transported into the CSF via exosomes. From the CSF, folate can then enter the brain parenchyma and have its favorable positive actions in the developing and in the mature brain.

In the last part of my talk, I'd like to touch on some of the recent developments and findings investigating the active instructive roles of CSF-distributed factors on brain development.

And here we have a coronal section of a human fetal brain, and we can appreciate that the cerebral spinal fluid really occupies a tremendous amount of real estate in this developing brain. The choroid plexus is the white tissue, the bilateral white tissue shown in this image, and on the left is an EM of actually eroded ventricular surface.

And so there's a growing body of work that's begun to investigate how the cerebral spinal fluid composition changes during early stages of brain development and how secreted signals by the choroid plexus are delivered to these neural progenitor cells shown on the left, which are directly in contact with the cerebrospinal fluid.

These neural stem cells interact with the secreted signals in the CSF, and these signals then can specify the survival, identity, and division of these neural stem cells and contribute to brain development.

Many of these studies have been carried out using rodent

models, and I'll show some of those data here.

Here is an example of the total protein concentration in a developing fetal rat CSF, and we can see that the total CSF concentration peaks during its embryonic field development, peaking at birth, P0, and then it rapidly declines postnatally into adulthood. And these observations have actually been confirmed and observed in many other species as well, shown here on the left from work of a number of labs around the world.

If we sample the CSF at individual time points during embryonic development and we analyze its protein composition, we can see great variance in the proteins that are delivered by the CSF.

And on the right is a silver staining analysis which shows the general protein banding patterns that are present in the CSF over the course of rat embryonic development and into adulthood. Each band represents an individual protein, and what we can see is there are proteins that are available very early on and then disappear. We observed the transient availability of proteins, and there are also proteins in the CSF that are present later on in adult life.

Here's an example of one factor that we've investigated in my lab, called insulin-like growth factor 2 or Ifg2 for short. This is a growth factor that's very important for the regulation of stem cells for many organs in our bodies during

development, and we've identified its transient availability in the developing rat cerebrospinal fluid.

In this example, shown here are bands on a western blot on the top panel. And consistent with an active secretion into the CSF by the choroid plexus on the right, we have an in situ showing its expression levels in the choroid plexus.

And so it's studies such as this that have really led to an analysis of the CSF proteome using many different techniques. And because many of the proteins in the CSF are thought to arise from the choroid plexus, this has opened up a field of research where a number of labs are starting to investigate how the choroid plexus epithelial cells, shown on the right, are actively sensing and receiving signals to modulate their activity and how the transcriptome of these cells may develop, may vary during the course of development and into adulthood to modulate CSF composition.

I will show some of the data from these rodent studies. We have an example here of a mouse brain at late embryonic development where the lateral ventricle choroid plexus and the fourth ventricle choroid plexus have been isolated. We've analyzed the gene expression profiles of these different tissues using a technique called RNA sequencing, and the heat map on the right is a color code of genes that are differently expressed between the different choroid plexus tissues located in different ventricles of the brain.

And this is a very complicated diagram, but I'd like to show it just to point out that the take-home message really is that there is regional diversity in the choroid plexus tissue. So we speak of the choroid plexus, but it actually has a unique identity in each ventricle in the brain.

Many of the regional gene expression patterns that we've observed actually parallel regionalization that's known to exist in the developing -- in developing organisms that are -- in these developmental changes, and patterns are conserved evolutionarily. In our model, we interpret these results to really then demonstrate that there is a regionalization or a basic patterning of the body plan that's retained in the different choroid plexus tissues and the different ventricles in the brain. That leads to a regionalized gene expression of the choroid plexus.

We see that many of these differences in regional gene expression patterns are conserved from the mouse to both macaque and human brain, actually sort of reinforcing the translational value of this research.

And when we go back to our mouse/rodent models where we have attempted to evaluate how these regional gene expression changes might contribute to the production of regionalized CSF, we find that the regionalization does lead to a selective secretion of different proteins into the different brain ventricles.

So while there is flux mixing and flow of CSF from the lateral ventricle to the third and the fourth at the initial sites of production, there are different proteins that are actively being secreted into the CSF.

Interestingly, while many of these studies have really focused on the developing embryonic rodent brain and the choroid plexus therein, when we examine these gene expression patterns in the adult choroid plexus in rodents, we see that these gene expression patterns change. And so that really means that there is a dynamic regulation of the choroid plexus transcriptome between embryonic and adult that really still remains to be understood at the mechanistic level.

These gene expression changes at the level of the cells and tissues themselves lead to the differential secretion of factors into condition medium in experiments where we've isolated the tissues.

And also, we're able to observe these regional differences in many different proteins, including some morphogens that are really key factors for driving and instructing brain development, including sonic hedgehog and IGF2. And in our studies, we found that these regional patterns are conserved in the primate brain as well.

And so to summarize, I've given you an overview of the current beliefs on the models of choroid plexus and CSF functions. The choroid plexus tissues in the brain's

ventricles are regionalized, they produce CSF for the nervous system, and the CSF flows throughout the nervous system. There's a tremendous turnover of the CSF during a 24-hour period, and the CSF composition varies tremendously from early stages of brain development into adulthood.

We know that the CSF has -- in addition to its very well-described passive roles for providing a fluid cushion for the nervous system, it also delivers important morphogens and growth-promoting factors for the developing brain. It's implicated also in a number of pathologies in the brain, including tumor genesis, hydrocephalus, and A-beta clearance, for example, which I mentioned in the previous slides.

And so with that, I'd like to thank you, and I'd like to acknowledge and thank our collaborators who have helped to contribute to many of the studies that I described, and we're grateful for our funding sources that enable us to carry out this research in this field. Thanks very much.

DR. STOWELL: Thank you.

We'll now proffer questions of the speaker.

DR. BASAVARAJU: So you talked about the choroid plexus and a change in stroke and schizophrenia and things like that. Do you know how -- what the changes on the choroid plexus are in other like common pediatric cognitive or behavioral disorders, you know, like ADD and things like that, or are there any known changes to the choroid plexus?

DR. LEHTINEN: So this is a really important question. The basic science is really starting to suggest that there are important roles for the choroid plexus CSF, and CSF and hydrocephalus is also associated with many different neurological conditions. But the specific changes in many of these conditions that you are referring to are really poorly understood at the level of individual cells in the choroid plexus.

DR. STOWELL: Dr. Garman.

DR. GARMAN: That was a very excellent overview, and we used to just think of lysosomes as being the trash cans of the cell, and now it's being realized that lysosomes are very important in cell functioning and are critical for a certain pathway such as autophagy.

So my question to you, you're more of a cell biologist than I am, if I take an ependymal cell and I stuff it full of PEG-containing lysosomes, how do you think that would affect the function of that cell in doing some of the protein secretion processes that are so important?

DR. LEHTINEN: That's a really important question and I have to say I'm not aware of any specific studies that have addressed that question directly. If I have to hypothesize, we know that the choroid plexus epithelial cells are really important for the clearance of A-beta, for example, and lysosomal clearance and breakdown mechanisms are important for

degradation of many different factors.

No, I think that these things would -- it would be important to design tests to study at least a couple of activities or factors that are known to be cleared or known to transit through the choroid plexus to begin to address these questions.

DR. SHAPIRO: I have two questions that are somewhat related. And as you know, we're trying to figure out whatever we can about how the accumulation of PEG in choroid plexus epithelium might affect choroid plexus function and, more broadly, nervous system development.

So the first question is how specific is transcytosis across the choroid plexus epithelium? So if there is accumulation of PEG within the choroid plexus epithelium, is it reasonable to think that that might be then secreted into the CSF and that there might be accumulation of PEG in the CSF? I realize this is speculative and you might not know the answer.

And the second question is, are there differences in permeability of the blood CSF barrier and transcytosis of substances across choroid plexus epithelium with development? So, for example, do you see more permeability in infants and young children compared to adults or older adults?

DR. LEHTINEN: Okay. So there are a lot of questions in there, so I'll try to address the first question first, but if I'm missing something, please remind me.

So the first question was if the PEG can accumulate in the choroid plexus epithelial cells and if there might be indication that that could interfere with normal transcytosis or if the PEG can end up in the CSF?

DR. SHAPIRO: Right. Or if the PEG could end up -- well, actually -- yeah, both. So you unpacked that into questions, but one is whether the PEG could then end up in the CSF, and the second is whether it would interfere with normal transcytosis.

DR. LEHTINEN: So I think if the PEG is being transcytosed, then I would predict that it could be present in the CSF, and I think that would be worth testing. In terms of interfering with transcytosis, other mechanisms or other molecules that are being transcytosed and transported that need to be transported, that would certainly be something that could be tested, I would imagine, with perhaps folate as a candidate marker because the assays seem to be well established.

In terms of the age-dependent changes in transcytosis, those are not very well understood and characterized at this point. We know that the CSF protein concentration peaks near birth in rodents and then declines, but even the mechanisms for rapid decline in CSF protein concentration is not very well understood, and it may be that that may have something to do with the maturation of the brain -- of lymphatics and arachnoid granulations. And there really are limited studies, limited to

no studies examining these developmental processes.

DR. PACKER: I've read more about the choroid plexus in the last 48 hours than I have in the last 20 years, so I'm trying to understand if vacuolation, which keeps being brought up, is just a compensatory mechanism of the macrophages in the choroid plexus and pericytes or whatever they are and that is just compensatory and then they -- when the PEG is gone, they settle down and they disappear, the vacuolation, or does vacuolation really represent any real damage to the choroid plexus?

DR. LEHTINEN: These are good points. It would be something that we could think of different ways to test that in animal models, for example, if there's PEG that's presented, and we could really look at tests for the accumulation of these vacuoles and see if they're eliminated later on. I don't know of any specific study that has looked at that.

DR. PACKER: And the follow-up to that is we've heard from the FDA that we don't really want to talk about other PEG studies because PEG is different in different ways.

Is there any evidence that PEG is that much more toxic or less toxic at different weights or different configurations, or is this a relatively inert object that sort of gets swallowed by the choroid plexus and disappears? How much variation have you seen, and do you think that the PEG causes different types of PEG?

DR. LEHTINEN: I'm not aware of that at all actually, so it may be that data are out there to answer that question, but I'm not aware of those studies.

DR. STOWELL: Dr. Elmore, I believe you have a question.

DR. ELMORE: Thank you. Susan Elmore. Thank you for that wonderful presentation. I think that you're really doing some good work in your lab, and that really underscores the complexities of the choroid plexus.

What we know about this -- and, you know, we know a lot about the choroid plexus; of course, there's also a lot that we don't know, as you're aware. And in newborn mice, we know that the choroid plexus epithelial cells function as neural progenitor cells, at least for a period of time. They can give rise to, for example, astrocytes, and that disability decreases with age.

We also know that for a time there's almost a fivefold increase in the number of newly divided cells which are proliferating immature neurons in the choroid plexus of mice at 1 year of age. So, you know, this really underscores that it's a very important stem cell niche for a period of time, and you did allude to that earlier.

And then when we look at the aged, at aged mice, we also see that there are some structural changes like lipid droplets, like dense bodies, changes in the microvilli, they become longer. So there are changes that occur, you know, in the

choroid plexus of aged mice, as well.

So these are just looking at rodents. So I guess, you know, there really should be a concern whether or not, as Dr. Garman alluded to, PEG accumulation within the choroid plexus could cause some functional change.

So I guess mine is just really a comment, not so much of a question, but again just underscoring the complexity of the choroid plexus.

DR. CHITLUR: Do you see vacuolation -- first of all, thank you very much. That was an excellent presentation. Do you see vacuolation in the choroid plexus as a result of some infectious complications? Is that something that's been seen or studied? And if there is increase in vacuolation of the choroid plexus, does it actually affect the function of -- you described various functions of these cells. Do we know if that directly translates into dysfunction?

DR. LEHTINEN: Yes. So I'm not aware of studies that have looked at specifically the vacuolation under those conditions. As was brought up in some of the earlier discussions, it's very -- we don't have a lot of great assays for evaluating the functions of the choroid plexus, to begin with, in a dish because it's so much a part of the whole body physiology. It's really at the receiving the blood supply; it's at the interface between the blood and the brain.

And so this is really something that is an area of active

research at this time to try to establish assays that can evaluate what normal choroid plexus function is under these different categories that we think of tasks that it is -- we believe it's accomplishing in the brain.

DR. STOWELL: So last question. Dr. Ortel.

DR. ORTEL: So in one of the presentations from the Sponsor, there was discussion about one of the studies, that vacuolation was not observed at an increased rate in the N9-GP compared to just vehicle, and it was overall fairly uncommon.

I was just curious, in the normal anatomy or review of the choroid plexus, are vacuoles seen at some percentage in normals, if you just look across the spectrum of people? Because this is just comparing vehicle with drug, so I'm not quite sure -- I don't have an idea of what baseline is.

DR. LEHTINEN: So I'm not aware of any study that has systematically documented that.

DR. STOWELL: Dr. Lehtinen, thanks very much for your very helpful talk.

At this point, we'll move to the Open Public Hearing part of this session today. We have got three speakers that we're aware of at this point. I need to read for you the Open Public Hearing statement.

So both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open

Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So the first person, I believe, who we'll have speak is Mark Skinner, who is representing the National Hemophilia Foundation.

MR. SKINNER: So good morning, Mr. Chairman. Does this work? Is this where you want us?

DR. STOWELL: Please, go ahead. And for all speakers, if you'd please confine yourself to about 5 minutes.

MR. SKINNER: Correct. So I am Mark Skinner, and I guess the first thing that I should clarify is I'm not speaking officially on behalf of the National Hemophilia Foundation.

Although I have a long history of leading both national and international patient organizations, I'm speaking today as an individual, a patient who lives with severe hemophilia.

The disclosure that would be appropriate for me to make is I am the principal investigator on an independent initiated research study looking at patient outcomes of hemophilia. Novo Nordisk, along with the competitors of Novo that make competing products for factor IX, also are studied, so it's a multi-sponsor funded study that includes Novo. And I am a paid consultant of the National Hemophilia Foundation.

Patients very much appreciate the recognition that it is appropriate to consider patient perspectives in drug development approvals. Patients do, in fact, consider things very differently than clinicians, researchers, or regulators.

As part of the FDA Patient-Focused Drug Development Initiative, which included hemophilia and bleeding disorders as one of the topics, the National Hemophilia Foundation and the Hemophilia Federation of America jointly surveyed patients, and patients were specifically asked about the advantages and disadvantages of the current treatments and what characterized their ideal treatment.

Responses to these questions support the community's desire for longer-lasting products. Sixty-four percent of the patients to the survey said the ideal treatment would last longer so they could infuse less frequently, and 41% said the

most significant disadvantage of their current treatment is that they have to treat too frequently. The full study and the results are actually part of the FDA record, which is available.

Additionally, in a 2014 multinational patient perspective study, which included the United States, patients were asked to choose would they prefer higher trough levels or reduced frequency in infusion, and the responses were actually split about 50/50 across the national -- the international sample. However, it was also clear from this research that if patients had their choice, they want both, which seems logical.

And so part of my comment today is patients really should not have to choose between a longer-lasting product and one that is more efficacious.

In published medical peer-reviewed literature, I previously challenged the notion that the target treatment level should continue to maintain a trough level of greater than 1%.

Patients and clinicians have been conditioned to accept converting their phenotype from severe to a moderate state, and this has been the treatment standard since the 1960s, and this has been interpreted to be a treatment level of greater than 1%. Given product advances over the past 50-plus years, it is time to consider whether the 1% treatment is really sufficient to prevent bleeding or whether it's simply based on historical

considerations, product limitations at the time, the treatment burden that would ensue, or the cost of the product.

Science has brought us to a point where a new paradigm with new treatment goals are actually at hand and where treatment could actually mimic a more normal state approaching 50% of a range of normal. Patients, in fact, have a desire to be normal, to live a life spontaneously without the risk of spontaneous bleeds.

There's an ongoing need for new and additional treatments for factor IX products, and the National Hemophilia Foundation's Medical Advisory Committee, in fact, has called for the full range of clotting factor products to be available. They're not pharmacologically equivalent, and they vary based on their purity and a number of other factors, including the mechanism of extension.

The characteristics of each product, the resultant product choice are for an individual patient and their clinician to make. It is a complex decision-making process and one which the community has great familiarity. And although the community was asked to narrowly consider and focus its attention on this core set of issues today, it is really hard to separate the issues being considered today from the overall risk-benefit profile. Whether or not and how patients would choose to transition to a new product is something that patients and clinicians can make.

The safest, most effective drug that is not available to patients is of no benefit to a patient. And so post-authorization surveillance studies, in fact, are a typical way to monitor for long-term safety concerns.

If we analogize to the history of inhibitors where we've tried to predict the immunogenicity of different products premarket, we've learned that we've been wrong, and it may take 10 or 20 or 30 years of postmarket surveillance work to actually understand. We believe that the issues being faced today are very analogous to history and probably ones that we'll face again soon when gene therapy and other products are before us.

So, lastly, I would say if the Committee or the FDA has ongoing questions or concerns about patient perspectives or how clinicians are managing these decisions in their clinical decision making today, we would encourage you to take the time to reach out more broadly and talk to the community about it.

Unfortunately, the Committee questions were just published this past Friday, and so the time between understanding the narrow specificity with which the Committee was being asked to consider and today's hearing was relatively short, and we would encourage time to look at that more broadly.

Thank you.

DR. STOWELL: Thank you very much.

The next speaker is Wayne Cook, who is the president of

the Coalition for Hemophilia B.

MR. COOK: Thank you, Mr. Chairman.

I was invited here, and I was compensated for my travel and lodging by Novo Nordisk.

As the Chairman said, my name is Wayne Cook. I'm President of the Coalition for Hemophilia B. I also have severe factor IX hemophilia along with two daughters with hemophilia and a grandson with severe factor IX hemophilia. I'm here today just to, you know, just to give my perspective of, you know, what's going on in the community with people that I deal with through the coalition as a community advocate. I've been a community advocate for over 30 years now and dealt with people in our factor IX community, and it's been a long-term thing that we have looked forward to for many, many years of having new products when we didn't have many choices.

Patient choices is a big thing in our community, especially in the factor IX community, you know, and anytime that there is a new drug that comes out or is being introduced to the community, our group, the factor IX group, really looks forward to it and anything that can help. These long-term drugs that are being -- that are coming out with the longer half-lifes and stuff like that, these are great things for not only just people like myself, but our younger generations and our younger kids.

One thing that comes to my mind is Dr. Christopher Walsh,

when he speaks, he always says, he says how many bleeds are enough, you know, how many bleeds does it need to take before you start stopping the bleeds? And that's what we need; we need to have these drugs to come out so we can live the normal lives that we should have had.

Myself, I mean, the multiple surgeries and joint replacements and everything that I've gone through, or my 56 years of being alive, you know, I cherish what these kids in the new generation has. It's a great time in our community, and I personally think that I would never have ever thought that in my lifetime I would see the drugs and the medication that's out there to control our bleeding and a possible cure for hemophilia.

So, you know, we need these, we need patient choices that we can work with, and whatever works for our community, that's what we need.

So thank you for giving me this opportunity to speak, and I appreciate it. Thank you.

DR. STOWELL: Thank you, Mr. Cook.

The third person is Ben Shuldiner.

MR. SHULDINER: Hello. Good afternoon almost, I guess. It's 11:55. My name is Ben Shuldiner. I was compensated with my travel and lodging, but to put that in perspective, I was just at the Final Four in Phoenix, took a red-eye, got in at about 7:10 this morning. I am doing this on my own volition,

to say the very least. And the reason why I am here is, as Wayne and Mark said, this is really important stuff. I, too, have severe factor IX hemophilia, wonderful joint degradation and all sorts of issues that come along with having hemophilia and being a little bit older.

The medicine that we grew up with saved our lives, but it also wasn't that good. And so when you look at people who have hemophilia between the ages of 30, 40, 50, 60, a lot of us have really bad joints. And one of the reasons for that was we also tend to be terrible patients. We don't like taking our medicine when we're supposed to. We like to pretend that we don't have these bleeding disorders and instead do stupid things like, you know, play basketball and football.

But the problem, of course, was that we did have this disease, and the disease causes all sorts of issues in terms of internal bleeding. And the medicine, for years, had been, you know, infusions that you would have to take multiple times a week, sometimes three, four, even five times depending on how active you were.

And I will speak for myself here. I, like those remarks, was a terrible patient, and even though I was supposed to be taking my medicine all the time, who the hell really wants to put a needle in their arm and then inject yourself with a bunch of stuff? The long-lasting factor that this represents, and others do, has been a paradigm shift in the way that our

community handles itself, and I can say personally, it's been a paradigm shift to how I handle myself. I now get to take my medicine once a week. Oh, it's part of the trial.

This was the first time in my life that I was ever able to kind of stick to the program, and by sticking to the program, it has changed me physically and mentally. I am in much better shape, I feel much less pain, I am able to -- I mean, basically I'm an idiot for not having taken my medicine, you know, previously, but the fact that we have this stuff where you can take it once a week and feel good is really incredible.

But the reason why, I guess, I want to speak a little bit more is that the community also needs choice. To say that there is one medicine, that's fine, but it doesn't always work with everybody. And you guys are all the lauded doctors and folks who have studied this. All this stuff works differently on different folks. And what we find, of course, in the community -- it's a pretty tight-knit community. I know Wayne, I know Mark; they're really great guys. The fact that I get to speak after them is pretty great for me. You should listen to them much more than you should listen to me. But the idea is that this all works differently for different folks, even the same exact medicine. And so having a choice, knowing that there is a long-lasting factor out there -- I mean, there is also probably going to be competition and price, which is also helpful because this stuff is stupid expensive. And so that

kind of stuff is really, really helpful to us.

And the last thing I'd say is, you know, I'm actually -- you know, I'm a professor at Hunter, and I run a bunch of programs and, you know, I like research, and I like the idea that we can have multiple things and multiple choices.

But just to understand kind of very deeply the paradigm shift that this kind of medicine represents has changed dramatically the way that people in the hemophilia community live, and I am a product of that, and I can tell you just how happy I am to be on a long-lasting factor now, to have been part of this study, to have kind of been exposed to what this looked like and to know that it really does change me for the better. And I just urge that everybody at the table, you know, allows for this and other medicines that help this incredibly powerful and dynamic but very small community. We need your support and your help in allowing us to get the best medicine possible.

So, with that, I want to thank you guys all, and I think I'm the last one, so have lunch, right? And thank you.

DR. STOWELL: Thank you very much, Mr. Shuldiner.

Are there any other individuals from the public who would like to speak at this time?

(No response.)

DR. STOWELL: Seeing none, then, we will adjourn for lunch, and we will reconvene at 1:15.

(Whereupon, at 12:00 p.m., a lunch recess was taken.)

AFTERNOON SESSION

(1:14 p.m.)

DR. STOWELL: Welcome back, everybody, from lunch. Thank you for coming, returning.

In this session this afternoon, we will be considering the five questions which the FDA has posed to the Committee. We'll go through them one by one. The FDA has asked different members of the Committee to have a few comments about each of these points to sort of get the discussion going, and so we will go through that.

During the morning session, there were several questions which were posed to the folks at Novo Nordisk for some pieces of information. They have found that information and have a few slides. So I'll give them a chance to reply to those questions from earlier this morning.

DR. SEREMETIS: Hello. Okay. Good, thank you. Thank you, Dr. Stowell.

You asked a number of questions for which you wanted additional data, and with regard to the first question -- I'll take the last question that was asked, asking for more data, and that's about sectioning of the brain. And I'm going to ask Dr. Lars Madsen to come to the microphone.

DR. MADSEN: Lars Madsen, nonclinical.

So yes, I was asked about the sectioning of the monkey brain, and this is the actual section. Oh, it's not. Yes,

this is the actual sectioning that was done. So in contrast to what I said, it's actually five sections. It does include both the cerebellum, the midbrain, the cerebrum, and the medulla oblongata, and these slides were the standard done at that time.

So with these data, we were able to evaluate the histopathology. This is a representation of the choroid plexus, specifically in a control and a high-dose rat, and this is where we -- this is the type of analysis that we base our conclusion that there is no adverse effects. But this was further substantiated also by the fact that we did electron microscopy.

And I think maybe dwelling a little bit on this picture. So to the left, you have a control rat and to the right a high-dosed, 26-week dosed rat, and everything in the ultrastructure was normal. The only finding was, as we have discussed also this morning, the fact that we could see microvesicles with PEG, or lysosomes, that is. But maybe to sort of put our analysis into perspective, if I can briefly ask Dr. Henry Wall, our consultant pathologist, to give his perspective.

DR. WALL: Good afternoon. I'm Dr. Henry Wall, an independent consulting veterinary pathologist with over 35 years of experience in toxicologic pathology, including use of electron microscopy quite extensively, and I have experience evaluating and interpreting effects of PEGylated compounds.

I had an opportunity to look at study reports and closely evaluate the data, and the testing was quite comprehensive and went well beyond normal testing, to include light microscopy, immunohistochemistry, and transmission electron microscopy. And I also noted that the data was reviewed by two external pathologists, and I concur with their findings, that there was no treatment-related vacuolation.

And I also wanted to just get back to the point that the immunohistochemistry and EM demonstrated the presence of PEG and vesicles, but that was not quantitative. Dr. Madsen showed four graphs of the elimination curves of PEG, and I want to just emphasize that PEG was eliminated from all the tissues, including the choroid plexus.

DR. SEREMETIS: Thank you, Dr. Wall.

We were also asked about breakdown by age in the pediatric study. So we're only looking now at the 0 to 2 age group, and that was within the cohort of 0 to 6. These are the four patients who were enrolled in the previously treated patient study, who would be below the age of 2, and there were an additional eight over the age of -- 3 or over. And you can see the country distribution.

With regard to what we saw in these patients, this is the summary of all adverse events reported in children, both age cohorts 0 to 2 and 3 to 6, and as you can see, the majority were mild and unlikely related to N9-GP. The one anticipated

question that was considered possibly related was a gastrointestinal disorder, and there was some uncertainty about the relationship. So it was related to this possibly.

As you can also see, there were no nervous system disorders reported in either the 0 to 2 or 3 to 6 years age groups and no psychiatric disorders reported in these age groups.

That sufficiently addresses that question. And then I also wanted to mention that, beyond the previously treated patients, which has been what we focused on today, we have also enrolled the previously untreated patients. Actually to date, summary with regard to the number of previously untreated patients, we've enrolled 23, and 20 of these are below the age of 2. The longest time in assessment of these patients is 2½ years. So we have a larger cohort of previously untreated patients who have been followed for as long as 2½ years.

Now, with regard to the question raised regarding what treatment centers enrolled patients, this is a summary of the treatments centers from the U.S. that were involved in the clinical development program for N9-GP. As you can see, this is basically a distribution across the country, and it includes a lot of centers that I'm sure you're familiar with. So a quite broad distribution, 32 patients in 21 U.S. sites throughout the U.S. And we did not note any demographic or baseline information that differed amongst the enrollees from

the various sites, although there were very small numbers with each site.

And you asked a question about specifics with regard to demographics for the U.S. patients, and here is a summary of demographics for U.S. patients coming up. Oops, we've just lost it. Let's do it again. We're having a little technical difficulty. Let's try again. Okay. So yeah, good, it's stable now. This is both by age and by race. It's broken down: white, Hispanic, and black. And I think that the data speak for themselves as to the distribution that we were able to enroll in the study.

Okay. And just to perhaps reiterate based on some of the commentary in the open session. We are able to, with N9-GP, achieve very high levels of circulating factor IX. That allows for the elimination, largely elimination of spontaneous bleeding and specifically the significant mitigation of traumatic bleeding, the correction of target joint bleeding, and enhanced quality of life.

So we expect that this is an important consideration, as was articulated by the hemophilia patients, and hope that this will be considered when we think about going forward and understanding how to monitor these patients in the post-approval study.

Thank you very much.

DR. STOWELL: Okay, thank you very much.

All right. So they put up the slides with the series of questions, and the questions that the FDA has posed to us really focus around safety concerns. We're not really here today to vote on whether or not to recommend licensure or not for this product. Where the FDA is really looking for input is our thoughts about the safety profile of this material and whether there are concerns about it.

So the first question, basically, is they would like our thoughts about the clinical significance of the preclinical findings that they have noted, which have been presented to you today.

I think Dr. Garman was going to make some comments on that regard.

DR. GARMAN: Thank you.

I was originally going to talk a little bit about choroid plexus function, but Dr. Lehtinen did such a beautiful job of doing that, I'm going to skip all of that. And I believe, at this point in time, you all know as much about the choroid plexus as I do. So my comments are going to be based upon peer reviews that I've performed on five or six different PEGylated compounds, some of which have been approved and others which were removed from consideration. And I'd say that all of the ones, all of the compounds that I've looked at had greater amounts of PEG in the choroid plexus than this particular formulation.

Let me address this whole business of vacuolation a little bit because I think, for non-pathologists, the word "vacuolation," is that biologically significant? What is this?

In my experience, as PEG is taken up into the choroid plexus epithelial cells, you don't get vacuoles right away. The cells swell a little bit and they look a little bit more granular, and this is because the PEG is being sequestered into lysosomes, and eventually, at least for some compounds, you'll see choroid plexus epithelial cells that are just stuffed with lysosomes containing PEG.

It's later on, as the lysosomes either combine or you'll get combination with other endosomal portions, that you get these larger vacuoles. And so basically, what these vacuoles are is a combination of the lysosome-containing PEG and the PEG.

Now, sometimes these vacuoles don't stain with immunohistochemistry, and this may have to do with tissue processing. And for those of you that don't understand about paraffin sections, the tissue has to go through various changes of alcohols and xylenes, and some of this PEG may come out during the tissue processing.

So the bottom line is, to really assess if PEG is present in the choroid plexus epithelial cells, you can't just look for vacuoles; you really need to do the immunohistochemistry, and even that is somewhat controversial, or you need to do EM,

which is probably the gold standard.

So the question is, and I don't have an answer for this, if you fill these choroid plexus epithelial cells up with lysosomes containing PEG, how does that impact on the function of the epithelial cell per se? And Dr. Lehtinen talked about various pathways that potentially might be affected, but nobody has shown any definitive effects of this accumulation of PEG.

So getting back to Question 1, I mean, I think the only thing that is of any concern is this accumulation of PEG within these epithelial cells, and nobody really has a clue what that means from a safety standpoint.

I would point out one other thing, and that is that you really can't compare grades of vacuolation between studies. These are subjective grades. Now, sometimes pathologists will take -- you know, if there are multiple dose groups, they might take a very mild degree of vacuolation in the high-dose group and call that marked because they want to see if there's a treatment-related effect. So if you go to a lower dose, you call that moderate. You can't compare. And again, the vacuoles develop later, and so the degree of vacuolation may not necessarily indicate the PEG load for that cell.

Now, the Society of Toxicologic Pathology has a group that's looking into this. These are pathologists that are familiar with these studies, and they're going to try to come up with a standardized grading scheme which might allow for

these studies to be compared more accurately.

So I think that's it, unless there are questions.

DR. STOWELL: Thank you.

Dr. Manuelidis.

DR. MANUELIDIS: So I agree totally with what you say, as a pathologist. I think, though, that more can be done in terms of two issues. I haven't studied PEG in the choroid plexus, so you know a great deal more about it than I do, and there is no apparent toxic effect. But it does concern me, the children concern me still because I don't see any experiments where you're injecting even something like just PEG 40 at a very young age and not letting it subside and go away but really seeing what is the distribution of it.

And I asked somebody here, which I would love the answer to as well, is one of the interesting places is the eye, which is a direct way of seeing the brain, if there is a lot of PEG there and whether you see anything happening in the eye because it's so accessible, especially with some new types of technologies that are not wildly expensive.

So the second thing is I was very happy to see the ultrastructural studies were done. I do think that they could've been done a little bit more extensively in terms of function. So it's known that choroid plexus cells take up certain kinds of molecules, and they can actually -- some of them can be labeled in a very simple way so you can follow them

there, antibodies to certain small molecules.

And the question is would those molecules be changed in the way they're taken up in a cell that has a lot of lysosomes with PEG in it? And the reason I say that is because it's not just the choroid plexus, but macrophages are an important part of the innate immune system, and from what I've done with PEG in my life, that actually can make macrophages to be able to take up certain kinds of things much less effectively after they are stuffed with PEG.

So those are two of the questions. And the third question, as I mentioned, we're talking about the older people. You've heard about the functional changes and the decrease, and I think it would be really interesting, again, to have some kind of at least short experimental study seeing what happens in an older brain in an older animal, what is the change and the difference?

Another thing that I think I would like to suggest as a possibility is that CSF is pretty much simplified as comparison with a cell, and I think one can do proteomic types of studies very, very reasonably and seeing is the CSF really changed after PEG. Is there a difference within a certain age group? Okay. And then you can say does that mean something is de-differentiating or having less of a function? Is it not handling some of the factors the same way, or the enzymes that actually deal with these things? So that's a second thing.

And then finally, I'd like to say that, having seen lots of human brains with metabolic compromise at the end of life, you can get vacuoles from many, many different things. It's a phenotype, and it doesn't really tell you what the cause is.

DR. GARMAN: I should have mentioned that in some of these studies, we have seen vacuolated macrophages. Well, I'm not sure they're macrophages -- vacuolated cells in the choroid of the eye. And we also have sometimes seen them around some of the circumventricular organs.

And I should mention the CVOs, because there are six of them in the midline. Some people consider the choroid plexus as being the seventh CVO, circumventricular organ. And these are important because they don't have a complete blood-brain barrier, and I have seen some evidence of PEGylation either around some of the CVOs or in areas that they project to.

And this is why I asked the question earlier about how extensively the brain was sampled. I mean, typically in a monkey brain, if you're going to be looking at a potentially CNS-active compound, you're going to have at least, at minimum I would say, a dozen sections, and you want to sample all of these CVOs and also do immunohistochemistry on those to see if there's evidence of penetration of the PEG.

DR. STOWELL: Thank you.

Do other people have comments on this question? I think the focus here is on whether or not the observations made

during these preclinical studies have portended the clinical outcomes, have significance for clinical outcomes, and whether there is a reason to be concerned about those.

DR. PACKER: I don't think there's an excessive concern, but I think it's really fair to say that the studies are still relatively short term and you're talking about -- and if we were only thinking about giving the drug intermittently, preoperatively, or at times of bleeding, I think the preclinical studies, although maybe not absolutely complete, if you would do every -- everything would be quite reassuring.

Where I get lost in the process is if you're going to give this drug every week, 52 weeks out of the year for the next 10 years in the population that might have the most to gain from it, I don't think the preclinical studies have really addressed all the things. I don't know if they can, but if you ask me, honestly, that's where I'm a little bit lost in the process.

DR. STOWELL: Actually, the second question that the FDA has posed really kind of follows from the issues that both of you raised, and this is namely, sort of what is our level of concern, what's our level for potential safety concerns with this product, and particularly with regard to the vulnerable populations, so the very young and the very old.

So I think, so the FDA would like to have a feeling from us, if this is alarming, not concerning, some place in between, and if it's different depending upon the age group that you're

talking about.

So I think Dr. Shapiro may want to comment.

DR. SHAPIRO: Yeah, thank you. Yeah, I was asked to start the discussion on this question, and I think it does follow from the comments that were made in response to the previous question.

There are a lot of unknowns, so we're sort of asked to speculate based on a preclinical or a nonclinical finding of uncertain significance. But I guess it's incumbent on us to discuss this because the absence of evidence is not the same as evidence of absence.

So as I see it, there are two possible ways in which the accumulation of PEG in choroid plexus epithelium could have an effect on CNS development and function. One is relatively straightforward, I think, having to do with alteration of CSF fluid dynamics perhaps by transcytosis of PEG and accumulation of PEG and CSF or effects on, you know, other protein concentration and CSF leading to changes in CSF pressure.

And the other mechanism that I think could potentially be significant, although we don't know, is perhaps the function of choroid plexus epithelial cells might be altered in such a way that there is secretion of factors that are important for CNS development and is altered, for example, transthyretin or folate. And again, we don't know if that's the case, and as far as we can tell, there doesn't seem to be a function, an

effect on choroid plexus function. But again, we don't know.

So for either of those mechanisms, I think our highest level of concern would be in the youngest patients, so you know, perhaps in the 0- to 6-month age range, especially around the newborn period when transcytosis of proteins through the choroid plexus epithelium seems to be highest based on the studies that I've looked at. So there's more movement of protein into the CSF. The effects on CNS development are probably more active during that age range. And so we might expect that the developmental impact of either choroid plexus dysfunction or of accumulation of some material in the CSF that's not usually there is going to have a biggest impact on that age group, let's say 0 to 6 months.

Thankfully, it looks like no patients enrolled in this trial were within that age group, and it sounds like there are sort of limited indications for this product in that age group. So I'm not sure it's something that, practically speaking, you need to worry about very much, although the proposed indication does go down to birth.

In older children, let's say up to 6 months to 2 years, you'd still perhaps worry about effects of CSF dynamics and of regulatory factors secreted by the choroid plexus on neurodevelopment. And my concern about following up with children in that age range is that there might be changes that are of some clinical significance that we're not really able to

by the animal data.

So I think I heard a suggestion from a combination of two speakers on the other side, two panelists on the other side of the table, to go forward with approval in general but to limit the use from age -- from birth perhaps to 6 months, to comprehensive hemophilia treatment centers that have the resources to systematically monitor for neurologic effects through a mechanism that's decided upon and skilled pediatric neurologists doing the evaluations at those centers. And then one would have to decide what number of subjects are followed and for how long and you feel comfort with before reviewing that again.

So, again, just to limit the use in the very young age population to centers that have the skills and the knowledge to follow it, and that would include an informed consent to go over with the parent about what's known and not known in the very young age group.

DR. STOWELL: So I guess your suggestion then would be that the safety concerns really are this particular vulnerable population, and that for the other patients, it should otherwise go forward on its merits in terms of benefits and risks and so forth.

DR. LEITMAN: I personally don't have a great concern in the very -- based on everything I've heard, I do not have a significant concern. So my recommendation is to try and come

to some consensus that --

DR. STOWELL: Um-hum.

DR. LEITMAN: -- FDA might be comfortable with. But I personally feel, if I was given that informed consent as a parent, I would probably sign it if I had a child. So I feel assured by what I've heard today.

DR. STOWELL: Dr. Shapiro.

DR. SHAPIRO: So I think that that's an entirely reasonable proposal, and I just -- you know, from the comments I made earlier, I don't have any evidence-based reason to have a significant concern other than that we just don't have evidence. So I think it's unfortunate that that's what we need. Especially if there are going to be, at some point in the future, more PEGylated products of this type that are going to be administered chronically to children, we really need some kind of nonclinical data that indicates how the PEG is cleared and what effects it has on choroid plexus function.

But in the absence of that, you know, all we have is this evidence showing that PEG accumulates in the choroid plexus cells, which we don't know what it does, if anything.

So I think it makes a lot of sense, given that the theoretical concerns are probably highest, at least in my mind, for young children, that special care be taken to monitor and protect that population but recognize that, you know, despite our concerns, it may still be an extremely useful drug for that

population under certain circumstances and to make those -- to make our concerns into, I guess, a plan for protection of those patients explicit. I would say probably -- I mean, from my perspective, it probably would be a birth to 2-year age range, but that certainly is a topic of further discussion.

DR. BASAVARAJU: What you're proposing really is approval for older populations, but a study essentially for the younger population, right, before it would be approved for that group because that's what it sounds like. I mean, I would say that from what I'm hearing is that 2 and higher, up to 65 or something like that, it would be deemed to be safe, but in the younger population you'd want a study to sort of have more targeted neurologic or neuropsychiatric endpoints that are monitored first.

DR. STOWELL: Dr. Chitlur has a comment.

DR. CHITLUR: The problem with picking 2 years as the cutoff is that most children will require treatment before that. And if I'm going to start somebody at 9 months or 8 months, or whenever the kid starts walking, on a product, I'm not going to switch at 2 years if everything is going well. So it makes no -- I mean, if it's safe --

DR. STOWELL: Dr. Chitlur, could you speak into your microphone? Thank you.

DR. CHITLUR: Sorry. So what I'm saying is that if you pick 2 years as the cutoff age, the problem is most kids are

already on prophylaxis by the time they hit a year or a little over a year of age. As soon as they start walking is when we put kids on primary prophylaxis so that we can prevent any joint bleeding that can occur in these kids. So if I waited, there's going to be a very small population of kids that are actually going to be able to wait until they're 2 to be able to start treatment.

DR. STOWELL: Dr. Ortel.

DR. ORTEL: So as I'm listening to this, I'm wondering is it better, instead of having a certain age cutoff, to have a certain length of time that patients are followed from when they are put on the drug, because the question is accumulation or exposure over time. So if you have a child starting at 6 months versus one starting at 18 months, you would follow both of them for some length of time rather than mandated by a certain age cutoff.

DR. BAKER: In terms of the follow-up, I was very heartened to see the data that there were indeed 21 U.S. hemophilia treatment centers as opposed to 5 or just 10. That was very, very heartening. And to see that they were spread geographically throughout the U.S., that was also very heartening.

And I wish to just inform the Committee perhaps a little further that there is a very robust, mature U.S. hemophilia treatment center network that has been regionally organized

since about 1990 when the HIV crisis hit, and we are regionally organized with oversight and required involvement of CDC surveillance, initially for HIV but has expanded greatly. And also we can be quickly mobilized in terms of the sub-disciplines, meaning the nurses, the psychologists, the social workers, the physical therapists, who each in their own ways are looking at the neurodevelopmental, the cognitive delays.

So this is a very mature, rapid, highly organized group of team-based healthcare professionals for this rare disorder in the United States that can -- with sufficient resources could be mobilized to conduct the necessary robust, uniform, validated studies to look exactly at the particular endpoints to address the concerns that have been expressed around the room. So I wanted to let people know that, who might be less familiar with the U.S. hemophilia treatment center network.

And I want to also address my colleague across the table in terms of the access barriers. There are absolutely only about -- only about 70% of the U.S. population, hemophilia population, is seen in this network. Some of that is due to patient choice, but a lot of it is due to insurance restrictions. And not just insurance restrictions among the commercial insurers, but increasingly among the public insurers, and I am specifically referring to managed Medicaid.

So yes, we have many vulnerable populations, both among

the commercial insured and the Medicaid population, who have less and less access to these centers of excellence that the U.S. government, through HRSA and the CDC, have invested many, many dollars over the years. That is a treasure in this country.

DR. STOWELL: Dr. Leitman.

DR. LEITMAN: I just wanted to clarify what I said. I wasn't implying that I was in favor of a randomized controlled study for the young age, and it helps to hear that the network of comprehensive hemophilia treatment centers is so very well organized and has so many resources as a group, a very cohesive group, to collect data as a post-approval safety study from birth forward.

And I was only concerned about the very, very young infant, 0 to 6 months, who I thought was not well represented, represented by perhaps one or two subjects in the trials mentioned by the Sponsor, not by the 6-month plus, so just a clarification.

DR. STOWELL: Dr. Packer.

DR. PACKER: As a child neurologist, I would really push back that if you're looking for the very vulnerable and you're also trying to balance that they aren't walking, that you can certainly go 0 to 1 year of age. I don't think it's that easy to evaluate some of the developmental issues in a 6- or 7-month old, if you're going to really be taking the information.

And I keep coming back, and we'll talk about it in a different point, that these centers may be wonderful, and I'm very proud that we have all of these centers, but that doesn't mean unless there's a systematic way to obtain developmental data, some neurocognitive data, whatever you are concerned about in this young population that we'll talk about, that even the best center is going to give you data that's going to be useful and analyzable at the end.

So if we're going to approve this for a young patient population for prophylactic use, there are ways to build things in to be better off answering the question 3 to 4 years from now than we are. Now, if you take this with anecdotal data, even at the best center, we'll be talking about this for the next 5 years with no data, my opinion.

DR. DOBBS: I would just also, as a neurologist, second what Dr. Packer just said, that if approved, this is really an opportunity to learn more about the safety of these compounds neurologically and neurodevelopmentally, which is really missing from the current body of literature.

DR. PACKER: One last thing. These compounds will be expensive enough, will be enough of a financial issue that I think it will be -- there will be a way to finance, I believe, that kind of neurocognitive issue data that you need. No one's going to give this drug away. Someone is going to be paying a lot of money for it, and some of that could be potentially

reinvested and to answering that question for the younger patient population.

DR. STOWELL: Dr. Chitlur, you had your hand up.

DR. CHITLUR: I completely agree. I think at this point the best way forward would be to allow the drug to be used by the patients that really need it, which are the kids, and they are the really young ones, and for us to systematically collect the data so that moving forward we will be able to answer the question intelligently rather than based on rat models.

DR. STOWELL: I believe Dr. DeKosky on the phone has a comment for us. Dr. DeKosky?

DR. DeKOSKY: Yes, thank you very much. Can you hear me?

DR. STOWELL: Yes, we can.

DR. DeKOSKY: Yeah, I apologize. I was disconnected inadvertently for about 10 minutes and probably missed a bit of the discussion.

My last comments were that we know that it fills vacuoles. We don't know how much or how harmful it is, and we don't know the half-life. However, finding a way not only to monitor the children, because we can always stop it and we know that it does go away if it is kept on long enough, if it's withheld long enough, we could focus on trying to find a noninvasive way to answer this question for this PEG compound and perhaps for others, and that would be with MR spectroscopy, noninvasive.

It could be done on small children and would hopefully,

once we find ways to determine sensitivity of the methodology, answer the question from a developmental standpoint as well as from a longitudinal standpoint. I don't think there is much of a significant problem in the overage population, one of the groups that I was asked to think about specifically. But this would also be an excellent group if they stay on the medication in midlife for a significant period of time to be able to determine whether or not there is accumulation, which in and of itself does not necessarily mean there would be disruption of the metabolic, and the CSF provision effects of what the plexus does.

Again, if there was a way to do lumbar punctures, that would help us immediately with some of the trophic and transthyretin concerns. But unless there is an easy way to do that with guaranteed safety, I think we're limited to noninvasive things and to assessments of people over time. Overall, it may be safer to give the drug than not to give it.

DR. STOWELL: Other comments?

DR. SHAPIRO: Just to follow up on the last comment by Dr. DeKosky, I think it would certainly be interesting to do MR spectroscopy to look at various metabolites in the brain, but I would not advocate doing that for -- as part of the follow-up for children receiving this medication, mainly because in the young children that we're interested in, it would require anesthesia, and I think the risk of anesthesia probably

outweighs any benefit that we might derive from this kind of MR spectroscopy study. So it would be interesting, and I definitely think that we need more animal studies about the metabolism of PEG compounds.

DR. STOWELL: Dr. Packer.

DR. DeKOSKY: Well, I have no --

DR. STOWELL: Sorry. Dr. DeKosky.

DR. DeKOSKY: I have no --

DR. STOWELL: Go ahead.

DR. DeKOSKY: I have no objection to that. I agree. My thought was, number one, do this longitudinally to people who would be able to cooperate in the scanner. I wasn't thinking of going immediately to children. We first need to know if it does build up or not.

And second, we don't know how long this will take, but we certainly could do an animal study to prove the principle that you could reliably detect different levels in MRS and doing this in cyns, or in cynomolgus monkeys, would give us an answer to whether or not it is detectable or not. Yeah, I wouldn't anesthetize anyone to do something like this.

DR. PACKER: And I just wanted to jump in about the sedation issue and the LP issue. Even if you have biomarkers, you'll have nothing to correlate it with unless you know if it is two classes of patients, some who have developmental issues and some who don't have developmental issues. So first, you've

got to decide if there's a problem. Then you can potentially use a biomarker to help separate patients who decide to have the problem.

So I have difficulty in jumping into any MR or CSF studies or anything that even hints of being invasive unless we really know that there's a problem to follow so we can separate the patient populations. Animal data would be great.

DR. MANUELIDIS: In terms of the animal data, I think the FDA has their own CSF that's collected. It's right there, it's sitting, it's waiting to be used. I mean, it seems to me that one of the recommendations that we could use is to say this should be supporting in some way to look at some of these things. What is the CSF stuff that they have already on board? And maybe as well to recommend that it be done independently, you know, by those who have the drug.

DR. STOWELL: I think I'd like to move along to the third question, which is basically the same question, except here we're looking at if we think there are differences in the risks for patients or the possible safety risks for patients who would receive this product intermittently versus those who would be on maintenance therapy over the long term.

And I think Dr. Chiadi Onyike is going to make a few comments.

DR. ONYIKE: So firstly I'd say, in my estimation, it seems that the discussion has taken the format in the sense

that the comments have already bled into Questions 3, 4, and 5, so I'll stay short because there's not going to be much to add.

The first thing I would say is that the only difference between intermittent use and chronic use is uncertainty. I don't think that we have any data on the table from the clinical trial or from any other source suggesting that there is more danger or that there's more suffering, let me put it that way, in taking it chronically versus say intermittent use in a perioperative sense or in a trauma sense.

And so really, what we have is the absence of any indication that this is dangerous and therefore, and I think very persuasive arguments from my perspective, that we should not be using arbitrary age cutoffs, especially if those arbitrary age cutoffs will prevent people who will need the medication from getting it when they should.

So what we're really talking about, then, are vulnerable populations, very young people, maybe older people who might, you know, who might be suffering age-related cognitive decline or something more sinister, perhaps people with other neurodegenerative or neurological or neuropsychiatric conditions where there might then be interplay between whatever effects we imagine might come from this drug and whatever else might be happening in the brain.

And I think people have spoken eloquently to the need for careful monitoring. I think if there is anything about the

clinical -- the adverse effects data from the trial is that their monitoring was not sufficiently broad or deep or systematic. I have confidence these are very solid investigators and experienced experts in this field, so I have no doubt that they would not have missed anything important.

But nevertheless, vulnerable populations do not necessarily make it into clinical trials or do not make it in sufficient numbers, as Dr. Lerner has pointed out. And so it's very important therefore to have a robust post-surveillance program. I think it should be formal and informal. Mr. Templin has spoken very clearly about the issue of fidelity to any guidelines that require that people -- that the prescriber be in a center. And so it's important that any -- you know, there's a best precedent, for example, for postmarketing constraints that follow the drug.

Clozapine is very good example of this. I don't know if everyone is familiar with clozapine. It's an antipsychotic medication with rigid monitoring guidelines for people who are prescribed this medication, and in the first year they have to have blood draws every week. And then, over time, the constraint is relaxed as there's greater and greater confidence that the medication is safe. And I think a similar regime would be appropriate in this situation, not necessarily as rigid. And I'm not a subject matter expert, so I don't presume to say what kind of monitoring is essential.

Finally, I would say it's not obvious to me that we can sort out, in this meeting, what kinds of technologies or psychometric instruments -- actually, as mentioned, by the way, that I am a neuropsychiatrist, an expert in neurodegenerative disease, a clinical epidemiologist with specific interest in phenotype measurements, and I don't know that you can necessarily flesh it out here which instruments specifically should be used to monitor cognition or behavior or function. But it is essential that people with experience with this condition and with experience in measurement of cognition, whether it's in children or in elders, be engaged to help fashion the appropriate monitoring regime, at least for a formal program.

And then in that informal program, there might be something that is more -- there might be measures that are more amenable to bedside use and that are more focused, I would say, on serious things so you're not burdening every prescriber across the land with a battery of things that will essentially make it tedious to care for these people.

That's it in a nutshell.

DR. STOWELL: Dr. Ortel.

DR. ORTEL: So as has been said, we've kind of touched on this for the last couple of hours, the big issues, in my mind, are with intermittent use. Here, we're looking at the potential -- you're talking about maybe once a year or even

less frequently that a patient could be exposed to this type of agent at one extreme. It could be several times a year at the other extreme. So how to analyze that patient, I think, is something very different than the patient who's being put on this for prophylaxis with the intent being that they would continue that drug ongoing.

I think that here, trying to design additional studies in the preclinical sense can answer specific questions, but I'm not sure if they can help at this point.

I do like the idea of a very systematic approach. I think something that's drawn up and recommended as far as what types of assessments, at what age those should be made in the chronic, possibly lifelong patient population would be of value. I think making sure that the people administering those tests have done them repeatedly and feel comfortable doing them so that therefore you could compare across.

This is an uncommon disease, and from the perspective of even the hemophilia treatment centers, the number of patients who actually would fall in 0.2, the hemophilia B, the chronic treatment, you're not talking about a lot of patients at any given center. So having the expertise built in for the neurologic assessments or for the development assessments and making sure that it's following some systematic protocol is important, and then having some idea of what would this -- what will the signal be that will trigger a response and what should

that response be. What are you going to look for?

DR. STOWELL: We have a situation here -- we have a drug for a rare disease. If we want to -- we feel as though we need more information to make a decision about its safety and so on. The problem is we could do more studies over the next 5 years and accrue another 50 or 60 patients or something like that and not be that much farther along.

So I think the mechanism for this, as for a lot of rare diseases, is some sort of postmarketing mechanism whereby we can collect data prospectively, and it probably will end up being a larger number of people, and then use that to put together to inform us, because we do another study, but we're not going to detect a low-frequency event and especially amongst the very small population.

Dr. Leitman.

DR. LEITMAN: So I know the FDA asked questions in a specific way, and they'd like to hear the specific discussion. So there are two, there are Point 1 and Point 2 in this question. So I feel that I don't need any further evidence, that I'm convinced of safety by the evidence I've seen today for Point 1, which is intermittent use, because whatever storage in whatever cells it occurs, it is transient and reversible. So on demand, as needed for bleeding or pre-op, I feel comfortable that there is sufficient information and data provided by the Sponsor to assure comfort with the safety of

the drug.

DR. STOWELL: How do other people feel about this issue of intermittent versus chronic use?

DR. PACKER: As I said previously, I think there's no major issue on intermittent use, and we can talk about safeguards for chronic use. But intermittent use is fairly straightforward.

DR. ONYIKE: I don't see -- if I may.

DR. STOWELL: I see a few people also nodding.

DR. ONYIKE: Yeah, I don't see any issue for intermittent use at all. I don't see any danger for chronic use, only unanswered questions.

DR. STOWELL: So let's move along, then, to the next question, which is Question 4 and which has to do with what additional assessments might be done, either short term or long term, to help ensure the safety of this product. And I think we've already really begun that discussion in terms of some of the postmarketing types of data that we would like to collect. People have mentioned developmental and cognitive milestones, neurologic assessments and so forth.

Dr. Packer, you have a comment?

DR. PACKER: I think a lot of this has been mentioned. I think the basic things that you would do in an older child and an adult, headaches, confusion, unsteadiness, seizures, unexplained somnolence or other disturbances of consciousness,

ATHN database. So all of the information is collected on these patients, so adding a section on that database that specifically caters to looking at cognitive outcomes for the age groups that we are concerned about, which should not hopefully be too difficult to do.

So I think at this point of time, I feel comfortable taking this to my patients and saying that here's another option for you to be able to avail of.

DR. MANUELIDIS: I'm afraid I'm a little less sanguine because I think that there are two things I totally agree with Dr. Packer. I think that that can be put in, and it can be very safe. I still feel it's not 30 years to do an experiment that takes 1 year to test some of the functions and to do some of the injections and see what happens acutely in the young animal, a very young animal, and follow it and see if there are functional studies. I suggested some that take almost no time, like the proteomics, etc., of the CSF, like the amount of collection with two chronic doses, and then testing some of the functional uptake of molecules and the transient stuff and the edema and the hypotonicity and the protein and the CSF.

I think those are very straightforward studies that can be done, and I would love to see those studies done, so much so that they say when those studies are done, which I think can be done very rapidly, they can just basically say that's going to be one of the things that would say 0 to 2 years old can be

treated with it.

DR. STOWELL: Dr. Dobbs, do you have any comments that you would like to add?

DR. DOBBS: I thought I was Question 5.

DR. STOWELL: Yes, you are Question 5, but I think we have really sort of segued into Question 5.

DR. DOBBS: Then let's go with Question 5. You're right, sir, it actually is a very similar question.

A lot of Question 5 has already been discussed around the room. I would say that I don't have a recommendation for any additional clinical studies. I do agree that with the CSF, the animal CSF that's already available that -- I mean, it should be assayed.

What could we do going forward with postmarketing studies? Well, the idea of checking CSF or doing MRIs in the patients, I agree, that's probably out as a routine matter. However, if it's done for other reasons, other clinical reasons, I think that we should look at it and that we should examine that CSF if it's collected for other reasons.

I think we should follow cognitive outcomes in the postmarket data, probably requiring more neurocognitive data in pediatrics with some validated standardized tests.

It would be reasonable to require a full neurological exam, pre and post, especially in those folks that are at a fixed developmental stage, such as adults.

It would be reasonable to monitor children for signs and symptoms of hydrocephalus. It would be reasonable to monitor for papilledema or other visual disturbances.

But again, most of all in all of this, whatever we really do recommend, we need standardization, validation to do this the same for all of the patients. I could have more discussion, but that's really all that I have to recommend on this.

DR. STOWELL: Does anyone else have any comments?

DR. DeKOSKY: Yeah, this is Dr. DeKosky.

DR. STOWELL: Yes, please.

DR. DeKOSKY: With respect to -- and with all due respect to Dr. Packer, biomarkers were developed as a way to try and anticipate and potentially follow changes that might lead, at least in my world -- I'm also a neuropsychiatrist -- to be able to head off or shorten the time to know something before it would affect cognition, or if it is.

And I'm sitting here listening to the discussion about how we don't want to wait terribly long to find out, and yet we are dealing with vacuole storage of a compound, the toxicity of which is not known, hasn't been demonstrated, and it's uncertain as to whether it will continue to build up or, as with all of the animals and therefore likely in us as well, it will reach a steady state.

So I think the question is going to be if it reaches a

steady state, meaning it is removed, is it going to be toxic at the level of steady state that it achieves? No evidence of that from the admittedly few people that we have data for so far. But I do think that it's appropriate to dismiss biomarkers such as LP in anybody with hemophilia, unless it's absolutely necessary or unless they're under the big cover of a recent injection of factor IX, and it is also easy to say, well, we wouldn't want to give anesthesia to a small child, which I certainly agree with. I didn't decide to say it, but I recognize I should be very clear about this since I spend more of my time in the demented and elderly population.

On the other hand, animal studies that show us the metabolic output, we've already said, aren't going to be all that helpful in humans because both the time courses as well as the tox aren't exactly comparable. Nothing terrible happened, but if we came up with some kind of, for example, interference with folate metabolism or TTR, with transthyretin, if we were using doses that were tens multiples of the standard dose, how would that help us with respect to the humans?

I think this is a case in which we need to get down to some kind of reasonable dose, not just excess dose, and it's my own view, to determine exactly how disruptive it might be, given how high, although briefly, the levels go up and then come down even within a week.

So I would say that although it is easy enough to look at

specific cognitive testing, especially in anyone from their teenage years on up, but especially 25-year-olds who are relatively mature with respect to brain formation, I think it would be very useful to look hard for markers that would help us without having to wait to see a problem with children because there was some problem with the medication that we did not anticipate would happen.

I think it's useful to -- I keep reminding myself there's nothing but histology, there is no evidence of harm from this deposition, but none of us like depositing anything in the brain or the CSF or the choroid plexus of any child.

Now, there is a benefit-risk ratio here, which I believe, based on the data we have about harm, certainly says that this has great potential to be very helpful. The only question, how do we do this and how invasive should we make it, is for the oversight over time, keeping in mind both that we don't want to do anything to children below a certain age. And I would defer to the pediatricians about when you might have to use anesthesia or if you should or you just wait and do adults. But I would also look hard for a way to assess accumulation of this material in people over time, or accumulation in people, maybe even volunteers who get it, and then see how long the half-life is in a human, something which we don't have.

So to some extent, this is a big shadow on the wall of what might be, and I don't know that monitoring should be worse

than the disease or more problematic than taking care of the disease. I think we have kind of swung back and forth between there's some feeling of certainty that there is going to be a problem because we see changes in histology and the idea that this is a relatively benign product that does not appear to be doing any harm. At least it hasn't so far.

The only other comment I have is that while someone said that PEG products are all different, that's true, but it would be useful to look at the PEG which was the same molecular weight as the PEG used here and see if there are any data in that group or any safety studies being followed in some of those other patients. That would help to add to a thin database which is thin in large part because this is an uncommon disease.

Thank you.

DR. STOWELL: Okay, any -- oh, Dr. Chitlur.

DR. CHITLUR: Sorry, I should have asked this earlier. Is there any data of use in pregnant women?

DR. STOWELL: Is there any data --

DR. CHITLUR: Of use of a PEGylated product in pregnant women and if there is any effect on --

DR. SEREMETIS: Yes, there are data available, particularly with Cimzia, which is a 40k PEG molecule. And do you want to hear about that data, or is a yes sufficient?

DR. CHITLUR: Does the data show -- indicate any issues

with the fetus or the mother?

DR. SEREMETIS: Let me ask Dr. Sims to come to the microphone.

DR. SIMS: We can give you the reference. There is a published paper on pregnant women where they were given Cimzia all the way through gestation, all the way through pregnancy. Some women had -- were on Cimzia before pregnancy as well as being on it long term, and they measured maternal plasma PEG levels and core blood levels.

DR. CHITLUR: Okay.

DR. SIMS: There's no information about the outcome in the children.

DR. STOWELL: Dr. Leitman.

DR. LEITMAN: Does 40-kDa PEG cross the placenta? Because the developing brain in the fetus, it has to be the most vulnerable time of development.

DR. SIMS: I can't remember all the details of that paper. We can give you the reference so you can look for yourself. But my memory is, is that there was no evidence for that.

DR. STOWELL: Any other comments?

(No response.)

DR. STOWELL: So before we conclude this session, I'd like to ask the FDA if there are other points that they wish that we would address or --

DR. BRYAN: No. I really appreciate this thorough

discussion by the Committee. It's really been very helpful to us, and we'll appreciate and consider all of your comments in reviewing the BLA. And again, thank you to Novo Nordisk for developing this product.

DR. STOWELL: So we'll start our break a little bit on the early side, and let's plan to reconvene at 5 after, so 15 minutes from now.

(Off the record at 2:49 p.m.)

(On the record at 3:05 p.m.)

DR. STOWELL: So for this afternoon we have one item on the docket. This is an informational item, an update to the Committee from the FDA. The FDA is not seeking advice or guidance on this particular topic, but we should feel free to ask the FDA or any of the speakers questions, should they come up.

So this is regarding to a request for information that the FDA put out last summer about the MSM deferral policy, and Jennifer Scharpf from the FDA is going to be summarizing those results for us.

MS. SCHARPF: Good afternoon. My name is Jennifer Scharpf, and I'm the Associate Director for Policy in the Office of Blood Research and Review in CBER. My presentation will provide you with a summary of the responses to the FDA docket titled "Blood Donor Deferral Policy for Reducing the Risk of HIV Transmission by Blood and Blood Products." And as

noted on the slide, this docket was opened in July of 2016.

During my presentation I will present FDA's current recommendations to reduce the risk of HIV transmission through blood and blood products, review the rationale for the recent change to the donor deferral policy for men who have sex with men, referred to as MSM throughout the remainder of the presentation. I'll summarize comments to the public docket, which was opened in July of 2016, regarding HIV deferral policies. And then I'll share progress on the Transfusion-Transmissible Infection Monitoring System, referred to as TTIMS. And I'll conclude the presentation by briefly discussing FDA's future plans.

FDA's current recommendations are provided in a guidance document titled "Revised Recommendations for Reducing the Risk of HIV Transmission by Blood and Blood Components." This final guidance was issued in December of 2015.

The recommendations contained within the guidance replaced the 1992 memorandum to blood establishments and applies to the collection of blood and blood components, including source plasma.

The guidance provides FDA's revised recommendations for donor educational materials, donor questioning, deferral, and requalification, as well as blood product management with respect to HIV risk.

FDA's current donor deferral recommendations are as

follows:

The guidance recommends indefinite deferral from an individual that has ever had a positive HIV test, exchanged money for sex, or has a history of non-prescription injection drug use. And there's a related recommendation for a deferral for 12 months for a donor who has had sex with an individual having this history.

We recommend a 12-month deferral for receipt of allogenic blood transfusion, exposure to someone else's blood through needle stick, or receipt of a tattoo, ear, or body piercing, with certain exceptions as noted below.

We recommend a 12-month deferral following treatment or diagnosis of syphilis or gonorrhea, and finally, a 12-month deferral for men who have had sex with another man, and a related 12-month deferral for a woman who has had sex with a man having this history.

Over the next few slides I will review how FDA reached the current policy decision for deferral of MSM.

Since testing for HIV first became available in 1985, there have been calls for revising the blood donor deferral policy.

In June of 2010, the HHS Advisory Committee on Blood Safety and Availability recommended that the current donor deferral policies are suboptimal but that available scientific data are inadequate to support change to a specific alternative

policy, and the Committee recommended research to inform a possible policy change.

Subsequently, the Public Health Service, Blood, Organ and Tissue Safety working group designed and implemented one operational assessment and three research studies to help inform a potential policy change. And I'll outline these studies in the next slide.

So a number of different lines of evidence, including the studies recommended by the HHS Advisory Committee and designed by the PHS working group, supported a policy change. They included the QRE, or Quarantine Release Error Task Force Assessment. This operational assessment examined quarantine release errors or accidental release of an unsuitable unit and concluded that QREs contribute minimally to the risk of HIV transmission to the blood supply.

The Donor History Questionnaire Study conducted cognitive interviews with potential blood donors and found that individuals responded to the questions posed in the donor history questionnaire subjectively by answering is my blood safe, rather than providing the response to the literal questions posed in the questionnaire. The study also made recommendations for potential improvements to the donor history questionnaire and educational materials.

The REDS-II study, noted on this slide, was a pilot surveillance study that evaluated HIV, HBV, HCV, and HTLV in

50% of blood donors and assessed behavioral risk factors. An important finding of this study was that sex with an HIV-positive partner and history of male-to-male sex were the leading independent risk factors associated with HIV-positive blood donors, and this is consistent with the known epidemiology of such infections in the U.S.

The REDS-III BloodDROPS study examined the opinions of MSM regarding FDA's blood donor deferral policy and found a potential increase in the proportion of blood donors reporting MSM behavior, suggesting a decrease in compliance with the indefinite deferral policy.

And finally, FDA considered experience in Australia, a country with similar demographics and HIV epidemiology as in the U.S. A study of Australian blood donors reported no change in HIV-positive donations in the 5 years before and 5 years after Australia made a change in their deferral policy to 1 year for MSM.

So the results of the studies that I described above were presented to the HHS Advisory Committee on Blood and Tissue Safety and Availability in November of 2014. The committee voted 16 to 2 to recommend a policy change to a 1-year MSM deferral.

The committee also recommended the establishment of a robust system to monitor the safety of the blood supply and a communication plan on the policy change targeted to all

stakeholders.

The outcome of the Advisory Committee was then summarized at the FDA Blood Products Advisory Committee in early December 2014. And FDA announced that it would consider a change to a 1-year deferral policy for MSM in late December 2014.

FDA then issued draft guidance containing recommendations for reducing the risk of HIV transmission by blood and blood products in May of 2015.

We received approximately 700 comments to the docket in response to the draft guidance. The comments were evenly divided between calls for FDA to recommend a shorter deferral period for MSM or to move to individual risk assessment strategies and calls for FDA to leave the policy, indefinite deferral policy for MSM unchanged.

After careful consideration, FDA determined that the best available evidence supported a change to a 12-month deferral for MSM, as well as the implementation of the Transfusion-Transmissible Infection Monitoring System, which I'll describe in more detail in future slides. And as I mentioned earlier, FDA issued a final guidance in December of 2015.

However, when we announced the revised donor deferral policies at that time, we noted a commitment to continuing to further evaluate and potentially progress policies based on available scientific evidence.

We anticipate collaboration with other government agencies

and with stakeholders to consider whether emerging scientific evidence and information gained from the TTIMS will support alternative strategies to time-based behavioral deferrals. And one strategy to be further explored includes the evaluation of individual risk assessment questionnaires for all blood donors.

So one strategy employed by FDA to gather relevant scientific evidence was to open a public docket. We issued a *Federal Register* notice in July of 2016 announcing the establishment of the docket and requesting comments, supported by scientific evidence, regarding potential blood donor deferral policy options to reduce the risk of HIV transmission.

Specifically, we requested comments on alternatives to time-based deferral policies and the feasibility of individual risk assessment strategies, as well as the design of potential scientific studies on the feasibility and effectiveness of alternative deferral options.

And the notice posed six questions addressing deferral policies based on individual risk assessment. The six questions posed in the notice were as follows:

1. What questions would most effectively identify individuals at risk of transmitting HIV through blood donation?
2. Are there specific questions that could be asked that might best capture the recent risk of a donor acquiring HIV infection, such as within the

2 to 4 weeks immediately preceding blood donation?

3. How specific can questions be regarding sexual practices while remaining understandable and acceptable to all blood donors? For example, could questions about specific sexual behaviors be asked if they helped to identify which donors should be at least temporarily deferred because of risk factors? To the extent the questions are explicit about sexual practices, how willing will donors be to answer such questions accurately?

4. Under what circumstances would a short deferral period for high-risk behavior be appropriate? And for each short deferral period identified, please specify the duration of the deferral and provide scientific rationale.

5. What changes might be necessary within blood collection establishments to assure that accurate, individual HIV risk assessments are performed? And finally,

6. How best to design a potential study to evaluate the feasibility and effectiveness of alternative deferral options such as individual risk assessment?

As I mentioned, the docket was established on July 26th,

2016, and it was closed on November 25th of the same year.

We received a total of 670 responses from a variety of stakeholders, including:

- Individuals
- Blood donors
- Advocacy groups
- Academic and research institutions
- Healthcare providers, including HIV physicians
- Local and state governments, including health departments
- Medical associations
- Blood product recipients, as well as the
- Blood collection industry and device manufacturers

The 670 responses can be categorized as follows:

- 517 comments were against further change in the deferral policy.
- 86 comments were in support of further change in the deferral policy, and this includes one petition with 300 signatures.
- 35 comments were not responsive to the request for comments.
- And 32 of the comments provided were responsive to the specific questions posed in the notice.

And I should note that among the 517 responses that were against a further change, 252 of those comments appeared linked

to a single write-in campaign because of the similar responses.

So this slide is simply a pictorial representation of the types of comments we received, and as you can see, the majority of commenters did not support further change in FDA's policy.

So the policies suggested by the respondents covered a broad spectrum. Many commenters advocated for no further policy change or a return to the indefinite deferral period for MSM, while others recommended no deferral period for low-risk MSM and an abbreviated 2- to 3-week deferral for MSM at high risk for HIV.

Multiple commenters noted the need for an improved donor questionnaire for all donors that more accurately assesses risk.

And commenters made note about the need for privacy and the potential benefit of electronic responses or specially trained staff to administer the questionnaire.

Several commenters called for continued improvement in donor testing technology to reduce the window period or for the implementation of pathogen reduction technology for blood components.

Some commenters suggested additional interventions by blood collection establishments, such as the implementation of rapid HIV testing and counseling of high-risk donors at blood centers.

The responses included a wide range of recommendations for

assessing risk. While some respondents favored a more simple, streamlined questionnaire, others suggested a complex set of questionnaires to assess risk. Some commenters recommended questioning all donors for risk, while others supported a more customized approach. And respondents also provided varying definitions of high-risk MSM activity.

Finally, a cross-section of commenters concluded that data are not yet available to evaluate the recent change to a 12-month deferral for MSM.

Over the next several slides I will summarize the responses received to the six questions in the notice.

The first question asked: What questions would most effectively identify individuals at risk of transmitting HIV through blood donation? In response to this question, commenters recommended extending risk questions to all donors.

Several commenters suggested to ask potential donors about monogamy, unprotected sex, new sexual partners, sexual partners of unknown or positive HIV status, specific sexual practices, and injection drug use.

Another commenter suggested to model questions based on risk index tools developed for healthcare providers to identify MSM at high risk of HIV. These questions included addressing certain risk factors in the past 6 months to 1 year, such as number of partners, episodes of unprotected sex, and use of methamphetamine.

Question 2 asked: Are there specific questions that could be asked that might best capture the recent risk of a donor acquiring HIV infection, such as within the 2 to 4 weeks immediately preceding blood donation?

One commenter recommended asking all donors about monogamy, number of sexual partners, and use of safe sex practices in the weeks immediately preceding donation, as well as exposure to blood products, tattoos and piercings, and certain medical procedures in the past 3 months and injection drug use in the past year.

One commenter suggested, for MSM, new sexual partners in the past weeks should be assessed.

Another commenter suggested stratifying potential donors into high, medium, and low-risk groups as follows:

The high-risk group would include injection drug users and commercial sex workers. This group would have the longest deferral period, possibly an indefinite deferral period.

The medium-risk group would include MSM with multiple male partners, a history of unprotected sex, one or more HIV-positive partners in the past 2 to 4 weeks. And this group would be deferred for 30 days.

The low-risk group would include MSM with consistent condom use and/or pre-exposure prophylaxis, or PrEP. The commenter recommended that this group would have no deferral period.

With respect to Question 3, how specific can the questions be regarding sexual practices while remaining understandable and acceptable to all blood donors, we received the following responses:

- Yes/no questions with respect to monogamy, new partners, and condom use could be considered acceptable.
- All donors should be asked high-risk questions, but the questionnaire could be structured to ask MSM-specific risk questions.
- Specific questions are likely to result in more accurate responses, and
- Recommendations to administer the questionnaire electronically and privately.

In Question 4 we asked: Under what circumstances would a short deferral period for high-risk behavior be appropriate? And for each short deferral period identified, please specify the duration of the deferral and provide the scientific rationale.

One commenter stated that a 3-month deferral would be acceptable for a new partner without condom use, and another commenter recommended a 1-month deferral for high-risk behavior would be acceptable given the accuracy of nucleic acid testing.

The fifth question in the notice asked: What changes might be necessary within blood collection establishments to

assure that accurate, individual HIV risk assessments are performed?

The commenters recommended questioning in a private environment, electronic administration of the questionnaire, staff training in cultural competency to ask sensitive questions, and to include an option of responding "I don't know" to discourage donors from guessing.

And finally we asked how best to design a potential study to evaluate the feasibility and effectiveness of alternative deferral options such as individual risk assessment.

One commenter suggested the incidence of HIV infection under the current deferral policy should be compared to the incidence under a new policy.

Another commenter suggested that studies should be conducted to assess the feasibility and effectiveness of integrating onsite rapid antibody testing at blood collection sites.

A pilot study was recommended by another commenter in which the control arm would use current eligibility and deferral criteria. Potential MSM donors could be recruited to participate in the intervention arm that would use an individual risk assessment questionnaire and a 30-day deferral for those identified at medium risk. All donations would then be tested using current technology to assess for an increased HIV risk.

The study would also pilot whether the individual risk assessment questions are understood and acceptable to potential donors.

In response to the same question, another commenter recommended a four-step study to validate screening questions and their effectiveness in identifying individuals at high risk for HIV.

The first step would be to collect blood samples from participants that have been asked specific questions about certain risk activities in the last month. Next, the samples would be tested for HIV. The third step would be to retest the participant for HIV in 1 month. And the final step would be to ask follow-up questions depending on whether the second test was positive or negative to evaluate the effectiveness of the initial questionnaire.

A third commenter recommended a staged approach for research to identify and test new donor deferral criteria.

The first stage would be to conduct research to identify low-risk MSM through donor questions and assess whether the respondents find the questions acceptable and comprehensible; next, to conduct research to understand the impact of these questions on other donors with respect to (a) acceptability and (b) eligibility, in other words, would currently eligible donors become ineligible with the proposed new criteria?

And finally, it would be important to develop methods for

testing the safety of the new questions, including testing of blood establishment computer software, or BECS, to validate controls sufficient to prevent crossover of study and donor population donations, as well as to establish safeguards to permit the study populations to donate, for example, to consider a pathogen reducing the blood donations collected from the study population.

And a final commenter on this question suggested that the highest priority in study design should be to test the efficacy of classifying MSM donors as high or low risk, although data on non-MSM donors would also be desirable.

The proposed study design included administering the questionnaire to MSM and non-MSM subjects to assess low or high risk for recent HIV infections. The subjects would provide a blood sample for HIV testing by nucleic acid testing, and then follow-up testing would be performed at 1 month to identify subjects who converted from NAT negative to NAT positive during that time frame.

For those subjects that tested positive on follow-up, analysis would be conducted on the initial sample to determine whether the individual was in the window period when tested or that the individual acquired a new infection since the initial test was performed.

And with this slide, I'm completing the summary of the responses that we received to the public docket, and at this

time I will share progress on the development of the Transfusion-Transmissible Infections Monitoring System, referred to as TTIMS. So TTIMS is a joint CBER-NIH program that's a long-term representative U.S. blood safety monitoring system that provides information on approximately 50% of the U.S. donor base.

The primary functions of TTIMS include monitoring for HIV, HBV, and HCV incidence and prevalence in U.S. blood donors, and there's a potential for comparison of the data collected through TTIMS to the data collected in the REDS-II study that I mentioned earlier that was conducted from 2011 to 2013.

TTIMS will also serve to evaluate the molecular epidemiology and recency of HIV infection in blood donors and assess behavioral risk factors.

TTIMS will provide a framework for rapid data collection to inform blood safety responses to new emerging infectious diseases, and the system may allow for alert levels, once defined, to indicate if potential blood safety intervention is needed.

And finally, the system will facilitate ongoing data availability to objectively assess the value of new blood safety initiatives, including changes to donor deferral policies.

There are two main components of TTIMS. The first component is the Donor Database Coordinating Center. The

American Red Cross is contracted to serve as the coordinating center and also serves as one of the five data collection sites.

Through the establishment of a central database, greater than 50% of the blood supply is monitored for HBV, HCV, and HIV. Consensus test result definitions have been established to ensure all contributing centers are using consistent terminology, and the use of a validated data exchange ensures the validity of the submitted data. There will be quarterly data analysis of HIV, HBV, and HCV prevalence and incidence rates in the donor population.

The second component of TTIMS is a Laboratory and Risk Factor Coordinating Center. Blood Systems Research Institute was awarded the contract to serve as this coordinating center, and the center will conduct risk factor interviews with all donors that test positive for HIV, and repeat donors that are newly positive for HBV and HCV, as well as integrate risk factor data with marker data and compare it with control interviews.

A biospecimen repository has been established that will test the recency of HIV infection in blood donors and perform viral genetic sequence analysis that will be useful to determine if there is a shift in genetic sequences that could necessitate a change in blood donor screening or testing.

The risk factor interview questionnaire that will be

utilized to interview donors was modeled on the REDS-II risk factor study interview, with the following enhancements:

Transgender categories have been included on the questionnaire, and questions will be asked with respect to employment, monogamy, specific sexual practices, pre- and post-exposure prophylaxis use, and antiretroviral therapy. The questionnaire will also be administered online and is available for Spanish translation. And this questionnaire is under final review.

So this final slide on TTIMS provides a summary of the blood safety related outcome measures through the system. These anticipated outcome measures will serve to monitor effects of recent policy changes as well as other potential changes in donor epidemiology and help to inform future blood donor policy decisions.

In summary, these measures include the prevalence and incidence of HIV, HBV, and HCV among U.S. blood donors, as well as risk factor assessments obtained through the donor interviews.

So as I conclude this presentation, I will briefly discuss FDA's future plans.

In consideration of the comments we received to the docket and the current progress of TTIMS, FDA's potential next steps include the following:

- To assess the impact of FDA's current donor

deferral recommendations, including the change to a 12-month deferral period for MSM;

- Consider the design of alternative donor history questionnaires, and
- Study the feasibility, effectiveness, and operational impact of individual risk assessment strategies for assessing eligibility of all donors.

And finally, FDA is committed to the following principles moving forward:

Our process will be based on gathering the necessary scientific evidence regarding policy change, while ensuring the continued safety of the blood supply. We will consider the epidemiology of infectious diseases and behavioral risk factors among donors; laboratory science, including nucleic acid testing technology and advancement in packaging reduction of blood components, as well as social science, including strategies to improve donor education and donor questioning.

And importantly, FDA will work to maximize transparency of this process through stakeholder engagement and the use of public meetings, including scientific workshops and Advisory Committee meetings.

And with that, I'll conclude my presentation. Thank you very much for your attention, especially at this late hour in the afternoon. Thank you.

DR. STOWELL: Thank you very much.

Are there any questions for the speaker?

(No response.)

DR. STOWELL: No questions? Very good then. We'll go into the Open Public Hearing part of this session, and so I will reread that statement for you.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at this Open Public Hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product, or if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, the FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So I believe we have the names of two people who have said

that they want to speak. The first of these is Sharon Carayiannis from the American Association of Blood Banks.

MS. CARAYIANNIS: Good afternoon. I'm Sharon Carayiannis, I'm employed by AABB. I'm the deputy -- I'm, rather, the Director of Regulatory Affairs. Yeah, I used to be the deputy. I'm the Director of Regulatory Affairs, and I have no other financial disclosures or any other conflicting considerations.

I have a very brief statement to read, and I appreciate the presentation that Jennifer offered to us. We learned a lot from it.

AABB is pleased to have this opportunity to express our support for FDA's commitment to reevaluate and update blood donor deferral policies as new scientific information becomes available.

AABB's top priority remains the safety of our volunteer blood donors and patients in need of lifesaving blood products.

AABB, America's blood centers, and the American Red Cross submitted joint comments in November of 2016 in response to the July 2016 *Federal Register* notice. Our joint comments identify key issues that should be considered as part of risk-based decision making on the feasibility of moving from the existing time-based deferrals related to risk behaviors to alternate deferral options.

We wish to underscore the importance of maintaining a safe and adequate blood supply while these studies are completed and

after implementation of new deferral policy.

Additionally, any changes in the deferral policy should focus on an effective assessment of individuals to identify risks for transfusion-transmitted infections. The views of all stakeholders should be considered and adequately addressed, including the concerns regarding the continued safety of transfusion recipients served by this blood community.

AABB is an international not-for-profit association representing individuals and institutions involved in the field of transfusion medicine and cellular therapies. Our association is committed to improving health by developing and delivering standards, accreditation, and educational programs that focus on optimizing patient and donor care and safety.

AABB's membership consists of nearly 2,000 institutions and 8,000 individuals, including physicians, nurses, scientists, researchers, administrators, medical technologists, and other healthcare professionals. AABB is located in more than 80 countries.

Thank you for the opportunity to provide these comments today.

DR. STOWELL: Thank you.

Our second speaker is David Hardy from the Whitman-Walker Clinic. Is David Hardy here?

DR. HARDY: Thank you. My name is Dr. David Hardy. I am an infectious disease and HIV-trained physician, formerly a

Professor of Medicine in the Division of Infectious Disease at UCLA School of Medicine for 25 years. I currently serve as the Senior Director of what's called Evidence-Based Practices at Whitman-Walker Health.

Whitman-Walker Health is a historic LGBT-focused, HIV-specializing clinic here in Washington, D.C. We care for approximately 16,000 individuals, about 3- to 4,000 of which are HIV positive, here in the District, and we're one of the first institutions to step forward in terms of the HIV epidemic here in Washington, D.C.

We certainly understand the Committee's concern for wanting to keep the blood supply safe, effective, and adequate, and we certainly do want to always support that.

We have submitted detailed comments to the Committee as of November 2016, and in those comments we agree with the Committee -- agree with the FDA's two-pronged approach, further evaluating individual-based testing for risk for HIV infection and transmission through blood donation. And number two, we also submitted a detailed but simple four-point plan or step plan, I should say, in a trial that could be conducted to be able to test the adequacy of an improved deferral individual-based sort of donor questionnaire.

We support the FDA's willingness and commend its ability to continue to consider the scientific evidence that's available for HIV infection, the current technology that's

available, such as NAT testing, and what is known about HIV transmission, to continue to inform a safe and effective blood donor policy.

Thank you.

DR. STOWELL: Thank you very much.

Is there anyone else from the public who would like to speak at this point?

(No response.)

DR. STOWELL: Seeing no one, then we'll close the Open Public Hearing, and unless I hear objections, I think it's time to adjourn for the day.

(Whereupon, at 3:41 p.m., the meeting was continued, to resume the next day Wednesday, April 5, 2017, at 8:30 a.m.)

CERTIFICATE

This is to certify that the attached proceedings in the matter of:

115TH MEETING OF THE BLOOD PRODUCTS ADVISORY COMMITTEE

April 4, 2017

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Biologics Evaluation and Research.

_____

Tom Bowman

Official Reporter