

**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Epidemiology (OBE)
Division of Epidemiology (DE)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

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Subject: Pharmacovigilance Plan Review

Sponsor: Novo Nordisk

Product: Esperoct[®], Turoctocog alfa pegol (N8-GP)

Submission Type: Original BLA

STN: BLA 125671/0

Proposed Indication: For use in adults and children with hemophilia A for: on-demand treatment and control of bleeding episodes; perioperative management; and routine prophylaxis

Submission Date: February 27, 2018

Action Due Date: February 27, 2019

1. Objective

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) based on the safety profile of Esperoct®.

2. Product Information

2.1 Product Description

Esperoct®, Turoctocog alfa pegol (N8-GP) is a glycopegylated recombinant human factor VIII (rFVIII) product that is administered intravenously. A 40 kDa polyethylene-glycol (PEG) moiety is covalently attached to an O-linked glycan site on the truncated B-domain of the (b) (4)

The pegylation results in an (b) (4) with a prolonged half-life compared to the unpegylated molecule. When Esperoct is activated by thrombin at the site of injury, the pegylated truncated B-domain is cleaved off, generating activated FVIII (FVIIIa), which is similar in structure to native FVIIIa.

The rFVIII drug substance intermediate of Esperoct is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. There are no human or additional animal-derived materials in the production process of Esperoct.

Esperoct will be available as a lyophilized powder in single-use vials of 500 IU, 1000 IU, 1500 IU, 2000 IU, and 3000 IU reconstituted with 0.9% sodium chloride solution.

2.2 Proposed Indication

The sponsor has proposed the following indications for use of Esperoct in adults and children with hemophilia A for:

- Control and prevention of bleeding
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

Esperoct will not be indicated for the treatment of von Willebrand disease.

2.3 Pertinent Regulatory History

None- Esperoct has not been licensed in the US or elsewhere.

2.4 Worldwide Distribution Data and Post-Marketing Exposure

Esperoct is not licensed in any country. Consequently, there are no post-marketing data as of the data lock point of this BLA.

3. Known safety Information for Class of FVIII Products

Esperoct belongs to the recombinant antihemophilic factor class of pharmacological products. The most important complication of treatment with antihemophilic factor products is the development of neutralizing antibodies (inhibitors). These inhibitors neutralize the infused antihemophilic factor thereby reducing the efficacy of treatment and increasing morbidity and costs.¹ It is estimated that the development of inhibitors

¹Peyvandi F, Ettinghausen CE, Goudemand J, Jimenez-Yuste V, Santagostino E, Makris M. New Findings on inhibitor development: from registries to clinical studies. *Hemophilia* 2017; **23**(Suppl 1): 4-13.

occurs in approximately one-third of previously untreated patients (PUPs) with severe hemophilia A, with the highest risk of inhibitor development during the first 20-30 days of exposure to FVIII.^{1,2} The incidence of new inhibitor development in previously treated patients (PTPs) is significantly lower than in PUPs but it is not negligible; a recent study demonstrated an overall incidence rate of inhibitors in PTPs of 2.06 per 1000 person years (95% confidence interval of 1.06-4.01).^{1,3}

The risk factors for development of inhibitors can be patient- and/or treatment-related.³ Patient-related risk factors include the severity of hemophilia, FVIII gene mutation, family history of inhibitor development, ethnicity, and polymorphisms in immune-response genes.³ Treatment-related risk factors for development of inhibitor include the number of exposure days (EDs), the intensity of treatment, the age at first exposure, type of FVIII concentrate, and the current infection or inflammatory state of the patient.³ The presence of inhibitors is determined by laboratory studies. A neutralizing antibody level of >0.6 Bethesda Units (BU)/mL, on at least two consecutive tests confirms the presence of inhibitors. High-titer inhibitors are defined as levels ≥ 5 BU/mL, and a low-titer inhibitor is between 0.6 – 5 BU/mL.⁴ Patients with low-titer inhibitors are further divided into two groups according to a secondary anamnestic (memory) response of antibody production to factor infusion. Patients who have a rapid response are classified as high-responders, and those without a similar response are classified as low responders.⁴ Low titer and low responding inhibitors can be treated with standard FVIII replacement therapy at higher doses to overcome the effect of the inhibitors.⁴ Patients with a high titer or high responding inhibitors require treatment with bypassing agents (on-demand or prophylaxis) or by immune tolerance induction (ITI) with the aim of eradicating the inhibitor, which is effective in about 65-70% of patients.³

The second most important complication of treatment with antihemophilic factor is allergic type hypersensitivity reactions, including anaphylaxis/anaphylactoid reactions. Reactions can be IgE-mediated (including anaphylaxis, angioedema, and urticaria) and/or delayed-type hypersensitivity (including various types of skin rashes).

Additional important safety context can be derived from examining the safety profiles of other licensed pegylated factor products, Adynovate[®], Jivi[®], and Rebinyn[®]. Adynovate is a full-length rFVIII (Advate[®]) and is comprised of a (b) (4) FVIII. Jivi is a B-domain truncated FVIII that has a 60 kDa PEG attached to an engineered cysteine residue. Safety risks that have been identified for these products include formation of inhibitors and hypersensitivity reactions. In addition, Jivi is not indicated for use in children < 12 years of age due to risk of PEG-related immunogenicity that manifests as development of anti-PEG

² Van den Berg HM. Epidemiological aspects of inhibitor development redefine the clinical importance of inhibitors. *Haemophilia* 2014; **20**(Suppl 4): 76-9.

³ Hassan S, Cannavo A, Gouw SC, Rosendaal FR, van der Bom JG. Factor VIII products and inhibitor development in previously treated patients with severe or moderately severe hemophilia A: a systematic review. *J Thromb Haemost* 2018; **16**: 1055-68.

⁴ Peyvandi F, Garagiola I, Young G. The past and future of hemophilia: diagnosis, treatments, and its complications. *Lancet* 2016 Jul 9; **388**(10040): 187-97.

antibodies and loss of product effect (primarily seen in patients <6 years of age). There are currently no long-term surveillance data for Adynovate or Jivi.

Rebinyn, Nonacog beta pegol (N9-GP), is a glycopegylated recombinant human factor IX (rFIX) product. A 40 KDa PEG moiety is (b) (4) to the activation peptide of rFIX. In addition to safety risks of inhibitor development and hypersensitivity reactions, pre-clinical studies in mice detected accumulation of PEG in the choroid plexus. Although no evidence of such accumulation was detected during clinical studies, concern about the potential risk of this safety issue after prolonged use led to restricting the approved indication to only acute uses (control of acute bleeds and peri-operative use).

4. Materials Reviewed

The materials submitted by the sponsor, which were reviewed in support of this submission are listed in Table 1.

Table 1: Materials Reviewed

Document Date	Document Type	Document	Source
17-Dec-14	Clinical Trial Report synopsis & Body, Module 5.3.5.2	NNC 0129-0000-1003, Trial ID: NN7088-3859 Main, Clinical Trial Report Synopsis & Body	Novo Nordisk, 125671/0
23-Nov-15	Clinical Trial Report synopsis & Body, Module 5.3.5.2	N8-GP, Trial ID: NN7088-3885, Clinical Trial Report Synopsis & Body	Novo Nordisk, 125671/0
24-Apr-17	Clinical Trial Report synopsis & Body, Module 5.3.5.2	Turoctocog alfa pegol, Trial ID NN7088-3859 Ext 1, Report Synopsis & Body	Novo Nordisk, 125671/0
6-Nov-17	Clinical Trial Report synopsis & Body, Module 5.3.5.2	Turoctocog alfa pegol, Trial ID: NN7088-3885 Ext 1, Clinical Trial Report Synopsis & Body	Novo Nordisk, 125671/0
4-Dec-17	Clinical Trial Report synopsis & Body, Module 5.3.5.2	Turoctocog alfa pegol, Trial ID NN7088-3859 Ext 2, Report Synopsis & Body	Novo Nordisk, 125671/0
4-Dec-17	Clinical Trial Report synopsis & Body, Module 5.3.5.2	Turoctocog alfa pegol, Trial ID: NN7088-3860-Report Synopsis & Body	Novo Nordisk, 125671/0
22-Dec-17	Summary safety report, Module 2.7.4	Turoctocog alfa pegol. Summary of clinical safety	Novo Nordisk, 125671/0
22-Dec-17	Clinical Overview, Module 2.5	Turoctocog alfa pegol. Clinical overview	Novo Nordisk, 125671/0

22-Dec-17	Summary of Immunogenicity, Module 5.3.5.3	Turoctocog alfa pegol, Integrated summary of Immunogenicity	Novo Nordisk, 125671/0
18-Jan-18	Risk Management Plan, Module 1.16.1	Risk Management Plan-turoctocog alfa pegol	Novo Nordisk, 125671/0
22-Jan-18	Nonclinical Overview, Module 4.2.3.7.7	Turoctocog alfa pegol, Non-Clinical Overview	Novo Nordisk, 125671/0
6-Jun-18	120-Day safety Update	Turoctocog alfa pegol, 120-Day Safety Update	Novo Nordisk, 125671/12
	Case Report Forms, Module 5.3.5.2	NN7088-3908- Case Report Forms	Novo Nordisk, 125671/0
	Pre-Clinical Study Report, Module 4.2.3.7.7	Comparison between N8-GP and N9-GP-nonclinical safety package	Novo Nordisk, 125671/0
	Pharmacovigilance Plan Review	OBE/DE Pharmacovigilance Plan Review- Adynovate	OBE/DE
	Pharmacovigilance Plan Review	OBE/DE Pharmacovigilance Plan Review- Rebinyn	OBE/DE
	Pharmacovigilance Plan Review	OBE/DE Pharmacovigilance Pan Review- Jivi	OBE/DE

5. Pharmacovigilance Plan Review

5.1 Key Non-Clinical Safety Findings

In repeat-dose toxicity studies the highest dose levels tested were identified as no observed adverse effect levels (NOAELs) based on non-immunogenic effects.⁵ The studies involved single doses of Esperoct up to 25,000 IU/kg in rats, repeat dosing up to 2,500 IU/kg every 2nd day for 2 weeks in rats, up to 1,200 IU/kg every 4th day for 26 weeks and 52 weeks in (b) (4) rats, and up to 2,500 IU/kg every 3rd day for 2 weeks in (b) (4) monkeys. Of note, PEG was not detected by a PEG-specific immune histochemical (IHC) staining of brain tissue (including the choroid plexus) after 52 weeks of repeated dosing of Esperoct up to 1,200 IU/kg every 4th day in (b) (4) rats.⁵ Non-clinical studies on excretion and distribution with (b) (4) PEG moiety of Esperoct showed that PEG is widely distributed, gradually eliminated from organs and tissues, and excreted in urine and feces.⁵ The terminal elimination half-life of PEG was estimated in all tissues and ranged from 14 days in plasma to 89 days in the choroid plexus.⁵ No effects of Esperoct were observed up to the highest dose of 2,500

⁵Risk management plan, module 1.16.1 (b) (4)

IU/kg on blood pressure, electrocardiography, respiratory rate, temperature, neurological/central nervous system endpoints and urinalysis during the 2-week repeated dose toxicity study.⁵

5.2 Clinical Safety Database

The clinical development program for Esperoct consists of trials in PTPs (adults and children) and in pediatric PUPs (Table 2). The clinical trials for Esperoct have all been conducted in male patients with severe hemophilia A with no history of inhibitors.

Table 2: Overview of Clinical Trials for Esperoct

Trial ID	Status	Esperoct Trial Design	Actual age range	Number of Subjects
Previously treated patients				
Trial 3776	Completed	<i>First human dose trial</i> - To evaluate safety and Pharmacokinetics (PK)	20-60 years	26
Trial 3859 (<i>Pivotal Trial</i>)- Main Phase	Completed	To evaluate safety and efficacy for long-term prophylaxis & treatment of bleeding episodes	12-66 years	186
Trial 3859 - Extension Phase Part 1	Completed	To investigate safety & efficacy of every 7 th day prophylactic dosing regimen	12-66 years	150
Trial 3859 - Extension Phase Part 2	Ongoing	To investigate long term safety & efficacy in patients on every 4 th day and every 7 th day dosing regimens	12-66 years	139
Trial 3860	Ongoing	To evaluate efficacy and safety during major surgical procedures	15-69 years	34 (45 surgeries)
Trial 3885 - Main phase	Completed	<i>Pediatric trial</i> - To evaluate safety and efficacy for prophylaxis & bleeding episodes in pediatric PTPs	1-11 years	68
Trial 3885 - Extension Phase	Ongoing	Pediatric PTPs trial		

Trial 4033	Completed	Comparison of single dose PK and safety of N8-GP from pivotal and commercial process	25-71 years	21
Previously untreated patients				
Trial 3908	Ongoing	To investigate safety and efficacy of N8-GP in pediatric PUPs	<6 years	32 (125 planned)

Excerpted from Table 1-2 of Clinical Overview, Module 2.5 (b) (4)

Safety population and pooling of data

A total of 270 unique PTPs have been exposed to Esperoct in the clinical trials. PTPs entered the program through trials 3776 (PK trial), 3859 (pivotal trial), and 3885 (pediatric trial). Many patients participated in more than one trial. During the development program, the manufacturing process for Esperoct changed from the (b) (4) to an optimized manufacturing process. Trial 4033 was a comparison of the single dose PK and safety of Esperoct from (b) (4) manufacturing processes.⁶ As of the cut-off date, 92 out of 254 patients had been switched from Esperoct from the (b) (4) to Esperoct from the commercial process.

The sponsor reports that since there were no apparent differences in the safety profile of Esperoct between age groups or dose levels, the safety data from all completed trials and ongoing trials in PTPs (trials 3776, 3859, 4033 and 3885), except for safety during surgery trial (trial 3860), can be pooled for the purpose of safety analysis.

The safety information collected during the clinical trials included adverse events (AEs), medical events of special interest (MESIs), laboratory assessments for safety [VIII inhibitor testing, hematology, biochemistry, coagulation-related parameters, anti-Chinese-hamster-ovary (CHO) host-cell-protein (HCP) antibodies, anti-Esperoct antibodies, anti-PEG antibodies, urinalysis], physical examination, vital signs, electrocardiography, and injection site tolerability.⁹ MESIs were defined in the trials as medication errors, suspected transmission of an infectious agent via trial product, thromboembolic events, development of FVIII inhibitors, and hypersensitivity reactions, including anaphylaxis/anaphylactoid reactions.⁹ A positive inhibitor test was defined as ≥ 0.6 BU, and a patient was diagnosed with inhibitors if he tested positive at 2 consecutive tests preferably within 2 weeks. Inhibitors ≥ 0.6 BU but < 5 BU were classified as low titers, and high titer was defined as ≥ 5 BU.

Table 3 is the summary of the baseline demographics by age for trials 3776, 3859, 4033, and 3885. All patients were diagnosed with severe hemophilia A with a FVIII activity level $< 1\%$. One hundred and twenty (120) out of 177 of the adult patients were hepatitis C positive, 6 patients were hepatitis B positive (with 3 of these patients also positive for

⁶ Summary of clinical safety (b) (4)

hepatitis C), and 13 of the patients with available information of HIV status were HIV positive.⁹

Table 3: Summary of baseline demographics by age- trials 3776, 3859, 4033 and 3885

	0-5 years	6-11 years	12-17 years	>=18 years	Total
Number of patients	34	34	25	177	270
Mean age at baseline in first trial (year)	3	8.9	14.9	33.8	25.1
Ethnicity					
Hispanic or Latino	-	3	3	10	16
Not Hispanic or Latino	34	30	22	167	253
Not Available	-	1	-	-	1
Race					
Asian	1	4	1	37	43
Black/African American	2	1	3	9	15
White	30	25	19	129	203
Other	1	1	2	1	5
Not Available	-	3	-	1	4

Excerpted from Table 1-5 of Summary of Clinical safety (b) (4)

For the surgery trial 3860, the mean age for the 34 patients enrolled was 40 years (range 15-69 years) when they enrolled in the trial. Except for one adolescent patient age 15 years, all the remaining patients were ≥18 years. Eighty-two percent (82%) of the patients were White, 15% were Asian and 3% were Black or African American.⁹

Key Safety Findings

Common Adverse Events (pooled data from trials 3776, 3859, 4033 and 3885):

- A total of 2307 adverse events (AEs) were reported in 239 (89%) of patients. The most frequent AEs occurring in more than 5% of patients were viral upper respiratory tract infection (28.9% of patients), upper respiratory tract infection (21.1%), influenza (10.7%), gastroenteritis (7.5%), tonsillitis (6.7%), rhinitis (5.6%), bronchitis (5.6%), arthralgia (15.9%), pain in extremity (8.1%), musculoskeletal pain (6.3%), back pain (5.6%), contusion (7.4%), laceration (7.0%), fall (6.3%), limb injury (5.9%), diarrhea (11.5%), vomiting (7.4%), nausea (6.3%), toothache (5.6%), cough (13.7%), oropharyngeal pain (10.7%), rhinorrhea (5.6%), headache (20.7%), eczema (5.6%), rash (5.2%), pyrexia (9.3%), alanine aminotransferase increased (5.2%), hypertension (7.0%), and seasonal allergy (5.2%)
- A total of 67 serious adverse events (SAEs) were recorded in 47 (17%) of patients. Except for the SAEs of cellulitis, device related infection, bacterial sepsis, fall, and duodenal hernia for which there were 2 reports each (0.7%), all the remaining SAEs had one report each (0.4%). Thus, there were no discernible symptom patterns or organ system clustering of SAEs suggestive of a safety issue.

- One fatal event of metastatic pancreatic carcinoma was reported in a 67-year-old patient (patient ID (b) (6) in trial 3859 after 88 exposure days to Esperoct. The patient's only reported past medical history was hemophilia A.
- One (0.4%) subject across all studies developed confirmed high titer neutralizing antibodies to Factor VIII. Four additional subjects developed transient non-neutralizing antibodies to Factor VIII, two of whom had pre-existing low titer FVIII antibodies and were late screen failures. Anti-PEG antibodies were detected in 45 (17%) subjects and pre-existing anti-PEG antibodies were detected in 32 (12%) subjects. Nine subjects developed anti-CHO HCP antibodies. Two additional subjects had positive anti-CHO HCP antibodies prior to treatment with Esperoct.
- Other MESIs:
 - No subject sustained a thromboembolic AE.
 - There were no events of suspected transmission of an infectious agent via the product among trial subjects.
 - 13 AEs related to hypersensitivity in 7 subjects were reported; all AEs were mild except for one AE of rash that was judged as moderate, and one case of rash accompanied by vomiting in a 3-year-old that was judged as severe. All 7 subjects fully recovered from these AEs. No cases of anaphylaxis were reported.
 - Evaluation of the effect of accumulation of PEG in various organ systems was limited by the lack of long-term follow up data; however, AEs related to SMQs 'acute renal failure' (6 AEs in 4 subjects), 'drug-related hepatic disorders' (74 AEs in 34 subjects), 'nervous system disorders' (163 AEs in 78 subjects), and 'psychiatric system disorders' (25 AEs in 24 subjects) were reviewed. The vast majority of reports were of transient nature (transient elevations of serum creatinine/hepatic enzymes, transient headaches).

Common Adverse Events- surgery trial 3860:

- A total of 118 AEs were reported in 37 out of 45 (77%) surgeries performed. The most common AEs reported in >5% of patients were constipation (22.9%), nausea (12.5%), diarrhea (6.3%), and vomiting (6.3%), increased c-reactive protein (8.3%), decreased hemoglobin (6.3%), post-procedural inflammation (6.3%), and pyrexia (8.3%). The remaining adverse events, which were the majority, occurred only once or twice.
- There were 5 SAEs reported in 4 surgeries. The SAEs were hemorrhage, ischemia, acute pancreatitis, decreased mobility and tooth extraction. The SAEs of hemorrhage and ischemia were reported in the same patient while undergoing a total knee replacement.
- There were 2 MESIs reported in 2 surgeries, namely blister and allergic dermatitis.
- No FVIII inhibitors or thromboembolic events were reported
- No deaths were reported

Adverse Events- ongoing trial 3908:

- Of the 32 PUPs exposed to Esperoct, 4 patients had developed FVIII inhibitors as of the cut-off date of the sponsor's report. There was 1 high-titer inhibitor of 6.1 BU and 3 low-titer inhibitors of 1.0, 1.6 and 4.9 BU respectively. One additional patient had one initial single positive FVIII inhibitor test followed shortly by a negative central laboratory test.
- Five patients had been withdrawn from the trial as of the cut-off date of the report. The reasons for withdrawal were therapy non-responder, FVIII inhibition, spinal epidural hematoma, unresponsiveness to Esperoct, and family decision.
- A total of 14 SAEs were reported in 9 patients. The SAEs were FVIII inhibitors (4 patients), single events each of head injury, therapy non-responder, spinal epidural hematoma, tongue injury and contusion, and 3 events of pneumonia reported in 1 patient who also had 1 event of haemophilus pneumonia.

5.3 Review of Postmarketing Data in US and Worldwide

Not applicable because Esperoct has not been licensed in the U.S. or worldwide.

5.4 Review of Sponsor's Proposed Pharmacovigilance Plan

The sponsor's proposed pharmacovigilance plan (PVP), including identified risks, potential risks, missing information, and intended risk minimization activities for each category, is summarized in Table 4.

Table 4: Summary of Sponsor-proposed PVP (adapted from Risk Management Plan, pg. 47)

Safety Concern	Risk Minimization Labeling	PVP Activities
<i>Important Identified Risks</i>		
Inhibitor development	<i>Warnings and Precautions</i> (both 'Highlights' and Section 5.2): Inclusion of warning regarding "development of neutralizing antibodies (inhibitors)" with instruction to perform serum assay for inhibitors in event of persistent uncontrolled bleeding	<ul style="list-style-type: none"> - Routine pharmacovigilance - Immunogenicity questionnaire - PASS*

Allergic/hypersensitivity reactions	- <i>Contraindications</i> (both ‘Highlights’ and Section 4): Contraindication instruction for patients who have known hypersensitivity to ESPEROCT or its components “including hamster protein”	-Routine pharmacovigilance -Hypersensitivity questionnaire - PASS*
	- <i>Warnings and Precautions</i> (both ‘Highlights’ and Section 5.1) : Inclusion of warning indicating that “hypersensitivity reactions, including anaphylaxis, may occur” with instruction to discontinue use and administer treatment	
<i>Important Potential Risks:</i> None		
<i>Missing Information</i>		
Previously untreated patients	None	- Routine pharmacovigilance -Ongoing PUP study (Trial 3908)
Patients with HIV with high viral load and low CD4 T cell count	None	-Routine pharmacovigilance
Patients with history of FVIII inhibitors	No specific safety-related labeling aside from previously described Warning regarding risk of inhibitor development	-Routine pharmacovigilance -Immunogenicity questionnaire
Patients with history of thromboembolic events	None	-Routine pharmacovigilance
Patients on ITI regimen	None; Esperoct will not be indicated for ITI therapy	-Routine pharmacovigilance

*PASS=Post- authorization Safety Study

Current information about the status of the trials that were ongoing as of submission of this BLA was obtained from clinicaltrials.gov and is as follows:

- Trial 3859 (adolescent and adult PTPs)
 - Completed
 - Actual primary completion date- December 10, 2018; Actual study completion date- December 10, 2018.
- Trial 3860 (surgery)
 - Recruiting

- Estimated primary completion date- December 3, 2018; Estimated actual completion date- December 3, 2018
- Trial 3885 (pediatric PTPs)
 - Completed
 - Actual primary completion date- September 15, 2014; Actual study completion date: September 28, 2018
- Trial 3908 (pediatric PUPs)
 - Enrolling by invitation
 - Estimated primary completion date- November 13, 2021; Estimated actual completion date- November 13, 2021

In addition to routine pharmacovigilance, completion of study reports for extension trials 3859 and 3885, and completion of Trials 3860 and 3908, the sponsor is planning a non-interventional post-authorization safety study (PASS). This multinational, non-randomized, non-interventional study will evaluate the long-term safety of ESPEROCT in hemophilia A PTPs without inhibitors and is being undertaken to meet EMA requirements.

The PASS will include safety follow-up assessments at routine comprehensive care visits for at least 4 years for up to 50 patients. Beyond the standard assessments of routine comprehensive care of patients with hemophilia A by physicians, nurses, physiotherapists, psychologists, etc. The study aims to capture in more detail the routine assessment across all age groups, including neurodevelopmental milestone achievements in children using pre-specified screening tools.

Safety updates from the study will be provided in ESPEROCT Periodic Safety Update Reports (PSURs). Planned duration of recruitment period is 2 years. Proposed milestones are as follows:

- Planned first patient enrollment: 01 Mar 2020
- Planned last patient enrollment: 01 Mar 2022
- The end of the study is defined as: planned last patient follow-up: 01 Mar 2026

Finally, the sponsor plans to attempt to collect follow-up questionnaires when they receive reports related to immunogenicity or hypersensitivity. The immunogenicity questionnaire includes questions on treatment and inhibitor history as well as questions on the reported event. The hypersensitivity questionnaire will collect documentation of signs and symptoms of a reported allergic reaction as well as relevant medical history and laboratory tests performed, in order to make a determination of causality between the product and the AE.

6. Integrated Risk Assessment

The design of the PVP for Esperoct is based on clinical trial data for 270 unique patients. Of note, these patients were all PTPs. The reviewer also makes note of limited data derived from an ongoing trial in PUPs. However, insufficient information is currently available for PUPs to fully characterize the safety profile of product use in this population. Additionally, the trials excluded subjects with a previous history of inhibitors, or subjects with immunodeficiency syndromes such as HIV infection in order

to prevent confounding during evaluation of efficacy endpoints. Similarly, only incomplete safety information is assessable concerning use in patients with a history of severe renal or hepatic impairment, as those patients were also excluded from the trials to prevent confounding of assessment of efficacy endpoints. These limitations are commonly seen during evaluation of clinical safety databases for FVIII products.

The sponsor identified inhibitor development and hypersensitivity as safety concerns associated with use of the product. Review of the clinical safety database identified no other substantial safety concerns. SAEs occurred infrequently and were usually readily discerned to be unlikely to be attributed to the product. There were no apparent patterns/clustering of AEs with regards to involved organ system. Notably, no thrombotic events (TEEs) were documented. Thus, available safety data for the product were largely reassuring. Given that inhibitor development and hypersensitivity are well-recognized identified risks of factor replacement products, the sponsor's risk mitigation plan of routine pharmacovigilance and follow up questionnaires for both issues is adequate.

Although the sponsor has not included safety risks associated with the PEG moiety in the PVP, this safety issue warrants consideration. The PEG molecule is primarily excreted renally. Larger (40 kDa and above) PEG molecules have been shown in animal studies to vacuolize and accumulate in the kidney, liver, and choroid plexus, with the potential to lead to organ dysfunction. As previously noted, multiple pegylated biologic products are currently marketed in the US, with little evidence of safety issues.⁷ Additionally, no AEs related to the PEG were noted in the safety database for Esperoct. However, given the lack of long-term follow up information, it may be reasonable to consider 'potential long-term PEG-related adverse reactions' as 'Missing Information.' Such information could be obtained by the development of hepatic and renal questionnaires as an adjunct to routine pharmacovigilance. These questionnaires could supplement information gathering after receipt of reports of hepatic or renal impairment following prolonged use of Esperoct.

7. Recommendations

OBE/DE agrees with the proposed pharmacovigilance activities and postmarketing studies proposed by the sponsor, including routine pharmacovigilance and reporting of postmarketing adverse experiences to FDA in accordance with 21 CFR 600.80, completion of study reports for clinical trials 3855, 3859, 3860, and completion of Trial 3908, and conducting the PASS according to the proposed milestones. OBE/DE recommends that in the future the sponsor considers adding risks associated with long-term use of this pegylated product to the 'Missing Information' section of the PVP. OBE/DE also recommends that the sponsor considers developing and implementing questionnaires for gathering information on hepatic and renal impairment to supplement routine pharmacovigilance for this safety concern.

⁷ Stidl R, Denne M, Golstine J, Kadish B, Korakas KI, Turecek PL. Polyethylene Glycol Exposure with Antihemophilic Factor (Recombinant), PEGylated (rurioctocog alfa pegol) and Other Therapies Indicated for pediatric Population: History and Safety. *Pharmaceuticals (Basel)*. 2018; **11**(3):75. Published 2018 Jul 26. doi:10.3390/ph11030075