BLA Clinical Review Memorandum

Application Type	Original Application
STN	125671
CBER Received Date	February 27, 2018
PDUFA Goal Date	February 27, 2019
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	No
Reviewer Name(s)	Najat Bouchkouj, MD Bindu George, MD
Review Completion Date / Stamped Date	February 13, 2019
Supervisory Concurrence	Tejashri Purohit-Sheth, MD
Applicant	Novo Nordisk, Inc.
Established Name	Turoctocog alfa pegol (N8-GP)
(Proposed) Trade Name	ESPEROCT
Pharmacologic Class	Recombinant human factor VIII, pegylated
Formulation(s), including Adjuvants, etc.	Intravenous Injection
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder for Injectable Solution, Intravenous
Dosing Regimen	Proposed by the Applicant: • Routine prophylaxis: o In adults/adolescents: ▪ 50 IU/kg every 4 days; (b) (4) o In children (<12 years): ▪ (b) (4) IU/kg twice weekly • Perioperative management and on-demand treatment and control of bleeding episodes: o Frequency of administration is determined by the type of bleeding episode or surgical procedure and the recommendation of the treating physician.

	Proposed by the clinical reviewer: • On-demand treatment/Control of bleeding episodes: (b) (4)-40 IU/kg body weight for minor and moderate bleeds, and 50(b) (4) IU/kg body weight for major bleeds. • Perioperative management: For minor or major surgery: o In adolescents / adults: Pre-operative dose of 50 IU/kg body weight o In children (<12 years), pre-operative dose of 65 IU/kg body weight Frequency of administration is determined by the treating physician. • Routine Prophylaxis: The recommended initial regimen is: o In adults / adolescents: ▪ 50 IU/kg every 4 days o In children (<12 years): ▪ 65 IU/kg twice weekly A regimen may be individually adjusted to less or more frequent dosing based on bleeding episodes.
Indication(s) and Intended Population(s)	For use in adults and children with hemophilia A for: • On-demand treatment and control of bleeding episodes • Perioperative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

GLOSSARY

ABR	Annualized Bleeding Rate
ADR	Adverse Drug Reaction
AE	Adverse Event
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BU	Bethesda Unit
CMC	Chemistry, manufacturing, and controls
CI	Confidence Interval
eCTD	Electronic Common Technical Document
ED	Exposure Days
GCP	Good Clinical Practices
IU	International Units
MESI	Medical Event of Special Interest
PK	Pharmacokinetic
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PREA	Pediatric Research Equity Act
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
PVP	Pharmacovigilance Plan
rFVIII	Recombinant FVIII
SAE	Serious Adverse Event
$T_{1/2}$	half-life
TEAE	treatment emergent adverse event

1. EXECUTIVE SUMMARY

Novo Nordisk submitted STN 125671 as an original biologics license application (BLA) submitted for N8-GP with the proposed trade name ESPEROCT. ESPEROCT is a novel recombinant factor VIII (rFVIII) product based on the currently licensed Novoeight® (turoctocog alfa) with an extended half-life due to the covalent conjugation of a 40 kDa polyethylene glycol (PEG) moiety(b) (4) to an *O*-linked glycan site on the B-domain of turoctocog alfa. The mechanism of action for N8-GP (ESPEROCT) is replacement of the deficient or absent FVIII in patients with hemophilia A.

Clinical trials that provided the evidence for safety and efficacy of ESPEROCT were conducted under IND 14410. Data from the pharmacokinetic (PK) (Protocols NN7088/Study 3776 and NN7088/Study 4033), adolescent and adult (Protocol NN7088/Study 3859) and its extensions part 1 and 2, pediatric (Protocol NN7088/Study 3885) and its extension, and surgery (Protocol NN7088/Study 3860) studies were included for review. Studies 3859 and its extension part 1, 3885 and 3860 were the primary studies intended to support the marketing approval of ESPEROCT under this BLA submission. These studies were reviewed to evaluate the efficacy and safety of ESPEROCT for the following target indications for use in adults and children with hemophilia A for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

The safety and efficacy of ESPEROCT were evaluated in a total of 270 and 254 individual previously treated patients (PTPs) with severe Hemophilia A (factor VIII less than 1% of normal), respectively. Subjects received at least one dose of ESPEROCT in the multicenter, open label clinical studies submitted in support of this application. **Study NN7088-3859 (or 3859)** included 186 subjects, 161 adults (18 to 65 years old) and 25 adolescents (12 to 17 years old); it consisted of a Main Phase and two Extension Phases. Main Phase and Extension 1 have been completed and Extension 2 is still ongoing at the time of the submission. During the **Main Phase**, 175 subjects received the prophylaxis regimen which consisted of 50 International Units (IU) every 4 days (Q4D), while 12 adults chose to be treated on-demand. (One subject changed from on-demand to prophylaxis and is counted in both groups). Twelve (7%) of 175 subjects on the prophylaxis arm modified their regimen to Q3-4D (i.e., twice weekly) for ease of use. All subjects received at least one dose of ESPEROCT and are evaluable for safety and efficacy. A total of 165 subjects (91%) completed the Main Phase of this trial. The co-primary endpoints in the Main Phase are the incidence rate of FVIII inhibitor ≥ 0.6 Bethesda Unit (BU) and annualized bleeding rate (ABR) for subjects receiving prophylaxis treatment. One adolescent subject developed FVIII inhibitor which resulted in an estimated inhibitor rate of 0.6% and a one-sided 97.5% upper confidence limit for the inhibitor rate of 3.8%. As this is below the pre-specified limit of 6.8 %, this co-primary endpoint was met. The median ABR for treated bleeds in adults and adolescents treated Q4D was 1.18 (IQR: 0.00:4.25), and mean ABR was 3.00 (SD: 4.66). When including all bleeds (treated and non-treated with ESPEROCT), the median ABR was 1.20 (0.00;4.73) and the mean ABR was 3.26 (SD: 4.92). These ABRs are consistent with other FVIII products. A total of 105 (60%) of 175 subjects in the prophylaxis arm experienced bleeding episodes of which 69% were spontaneous bleeding events. Out of the 968 bleeding episodes that required treatment in 117 subjects, 964 bleeds were rated. Additional 26 bleeds that occurred in 23 subjects were not treated and therefore treatment response was not applicable. The treatment response was assessed as “good” or “excellent” in 88.4% of all bleeds (when counting the missed ratings as failure).

Extension 1 (Ext 1) compared two dosing regimens: 75 IU/kg every 7 days (Q7D) and 50 IU/kg every 4 days (Q4D). The randomization was open to subjects who experienced two or fewer bleeds during the last 6 months in the Main Phase. Of the 150 subjects who continued into Extension 1, 120 subjects met the randomization eligibility criteria, and 55 (46%) subjects chose to be randomized (2:1) to 75 IU/kg Q7D (38 subjects) and 50 IU/kg Q4D (17 subjects), respectively. Seven subjects were treated on-demand, 23 were not eligible to be randomized, and 65 eligible subjects chose to continue on 50 IU/kg Q4D. A total of 139 subjects (93%) completed Extension 1. Subjects randomized to Q4D with 50 IU/kg had a mean ABR of 1.68 (SD: 2.34). The median ABR was 0 (IQR: 0.00; 2.23). The mean ABR for all 38 subjects in the Q7D prophylaxis arm was 3.37 (SD: 6.19) and the median ABR was 0.00 (IQR: 0.00; 2.36). Nine (24%) of 38 subjects discontinued the Q7D regimen and changed to the Q4D regimen (eight subjects due to bleeding and one subject due to investigator’s choice). Mean ABR for the nine subjects who switched from Q7D to Q4D was: 11.8 and mean ABR for the remaining 29 subjects on Q7D was: 0.7. One additional subject in the Q7D arm discontinued the Q7D regimen due to an adverse event. Because the ABR was higher in subjects on the Q7D regimen as compared to the Q4D group, and significantly higher in a subgroup in whom characteristics that place them at a higher risk for bleeding are unclear, the Q7D regimen will not be included in the label. Out of the 1436 bleeding episodes in the Main

Phase and Ext 1 of the trial, 1420 bleeds were rated. The treatment response was assessed as “good” or “excellent” in 87.7% of all bleeds. During the Main Phase and two extensions of the trial, one death occurred in a 67-year-old subject with metastatic pancreatic carcinoma which was considered unlikely related to ESPEROCT. A total of 49 serious adverse events (SAEs) were recorded in 31 (17%) subjects. The event of factor VIII inhibition was evaluated as probably related to investigational product.

Trial NN7088-3860 (or 3860) included 33 previously treated adolescents/adults who underwent 45 major surgeries. The dose level of ESPEROCT was chosen so that FVIII activity, as recommended by the World Federation of Hemophilia (WFH) guidelines, was targeted. All subjects returned to the adult/adolescent trial after the surgery trial assessments were completed. The procedures included 15 joint replacements, nine arthroscopic orthopaedic interventions, 17 other orthopedic interventions, and four non-orthopedic surgeries. The hemostatic effect of ESPEROCT was rated as “excellent” or “good” in 43 of 45 surgeries (95.6%), while the effect was rated as “moderate” in two surgeries (4.4%). A total of five SAEs were reported in four surgeries. Two of the SAEs were possibly related to the investigational product. There were no deaths in the trial.

Trial NN7088-3885 (or 3885) included 68 subjects who were evenly divided with 34 in each age group, 0–5 and 6–11 years of age. All subjects were to receive the same prophylaxis regimen of approximately 60 IU/kg (50–75 IU/kg) twice weekly. A total of 63 subjects (93%) completed the Main Phase and were continuing treatment with ESPEROCT in the ongoing Extension part. **The Main Ph**ase was completed at the time of the submission. The primary endpoint of the trial was the incidence of inhibitory antibodies against FVIII ≥0.6 BU during the Main Phase of the trial (from 0-26 weeks of treatment). No FVIII inhibitors were observed. The mean ABR was 3.87 (SD: 9.68) for the 0-5 age group and 2.29 (SD: 2.86) for the 6-11 age group. The median ABR was 1.95 (IQR: 0.00; 2.79) and was comparable between the two age-groups. Out of the 70 bleeding episodes, 67 bleeds were rated. The treatment response was assessed as “good” or “excellent” in 78.6% of all bleeds. A total of 17 SAEs were reported in 15 (22%) subjects, of which two SAEs (increased bleeding due to decreased efficacy and hypersensitivity) were evaluated as probably related to trial product. There were no deaths in the trial.

Across all studies, one previously treated subject developed confirmed neutralizing antibodies to Factor VIII (13.5 BU). In addition, two subjects had transient low titer FVIII antibody (<5 BU) test results on one single occasion. Anti-polyethylene glycol (PEG) antibodies of no clinical consequence were detected in 45 subjects, 32 of whom had pre-existing anti-PEG antibodies. Nine subjects developed anti-Chinese hamster ovary (CHO)-host cell protein (HCP) antibodies with no clinical consequence.

This submission triggers Pediatric Research Equity Act (PREA) and the Pediatric Equity Research Committee (PeRC) meeting was held on September 19, 2018. There are no Post Marketing Commitments or post Marketing Requirements.

Conclusion and Recommendation:

Based on the review of the submitted data, ESPEROCT appears safe and efficacious in adults and children with Hemophilia A for the three indications being sought (on demand treatment and control of bleeding episodes; perioperative management of bleeding; routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with Hemophilia A). However, given the number of subjects who required rescue treatment and change to a more frequent dosing, and the higher ABR in the Q7D prophylaxis regimen, in addition to the inability to identify characteristics of subjects who are likely to benefit from this regimen, the clinical reviewer does not recommend including the Q7D dosing regimen in the label due to the increased risk of bleeding under this regimen. The Q7D regimen may be appropriate for a subset of patients. Individualized prophylaxis at prescriber discretion to less frequent dosing regimens could be considered for those patients who have control of bleeding on the Q4D dosing regimen. These recommendations will be included in the label. Although there are no data in pediatric subjects (<12 years) with perioperative management, hemostatic data in major bleeding and pediatric pharmacokinetic data were utilized to extrapolate the data to support a pediatric perioperative indication. The BLA is recommended for approval from the clinical perspective.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

All subjects were male. The median age in the adult/adolescent studies was 29 years of age. The median age in the pediatric study was 6 years of age. The predominant races represented in the studies were White and Asian. See Table 1 for details.

Table 1: Demographics and Baseline Characteristics

	<6 years	6 to <12 years	12 to <18 years	>18 years
N (%)	34 (100%)	34 (100%)	25 (100%)	161 (100%)
Male	34 (100%)	34 (100%)	25 (100%)	161 (100%)
Race				
White	30 (88%)	25 (74%)	19 (76%)	119 (74%)
Black	2 (6%)	1 (3%)	3 (12%)	8 (5%)
Asian	1 (3%)	4 (12%)	1 (4%)	34 (21%)
NA	0 (0%)	3 (9%)	0 (0%)	0 (0%)
Other	1 (3%)	1 (3%)	2 (8%)	0 (0%)
Ethnicity				
Hispanic/Latino	0 (0%)	3 (9%)	3 (12%)	10 (6%)
Age				
Mean (±SD)	3 (±1.3)	9 (±1.7)	15 (1.6)	34 (11.7)
Median (Min, Max)	3 (1-5)	9 (6-11)	15 (12-17)	31 (8-66)

Source: FDA analysis
NA: not applicable

Reviewer comment: *The limited sample size in blacks and Hispanics makes it challenging to reach conclusions about the efficacy of ESPEROCT in these races and ethnicities. Since the predilection for clinical bleeding is dependent on the degree of factor VIII deficiency, race and ethnicity related differences in efficacy are expected to be minimal. Therefore, it is reasonable to extrapolate from Whites/Asians to the other races and ethnic groups.*

1.2 Patient Experience Data

Table 2: Patient Experience Data Relevant to this Application

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	Sections: 6.1.8 and 6.1.11.2 6.3.8 and 6.3.11.2
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A (HA) is an X-linked congenital bleeding disorder caused by a deficiency of functional clotting factor VIII (FVIII) which manifests as bleeding episodes. It is the most common of the severe inherited coagulopathies with an incidence of approximately 1 in 10,000 births, with approximately 20,000 affected males in the United States. The relationship of bleeding severity correlates with clotting factor level. Patients with <0.01 IU/ mL or <1% of functional FVIII are categorized as severe with spontaneous bleeding into joints or muscles. Moderate severity and mild severity have clotting factor levels of 1-5% and 5 to<40%, respectively.

The average life expectancy is less than 20 years with quality of life severely limited by joint complications and intracranial hemorrhage. To prevent joint destruction, the standard of care in patients with severe HA is primary prophylaxis with infusions of FVIII.

These regular infusions are initiated at the time of the first bleeding episode in a joint or earlier aiming to prevent joint damage. However, inhibitory antibodies to infused FVIII products develop in a substantial percentage of patients treated with either plasma-derived or recombinant FVIII (rFVIII) products, making usual treatment with FVIII complicated. Prophylaxis has been shown to prevent complications later in life and to decrease the incidence of inhibitor formation.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently, there are over ten licensed rFVIII products some of which are full-length FVIII products and others that are beta domain deleted (BDD) products. These products are indicated for adults and children with HA for the control and prevention of bleeding episodes, and/or perioperative management, and/or routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage. The following are the currently approved FVIII products:

Table 3: Approved FVIII Products

Product	Category	Full Length(FL) or B Domain Deleted (BDD)	Cell Expression	Year Approved
Recombinate	Recombinant	FL	CHO	1992
Kogenate	Recombinant	FL	BHK	1993
Refacto	Recombinant	BDD	CHO	2000
Advate	Recombinant Plasma/Albumin Free	FL	CHO	2003
Xyntha	Recombinant	BDD	CHO	2008
Novoeight	Recombinant	BDD	CHO	2013
Eloctate	Recombinant Fc Fusion Protein	BDD	HEK	2014
Obizur	Recombinant Porcine Sequence	BDD	BHK	2014
Nuwiq	Recombinant	BDD	HEK	2015
Adynovate	Recombinant 20kDA PEGylated	FL	CHO	2015
Afstyla	Recombinant Single Chain	BDD	CHO	2016
Kovaltry	Recombinant	FL	BHK	2016
JIVI	Recombinant 60kDA PEGylated	BDD	BHK	2018

Source: FDA summary
BHK: Baby Hamster Kidney, CHO: Chinese hamster ovary, HEK: human embryonic kidney

2.3 Safety and Efficacy of Pharmacologically Related Products

Inhibitor formation and pathogen transmission are the main safety concerns when treating HA patients with FVIII replacement therapy. FVIII concentrates derived from human plasma first became available in the 1960s. The high risk of viral transmission from human plasma donors, underscored by the human immunodeficiency virus (HIV) epidemic in the 1980s, led to the development of rFVIII products which became available in the 1990s. The rFVIII products are genetically engineered and manufactured from animal cell lines, thus minimizing the risk of transmission of human pathogens. Full-

length and modified rFVIII have been produced in Chinese hamster ovary (CHO) or baby hamster kidney (BHK) cells. In addition to the risk of pathogen transmission, the development of neutralizing antibodies, or inhibitors, has been and remains the most concerning safety issue following the administration of FVIII concentrates. The etiology of the development of inhibitors is thought to be a host immune response triggered by non-human proteins contained in the final recombinant FVIII product. Purification steps in the manufacturing processes of successive generations of rFVIII aim to reduce both the transmission of pathogens and the development of inhibitors, which occurs in up to 30% of patients with severe Hemophilia A[1].

The development of inhibitors decreases the efficacy of replacement therapy, necessitates FVIII dosage increases and/or the use of "bypass" agents, increases the risk of unmanageable bleeding and increases cost of treatment (by 3-5 fold)[2]. The incidence of inhibitor development is approximately 30% in severe disease and less in mild or moderate disease. The highest incidence is in previously untreated patients with severe disease (reported incidence from 3-52%). Inhibitor development in previously treated patients who have not previously developed a FVIII inhibitor is less, reported as 0.9-4%. Potential risk factors for inhibitor development include genetic factors, such as the type of FVIII gene mutation, human leucocyte antigen (HLA) type, polymorphisms in immune regulatory regions, family history of inhibitors and ethnic background as well as immunologic environment during early treatment and high intensity of treatment (either peak acute treatment or high overall treatment frequency).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

At the time of the BLA submission ESPEROCT was not licensed in any other country.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

FDA had multiple interactions with the Applicant throughout the IND and BLA process. Pre-IND meeting was held in April 2009 and IND was initiated in July 2010. An end of phase 2 meeting was held in August 2011 and a type C meeting was held in February 2017 to discuss the Applicant's plan for converting the clinical study data from legacy format to Clinical Data Interchange Standards Consortium (CDISC) compliant format. A Pre-BLA meeting was held in December 2017 and discussion included the BLA content/format and timing for the submission. The Applicant indicated that Case Report Forms (CRFs) and narratives will be only reported for subjects who died, withdrew due to an adverse event, or experienced serious adverse events or Adverse Events of Special Interest (AESI). FDA requested that CRFs for all subjects be included. Applicant agreed to submit CRFs for all subjects within 90 days of initial BLA submission.

2.6 Other Relevant Background Information

This product contains a 40kDa PEG moiety that is expected to be comparable to the PEG moieties used with other approved rFVIII products. An approved FIX product showed preclinical findings of PEG accumulation in the choroid plexus. The implications of PEG accumulation are unknown. A Blood Product Advisory Committee (AC) was held

1 Gouw SC, van der Bom JG, Ljung R, et al. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med. 2013;368:231-9.
2 Goudemand J.Treatment of patients with inhibitors: cost issues. Haemophilia 2013;5:397-491.

to gain input on the assessment regarding safety in the intended population, particularly in the pediatric and elderly populations, and in the setting of chronic administration of the pegylated FIX product. FDA asked whether monitoring, specifically for neurocognitive function, should be done for the safety of the intended patient population. In addition, FDA asked whether additional data are necessary to evaluate the issue of PEG accumulation in the choroid plexus. Based on their discussion, the majority of the AC members suggested that a post-marketing study be conducted to assess neurologic and neurocognitive parameters in a standardized manner. All of the committee members agreed that short-term use (on demand treatment and perioperative use) of the study drug was not concerning. The committee members agreed that premarketing approval studies would be useful; and, postmarketing studies may be sufficient to collect more safety data with respect to neurocognitive function in patients.

ESPEROCT, a pegylated FVIII product, did not show any preclinical findings of PEG accumulation. No safety concerns that could be related to PEG were identified in the chronic toxicity studies in (b) (4) nude rats for up to 52 weeks of duration. PEG accumulation does not appear to be a concern with this product.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA was submitted electronically and formatted as an electronic Common Technical Document (eCTD) according to FDA guidance for electronic submission. This submission consisted of the five modules in the common technical document structure. It was adequately organized and integrated to conduct a complete clinical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Submission Integrity

CBER Bioresearch Monitoring (BIMO) issued inspection assignments for three foreign and two domestic clinical study sites that participated in the conduct of Study 3859. The sites were selected for inspection based on numbers of enrolled subjects, number of protocol deviations and prior FDA inspection history. The inspected sites comprise approximately 12% of the total subjects dosed with ESPEROCT in Study 3859. The inspections did not reveal any issues that impact the integrity of the data submitted in this BLA. Please refer to the BIMO review memo for full details.

Table 4: BIMO Inspection Sites

Study Site#	Site Name	Location	Inspection Final Classification
852	KD Haemophilia Centre & Thrombosis Unit	London, Great Britain	NAI
854	Oxford Haemophilia Centre	Oxford, Great Britain	NAI
856	Hemophilia Centre	Basingstoke, Great Britain	NAI
909	Children's Hospitals and Clinics of Minnesota	Minneapolis, Minnesota	NAI

Study Site#	Site Name	Location	Inspection Final Classification
914	Vanderbilt Clinical Trials Center	Nashville, Tennessee	NAI

Source: BIMO Reviewer
NAI: No Action Indicated; BIMO: Bioresearch Monitoring

Reviewer comment: *The European Medicinal Agency (EMA) communicated with the FDA concerns regarding clinical inspection findings for sites: KR0551, and US911. EMA stated that they have identified significant deficiencies in data quality and integrity, and rights and safety of patients. At the time of this communication, they were awaiting the final inspection report to verify if these sites were Good clinical practice (GCP) compliant, which is expected to occur in February 2019. CBER BIMO team did not identify any issues during their inspection, but the sites listed above were not inspected. However, sensitivity analyses were performed excluding these sites and the findings regarding the conclusions of all studies remain unchanged.*

3.3 Financial Disclosures

Complete financial disclosures were provided for the studies and reviewed. No significant financial interests or conflicts were identified that could potentially bias the conduct of the study. A complete list of clinical investigators and sub-investigators was provided and reviewed. A total of 23 investigators or sub-investigators (some of whom were investigators on more than one study) had disclosable financial interests / arrangements and submitted Form FDA 3455. Majority of these investigators received honoraria for participating in advisory boards, consultations, travel and educational events. A total of 60 subjects were treated at these investigators' sites. Table 5 summarizes the investigators' financial disclosures.

Table 5: Financial Disclosure Summary for All Investigators

Study	Total number of Investigators	Number of investigators with disclosable financial interests
3776	37	1
3859	408	20
3860	182	8
3885	209	4
4033	27	0

Source: Adapted from Financial Certification and Disclosure Module 1.3.4

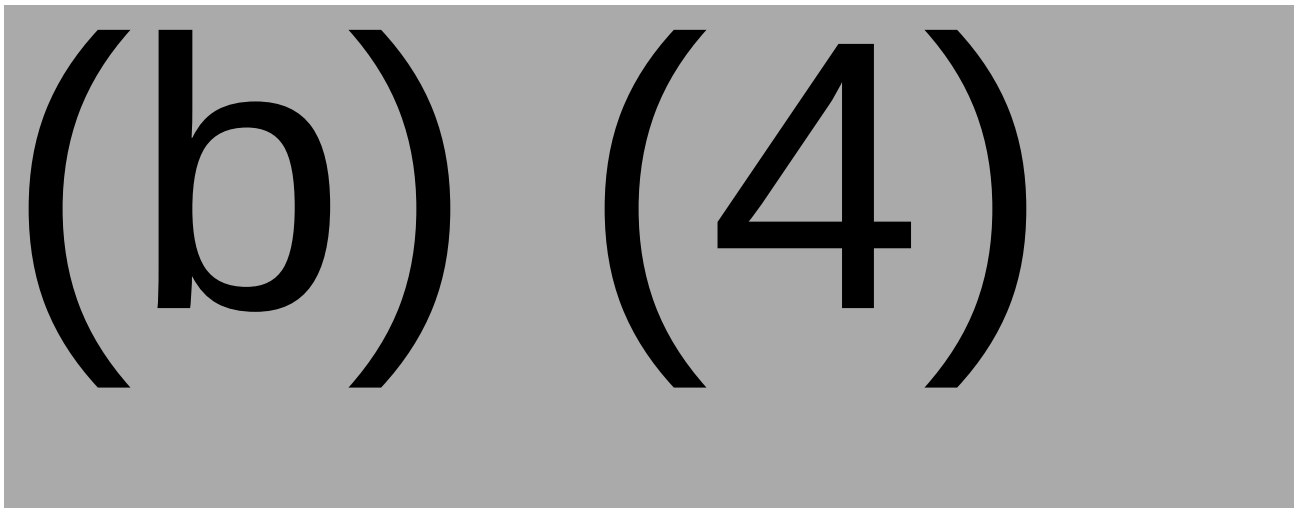
Reviewer comment: *If no information was provided by the investigators, then the sponsor described their efforts at due diligence in attempting to obtain this information. Certificates of due diligence were submitted for four investigators (one from Study 3859 and three from Study 3860). The details of the disclosable arrangements were provided. However, the Applicant did not specifically describe the steps taken to minimize potential bias. The majority of investigators' compensations were received by their respective*

institutions except for when they were used for travel, consultations and educational events. The clinical reviewer doesn't have any concerns regarding the trials conduct or outcome.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls (CMC)

ESPEROCT is a pegylated rFVIII product. The generic (INN) name is turoctocog alfa pegol. The N8-GP product is based on turoctocog alfa, which is a third-generation serum-free, hemostatic protein in which the B-domain of the FVIII molecule has been truncated. In ESPEROCT, the turoctocog alfa molecule is covalently coupled to a single 40K PEG at a unique B- domain O-glycan of turoctocog alfa, resulting in a product consisting of one exact molecular form. When activated by thrombin, the B-domain containing the pegylation is cleaved off, thus generating active FVIII (FVIIIa) which is similar in structure to native activated FVIII. Figure 1 shows ESPEROCT schema.



There were no significant issues related to CMC. Please refer to the CMC memo for details.

4.2 Assay Validation

Required validation of applicable methods and release specifications have been completed and no issues were identified. FVIII plasma activity was measured by two different assays, a clotting assay and a chromogenic assay. For both assays, analyses were performed using (b) (4) . Please refer to the CMC review memo for complete details.

4.3 Nonclinical Pharmacology/Toxicology

The activity, pharmacokinetics (PK) and safety of ESPEROCT were evaluated in several rodent and non-rodent HA and healthy animal models. PK analysis in dogs indicated a terminal half-life almost double that of N8 which suggested that the prolonged activity of ESPEROCT (N8-GP) is likely due to extended circulation of the PEGylated FVIII protein. The prolonged activity was also supported by studies in HA mice. PK studies were

conducted in mice, rats and monkeys to characterize PEG tissue distribution and elimination, and results supported the extended terminal half-life of ESPEROCT. Excretion studies revealed that the primary mode of elimination may be through feces followed by renal clearance.

Repeat administration of ESPEROCT once every 4th day in immunocompromised rats over 52 weeks followed by a 12-week recovery period did not result in notable toxicities at dose levels up to 1200 IU/kg. The "no-observed-adverse-effect-level (NOAEL)" was established at 1200 IU/kg administered intravenously every 4th day. This NOAEL dose level is approximately 20-fold higher than the clinical dose levels (50-60 IU/kg twice weekly).

As PEG accumulation in the choroid plexus and other organs was a concern raised with another PEG-conjugated recombinant FIX product (N9-GP). The Applicant submitted a comparative analysis of PEG distribution, accumulation and toxicity following administration of N8-GP (ESPEROCT) and N9-GP (Rebinyn). While distribution and elimination profiles appeared to be similar for the two compounds, no PEG was detected in the choroid plexus following long-term, repeat administration of ESPEROCT compared to Rebinyn at dose levels of 1200 IU/kg. This may be due to the lower amount of PEG per unit of activity for ESPEROCT (b) (4) PEG/IU) compared to Rebinyn ((b) (4) µg PEG/IU).

Reviewer comment: *The pharmacology toxicology (pharm/tox) reviewer concluded that there are no nonclinical deficiencies identified in the pharm/tox studies, and that the nonclinical data provided in this BLA submission support the approval of this licensure application. Please refer to the pharm/tox review memo for complete details.*

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

ESPEROCT, a glycoPEGylated form of recombinant anti-hemophilic factor temporarily replaces the missing coagulation FVIII needed for effective hemostasis in congenital HA patients. The FVIII in ESPEROCT is conjugated to a 40-kDa polyethylene glycol molecule, which slows down its removal from the blood circulation, prolonging its half-life.

4.4.2 Human Pharmacodynamics (PD)

The administration of ESPEROCT increases plasma levels of FVIII and can temporarily correct the coagulation defect in HA patients, as reflected by a decrease in activated partial thromboplastin time (aPTT).

4.4.3 Human Pharmacokinetics (PK)

All PK studies with ESPEROCT were conducted in previously treated subjects with severe HA (FVIII<1%). In total, 129 single-dose PK profiles of ESPEROCT were evaluated in 86 subjects (including 24 pediatric subjects, 0–11 years). Observed pre-dose (trough) and post-dose (peak) plasma FVIII activity levels at steady-state during prophylactic treatment with ESPEROCT are presented in Table 6 by dose regimen and age range.

Table 6: Steady-state Trough and Peak Plasma FVIII Activity by Age and Dose Regimen, Chromogenic Assay (Geometric Mean [95% CI])

Dose Regimen	65 IU/kg twice weekly* (50–75 IU/kg)		50 IU/kg Q4D**		75 IU/kg Q7D**	
Age range	0-5 years	6–11 years	12–17 years	≥18 years	12–17 years	≥18 years
# of subjects	N=31	N=34	N=23	N=143	N=6	N=29
Trough, IU/dL	1.2 (0.8; 1.6)	2.0 (1.5; 2.7)	2.7 (1.8; 4.0)	3.0 (2.6; 3.5)	0.6 (0.2; 1.6)	1.3 (0.9; 2.0)
Peak, IU/dL	125.0 (118.7; 131.6)	143.3 (136.8; 150.2)	125.1 (116.0; 135.0)	137.9 (133.9; 142.2)	198.0 (166.8; 235.2)	197.9 (184.9; 212.7)

*Data included in analysis are from Study 3885 main
**Data included in analysis are from Study 3859 Main and Extension 1
Only measurements collected at steady-state for the given prophylaxis treatment are included in the analyses

Of the 45 subjects with evaluable PK profiles after dosing with 50 IU/kg in Studies 3776, 3859 and 4033, 27 subjects had a body mass index (BMI) within normal range (18.5–24.9 kg/m^2), 12 subjects had a BMI 25–29.9 kg/m^2 and six subjects had a BMI ≥30 kg/m^2. One subject had a BMI of 16.9 kg/m^2. No clear effect of BMI on the PK of ESPEROCT was observed, when considering the variability of the individual profiles and limited number of subjects in the higher BMI groups.

Please refer to the Clinical Pharmacology review memo for complete details.

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses and key secondary endpoints cited by the Applicant were supported by the submitted data. Please refer to the biostatistic review memo for complete details.

4.6 Pharmacovigilance

The Applicant proposed a non-interventional post-authorization safety study (PASS); which is a multinational, non-randomized, non-interventional study to evaluate the long-term safety of ESPEROCT in HA PTPs without inhibitors. This study is being undertaken to meet an EMA requirement, but not FDA requirement.

This study is planned to include safety follow-up assessments at routine comprehensive care visits for at least four years for up to 50 patients. Beyond the standard assessments of routine comprehensive care of patients with HA by physicians, nurses, psychologists, physiotherapists, 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.

Study milestones: safety updates from the study will be provided in ESPEROCT Periodic Safety Update Reports (PSURs) and at the five-year renewal. Planned duration of recruitment period is two years. Protocol submission to be determined.

- 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

Please see the office of biostatistics and epidemiology (OBE) review for further details.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Clinical trials that provided the evidence for safety and efficacy of ESPEROCT were conducted under IND 14410. Data from the completed adults and adolescents (Study 3859) main and extension 1, pediatric (Study 3885), and surgery (Study 3860) studies served as the primary basis for the review. Data reviewed included the integrated summary of safety (ISS), summary of clinical safety (SCS), summary of clinical efficacy (SCE), individual clinical study reports (CSRs), patient narratives, numerous information requests (IRs), and data in the public domain. Integrated summary of efficacy (ISE) was not appropriate for the adult and pediatric studies due to different study designs and dosing regimens used in the trials. Supportive data from completed PK (3776) and ongoing adults and adolescents (3859) extension 2 and pediatric (3885) extension studies were briefly reviewed. Analyses were performed largely using JReview 12.0 and JMP 13 (SAS Institute, Inc.), to reproduce key efficacy and safety analyses, based on the submitted data analysis datasets, and to conduct additional exploratory analyses.

Review Responsibilities:
Chair/CMC – Andrey Sarafanov
Clinical – Najat Bouchkouj
Statistician – Lin Huo
Clinical Pharmacology – Iftekhar Mahmood
Pharm/Tox – Gaya Hettiarachchi
Epidemiology – Ohenewaa Ahima
APLB Labeling – Kristine Khuc
BIMO – Anthony Hawkins
DMPQ Reviewer – Hector Carrero
DBSQC Reviewer – Karla Garcia
RPM – Jean Dehdashti

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Documents pertinent to this review were provided in BLA125671/0 and IND 14410, including the overview, analyses datasets, clinical summary, and clinical study reports.

5.3 Table of Studies/Clinical Trials

An overview of ESPEROCT clinical trials is presented in Table 7. In summary: Study 3776 was a first in human PK study. Study 3859 consisted of a main phase followed by optional two extension phases. The main phase included an on-demand arm and a prophylaxis arm. Subjects on prophylaxis during the main part were offered to continue into extension phase part 1 with the option of being randomized to every 7 day (Q7D) or 4 day (Q4D) dosing. Subjects completing extension phase part 1 could continue treatment in extension phase part 2. Study 3885 consisted of a main phase followed by

one optional extension phase. Study 3860 was a surgery study and study 4033 was a PK study evaluating the commercial process (drug substance manufacturing process was optimized and moved to a different site) compared to the pivotal process in a randomized cross-over design with a wash-out period before each PK session.

Table 7: Overview of ESPEROCT Clinical Trials*

Trial ID/ Status	Trial design	N8-GP dose and treatment regimen[a]	Number of patients[b] (age range)
Previously treated patients			
Trial 3776: Completed	*First human dose trial* Open-label, dose escalation	*Single-dose PK*: 25, 50, 75 IU/kg	Total: 26 patients (20–60 years)
Trial 3859 Pivotal part of the trial (Interim report): Completed	*Pivotal trial* Open-label, non-controlled	Main phase: *Prophylaxis*: 50 IU/kg Q3–4D *Treatment of bleeds*: 20–75 IU/kg *Single-dose PK*: 50 IU/kg	Total: 186 patients (12–66 years) PK: 24 patients
Extension phase part 1 (Interim report): Completed		Extension phase part 1: *Prophylaxis*: 50 IU/kg Q3–4D or 75 IU/kg Q7D *Treatment of bleeds*: 20–75 IU/kg	Total: 150 patients (12–66 years)
Extension phase part 2 (Interim report): Ongoing		Extension phase part 2: *Prophylaxis*: 50 IU/kg Q3–4D or 75 IU/kg Q7D *Treatment of bleeds*: 20–75 IU/kg	Total: 139 patients (12–66 years)
Trial 3860 (Interim report): Ongoing	*Surgery trial* Open-label, non-controlled	*Pre-surgery period*: Preoperative dose aiming for a FVIII activity level of 80-100%. *Post-operative period* *Days 1–6*: At the investigator's discretion, aiming for a FVIII activity level above 50%. *Days 7–14*: At the investigator's discretion.	Total: 34 patients; 45 surgeries (15–69 years)
Trial 3885 Main phase (Interim report): Completed Extension phase (Interim report): Ongoing	*Paediatric trial* Open-label, non-controlled	*Prophylaxis*: ~60 IU/kg (50–75) twice-weekly with adjustment to every third day if necessary* *Treatment of bleeds*: 20–75 IU/kg *Single-dose PK*: 50 IU/kg	Total: 68 patients (1–11 years) PK: 27 patients
Trial 4033: Completed	*Pharmacokinetics & safety of N8-GP from the pivotal and the commercial process* Randomised, double-blind, cross-over	*Single-dose PK*: 50 IU/kg	Total: 21 patients (20–71 years)
Previously untreated patients			
Trial 3908 Ongoing	*Previously untreated patients* Open-label, non-controlled	*Prophylaxis:* 50–75 IU/kg every third day, twice weekly or every seventh day. *Treatment of bleeds*: 20–75 IU/kg	32 patients (planned 125 patients <6 years of age)

PK: pharmacokinetics; Q3–4D: patients starting dose was every fourth day, subsequently patients could switch to twice-weekly*; Q7D: every seventh day dosing.

*Dosing frequency could be adjusted at the discretion of the investigator based on patient response.

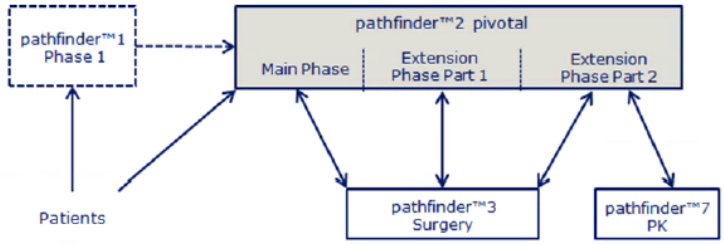
[a] Bleeds were treated according to the severity and location of the bleed. Additional doses for treatment of a bleed could be given at the investigator's discretion. [b] Number of exposed patients shown; all patients had severe haemophilia A with FVIII activity <1%.

Source: Adapted from BLA125671 Clinical Overview Table 1-2 Page 13.

* From PTP trials 3776, 3859, 3885, and 3860: Total number (#) of treated subjects is 270: (0-5 years: 34, 6-11 years: 34, 12-17 years: 25, ≥18 years: 171)

Figure 2 below summarizes the clinical program in adolescents and adults.

Figure 2: Overview of the ESPEROCT clinical trial program in adolescents and adults

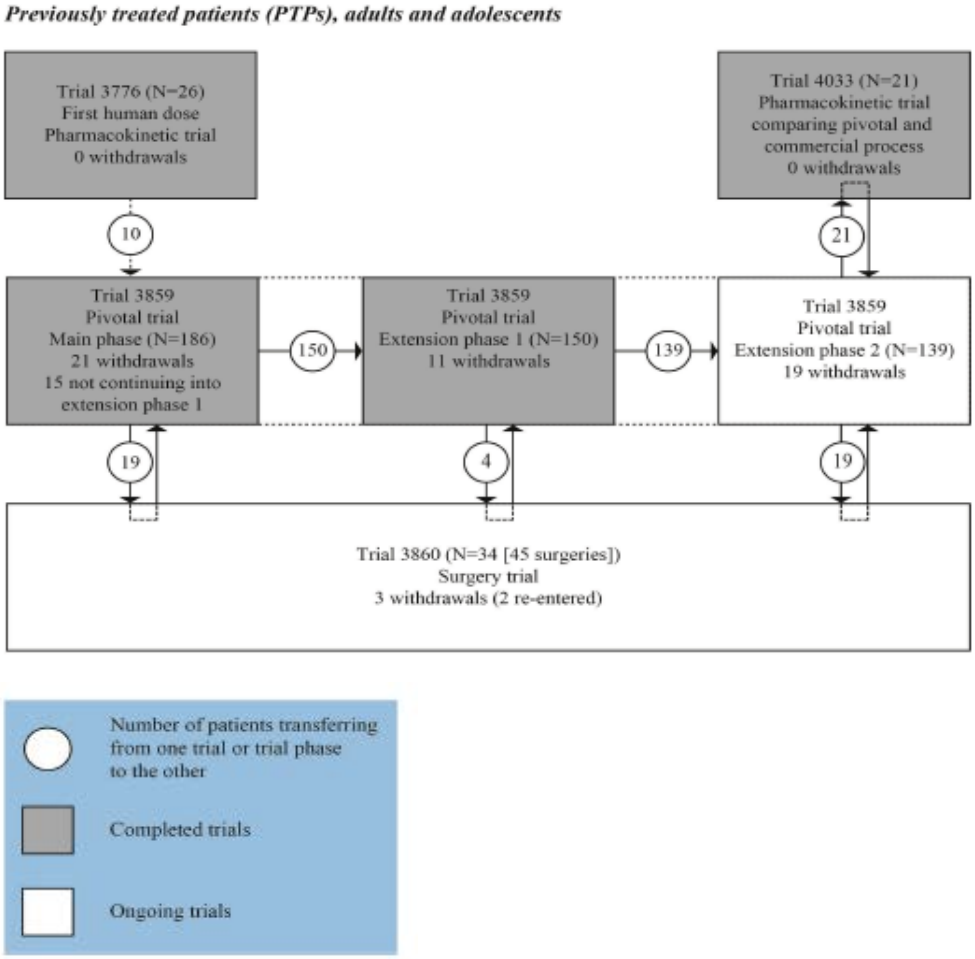


pathfinder™1 = NN7088-3776
pathfinder™2 = NN7088-3859
pathfinder™3 = NN7088-3860
pathfinder™7 = NN7088-4033
broken lines = NN7088-3776 was completed before NN7088-3859 was initiated. There was an interval before patients who had participated in NN7088-3776 could enter NN7088-3859

Source: BLA 125671 Study 3860 CSR Figure 7-1 Page 25/711

Flow of subjects in the 3776, 3859 and 3860 studies is shown in Figure 3 below.

Figure 3: Flow of Subjects in the ESPEROCT Clinical Development Program



Source: Adapted from BLA 125671 Clinical Overview Figure 1-3 Page 17/66

Reviewer comment: *All PTPs entered the program through Studies 3776, 3859 and 3885. Subjects from study 3776 could continue prophylaxis and on-demand treatment in the Study 3859. As the results of trial 3776 had to be analyzed and used for dose selection, subjects could not continue directly from Study 3776 into study 3859. Subjects from Study 3859 requiring major surgery were offered to participate in the surgery trial 3860 and to return to trial 3859 upon surgery completion. A subset of subjects from Study 3859 also participated in the PK study 4033, and after completion of this study they returned to Study 3859. As many subjects participated in more than one trial, the sum of subjects in the individual studies is higher than the total number of unique subjects.*

5.4 Consultations

No consultants were requested by the clinical team during the review of this BLA.

5.4.1 Advisory Committee Meeting (if applicable)

An advisory committee meeting was not convened because: the biologic is not the first in its class, and the safety profile particularly with regard to long-term PEG accumulation associated with pre-clinical findings from similar class of products are not a concern based on review of the pre-clinical studies in support of the BLA. Additionally, the design of the clinical study is similar to studies conducted to support other approved products, and the review of the application did not raise significant safety concerns that could not be addressed through information in the label. Consultative expertise was not required, and no public health concerns arose upon review of this file.

5.4.2 External Consults/Collaborations

There were no external consults or collaborations, that were requested by the clinical reviewer, in the review of this BLA.

5.5 Literature Reviewed (if applicable)

1) Gouw SC, van den Berg HM, et al: Intensity of factor VIII treatment and inhibitor development in children with severe hemophilia A: the RODIN study. Blood 121(20): 4046-4055, 2013.
2) Calvez T, Chambost H, et al: Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A. Blood 124(23): 3398-3408, 2014.
3) Collins PW, Palmer BP, et al: Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe hemophilia A, 2000-2011. Blood 124(23): 3389-3397, 2014.
4) Vezina C, Carcao M, et al: Incidence and risk factors for inhibitor development in previously untreated severe haemophilia A patients born between 2005 and 2010. Haemophilia 20(6): 771-776, 2014.
5) Fisher K, Lassila, R, et al. Inhibitor development in haemophilia according to concentrate: Four-year results from the European Haemophilia Safety Surveillance (EUHASS) project. Thromb Haemost 113.4, 2015.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: Study NN7088-3859 (or 3859)

Clinical Trials Identifier: NCT01480180
Trial initiated: 30 January 2012. Trial Completed: 28 January 2014.

Title: A Phase 3, multi-national trial evaluating safety and efficacy, including pharmacokinetics (PK), of ESPEROCT when administered for treatment and prophylaxis of bleeding in patients with hemophilia A.

General considerations: All endpoints were planned to be analyzed and reported separately for the Main Phase, the Extension Phase part 1 and the Extension Phase part 2 of the trial. The review of the Main Phase is based on all data up to the cut-off visit for each subject when they reached at least 50 exposure days (EDs) (except for subjects having had surgery as part of Study 3860). The last prophylaxis subject was expected to reach 50 EDs on 6 December 2013. Data on exposure and adverse events are based on subjects' cut-off visit dates. In addition, all serious adverse events until 28 January 2014 were included in the narratives.

6.1.1 Objectives (Primary, Secondary, etc)

Co-Primary objectives

- To evaluate the immunogenicity of ESPEROCT in previously treated subjects with hemophilia A
- To evaluate the clinical efficacy of ESPEROCT in bleeding prophylaxis (number of bleeds during prophylaxis)

Secondary objectives

- To evaluate the clinical efficacy of ESPEROCT when treating bleeds in subjects with hemophilia A
- To evaluate the safety of ESPEROCT when used for prevention of bleeds and treatment of bleeds in subjects with haemophilia A
- To evaluate PK properties of ESPEROCT
- To evaluate patient reported outcomes (PRO)
- To evaluate the health economic impact of ESPEROCT treatment
- Generation of a population based PK-model for ESPEROCT

The trial consisted of a Main Phase followed by an Extension Phase:
Extension Phase part 1: The primary objective was to assess the efficacy of the Q7D prophylaxis regimen compared to Q4D. Please refer below to section 6.1.11 for review of the completed extension 1 study.

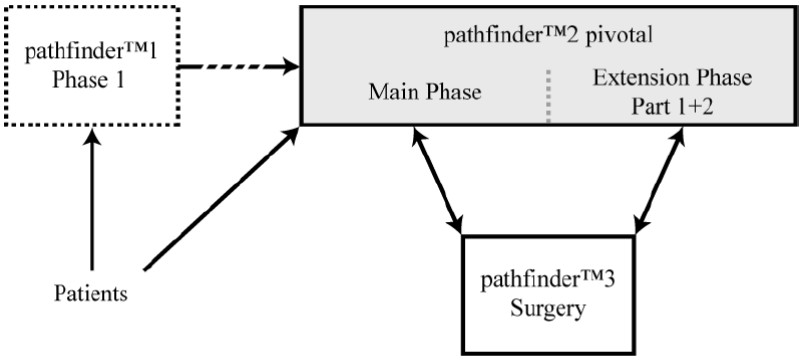
Extension Phase part 2: The primary objectives were to evaluate the immunogenicity of ESPEROCT in PTPs with hemophilia A and to evaluate the clinical efficacy of ESPEROCT in bleeding prophylaxis.

Reviewer comment: *Extension Phase part 2 was not reviewed in detail because the study is still ongoing and it hasn't been completed yet.*

6.1.2 Design Overview

The study was a phase 3, multi-center, multi-national, open-label, non-randomized trial evaluating safety, PK and clinical efficacy of ESPEROCT when used for treatment of bleeding episodes and for long-term prophylaxis. The trial consisted of a Main Phase followed by an Extension Phase; please see Figure 4. Subjects completing the first human dose (FHD) Study 3776 were offered to participate in this trial. Furthermore, if the subjects needed to undergo surgery during this trial they could switch into the surgery trial 3860 and upon completion of the surgery they could return to the 3859 trial. Minor surgery could be performed while participating in this trial by administering an additional dose of 50-75 U/kg ESPEROCT or a dose sufficient to increase the FVIII level to 100% prior to the minor surgery to prevent peri-operative bleeding. The surgery trial and the prophylaxis treatment in US were not initiated until at least 20 bleeds in at least 10 subjects were treated with ESPEROCT in the present trial.

Figure 4: Study Design



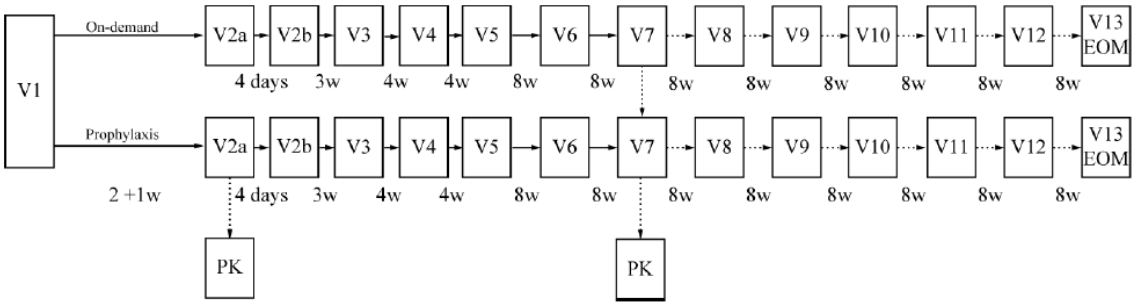
(pathfinder™ 1, NN7088-3776), (pathfinder™ 2, NN7088-3859), (pathfinder™ 3, NN7088-3860)

Source: BLA 125671 CSR Figure 9-1 Page 41/1561

In the Main Phase of the trial, subjects were to receive treatment with 50 U/kg of ESPEROCT every 4 days during a period of approximately 7-19 months. All subjects were to continue in the Main Phase until the last subject initiated in the prophylaxis arm had received at least 50 EDs of ESPEROCT (except for subjects having had surgery as part of Study 3860) and the average exposure to ESPEROCT would therefore be more than one year. An exposure day was defined as each date at which ESPEROCT was administered, hence if ESPEROCT was administered more than once during the same day, this would count as one exposure day.

The Main Phase of the trial also included a non-randomized on-demand treatment arm. A total of 12 subjects were to be enrolled in the on-demand arm in order to obtain 10 completed subjects, who had been treated on-demand with ESPEROCT during a period of approximately six months to ensure that sufficient bleeding treatment data were collected in the trial. When these subjects had completed approximately six months on-demand treatment, the on-demand subjects were offered to switch to the prophylaxis arm (if the prophylaxis arm was still open for enrollment), or to continue on-demand treatment until the end of trial. For an overview of visits in the Main Phase of the trial; please refer to **Figure 5**.

Figure 5: Overview of visits in the Main Phase of the trial



Source: BLA 125671 CSR Figure 9-1 Page 43/1561

The Main Phase of the trial included the following visits:

- Visit 1: Screening visit
- Visit 2a and 2b: Visits at the site.
    - All subjects had their first and second dose administered at the site.
    - Subjects in the prophylaxis arm undergoing PK evaluation underwent first PK evaluation at Visit 2a.
- Visit 3-12: Visits at the site.
    - Subjects in the prophylaxis arm were dosed during the visits
    - Subjects in the prophylaxis arm undergoing PK evaluation underwent the second PK evaluation at Visit 7
    - subjects in the on-demand arm were not dosed during the visits
- Visit 13: End-of-Main Phase visit. Visit at the site
    - End of Main Phase assessments (No subjects were dosed as part of the visit)

The two initial doses of ESPEROCT were to be administered in a hospital setting to observe for adverse reactions. The subjects were to be observed for at least 1hr after dosing. Thereafter, home treatment could be initiated. In both the prophylaxis arm and the on-demand arm, bleeds were to be treated with ESPEROCT doses between 20-75 IU/kg BW. A severe bleed should be treated immediately at home and the hemophilia site should be contacted without delay for further instructions and/or transport to the site. When the Main Phase was completed (Visit 13), all subjects were offered to continue treatment in the Extension Phase, if approved by the country.

The current report includes all data from the Main Phase of the trial analyzed and reported when all subjects had reached at least 50 EDs (except for subjects having had surgery as part of Study 3860).

6.1.3 Population

The key inclusion criteria were as follows:

- Male subjects with severe congenital haemophilia A (FVIII activity <1%)
- Documented history of at least 150 EDs to other FVIII products
- Age ≥12 years and body weight ≥35 kg (or male ≥18 years of age in countries where enrollment of minors was not permitted)
- Body Mass Index (BMI) ≤ 35

The key exclusion criteria were as follow:

- Known or suspected hypersensitivity to trial product
- Current evidence of inhibitor to FVIII with a titer ≥ 0.6 BU/mL, measured by the (b) (4) Bethesda assay at the time of screening (central laboratory)
- History of inhibitor to FVIII with a titer ≥1 BU
- HIV positive
- Congenital or acquired coagulation disorders other than hemophilia A
- Previous significant thromboembolic events
- Platelet count < 50,000 platelets/µL
- ALT > 3 times above upper limit of normal (ULN) or Creatinine level ≥1.5 times ULN
- Ongoing immune modulating or chemotherapeutic medication
- Significant concurrent illness that the investigator deemed to be incompatible with the subject's continued safe participation in the study

Withdrawal of subjects from therapy and assessment: A subject was to be withdrawn if the following applied:

- Hemostasis not achievable with ESPEROCT: The bleed cannot be controlled after 48 hours using adequate doses of ESPEROCT
- FVIII inhibitor (>5 BU) as confirmed by re-testing by Central Laboratory
- FVIII inhibitor (≥0.6 and ≤ 5 BU) as confirmed by re-testing by Central Laboratory
- Allergy/anaphylaxis to the trial product
- Use of Coagulation Factors FVIII, FIX and FVII-containing products other than ESPEROCT and other FVIII-containing products like fresh frozen plasma or cryoprecipitate
- Use of anti-coagulants such as heparin and vitamin-K antagonists

6.1.4 Study Treatments or Agents Mandated by the Protocol

The following investigational products were supplied by Novo Nordisk: ESPEROCT 2000 IU/vial 211µg/vial as a sterile, freeze-dried powder in a 2-8 °C (36-46°F) stable formulation single use vial to be reconstituted with (b) (4) of 0.9% sodium chloride (NaCl) for intravenous (i.v.) injection. The product had to be reconstituted prior to administration.

6.1.5 Directions for Use

The trial product was to be administered as a slow bolus i.v. injection over approximately 2 minutes. The maximum dose to be administered to a subject within 24 hours was 200 IU/kg BW. An electronic diary (eDiary) was kept to register all bleeding episodes and their treatment.

Per protocol, for the treatment of bleeding episodes, doses were based on World Federation of Hemophilia (WFH) guidelines. For treatment of a bleed, all on demand and prophylaxis subjects were to be treated with doses between 20-75 U/kg BW (the recommended standard dose was 50 U/kg).

Table 9–1 Overview of treatments

	Treatment	Dose	Frequency
Main phase	Prophylaxis	50 IU/kg BW	Every 4th day / Twice weekly*
	PK (for a sub group)	50 IU/kg BW	Twice (Visit 2a and 7)
	Treatment of bleeds	20-75 IU/kg BW	Investigator's discretion

Source: Adapted from BLA 125671 CSR Table 9-1 Page 48/1561
* Twice weekly dosing was only allowed for subjects at the discretion of the investigator and if deemed necessary for the individual subject

Reviewer comment: *Thirteen (7%) of 175 subjects in the prophylaxis arm modified their dosing regimen from Q4D to Q3-4D dosing (i.e., twice weekly) for ease of use.*

6.1.6 Sites and Centers

A total of 186 subjects received treatment in the Main Phase of the study at 77 sites in 22 countries, which included Australia, Brazil Croatia, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Malaysia, Netherlands, Norway, Russia, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, and the United States.

6.1.7 Surveillance/Monitoring

The trial was conducted in accordance with Declaration of Helsinki and International Conference on Harmonization (ICH) Good Clinical Practice. The 21 Code of Federal Regulations, parts 312, 50, and 56 were followed.

Prior to trial initiation, the protocol, the protocol amendments, the consent form, and the subject information sheet were reviewed and approved according to local regulations by appropriate health authorities, and by an independent ethics committee (IEC) / Institutional Review Board (IRB), i.e., a review panel responsible for ensuring the protection of the rights, safety, and well-being of human patients involved in a clinical investigation, which was adequately constituted to provide assurance of that protection.

Prior to any trial related activity, the investigator gave the subjects and/or the subjects' legally acceptable representative (LAR) oral and written information about the risks and benefits of the trial, in a form that the subject or LAR could read and understand. This included the use of impartial witness where required. The subjects and/or the subjects' LAR were informed that the subjects could withdraw from the trial at any time for any reason. Consent was obtained in writing at the screening visit, prior to any trial- related activities, and the investigators retained the consent forms.

6.1.8 Endpoints and Criteria for Study Success

Co-primary endpoints

- The incidence rate of FVIII inhibitors ≥0.6 BU
- Annualized bleeding rate (ABR) for patients receiving prophylaxis treatment

Secondary endpoints Confirmatory secondary efficacy endpoints

- The hemostatic effect of ESPEROCT when used for treatment of bleeds, assessed on a four-point scale for hemostatic response (excellent, good, moderate and none) by counting excellent and good as success and moderate and none as failure.

Additional supportive efficacy endpoints

- Consumption of ESPEROCT (number of injections and IU/kg per bleed and month and per year) during prophylaxis and on-demand treatment
- Hemostatic effect as measured by recovery and trough levels FVIII:C (in subjects receiving prophylaxis treatment)
- Patient Reported Outcomes (PROs) and Health Economic Endpoints

Reviewer comment: *The following definitions were used by the Applicant:*
Definitions of hemostatic response:

- *Excellent: Abrupt pain relief and/or clear improvement in objective signs of bleeding within approximately 8 hours after a single injection*
- *Good: Definite pain relief and/or improvement in signs of bleeding within approximately eight hours after a single injection, but possibly requiring more than one injection for complete resolution*
- *Moderate: Probable or slight beneficial effect within approximately eight hours after the first injection, but usually requiring more than one injection*
- *None: No improvement, or worsening of symptoms*

Definitions of severity of bleeding episodes:

- *Mild/moderate: Bleeding episodes that were uncomplicated joint bleeding episodes, muscular bleeding episodes without compartment syndrome, mucosal- or subcutaneous bleeding episodes.*
- *Severe: All intracranial, retroperitoneal, iliopsoas and neck bleeding episodes were categorized as severe. Muscle bleeding episodes with compartment syndrome and bleeding episodes associated with a significant decrease in the hemoglobin level (>3g/dL) were also considered severe.*

Classification of re-bleed: A re-bleed was defined as a worsening of symptoms in the same location after an initial period of improvement, either on treatment or within 72 hours after completed treatment. If a bleeding episode occurred in the same location later than 72 hours after completed treatment it was considered a new bleed.

Reviewer comment: *All definitions are acceptable.*

Safety endpoints

- Adverse events (AEs) and serious adverse events (SAEs)
- Changes in vital signs

Pharmacokinetic endpoints

- FVIII activity 30 min post-injection (C30min)
- Incremental recovery, ([IU/mL] / [U/kg]) (single dose and steady state)
- Trough level, (IU/mL) (single dose and steady state)

- AUC, (h*IU/mL)
- Terminal half-life (t½), (h)
- Clearance (mL/h/kg)
- Mean Residence time (MRT) (h)
- Vss (Volume of distribution at steady state) (mL)

Exploratory endpoints

- Incidence of binding antibodies to N8-GP

The safety analysis set and the full analysis set were identical and consisted of all dosed subjects. Thus, a total of 186 subjects were included in these analysis sets. No subjects were excluded from any analyses.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The study had two co-primary endpoints that both had to succeed. The evaluation was based on data from the Main Phase of the trial.

Incidence rate of FVIII inhibitors ≥0.6 BU:

- The rate of inhibitors is reported and a 1-sided 97.5% upper confidence limit is provided based on an exact calculation for a binomial distribution. For the calculation of the inhibitor rate, the numerator included all subjects with neutralizing antibodies while the denominator included all subjects with a minimum of 50 EDs plus any subjects with less than 50 EDs but with inhibitors. Adequate safety with regard to inhibitors would be concluded if the upper 1-sided 97.5% confidence limit was below 6.8% corresponding to the upper 97.5% confidence limit if two inhibitors out of 105 subjects were observed (3 or less if the study should get 127 or more patients with 50 EDs).

Annualized bleeding rate for subjects receiving prophylaxis treatment:

- The prophylactic effect of ESPEROCT was shown by comparison of the observed bleeding rates to historical data on ABRs for subjects treated on an on-demand and prophylaxis basis. Prophylactic effect of ESPEROCT would be concluded, if the bleeding rate was significantly below 50% of the historical on-demand bleeding rate (i.e. lower than 12) as well as within 25% of the historical prophylaxis bleeding rates (i.e. lower than 6.8*1.25 = 8.5). Since both must be met in practice it must be shown that the bleeding rate is significantly lower than 8.5.

One interim analysis was conducted during the Main phase of the study to evaluate if the sample size needed to be adjusted, and for regulatory purposes (in order to obtain regulatory permission to start the surgery and pediatric trials).

Reviewer comment: *For the historical control for hypothesis testing, the Applicant based the estimated ABR on the referenced studies that were provided in the study protocol. The Applicant suggested that representative numbers for mean ABR in severe hemophilia patients were 24 bleeds/year for patients treated on-demand and 6.8 for patients on prophylactic treatment. However, the references that the Applicant cited are all published prior to 2010. In general, in the current landscape of hemophilia treatment, a mean ABR of 8.5 would be considered unacceptable.*

Imputation: For subjects withdrawing prematurely, the number of bleeding episodes was imputed (whenever stated) up to what would be expected if they had completed the trial, as described in the protocol. For subjects withdrawing within one month, the annual bleeding rate was imputed as 24 episodes per year for the missing period.

Reviewer comment: *The Applicant proposes to use the Poisson estimates (95%CI) for ABR analysis in the label. However, the Poisson estimates are estimates based on the fitted model, and their primary purpose is for hypothesis testing while accounting for outliers. The clinical reviewer recommends including the Mean ABR (SD) instead of the Poisson estimated rates throughout the label since the mean (SD) is calculated based on the actual data, which is more comparable with the median (IQR) ABR presented (which is also calculate based on the actual data). Furthermore, the clinical reviewer based the primary ABR analysis on the observed ABRs without imputation.*

6.1.10 Study Population and Disposition

A total of 215 subjects were screened for this trial and 186 of these subjects were dosed with ESPEROCT, of which 25 subjects were adolescents (12-17 years). Twelve subjects received on-demand treatment and 175 subjects received prophylaxis therapy. A total of 24 subjects were enrolled for PK assessments, of which three were adolescents.

A total of 345 important protocol deviations were reported in this trial of which 33 were at trial site level and 308 were at patient level. None of the important protocol deviations at the trial site and patient levels were regarded as having a major effect on the trial outcome or on the safety of the patients. Most of the 82 treatment compliance deviations were related to non-compliance with the prophylaxis dosing regimen, for most cases due to administration of the prophylaxis dose just outside the treatment window specified in the protocol.

Table 8: Summary of Important Protocol Deviations at Subject Level

Protocol deviation category	Number of deviations
Informed consent	29
Inclusion/exclusion criteria	12
Withdrawal criteria	9
Trial drug handling	31
Treatment compliance	82
Visit window	2
Assessment deviations including laboratory samples	99
Other	44

Source: FDA analysis and adapted form BLA 125671 Table 10-6 CSR Page 116/1561

6.1.10.1 Populations Enrolled/Analyzed

This trial enrolled subjects with severe hemophilia A aged 12 to 65 years. There were 25 subjects between the ages of 12-17 years.

6.1.10.1.1 Demographics
The trial population consisted of male subjects with severe hemophilia A and a mean age of 31.1 years (ranging from 12 to 66 years old). Subjects' mean body weight was 75 kg (ranging from 39.0 to 122 kg). Most subjects were White (74%) followed by Asian (19%). A total of 25% of the subjects were from the US, 12% were from the United Kingdom, 8% were from Japan, 7% were from Germany, while the remaining subjects were distributed between the other 18 countries. Mean age was slightly lower in the prophylaxis arm (30.6 years) as compared to the on-demand arm (39.8 years), all 25 adolescents subjects enrolled in the trial were in the prophylaxis arm. No differences were observed between the 24 subjects in the PK population and the total trial population. Subject ID (b) (6) changed treatment from on-demand to prophylaxis at Visit 6 and therefore contributed to exposure time in the prophylaxis arm from Visit 6 and onwards. Details are provided in Table 9.

Table 9: Demographics and Baseline Characteristics

Characteristics	Statistics	Subjects N (%)
Sex	Male	186 (100%)
Age Group	<18 years	25 (13%)
	≥18 years	161 (87%)
Race	Asian	35 (19%)
	Black or African American	11 (6%)
	Other	2 (1%)
	White	138 (74%)
Ethnicity	Hispanic or Latino	13 (7%)
	Not Hispanic or Latino	173 (93%)
PK	PK Analysis	24 (13%)
Mutation	Deletions	28 (15%)
	Duplication	3 (2%)
	Insertions	7 (4%)
	Inversions	69 (37%)
	Other	8 (4%)
	Splice site mutation	3 (2%)
	Substitution	38 (20%)
Treatment Prior to Trial	Prophylaxis regimen	149 (80%)
	On-demand	37 (20%)
Treatment Arm During Trial*	Prophylaxis	175 (94%)
	On-demand	12 (6%)
Population	Safety Set	186 (100%)
	Full Analysis Set	186 (100%)

Source: FDA analysis
* One subject changed treatment regimen from on-demand to prophylaxis at Visit 6. Therefore, he is included in both the prophylaxis and on-demand arm but only counted once in the total.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
All subjects were males with severe congenital hemophilia A (FVIII activity <1%), according to medical records. All subjects were previously treated patients with a history of at least 150 EDs to other FVIII products without a history of inhibitors.

Before entry into the trial, 80% of the subjects received regular prophylactic treatment with either recombinant or plasma-derived FVIII products. The remaining 20% received on-demand treatment. A total of 65 (35%) subjects had clinically significant abnormal physical findings in the musculoskeletal system, because of their hemophilia A at study entry. At baseline, nine subjects were positive for HIV antibodies, 107 subjects were positive for hepatitis C antibodies and six subjects were positive for hepatitis B antibodies. The mean ± standard deviation (SD) number of bleeds in the previous 12 months was 9.9 ± 26.7 in 147 subjects.

6.1.10.1.3 Subject Disposition

At cut-off, a total of 19 subjects were withdrawn during the Main Phase of the trial; please see Table 10. Of these, seven subjects withdrew within the first month of exposure. Most common reason for discontinuation from the study was meeting the pre-specified withdrawal criteria (i.e., needs for surgery in countries where the surgery trial was not initiated yet, using other FVIII products, personal logistical issues, or non-compliance).

Table 10: Subjects Disposition

Characteristics		**Subjects N=186 (%)**
Withdrawal	# of subjects	19 (10%)*
Reason for Discontinuation	Lack of efficacy	1 (1%)
	Other	4 (2%)
	Protocol deviation	4 (2%)
	Withdrawal criteria	10 (5%)
	Adverse events	0 (0%)
End of Study Status	COMPLETED	167 (90%)**
	DISCONTINUED	19 (10%)
Study Disposition	SURGERY	16 (9%)
	MET WITHDRAWAL CRITERIA	10 (5%)

Source: FDA analysis
* 21 (11%) based on data submitted in Ext 1 part
**165 (91%) based on data submitted in Ext 1 part

Reviewer comment: *Subject* (b) (6) *felt that if he increased his activity, he would bleed so he withdrew from the trial. In addition, Subjects* (b) (6) *were dosed with other FVIII products than ESPEROCT and therefore were withdrawn in accordance with the withdrawal criteria.*

6.1.11 Efficacy Analyses

The safety analysis set and the full analysis set were identical and consisted of all dosed subjects. Thus, a total of 186 subjects were included in these analysis sets. No subjects were excluded from any analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Of the two co-primary endpoints, the primary efficacy endpoint was to evaluate the Annualized Number of Bleeds/Annualized Bleeding Rate (ABR) for subjects receiving prophylaxis treatment.

A total of 968 bleeds were treated with ESPEROCT in 117 subjects with bleeds during the trial. All 12 subjects on the on-demand arm had a bleed, and 105 (60%) of 175 subjects from the prophylaxis arm had a bleeding episode. Most of the bleeds (69%) were spontaneous, 30% were traumatic bleeds and 1% were after minor surgery. In the prophylaxis arm, 60% of the subjects had at least one bleeding episode treated with ESPEROCT, while all 12 subjects in the on-demand arm reported at least one bleeding episode. The most frequent location of bleeds was in the joint, which accounted for 66% of the 968 bleeds. The bleeds were classified as mild/moderate in 99% of the cases, and 8 bleeds (1%) were classified as severe. The mean duration of bleeds for the 916 bleeds with reported information on duration was approximately 28 hours.

The main differences between adolescents and adults were higher frequency of traumatic bleeds among adolescents (55%) compared with adults (28%), and a longer mean duration of bleeds among the adolescents (46 hours) compared with adults (27 hours).

Reviewer comment: *The Applicant stated that all bleeding endpoints were evaluated based on bleeding episodes requiring treatment with ESPEROCT. Non-treatment requiring bleeding episodes that coincided with regular prophylaxis doses were not included. Thus, the results of bleeds were underestimated. The Applicant explained that the main objective of the trials was to evaluate the prophylactic effect of ESPEROCT for prevention of clinically relevant bleeds. Non-treatment requiring bleeds (e.g., bruises, minor nose/gum bleeds) were not considered relevant for the assessment of ABRs in the clinical trials. These non-treatment requiring bleeds were bleeds that resolved by themselves or by the RICE principle (rest, ice, compression, elevation). However, upon our review, we noted that of the 26 non-treatment required bleeds, 16 bleeds occurred in the joints in 14 subjects. Some subjects had severe, spontaneous, or multiple joint bleeds and were not counted in the bleeding analyses of ABRs based on the subjects' or investigators' assessments. Therefore, upon further request, the Applicant submitted datasets and analysis program including all bleeds, whether treatment was required or not, for our review. In addition to the* ***968*** *bleeds, 26 bleeds in 23 subjects that didn't require treatment were identified. A total of 1609 joint bleeds occurred in the Main part of the trial. Of these, 16 were non-treatment requiring joint bleeds (13 in subjects on prophylaxis and three in subjects treated on-demand). None occurred during the randomized part of the extension phase of the trial. Hence, the total number of bleeds becomes* ***994*** *in 119 subjects.*

The ABRs for subjects receiving prophylaxis treatment was estimated using a Poisson regression model on number of bleeding episodes per subject allowing for overdispersion (using Pearson's chi-square divided by the degrees of freedom (i.e. Scale=Pscale in SAS) and using log planned observation duration as an offset.

Details of the ABRs are presented for all subjects and separately for adolescents, adults, spontaneous, traumatic and joints bleeds in Table 11. Additionally, Table 12 lists ABR details for all bleeds (treated and non-treated).

Table 11: Efficacy in Adult/Adolescent Prophylaxis, Median and Mean ABRs by Age, Treatment Regimen, and Bleed Type for Treatment Required Bleeds

	Prophylaxis			On-demand
Age Range	**12–17 years**	**18–70 years**	**12–70 years**	**18–70 years**
# of subjects	25	150	175	12
Mean treatment duration (years)	0.85	0.81	0.82	1.33
All treated bleeds*				
# of subjects (%)	19 (76)	86 (57)	105 (60)	12 (100)
# of bleeds	67	369	436	532
Median ABR (IQR)	2.22 (0.87;4.73)	1.17 (0.00;3.71)	1.18 (0.00;4.25)	30.87 (18.64;38.51)
Mean ABR (±SD)	3.47 (3.85)	2.92 (4.78)	3.00 (4.66)	31.90 (19.08)
*Estimated ABR (95% CI)***	*3.16 (2.06; 4.83)*	*3.02 (2.37; 3.85)*	*3.04 (2.45;3.77)*	N/A
Spontaneous bleeds				
# of subjects	11	65	76	12
# of bleeds	30	221	251	415
Median ABR (IQR)	0.00 (0.00;1.47)	0.0 (0.00;1.85)	0.00 (0.00;1.82)	19.35 (12.07;31.04)
Mean ABR (±SD)	1.39 (2.39)	1.80 (3.65)	1.74 (3.50)	24.46 (17.32)
Traumatic bleeds				
# of subjects	16	57	73	10
# of bleeds	37	146	183	110
Median ABR (IQR)	1.33 (0.00;2.58)	0.00 (0.00;1.42)	0.00 (0.00;1.74)	4.32 (0.77;9.93)
Mean ABR (±SD)	2.08 (2.88)	1.10 (2.21)	1.24 (2.33)	6.13 (6.15)
Joint bleeds				
# of subjects	16	74	90	12
# of bleeds	37	288	325	309
Median ABR (IQR)	1.22 (0.00;2.84)	0.0 (0.00;2.84)	0.85 (0.00;2.84)	19.35 (4.48;28.76)
Mean ABR (±SD)	1.76 (2.19)	2.32 (4.32)	2.24 (4.09)	19.67 (15.07)

Source: FDA analysis
*ABRs are the observed ABRs without imputation
**Poisson estimate of ABR (95% CI) from Table 11-3 CSR Page 125/1561

Reviewer comment: *The Applicant's primary prophylaxis analysis was based on imputed ABRs. Sensitivity analysis was repeated based on observed data without any imputation. The ABR was estimated to 3.04 (95% CI: 2.45 ; 3.77) when no imputation was performed for withdrawn subjects. The corresponding median ABR was 1.18 (IQR: 0.00 ; 4.25).*

Table 12: Efficacy in Adult/Adolescent Prophylaxis, Median and Mean ABRs by Age, Treatment Regimen, and Bleed Type for All Bleeds (Including Non-Treatment Required Bleeds)

	Prophylaxis			On-demand
Age Range	**12–17 years**	**18–70 years**	**12–70 years**	**18–70 years**
# of subjects	25	150	175	12
Mean treatment duration (years)	0.85	0.81	0.82	1.33
All bleeds				
# of subjects (%)	19 (76)	88 (59)	107 (61)	12 (100)
# of bleeds*	72	386	458	536
# of Re-bleeds**	0	6	6	8
Median ABR (IQR)	2.22 (0.87;6.02)	1.18 (0.00;4.33)	1.20 (0.00;4.62)	31.25 (18.64;38.90)
Mean ABR (±SD)	3.73 (4.06)	3.18 (5.06)	3.26 (4.92)	32.15 (19.12)
Spontaneous bleeds				
# of subjects	12	67	79	12
# of bleeds	32	231	263	418
Median ABR (IQR)	0.00 (0.00;1.47)	0.0 (0.00;2.00)	0.00 (0.00;1.99)	19.35 (12.07;31.78)
Mean ABR (±SD)	1.48 (2.39)	2.01 (3.97)	1.93 (3.79)	24.64 (17.39)

	Prophylaxis			On-demand
Age Range	**12–17 years**	**18–70 years**	**12–70 years**	**18–70 years**
# of subjects	25	150	175	12
Traumatic bleeds				
# of subjects	17	60	77	12
# of bleeds	40	153	193	111
Median ABR (IQR)	1.42 (0.00;3.14)	0.00 (0.00;1.44)	0.00 (0.00;1.74)	4.32 (0.77;9.93)
Mean ABR (±SD)	2.25 (2.91)	1.16 (2.24)	1.31 (2.37)	6.20 (6.18)
Joint bleeds				
# of subjects	16	76	92	12
# of bleeds	39	299	338	312
Median ABR (IQR)	1.22 (0.00;2.84)	0.71 (0.00;2.88)	0.87 (0.00;2.86)	19.86 (4.48;29.15)
Mean ABR (±SD)	1.82 (2.23)	2.55 (4.64)	2.45 (4.38)	19.86 (15.21)

Source: FDA analysis
*The total number of bleeds are based on observed bleeding episodes (without imputation) and includes non-treatment requiring bleeds and the exposure time is the observed time.
** Re-bleed is defined as a worsening of symptoms in the same location after an initial period of improvement, either on treatment or within 72 hours after stopping treatment.

Reviewer comment: *As expected, mean ABRs increased when the analysis included all bleeds (treated and not treated) in both the prophylaxis and on-demand groups. However, this increase is minimal. Overall, all ABRs in the prophylaxis arm (with or without imputation and with or without including non-treated bleeds) confirm the prophylactic effect of 50 IU/kg Q4D dosing, as the upper limit of 95% CI is below 8.5. (See statistical considerations Section 6.1.9). Additionally, the ABR for the prophylaxis group is consistent with other FVIII products. The ABR is expected to be lower in those who receive prophylaxis versus those subjects who receive on demand therapy.*

Table 13: Efficacy in Adult/Adolescent Prophylaxis, Median and Mean ABRs by Age, Treatment Regimen, and Bleed Type (For All Treated and non-Treated Bleeds)

	Prophylaxis			On-demand
Age Range	**12–17 years**	**18–70 years**	**12–70 years**	**18–70 years**
# of subjects	**25**	**150**	**175**	**12**
Mean treatment duration (years)	0.85	0.81	0.82	1.33
Treated bleeds				
# of subjects (%)	19 (76)	86 (57)	105 (60)	12 (100)
# of subjects with 0 bleed (%)	6(24)	64 (43)	70 (40)	0
# of bleeds	67	369	436	532
Median ABR (IQR)	2.22 (0.87;4.73)	1.17 (0.00;3.71)	1.18 (0.00;4.25)	30.87 (18.64;38.51)
Mean ABR (±SD)	3.47 (3.85)	2.92 (4.78)	3.00 (4.66)	31.90 (19.08)
Mean ABR (95% CI)*	3.16 (2.06;4.83)	3.02 (2.37;3.85)	3.04 (2.45;3.77)	N/A
All bleeds (treated and non-treated)**				
# of subjects (%)	19 (76)	88 (59)	107 (61)	12 (100)
# of subjects with 0 bleed (%)	6 (24)	62 (41)	68 (39)	0
# of bleeds	72	386	458	536
Median ABR (IQR)	2.22 (0.87;6.02)	1.18 (0.00;4.33)	1.20 (0.00;4.73)	31.25 (18.64;38.90)
Mean ABR (±SD)	3.73 (4.06)	3.18 (5.06)	3.26 (4.92)	32.15 (19.12)
Mean ABR (95% CI)*	3.39 (2.24;5.15)	3.16 (2.49;4.00)	3.19 (2.59;3.94)	N/A
Treated spontaneous bleeds				
# of subjects (%)	11 (44)	65 (43)	76 (43)	12 (100)
# of subjects with 0 bleed (%)	14 (56)	85 (57)	99 (57)	0
# of bleeds	30	221	251	415
Median ABR (IQR)	0.00 (0.00;1.47)	1.0 (0.00;1.85)	0.00 (0.00;1.82)	19.35 (12.07;31.04)
Mean ABR (95% CI)**	1.41 (0.75;2.65)	1.81 (1.35;2.43)	1.75 (1.34;2.29)	N/A

Treated traumatic bleeds				
# of subjects (%)	16 (64)	57 (38)	73 (42)	10 (83)
# of subjects with 0 bleed (%)	9 (36)	93 (62)	102 (58)	2
# of bleeds	37	146	183	110
Median ABR (IQR)	1.33 (0.00;2.58)	0.00 (0.00;1.42)	0.00 (0.00;1.74)	4.32 (0.77;9.93)
Mean ABR (95% CI)**	1.74 (1.13; 2.69)	1.19 (0.89;1.60)	1.28 (0.99; 1.64)	N/A
Treated joint bleeds				
# of subjects (%)	16 (64)	74 (49)	90 (51)	12 (100)
# of subjects with 0 bleed (%)	9 (36)	76 (51)	85 (49)	0
# of bleeds	37	288	325	309
Median ABR (IQR)	1.22 (0.00;2.84)	0.00(0.00;2.84)	0.85 (0.00;2.84)	19.35 (4.48;28.76)
Mean ABR (95% CI)**	1.74 (1.10; 2.76)	2.36 (1.79;3.11)	2.27 (1.76;2.92)	N/A

Source: FDA analysis
*Post-hoc analysis was performed to include non-treatment required bleeds
**Based on Poisson regression model that allows for over-dispersion. Values were provided by the Applicant and were confirmed by the statistical reviewer.

Reviewer comment: *During preliminary labeling negotiations, the Applicant proposed to mirror the Emicizumab (Hemlibra) Package insert (PI) and thus included data on treated bleeds and all bleeds (including non-treated) in the same table. Moreover, the Applicant proposed to include the mean ABR and 95% CI based on the Poisson model, replacing the mean ABR (SD) since this was the planned analysis and the Poisson model takes the exposure time into account. Because the primary analysis was prespecified to include only treated bleeds, and including non-treated bleeds was a post-hoc analysis, the clinical reviewer agrees to include information on both analyses in the label. Of note, the labels of prior FDA approved FVIII products did not include non-treated bleeds in the label, ABR analysis utilizing all bleeds (treated and untreated) have been performed (please refer to the clinical review memo for Eloctate). The clinical reviewer believes that information on treated and non-treated bleeds is important to the prescribers. In addition, the reviewer recommends including the mean ABR (SD) in the label rather than the Poisson estimate because the mean ABR represents the true value observed in the clinical trial as does the median ABR and therefore it is more accurate. It is noted that the Poisson estimate of the ABR is slightly lower than the mean observed ABR.*

Reviewer comment: *During Study 3859 Main Phase: 13 (7%) of 175 subjects switched from the Q4D regimen to a Q3-4D (every 4th day or twice weekly) dosing frequency for ease of use. Because only 7% of subjects used this regimen, it is acceptable to use the Q4D rather than Q3-4D as the starting dosing regimen. A statement regarding modifying this regimen to a less or more frequent regimen based on bleeding episodes will be included in the label.*

Reviewer comment: *An analysis excluding subjects treated at Sites KR0551 and US911 was performed because of the concern that was raised by EMA regarding the data integrity in these two sites. A total of eight subjects were treated in the prophylactic arm (five at the Korean site and three at the US site). No subject received on-demand treatment. Mean (±SD) and median (IQR) ABRs for all eight subjects were: 9.89 (±6.29) and 11.71 (5.00, 14.32) when counting only treated bleeds, and 10.17 (±6.32) and 12.08 (5.74, 14.34) when including all bleeds. Mean (±SD) ABR for the 167 subjects treated in the prophylactic arm decreases to 2.93 (±4.61) when these eight subjects are excluded. Exclusion of these subjects does not impact the efficacy analysis. As the CBER BIMO team has not raised any concerns regarding data integrity of these sites, the data from these eight subjects were included in the efficacy analysis.*

6.1.11.2 Analyses of Secondary Endpoints

Confirmatory secondary endpoint: Hemostatic effect of ESPEROCT when used for treatment of bleeding episodes: ESPEROCT's hemostatic effect was assessed on a four-point scale as excellent, good, moderate and none. If the hemostatic response was rated as excellent or good, the treatment of the bleed was considered a success. If the hemostatic response was rated as moderate or none, the treatment was considered a failure. In addition, any bleeding episode with missing response information was counted as failure. A summary of hemostatic responses and success rates by actual treatment arm is presented in Table 14 and by age in Table 15.

Out of the total 968 bleeding episodes in the trial, 964 bleeds were rated and a rating for four bleeds was missing. The success rate for all bleeds was 84.2 (95% CI: 80.0 ; 87.7) and thereby above the 80% which was the pre-specified goal for the success rate. The success rate for treatment of bleeds which occurred in subjects enrolled in the on-demand arm was higher compared with the success rate observed for bleeds treated in subjects enrolled in the prophylaxis arm. The success rates across treatment groups were slightly higher for adults 84.6% compared with adolescents 83.6%. Sensitivity analysis based on observed responses (when not including the four missed ratings as failure) demonstrated a success rate of 85.1%.

Table 14: Efficacy in Control of Bleeding Episodes by Treatment Arm

Treatment Arm		**On-demand 20-75 IU/kg N (%)**	**Prophylaxis 50 IU/kg N (%)**	**Total N(%)**
# of subjects		12 (100)	175 (100)	186 (100)
# of subjects with bleeds		12 (100)	105 (60)	117 (63%)
# of bleeds*		532	436	968
Hemostatic response**	Failure	42 (8)	70 (16)	112 (12)
	Success	490 (92)	366 (84)	856 (88)
	Success rate	**92.1%**	**84%**	**88.4%**

Source: FDA analysis
* Including treated bleeds only since hemostatic control cannot be assessed for untreated bleeds.
** Including four missing ratings as failure

Table 15: Summary of Efficacy in Control of Bleeding Episodes by Age

Age category		**12-17 years N (%)**	**≥ 18 years N (%)**	**Total N (%)**
# of subjects		25 (100)	161 (100)	186 (100)
# of subjects with bleeds		19 (76)	98 (61)	117 (63)
# of bleeds*		67	901	968
Hemostatic response**	Failure	11 (16)	100 (11)	112 (12)
	Success	56 (84)	801 (89)	856 (88)
	Success rate	**83.6%**	**88.9%**	**88.4%**

Source: FDA analysis
* Including treated bleeds only
** Including four missing ratings as failure

Reviewer Comment: *The clinical reviewer agrees with the assessment above regarding the adequacy of hemostasis. The adequacy of hemostasis (success rate) was judged to be excellent/good in 856/968 (88%) bleeds. There is no clear reason with the exception of patient related (intra-patient) variability to explain the differences in hemostatic outcomes in subjects on the on-demand vs. the prophylaxis arm. This observation is not explained by differences in dosing since the on-demand group experienced a higher hemostatic success rate despite a lower mean dose/kg (41IU/kg) for management of bleeding than the group in the prophylaxis arm (mean dose 64.6 IU/kg). Overall, the success rate for control of bleeding (84%) in the prophylaxis group is consistent with FDA approved products.*

The hemostatic response was also analyzed taking into account bleed characteristics (Table 16). The total success rate was higher for spontaneous compared with traumatic bleeds. Furthermore, differences between locations of bleeds were observed, but numbers of bleeds in some groups were small. Mucosal, subcutaneous and gastrointestinal bleeds had a higher success rate than the overall success rate, and muscular bleeds a slightly lower success rate. There was an association between increase in number of injections to treat a bleed and lower success rates. The proportion of successfully treated bleeds that were resolved with one injection was 94.6%.

Table 16: Hemostatic Response: Success Rates by Bleed Characteristics

	On-demand 20-75 IU/kg	**Prophylaxis 50 IU/kg**	**Total**
Total bleeds	532	436	968
Cause of bleed*			
Spontaneous # of bleeds	415	251	666
Success rate**	386 (93.0)	211 (84.1)	597 (89.6)
Traumatic # of bleeds	110	183	293
Success rate (%)	97 (88.2)	153 (83.6)	250 (85.3)
Location of bleed			
Joint # of bleeds	309	325	634
Success rate	292 (94.5)	272 (83.7)	564 (89.0)
Muscular # of bleeds	88	57	145
Success rate	72 (81.8)	46 (80.7)	118 (81.4)
# of injections to treat the bleed			
1	453 (96.2)	312 (92.3)	765 (94.6)
2	29 (64.4)	46 (65.7)	75 (65.2)
3	5 (71.4)	5 (41.7)	10 (52.6)

Source: FDA analysis
*Nine additional bleeds occurred after minor surgery (7 in the on-demand and 2 in the prophylaxis arm)
** N: Total number of successfully treated bleeds by bleed characteristics
(%): Percentage of treatment successes by bleed characteristics

Consumption of ESPEROCT per bleed: Of the total 968 bleeds in the trial, 83.6% were resolved with one injection of ESPEROCT, 11.9% were resolved with two injections; Therefore, 95.5% of bleeds were treated with ≤ two injections. In the prophylaxis arm 77.5% of the bleeding episodes were resolved with one injection of ESPEROCT, whereas the proportion was 88.5% for the on-demand arm. Furthermore, the highest

number of injections to treat a bleed was nine injections in the prophylaxis arm and 13 injections in the on-demand arm.

Reviewer comment: *Table 16 and its related text refer to successful treatment of bleeds. The treatment of a bleed was considered successful if the hemostatic response was rated as excellent or good. Whereas in the consumption of ESPEROCT per bleed, the percentages outlined, represent the number of injections needed for cessation of bleeds. Hence the slight difference in the numbers.*

The per protocol dose level to be used for treatment of a bleed was 20-75 IU/kg. The median and mean doses used to treat a bleed were 52 and 65 U/kg in the prophylaxis arm, 29 and 41 IU/kg in the on-demand arm, and 36 and 52 IU/kg for all bleeds.

Reviewer comment: *The Applicant proposes including dosing recommendation for the treatment of bleeds, in the label based, on the World Federation of Hemophilia (WFH) guidelines. In general, labelling recommendations for dosing should be based on clinical trial data. Since the majority of the subjects in the trial did not receive the lower range of the Applicant's proposed dose based on WFH recommendations, the dose range proposed does not coincide with trial data. Thus, the proposed dose for on-demand treatment will need to be revised to provide a range in dosing based on the median that was observed during the trials. Dose based on WFH or other guidelines should be deferred to the prescriber.*

PK analysis: The mean recovery was approximately 1.60 IU/ml (mean range from Visit 3 to 12a was 1.50-1.77) and the mean trough level was approximately 0.08 IU/ml (mean range from Visit 3 to 13: 0.07-0.09). At the first PK session, t½ was 18.27 hours and the incremental recovery was 0.031 (IU/mL)/(U/kg). At the second PK session, t½ was 18.18 hours and the incremental recovery was 0.034 (IU/mL)/(U/kg). PK parameters (including C_{30min} and $AUC_{(0\text{-}inf))}$ were similar at the two PK sessions (separated by 28 weeks).

Patient reported outcomes (PROs) and health economic outcomes: were collected at Visit 1 (screening visit) and at Visit 13 (end of Main phase). PROs included: the haemophilia-quality of life (HAEMO-QOL), the HAEM-A-QOL (haemophilia-adult-quality of life), the haemophilia-satisfaction (HEMO-SAT), the European QOL 5 dimension visual analogue scale (EQ-5D-VAS) questionnaires, the European QOL visual utility index (EQ5D-VAS), and the health economic aspects. At the cut-off date for the primary analyses, PRO analyses were not completed yet and were considered inadequate for any conclusions. Thus the PRO reports for the Main Phase of the trial were presented in a separate report at a later stage. See results below in Extension Part 1. For health economic analysis, the mean number of days of missed school or work was 0.5 day in the prophylaxis arm and 6.7 days in the on-demand arm, though the mean values were driven by very few subjects. The mean reported number of days using a mobility aid was 4.4 days in the prophylaxis arm and 11.1 days in the on-demand arm.

Reviewer Comment: *PRO endpoints were not reviewed by FDA clinical outcome assessment staff and were not agreed upon with the Agency during the trial and prior to the BLA submission; Therefore, PROs will not be included in the label for this product.*

Other secondary endpoints that are related to the safety of the product are reviewed in the Safety Analysis below.

Extension Part 1:
Trial ID: NN7088-3859 Ext 1 (or Ext 1)

The main objective of the extension phase part 1 (Ext 1) was to investigate the safety and efficacy of once weekly prophylaxis dosing of ESPEROCT in a subset of subjects who had low bleeds in the Main Part of the study.

Co-Primary Objectives

- To evaluate the immunogenicity of ESPEROCT in PTPs with Hemophilia A
- To evaluate the clinical efficacy of ESPEROCT in bleeding prophylaxis with Q7D dosing

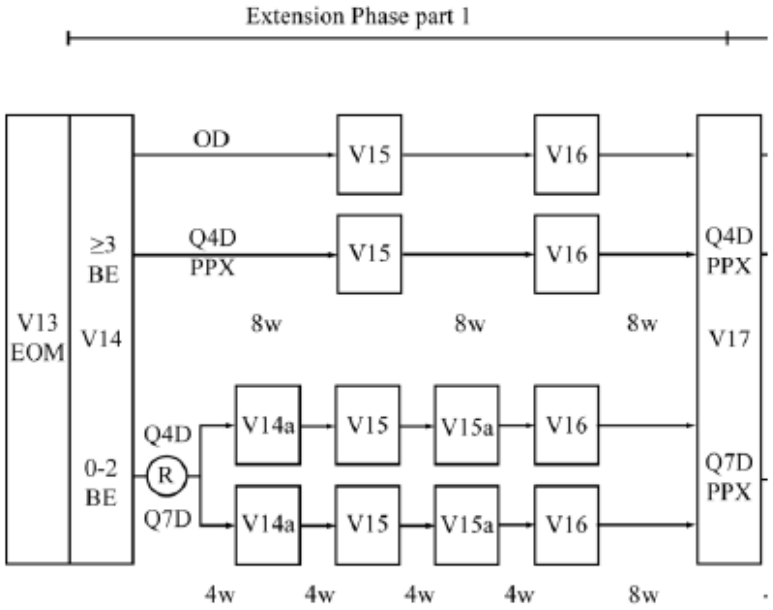
Secondary Objectives

- To evaluate the clinical efficacy of The IP when treating bleeds in PTPs
- To evaluate the safety of ESPEROCT when used for prevention of bleeds and treatment of bleeds in PTPs
- To evaluate PK properties of ESPEROCT
- To evaluate Patient Reported Outcomes
- To evaluate the health economic impact of ESPEROCT treatment
- Generation of a population based PK-model for ESPEROCT

Reviewer Comments: *Note that PROs were collected during the Main Part (at Visits 1 and 13) and in the Ext 1 Part (at visit 17) of Study 3859.*

Subjects who were on prophylaxis treatment and dosed every 4 days with ESPEROCT in the Main Phase of the trial and had 0-2 bleeding episodes during the last six months before entering the extension phase and agreed to treatment in Extension Part 1, were randomized to Q7D or Q4D treatment (2:1 randomization). Ineligible subjects from the Main Phase of the study included subjects with three or more bleeding episodes within the last 6 months of the main phase or subjects with low bleeding rates who were unwilling to be randomized. These subjects continued with the Q4D treatment regimen. Upon completion of Extension 1 (6 months of treatment), Extension phase part 2 was opened for subjects who were willing to continue on the study. Randomization was conducted via the Interactive Voice/Web Response System (IV/WRS). For an overview of visits in the Extension phase part 1; please refer to Figure 6.

Figure 6: Overview of Visits and Home Treatment Periods in the Extension Phase Part 1



Source: BLA 125671 Ext 1 CSR Figure 9-3 Page 57/2761
EOM = End of main phase, OD = on-demand, PPX = prophylaxis, BE = bleeding episodes, ® = randomization, Q4D = prophylaxis every 4 day, Q7D = prophylaxis every 7 day, w = weeks

Reviewer comment: *The study report and datasets include all data form the Main Phase and Extension Phase Part 1 of the trial. However, since the Main Phase of the trial was concluded, the focus of the Ext 1 analysis was on the subgroup who underwent randomization. Additionally, results of PROs and anti-PEG antibodies were included in this report.*

The prophylaxis dose of ESPEROCT was administered in the non-randomized group every 4 days (Q4D) or in the randomized group Q4D at 50 IU/kg or every 7 days (Q7D) at 75 IU/kg BW, depending on which treatment arm the subject was assigned to. Based on the bleeding pattern, the Investigator could change the Q7D prophylaxis treatment to a Q4D treatment regimen (the non-randomized arm) at any time. Changing vice versa was not permitted. A subject on Q7D prophylaxis was to be switched to Q4D prophylaxis if either of the following criteria were met over an 8 week period:

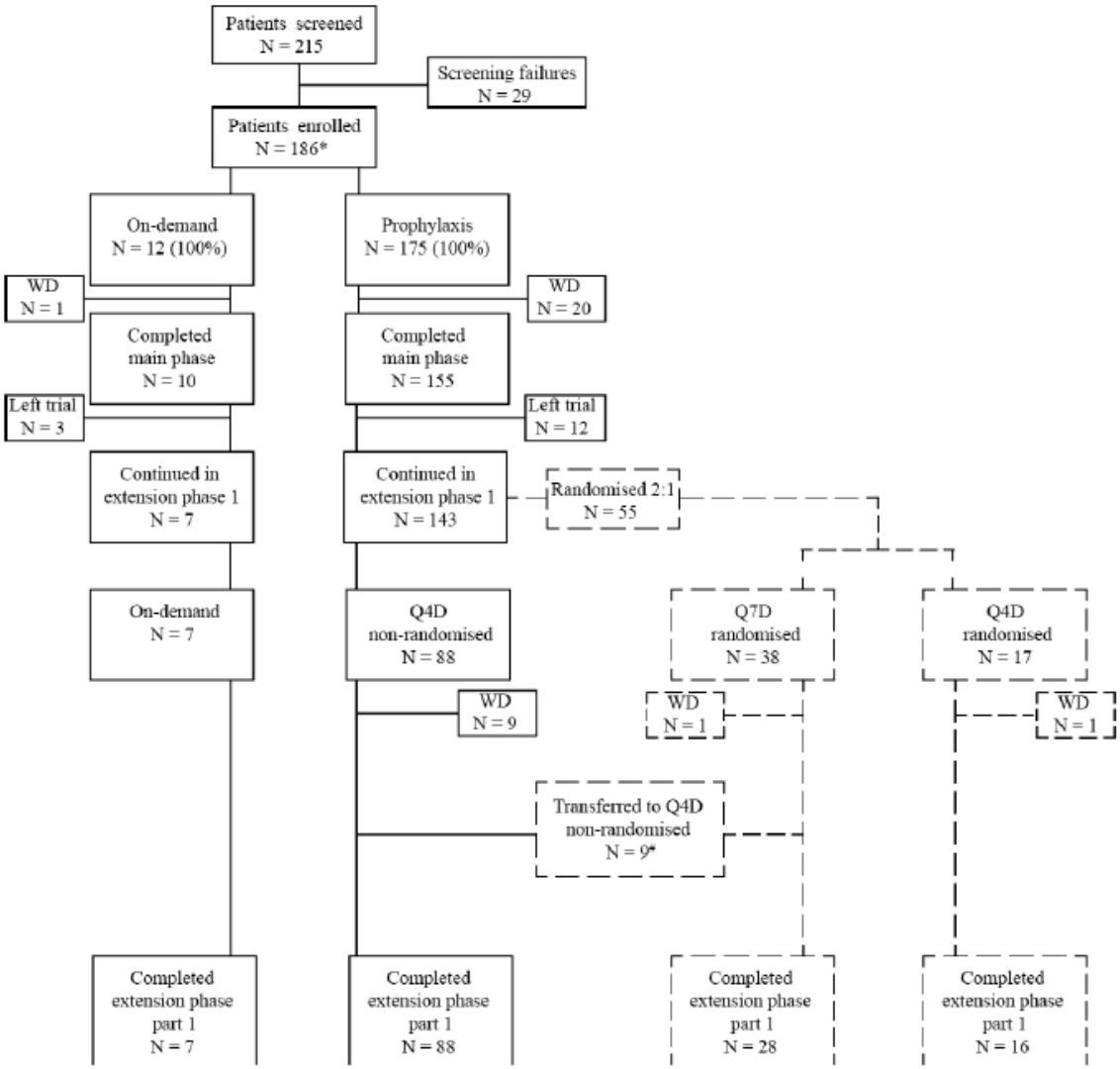
- Two or more spontaneous bleeding episodes
- One severe bleeding episode requiring hospitalization

The Applicant planned to terminate the Q7D treatment arm if at least 15 out of 30 subjects (or 50% of 30 or more) who had been randomized to the Q7D treatment arm were switched back to the Q4D treatment arm.

Statistical consideration: Prophylactic effect of Q7D dosing was concluded if the upper limit of the 95% CI was below 8.5. In addition, the two randomized treatment regimens were compared by reporting the estimated ratio between the two randomized treatment regimens with corresponding 95% confidence intervals. The Applicant pre-specified that only treatment requiring bleeding episodes were to be considered in the evaluations of ABR.

Disposition and baseline characteristics: A total of 55 subjects were randomized, 38 subjects were included in the Q7D arm and 17 in the Q4D arm. Mean age was slightly lower in the Q4D arm (26.4 years) as compared to the Q7D arm (30.9 years). Figure 7 below represents subjects flowchart during the main and Ext 1 part of the trial.

Figure 7: Flowchart Study 3859 Main Part and Ext Part 1



Source: BLA 125671 Ext 1 CSR Figure 10-1 Page 123/2761
* One subject changed treatment regimen from on-demand to prophylaxis during main phase, and is counted as exposed in both arms, but counted only once in the total.

Reviewer comment: *Sixty-five (54%) of 120 subjects at start of Ext 1 who met the randomization eligibility criteria chose not to be randomized to Q7D dosing and only 55 subjects agreed to be randomized. The Applicant did not provide justification for why many subjects chose not to be randomized. Upon further request, the Applicant stipulated that based on communication with some investigators, subjects' refusal to the randomization could be due to the requirement for more frequent monitoring if subjects were to be randomized. Since PK studies were completed in only eight of the 55*

subjects randomized to one of the two dose regimens, it is unlikely that a priori knowledge of PK characteristics influenced subject selection. Nevertheless, a substantial proportion of subjects eligible for randomization were not randomized, it is uncertain whether these subjects chose to avoid the potential risks of an extended regimen of Q7D based on their apriori knowledge of their bleeding phenotype.

Results:
Nine (24%) of the 38 subjects who were randomized to the Q7D regimen switched to Q4D dosing during Ext 1 (eight due to bleeding events and one due to investigator's discretion). Two of these subjects who switched to Q4D dosing regimen did so within the first month. One additional subject in the Q7D dosing discontinued from Ext 1 due to an AE of ankle fracture. Seventeen (17) subjects were randomized to 50 IU/kg Q4D and 16 of them (94%) completed Extension 1.

The Applicant's primary prophylaxis analysis was based on imputed ABRs for withdrawn subjects. The mean ABR (±SD) in the Q7D arm was 3.59 (±6.62) and median was 0.00 (IQR: 0.00; 2.36) compared to mean ABR (±SD) in the Q4D arm of 1.77 (±2.42) and median of 0.00 (IQR: 0.00; 2.23). Sensitivity analysis was repeated based on observed data without any imputation. The mean ABR in the Q7D prophylaxis arm was 3.37 (SD: 6.19). The median ABR was 0.00 (IQR: 0.00; 2.36). Subjects randomized to q4D with 50 IU/kg had a mean ABR of 1.68 (SD: 2.34). The median ABR was 0 (IQR: 0.00; 2.23). Mean ABRs for the nine subjects who switched from Q7D to Q4D was: 11.8 and mean ABRs for the remaining 29 subjects on Q7D was: 0.7. Table 17 below shows the ABR across the Main and Extension 1 parts of the study for the Q4 and Q7 day regimens.

Table 17: ABR rates for Routine Prophylaxis for Q4 Day and Q7 Day Regimen

Bleeding Outcome	**Main Phase (n=175)**	**Extension Phase (n=143)**		
		Non-randomized (n=88)	**Randomized (n=55)**	
		Q4 Day	Q4 Day (n=17)	Q 7 Day (n=38)
Mean ABR (SD)	3.26 (4.92)	3.98 (5.28)	1.68 (2.34)	3.37 (6.19)
Median ABR (IQR)	1.20 (0.00; 4.73)	1.74 (0.57; 6.02)	0.00 (0.00; 2.23)	0.00 (0.00; 2.36)

Source: FDA analysis

Reviewer comment: *ABR data will be presented in the label based on the observed bleeds without imputation.*

Additionally, because a risk-based approach according to bleeding risk in the Main Part of the study was used to select subjects to receive a less frequent regimen, subjects who were selected to be randomized represent a phenotypically different group than the subjects who were not randomized and continued on the Q4D dosing regimen. ABR assessment in Ext 1 demonstrates that subjects on the Q7D regimen had higher mean ABRs than the Q4D group. Although subjects who were at a lower risk of bleeding were randomized to receive the Q7D regimen, the ABR in subjects who received the Q7D regimen was higher (approximately twice the mean ABR rate for subjects who were on

Q4D regimen). In addition, given that the half-life of the product is approximately 18 hours as predicted by the PK studies, a dosing interval of 7 days in patients who had low bleeding rates (n=29) could be explained by the bleeding phenotype of the patient (i.e., patients with low bleeding tendency).

During Study 3859 Ext 1:

- *65 (54%) of 120 subjects at the start of Ext 1 met the randomization eligibility criteria; however, they chose not to be randomized to Q7D dosing, thus increasing the selection bias in the trial.*
- *Nine (24%) of the 38 subjects who were randomized to the Q7D regimen switched to Q4D dosing during Ext 1 (eight due to bleeding events and one subject due to investigator's recommendation). One subject discontinued the Q7D regimen due to AE of ankle fracture).*
- *The mean ABR (±SD) in the Q7D arm was 3.59 (±6.62) and median was 0.00 (IQR: 0.00; 2.36) compared to mean ABR (±SD) in the Q4D arm of 1.77 (±2.42) and median of 0.00 (IQR: 0.00; 2.23).*
- *Mean ABRs for the nine subjects who switched from Q7D to Q4D was: 11.8 and mean ABRs for the remaining 29 subjects on Q7D was: 0.7.*

In summary, those subjects with Q7D dosing had a higher mean ABR. Moreover, 24% of subjects in this arm switched to Q4D and one additional subject discontinued the Q7D regimen due to an AE [(total of 10 (26%) of 38 subjects]). The reviewer recommends that Q7D dosing not be included in the label for the following reasons:

- *Almost a quarter of the subjects in the Q7D arm required rescue treatment and a more frequent dosing*
- *Although subjects randomized to Ext 1 were from a group of subjects identified as having a lower risk for bleeding, the nine subjects on the Q7D regimen who switched to the Q4D regimen had very high ABRs, ABRs that would place them at substantial risk of bleeding. Characteristics/eligibility criteria to define the group that is at substantial risk of bleeding compared to those that are likely to benefit from a Q7D regimen are unclear.*

Therefore, the inability to identify characteristics of subjects who are likely to benefit from an every 7-day regimen, and in the absence of pre-specified eligibility criteria to define this group of subjects (who are at low risk of bleeding with a Q7D regimen) precludes inclusion of the Q7D dosing regimen in the label. Individualized prophylaxis at prescriber discretion to less frequent dosing regimens could be considered for those patients who have control of bleeding on the Q4D dosing regimen. These recommendations will be included in the label.

PK analysis: The mean trough level for Q4D subjects in the Main Phase was estimated to be 0.030 IU/ml, and was comparable to mean trough levels for all Q4D subjects in the Ext 1 phase with an estimate of 0.026 U/ml. For the Q7D subgroup, a lower estimated trough (0.012 U/ml) was observed as compared to the randomized Q4D subjects (0.031 U/ml).

Reviewer comment: *The Applicant excluded subjects who switched back to the Q4D dosing regimen from the Q7D regimen from the trough analysis because it was assumed that these subjects would not have reached steady state. Of note, in the first human*

dose trial (NN7088-3776), the mean half-life (t½) of ESPEROCT was 18.4 hours in adult PTPs with severe HA. This corresponds to a 1.6-fold prolongation of t½ of ESPEROCT when compared to the patients' previous FVIII product (plasma-derived or recombinant).

Details of bleeds and Hemostatic effect for combined Main and Ext 1: Of the subjects treated in the Q4D regimen (randomized and non-randomized) 66% had at least one bleeding episode treated with ESPEROCT. In the Q7D arm, 42% of the subjects had at least one bleeding episode treated with ESPEROCT. The mean duration of bleeds was 62.2 hours in the Q7D arm, 24.1 hours in the Q4D arm and 27.2 hours in the on-demand arm. Out of the 1436 treated bleeding episodes in the main and Ext 1 parts, 1420 bleeds were rated; the rating for 16 bleeds was missing. The success rate for all bleeds (including missing responses as failure) was 83.3%. The success rate was 80.8% in the Q7D regimen and 82.7% in the Q4D regimen. The success rate for treatment of bleeds was higher in subjects receiving on-demand treatment than in subjects receiving prophylaxis treatment and was consistent with what was observed in the main part of the study. In the Q7D prophylaxis arm, out of the 25 bleeding episodes in the trial, 23 bleeds were rated, while rating of two bleeds was missing.

Reviewer comment: *The hemostatic response for treatment of bleeds is comparable between the Q4D and Q7D regimens.*

Consumption of ESPEROCT: Of the total 1436 treated bleeds, 82.2% were resolved with one injection of ESPEROCT, 12.8% were resolved with two injections; Therefore, 95.0% of bleeds were treated with ≤ two injections. The per protocol dose level to be used for treatment of a bleed was 20-75 IU/kg. The mean dose used to treat a bleed was 67.8 IU/kg in the Q4D arm and 78.2 IU/kg in the Q7D arm, as compared to 39.3 IU/kg in the on-demand arm, reflecting that more bleeds in the on-demand arm were resolved with one injection and the on-demand subjects used a lower dose per injection.

Reviewer comment*: The mean dose used to treat a bleed was higher in the Q7D arm than the Q4D arm, reiterating the inadequacy of the Q7D dosing regimen.*

Patient reported outcomes and health economic endpoints: HAEM-A-QOL, HAEMO-QOL and HEMO-SAT were administered: Scores ranged between 0-100, with a lower score indicating better quality of life related to haemophilia. Therefore, a negative change score indicated an improvement of quality of life. Overall, there was a trend towards improvement in Quality of Life scores in the main phase. However, this effect was not seen in the extension phase for the adults.

Reviewer comment*: The QOLs assessment information was not prespecified nor agreed upon with the Agency prior to the BLA submission. These QOL instruments have not been validated for the specific context of use and the significance of the results is difficult to interpret. Therefore, QOL information will not be included in the label.*

6.1.11.3 Subpopulation Analyses

Although there were notable differences in the ABRs amongst countries, with ABRs ranging from no bleeds to 11.60, the small number of subjects in some countries makes it challenging to draw any conclusions. Furthermore, the ABR was investigated by race,

ethnicity, weight and by body mass index. No apparent differences in the ABRs were observed for these subgroups.

6.1.11.4 Dropouts and/or Discontinuations

At cut-off for the Main Part of the study, a total of 19 (10%) of 186 subjects were withdrawn during the Main Phase of the trial. Of these, seven subjects withdrew within the first month of exposure. Please see section 6.1.10.1.3 for details. However, based on the data submitted for the Main Part and Ext 1 combined, a total of 32 subjects were withdrawn during the trial, 21 in Main Phase and 11 in Extension 1. Five of the subjects withdrew due to AEs in the Ext 1. The most common reasons for subject discontinuation from the study were due to meeting the pre-specified withdrawal criteria (i.e., needs for surgery in countries where the surgery trial was not initiated yet, using other factor VIII products, personal logistical issues, or non-compliance). See Table 18 for details.

Table 18: Subjects Withdrawal in Main Phase and Extension 1

Characteristics		**Subjects N=186 (%)**
Withdrawal (Main Phase)	# of subjects	21 (11%)
Reason for Discontinuation	Lack of efficacy	1 (0.5%)
	Other	4 (2%)
	Non-compliance	3 (2%)
	Withdrawal criteria	13 (7%)
	Adverse events	0 (0%)
Withdrawal (Extension 1)	# of subjects	11(7%)
Reason for Discontinuation	Other	1 (0.7%)
	Withdrawal criteria	5 (3%)
	Adverse events	5 (3%)

Source: FDA analysis and adapted from BLA 125671; Study 3859 main and Extension 1 CSR, Table 10-1.

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

6.1.12.1 Methods

All evaluations of safety were based on the safety analysis set (SAS), including all 186 dosed subjects and thus being equal to the full analysis set (FAS). Of the 186 subjects in the SAS, 164 (88%) subjects had at least 50 exposure days (EDs). Total EDs was 14114. The mean number of doses was 77.1 (range 1–182) doses per subject in the prophylaxis arm and 56.5 (range 14–151) in the on-demand arm.

6.1.12.2 Overview of Adverse Events

Overall, 148 of 186 subjects experienced at least one AE during the Main Part of the study. AEs occurring before administration of the study drug were defined as non-treatment- emergent events. A total of 30 non-treatment emergent adverse events were recorded in 26 subjects. A total of 474 treatment emergent AEs were reported in 145 (78%) subjects. The most commonly reported AEs were nasopharyngitis in 27 (15%) subjects, headache in 27 (15%) subjects, upper respiratory tract infection in 14 (8%) subjects and arthralgia in 11 (6%) subjects. See Table 19 for details on most common

AEs >1% and Table 20 for all serious AEs. Of a total of 423 AEs reported in 135 (77%) subjects during prophylaxis, 26 events were evaluated by the investigator to be possibly or probably related to the IP. For subjects treated on-demand, four of the 51 AEs were evaluated to be possibly related to trial product. Most of the AEs were evaluated as mild (375 events) or moderate (104 events). A total of 14 AEs were evaluated as severe.

Reviewer comment*: The Applicant reported that 366 (375 per FDA analysis) AEs were reported as mild and 94 (104 per FDA analysis) AEs were moderate. There was no difference in the analysis of the severe AEs between the Applicant and the clinical reviewer.*

Table 19: Most Common Adverse Events >1%

Adverse Events	Subjects N (%)
Nasopharyngitis	27 (15%)
Headache	27 (15%)
Upper respiratory tract infection	14 (8%)
Arthralgia	11 (6%)
Oropharyngeal pain	10 (5%)
Nausea	9 (5%)
Alanine aminotransferase increased	7 (4%)
Rash	7 (4%)
Influenza	7 (4%)
Gamma-glutamyltransferase increased	6 (3%)
Dizziness	6 (3%)
Viral infection	6 (3%)
Cough	6 (3%)
Pain in extremity	5 (3%)
Diarrhea	5 (3%)
Limb injury	5 (3%)
Musculoskeletal pain	5 (3%)
Respiratory disorder	5 (3%)
Aspartate aminotransferase increased	4 (2%)
Fall	4 (2%)
Vitamin D deficiency	4 (2%)
Influenza like illness	4 (2%)
Abdominal pain upper	4 (2%)
Contusion	4 (2%)
Pyrexia	4 (2%)
Hypertension	4 (2%)
Bronchitis	4 (2%)
Dental caries	3 (2%)
Blood bilirubin increased	3 (2%)
Acne	3 (2%)
Acute tonsillitis	3 (2%)
Insomnia	3 (2%)
Epistaxis	3 (2%)
Seasonal allergy	3 (2%)
Toothache	3 (2%)

Adverse Events	Subjects N (%)
Myalgia	3 (2%)
Tonsillitis	3 (2%)
Lymphadenopathy	3 (2%)
Total subjects	**145 (78%)**

Source: FDA analysis.

Reviewer Comments: *The AEs of hypersensitivity are likely related to ESPEROCT and will be included in the Warnings and Precautions (W&P) section of the label. All other events are possibly or unlikely related to the study drug as they were not temporally related. Case report reviews and review of narratives for subjects with hypersensitivity reaction did not identify any subjects who experienced an anaphylactic reaction.*

6.1.12.3 Deaths

No deaths occurred during the trial that is considered related to ESPEROCT. *One death* occurred in a 67 year old subject with metastatic pancreatic carcinoma which is unlikely related to ESPEROCT.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 17 SAEs were recorded in 13 (7%) subjects. Two of these events (intervertebral discitis and factor VIII inhibition) were evaluated as possibly and probably, related to trial product by the investigator, respectively. These two events are classified as adverse reactions and met the criteria for reporting as suspected unexpected serious adverse reaction (SUSAR). No thromboembolic events occurred during the trial.

Table 20: All Serious Adverse Events

Serious Adverse Events	Subjects N (%)
Calculus urinary	1 (1%)
Cataract	1 (1%)
Catheter site infection	1 (1%)
Convulsion	1 (1%)
Enteritis infectious	1 (1%)
Extradural hematoma	1 (1%)
Factor VIII inhibition*	1 (1%)
Fall	1 (1%)
Femoral neck fracture	1 (1%)
Forearm fracture	1 (1%)
Gastric varices	1 (1%)
Infective spondylitis	1 (1%)
Intervertebral discitis	1 (1%)
Medical device complication	1 (1%)
Pancreatic carcinoma metastatic	1 (1%)
Toxicity to various agents	1 (1%)
Viral infection	1 (1%)
Total subjects	**13 (7%)**

Source: FDA analysis

* Subject was withdrawn from the study

Reviewer comment: *Based on the review of CRFs narratives provided in this submission, the clinical reviewer determined that all these SAEs (except for FVIII inhibitor) had competing causes and therefore do not recommend inclusion of any of these events in the W&P section of the label. See reviewer comment below in section 6.1.12.5 regarding Adverse Events of Special Interest.*

6.1.12.5 Adverse Events of Special Interest (AESI)

Inhibitor formation against FVIII, allergic reactions (including anaphylactic reactions), thromboembolic events and medication errors were defined by the Applicant as medical events of special interest (MESI) in this trial. Nine subjects (5%) had medical events of special interest (MESIs), six of which had allergic reactions. None of the observed allergic reactions required systemic treatment. One 18 years old subject (b) (6) developed inhibitory antibodies against FVIII after 93 EDs to ESPEROCT. All MESI are summarized in **Table 21**.

Table 21: Medical Events of Special Interest (MESI)

Adverse Events	Subjects N (%)
Allergy to arthropod sting	1 (1%)
Drug hypersensitivity (after fentanyl patch)	1 (1%)
Electrocardiogram ST segment elevation	1 (1%)
Erythema (at injection site)	1 (1%)
Factor VIII inhibition	1 (1%)
Pruritus allergic (to house mite dust)	1 (1%)
Rash (after investigational drug)	1 (1%)
Urticaria (unknown)	1 (1%)
Wrong technique in drug usage process	1 (1%)
Total subjects	**9 (5%)**

Source: FDA analysis

Reviewer comment: *The EKG finding of ST segment elevation did not correlate with any clinical findings of a thromboembolic event. There was consideration that this was due to early repolarization as a potential etiology in this 15 year old subject.*

Antibodies:

FVIII inhibitors:

The co-primary endpoint for the trial was the incidence rate of FVIII inhibitors ≥0.6 BU. One subject developed inhibitory antibodies against FVIII. This resulted in a one-sided 97.5% upper confidence limit for the inhibitor rate of 3.8%. As this is below the pre-specified limit of 6.8 %, the primary test for the incidence rate of inhibitor development succeeded.

Narrative: The single subject who developed FVIII inhibitors was an 18 year old (b) (6) who developed inhibitory antibodies against FVIII after 93 EDs to ESPEROCT. The subject had one bleed during the trial prior to the detection of the inhibitor. On (b) (4), the FVIII inhibitor was 1.3 BU. Repeat tests on (b) (4) showed titers of 1.9 BU. On (b) (4) (after the subject's cut-off visit date) FVIII inhibitor increased to 13.5 BU. The IP was discontinued on 31 Dec 2013.

N8-GP Binding Antibodies (Non-neutralizing):
Three subjects had pre-existing binding antibodies:

- One subject was positive at screening and at Visit 3 (no increase in titer levels)
- One subject was positive at screening and throughout the trial (no increase in titer levels)
- One subject was positive before treatment with the study drug

Two subjects developed binding antibodies during the trial:

- One subject was positive only at Visit 5
- One subject was positive from Visit 10 and onwards (with inhibitors at the same visits)

Reviewer comment: *For more details regarding PEG antibodies, please refer to ISS Section 8.4.8. The events of FVIII inhibitor and hypersensitivity are likely due to ESPEROCT and therefore will be included in the W&P section of the label.*

Extension Part 1:
Overall, no new safety signals were observed based on adverse events, vital signs, physical examinations or laboratory results as compared to the Main Phase of the study. No subjects developed FVIII inhibitors in the Extension Phase of the study. No thromboembolic events occurred during the trial.

6.1.12.6 Clinical Test Results

Standard laboratory panels for hematology, chemistry and coagulation-related parameters were measured over time. Clinically relevant changes in laboratory tests were to be reported as AEs. Adverse events of increased levels of hepatic parameters were observed: (alanine aminotransferase [9 events in 7 subjects], gamma-glutamyltransferase [8 events in 6 subjects], aspartate aminotransferase [5 events in 4 subjects], blood bilirubin [3 events in 3 subjects], aspartate aminotransferase abnormal [1 event] and hepatic enzymes [1 event]). None of the events were serious. All subjects, except for three, with increased levels of hepatic parameters were hepatitis C or B positive at screening, which most likely explains the increased values. None of hematologic or clinical chemistry labs that were reported as abnormal resulted in clinically significant sequelae in the subject population.

Reviewer Comment: *AEs of increased levels of hepatic parameters occurred in a small number of subjects and were low grade, transient and most resolved by the end of the study. Overall the abnormal lab values were judged not to be clinically relevant by the clinical reviewer. Therefore, no specific recommendation regarding special population with liver disease is being included in the label.*

6.1.12.7 Dropouts and/or Discontinuations

The Applicant states that as of the cut-off date for this report, no subjects were withdrawn from the trial due to AEs; However, the subject who developed FVIII inhibitor was withdrawn from the study.

6.1.13 Study Summary and Conclusions

Prophylactic infusion with ESPEROCT was effective for prevention of bleeds at dose intervals of every 4 days, as compared with a non-randomized control group of subjects

receiving on-demand treatment. Subjects in the Q4D treatment groups in the Main Part and Ext 1 Part of the study had comparable control of bleed. Subjects in the randomized Q7D group in Ext 1 Part of the study had a higher ABR compared to the Q4D group. Subjects in the Q7D treatment group had bleeding events which caused 24% of those in that group to discontinue treatment as they had a higher mean ABR. Under standard of care, these subjects would have individualized prophylaxis through escalation of doses or frequency to reduce the frequency of bleeding. Given the high ABR rate in the Q7D group, the potential for selection bias and the absence of PK data, namely half-life of the product to support a Q7 dosing regimen, this regimen will not be recommended and will not be included in label. A starting dose of 40 IU/kg Q4D is recommended, and based on the bleeding profile, the subject's regimen may be modified to a less or more frequent dosing based on the treating physician's recommendation.

Most bleeds were treated with 1-2 infusions and hemostasis was judged to be excellent or good. The study drug provided 'good' or 'excellent' hemostatic control during 34 major surgeries in adults and adolescents with severe hemophilia A. The blood loss was within expected ranges.

Dose calculations for perioperative and on-demand dosing were based on target dose and weight and the recommendations for dose calculations in the label will be based on these dose calculations.

One subject developed inhibitory antibodies to FVIII during the study. No unexpected adverse events occurred. There were two drug-related serious adverse reactions (intervertebral discitis and factor VIII inhibitor). Notably, allergic reactions occurred in 3% of subjects, of which, none required systemic therapy. These risks are expected and will be discussed in the label in the Warnings and Precautions (W&P) section. Overall, ESPEROCT exhibited a favorable safety and tolerability profile.

6.2 Trial #2: Study NN7088-3860 (or 3860)

Clinical Trials Identifier: NCT01489111
Initiated: 03 August 2012. Trial is still ongoing
Data cut-off: 15 August 2017

Title: Efficacy and Safety of ESPEROCT During Surgical Procedures in Patients with Hemophilia A (pathfinder™2).

General consideration: The trial was conducted in accordance with the Declaration of Helsinki (Seoul, October 2008), ICH Good Clinical Practice (Geneva, May 1996), and FDA 21 CFR 312.120. The results presented in this analysis reflect the data available in the clinical database for subjects who were included in the analysis of the pivotal trial 3859. Minor surgeries performed post-operatively during the trial were not counted as surgery.

6.2.1 Objectives (Primary, Secondary, etc)

Primary objective:

- To evaluate the hemostatic effect of ESPEROCT during surgical procedures in subjects with hemophilia A

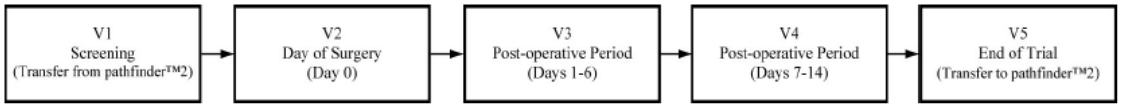
Secondary objectives:

- To evaluate the safety, including immunogenicity, of ESPEROCT when used for prevention and treatment of bleeding throughout the surgical period
- To evaluate the hemostatic effect of ESPEROCT during the post-operative period
- To evaluate health economic resource use (hospitalization days) due to surgery

6.2.2 Design Overview

The study was a multi-center, multi-national, open-label, non-randomized, single-arm, efficacy and safety trial evaluating ESPEROCT during surgical procedures in subjects with severe HA. The trial consisted of 5 scheduled visits (see Figure 8). The trial period was estimated to have a total duration of 2−5 weeks.

Figure 8: Study Design



pathfinder™2 = NN7088-3859

Source: BLA 125671 3860 CSR Figure 9-1 Page 27/711

6.2.3 Population

The trial enrolled PTPs aged ≥12 years with severe HA (Except for Croatia, France and Netherlands ,where the lower age limit was 18 years.). Subjects enrolled in this trial were recruited from the pivotal trial, 3859, and only if they had received ≥ 5 doses of ESPEROCT. Subjects were offered entry into the trial when they needed major surgery. Subjects were transferred from Trial 3859 in which subjects at inclusion were required to have a documented history of at least 150 EDs to other FVIII products.

Key inclusion criteria:

- Ongoing participation in Study 3859 and having received ≥5 doses of ESPEROCT.
- Undergoing major surgery requiring daily monitoring of FVIII activity and wound status for ≥3 days.
- The patient and/or Legally Acceptable Representative are capable of assessing a bleeding episode, keep an eDiary, capable of home treatment of bleeding episodes and otherwise capable of following the trial procedures.

Key exclusion criteria:

- Known or suspected hypersensitivity to trial product including allergy to hamster protein or related products.
- Previous withdrawal from Study 3859 after administration of trial product, except interruption due to inclusion in the present trial.
- The receipt of any investigational medicinal product (except EXPEROCT) within 30 days prior to enrolment into the trial.
- FVIII inhibitors ≥ 0.6 BU at screening.
- Previous arterial thrombotic events, deep venous thrombosis or pulmonary embolism

- Immune modulating or chemotherapeutic medication.
- Any disease (liver, kidney, inflammatory and mental disorders included) or condition which, according to the Investigator's judgement, could imply a potential hazard to the patient, interfere with trial participation or trial outcome.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Upon confirmation of eligibility at Visit 1, the subject was dosed once with ESPEROCT at a dose of 50 IU/kg in the clinic. The FVIII recovery level at this visit, as measured by the central laboratory, was used to determine the ESPEROCT dosing level to be maintained during and after surgery. Subjects on the prophylaxis arm continued on Q4D dosing and subjects on the on-demand arm continued treatment with 20-75 IU/kg at the investigator's discretion.

Therapeutic dose level of ESPEROCT was to be calculated to aim for a FVIII plasma level of approximately 80−100%. Subsequent dosing on the day of surgery was to be considered approximately 12 hours after the loading dose to maintain plasma levels of FVIII above 50%.

Surgery was performed on Day 0 (Visit 2). During Days 1−6 of the post-operative period, ESPEROCT dosing was adjusted to maintain FVIII plasma level above 50% and assessments were done every day at the site. During Days 7−14 in the post-operative period, dosing was done at the investigator's discretion and assessments were done once at the site. If the late post-operative period was extended beyond Day 14, subjects were evaluated once every week until the post-operative control of bleeding was confirmed. Upon completion of this trial, subjects returned to Trial 3859.

6.2.5 Directions for Use

The following trial product was supplied by the Applicant: ESPEROCT 2000 IU/vial as a sterile, freeze-dried powder in a 2−8°C (36−46°F) stable formulation single use vial to be reconstituted with (b) (4) of 0.9% NaCl for i.v. injection. Dosing was done at the investigators' discretion (except a fixed dose of 50 IU/kg at visit 1). The dose level was chosen based on FVIII activity levels as per WFH guidelines. The WFH guidelines for target FVIII levels for major surgery are as follows: pre-surgery (day 0): 80−100%; post-surgery Days 1−3: 60−80%; Days 4−6: 40−60%; Days 7−14: 30−50%. For treatment of a bleeding episode, all subjects were treated with doses between 20−75 IU/kg. The maximum dose to be administered to a subject within 24 hours was 200 IU/kg.

6.2.6 Sites and Centers

The trial was conducted at 25 sites in 13 countries as follows: Australia (1), Denmark (1), France (2), Hungary (1), Israel (1), Italy (2), Japan (3), Malaysia (1), Netherlands (1), Switzerland (1), Turkey (3), United Kingdom (4) and United States (4).

6.2.7 Surveillance/Monitoring

The trial consisted of 5 scheduled visits (see Figure 8).

6.2.8 Endpoints and Criteria for Study Success

Efficacy of ESPEROCT during surgical procedures was assessed using a four-point scale of ‘excellent’, ‘good’, ‘moderate’ or ‘none’. In addition, transfusion requirements, consumption and estimated blood loss were recorded as part of the efficacy assessment. Blood sampling for FVIII activity and laboratory safety parameters was done at all trial visits.

Criteria for efficacy evaluation:

- Hemostatic effect of ESPEROCT during surgery* evaluated on a four-point scale, assessed by the investigator/surgeon at the day of surgery (four-point response scale: excellent, good, moderate or none)
- Estimated blood loss during surgery
- Average consumption of ESPEROCT during surgery
- Hemostatic effect of ESPEROCT during the post-operative period Days 1−6
- Average consumption of ESPEROCT during the post-operative period Days 1−6
- Number of transfusions during the post-operative period Days 1−6
- Hemostatic effect of ESPEROCT during the post-operative period Days 7−14
- Health economics: length of stay in the hospital and days in intensive care assessed at the end of the trial

*During surgery was defined as the time from “knife to skin” until “last stitch”.

Criteria for safety evaluation:

- Adverse events and serious adverse events reported during the trial period
- Incidence rate of inhibitors against FVIII (≥0.6 BU)

Reviewer comment: *The primary efficacy analysis for surgery was based on outcomes from the day of surgery and was not inclusive of post-op bleeding outcomes. Therefore, if subjects had excellent response during surgery, per protocol specified criteria, the hemostatic rating would remain excellent even if they bled post-operatively.*

The anticipated blood loss was what the investigator documented prior to surgery. The estimated blood loss was the observed blood loss during surgery.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Power calculation: no formal sample size calculations were performed. Sample size was based on recommendations in the EMA guideline on the clinical investigation of recombinant and human plasma-derived FVIII products.

Analysis sets and excluded data: The safety analysis set and the full analysis set were identical and included all subjects exposed to ESPEROCT. No subjects were excluded from any analyses.

Statistical analyses: All endpoints were summarized and listed. No statistical analyses were planned or performed.

6.2.10 Study Population and Disposition

A total of 34 subjects were exposed to trial product. Of these 34 subjects, 33 subjects underwent 45 surgeries and completed the trial.

A total of 96 important protocol deviations were identified. Fifteen (15) were at trial site level, and 81 were at subject level.

Reviewer comment: *None of the important protocol deviations were considered to have an overall impact on trial conduct, subject safety or data interpretation.*

6.2.10.1 Populations Enrolled/Analyzed

The study population consisted of adolescent and adult males with severe HA.

6.2.10.1.1 Demographics

Mean age of all subjects was 40.8 years (range: 15−69 years). One subject was adolescent (15 years old), while the remaining subjects were adults (≥18 years old). The mean body mass index (BMI) was 25.4 kg/m^2 (range: 18.4−36.7 kg/m^2). Of all subjects, 28 (82%) were White while five (15%) were Asian and one (3%) was Black or African American. Subjects came from Australia (1), Denmark (1), France (3), Hungary (3), Italy (1), Israel (1), Japan (4), Malaysia (1) Netherland (1), Switzerland (1), Turkey (3), United Kingdom (8) and United States (6).

A total of 17 of the 34 subjects had relatives with HA. Of those 17 subjects, 12 subjects had relatives with inhibitors. At baseline (from Study 3859), 26 out of 34 subjects received prophylactic treatment with either recombinant or plasma-derived FVIII products. The remaining eight subjects followed an on-demand treatment regimen.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Subjects' medical history data were obtained from the baseline data recorded on Study 3859. Please refer to Section 6.1.10.1.2.

6.2.10.1.3 Subject Disposition

A total of 34 subjects were screened and all 34 subjects were exposed to trial product, and 33 subjects underwent surgeries and completed the trial. A total of 45 surgeries were completed; 10 of the 33 subjects re-entered the trial: four subjects had 2 surgeries, three subjects had 3 surgeries, one subject had 4 surgeries. Two subjects who initially withdrew re-entered the trial to have a surgery later and one subject withdrew from the trial due to cancelation of the planned surgery. The full analysis set and the safety analysis set included all 34 dosed subjects.

6.2.11 Efficacy Analyses

A total of 45 surgeries were performed on 33 subjects The details of the surgeries are summarized in Table 22. A total of 42 surgeries were elective and the remaining 3 were reported as emergency surgeries. The majority of the surgeries were orthopedic surgeries (41).

Table 22: Surgery Details

Surgery Location	N
Abdomen	1
Abdominal	1
Bilateral thumbs	1
Both ankles	1

Surgery Location	N
Chest	1
Left and right knee	1
Left ankle	6
Left elbow	3
Left hip	1
Left knee	5
Left shoulder	1
Penis	1
Right ankle	4
Right elbow	1
Right femoral neck	1
Right hip	2
Right knee	9
Right leg	1
Right talar	1
Total surgeries	**45**
Total subjects undergoing surgeries	**33**
Total subjects	**34**

Source: FDA analysis

Reviewer comment: *The number of major surgeries was adequate to draw conclusions regarding dose and efficacy in adult subjects >18 years of age. The limitations of the sample size in 12-17 year old are compensated by extrapolating data from control of bleeding data in the adolescents and the PK data from the main study to extend the indication in adolescents for the surgical indication. Although no pediatric subjects less than 12 years of age had undergone a major surgery, data from on-demand treatment of bleeds, PK data from the pediatric study, 3885, and target FVIII dosing allow adequate extrapolation to extend the surgery indication to the pediatric age group less than 12 years. This approach to extrapolation of data to support a surgical indication is consistent with review of other FDA approved products in hemophilia as surgical procedures particularly elective surgical procedures (emergency procedures are infeasible to include in a study) are uncommon in the pediatric population.*

6.2.11.1 Analyses of Primary Endpoint(s)

Hemostatic effect during surgery: The success rate for the hemostatic effect of ESPEROCT during surgery was 96% as 43 out of 45 surgeries had the effect rated as ‘excellent’ (49%) or ‘good’ (47%). Two surgeries (4%) had the effect rated as ‘moderate’. No surgeries had an outcome rated as ‘none’. All surgeries were effectively conducted with ESPEROCT and without change of treatment regimen. On the day of surgery (Day 0), two blood transfusions were given in 2 surgeries. The total volume transfused ranged between 800 and 1000 mL

Reviewer comment: *The surgeries with the hemostatic effect rated as ‘moderate’ (defined as ‘less than optimal for the type of procedure, but hemostatic response maintained without change of treatment regimen’) were seen in the following two subjects:*

- *Subject* (b) (6)*: total hip replacement lasting 2 hours and 21 minutes. This subject received blood transfusion (autologous).*
- *Subject* (b) (6)*: right ankle arthroscopic and open debridement with chondroplasty lasting 1 hour and 52 minutes.*

6.2.11.2 Analyses of Secondary Endpoints

Estimated blood loss (EBL) during surgery: The mean (SD) and median estimated blood loss (EBL) during surgery was 339 (779) mL and 50 mL, respectively, and the range was 0 to 4520 mL. The mean (SD) and median anticipated blood loss (ABL) during surgery was 293 (389) mL and 100 mL, respectively, and the range was 0 to 1500 mL. One subject (b) (6) had a markedly higher EBL (4520 mL) than the other subjects. See Table 23 for details of ABL, EBL, evaluation of hemostasis by surgery type.

Table 23: Summary of Evaluation of Hemostasis Response

Surgery Classification	Surgery Location	Anticipated Blood Loss mL	Estimated Blood Loss mL	Evaluation of Hemostasis	Surgery N (%)
Non-orthopedic	Abdomen	0	75	Excellent	1 (3%)
	Abdominal	1500	2000	Good	1 (3%)
	Chest	100	100	Excellent	1 (3%)
	Penis	0	2	Excellent	1 (3%)
Orthopedic	L and R thumbs	0	5	Good	1 (3%)
	L and R ankles	0	0	Excellent	1 (3%)
	L and R knee	.	.	Excellent	1 (3%)
	L ankle	0	0	Excellent	3 (9%)
	L ankle	.	0	Good	1 (3%)
	L ankle	5	5	Good	1 (3%)
	L ankle	400	30	Excellent	1 (3%)
	L elbow	.	50	Excellent	1 (3%)
	L elbow	0	0	Good	1 (3%)
	L elbow	.	.	Good	1 (3%)
	L hip	300	300	Excellent	1 (3%)
	L knee	100	100	Good	1 (3%)
	L knee	180	180	Excellent	1 (3%)
	L knee	250	150	Good	1 (3%)
	L knee	350	500	Good	1 (3%)
	L knee	400	700	Excellent	1 (3%)
	L shoulder	100	0	Excellent	1 (3%)
	R ankle	.	300	Moderate	1 (3%)
	R ankle	0	37	Good	1 (3%)
	R ankle	50	0	Good	1 (3%)
	R ankle	100	50	Good	1 (3%)
	R elbow	.	75	Good	1 (3%)
	R femoral neck	800	4520	Moderate	1 (3%)
	R hip	0	400	Excellent	1 (3%)
	R hip	800	500	Excellent	1 (3%)
	R knee	0	10	Good	1 (3%)
	R knee	.	.	Excellent	1 (3%)

Surgery Classification	Surgery Location	Anticipated Blood Loss mL	Estimated Blood Loss mL	Evaluation of Hemostasis	Surgery N (%)
	R knee	300	50	Good	1 (3%)
	R knee	300	200	Good	1 (3%)
	R knee	400	30	Excellent	1 (3%)
	R knee	500	500	Good	1 (3%)
	R knee	500	.	Good	1 (3%)
	R knee	600	556	Excellent	1 (3%)
	R knee	700	1190	Good	1 (3%)
	R knee	1000	1000	Excellent	1 (3%)
	R knee	1400	300	Good	1 (3%)
	R leg	0	0	Excellent	1 (3%)
	R talar	0	0	Good	1 (3%)
Subjects				**Good**	**33 (100%)**

Source: FDA analysis
R: right, L: left, ".": Missing.

Reviewer comment: *The mean EBL did not differ markedly from the mean ABL and is considered acceptable for the surgeries performed during the study.*

Average consumption of ESPEROCT during surgery**:** A pre-surgery dose of ESPEROCT was administered to all subjects at the day of surgery; the mean and median dose was 55.3 and 51.2 IU/kg (range: 27.2−86.2 IU/kg). In one surgery, a dose of ESPEROCT was administered during surgery (21 IU/kg). In 29 surgeries, a post-surgery dose was administered on the day of surgery; the mean and median dose was 31 and 26 IU/kg, respectively (range: 10.1−58.8 IU/kg). On the day of surgery, subjects received 1−3 doses of ESPEROCT: In 16 surgeries, subjects received 1 dose, in 27 surgeries subjects received 2 doses and in two surgeries subjects received 3 doses.

Reviewer comment: *For pre-op dosing, the median dose was 50-60 IU/kg. The Applicant's proposed dose for peri-operative management of 40-50 IU/kg for major surgeries is less than what the majority of subjects actually received during the study. Therefore, the clinical reviewer recommends revising the dose to 50-55 IU/kg based on the observed data from the clinical trial. A recommendation regarding precise post-operative dose is challenging in hemophilia trials as post-operative dosing is subject to the clinician's judgment, type of surgery and observed extent of post-operative drainage and intraoperative complications.*

Post-surgery period, days 1−6: Two bleeds occurred in two subjects. The success rate was rated as 'good' in one subject and was 'missing' for the other). The mean ESPEROCT consumption during days 1−6 post-surgery was 33.5 IU/kg (kg (range: 15.5−59.6 IU/kg). Nine blood transfusions were administered in five surgeries.

Reviewer comment: *One subject* (b) (6) *bled for several days after total right knee replacement surgery and did not receive 'treatment of bleed' doses (even though the bleed was 'severe').The Applicant stated this was because the bleed was a re-bleed from the surgery, and that the dose given was a prophylactic dose due to the surgery and not as a treatment of the bleed. In addition, this subject had discordant results*

between FVIII dosage and anticipated FVIII trough level. The hemostatic response for this subject was recorded as "Good" because this evaluation was based on the bleeding outcome during surgery not during the post-op period as pre-specified in the protocol.

Post-surgery period, days 7-14: Two bleeds occurred; one was assessed as 'excellent' and the other as 'good'.

***Reviewer comment**: In addition to the bleeds recorded during Days 1−6 and 7−14 as presented above, two bleeds before surgery (spontaneous), and one bleed after Day 15 (traumatic and located in muscle) occurred. All three bleeds were treated successfully with ESPEROCT. One additional non-treatment required bleed was reported.*

Post-surgical wound hematomas were observed in 13 surgeries. The mean number of days at the hospital during the trial was 10 days (range: 0−39 days) and median was 7 days. One subject was admitted for one day to the intensive care unit during this trial.

Endpoints that are related to the safety of the product are reviewed in the Safety Analysis below.

***Reviewer Comment:** This clinical reviewer agrees with the assessment regarding adequacy of hemostasis for these major surgeries, which supports the proposed perioperative indication. There were a total of 11 blood transfusions in 7 surgeries in two subjects who received blood transfusions post operatively due to the blood loss that occurred perioperatively. The blood loss observed is within the expected range for the major orthopedic surgeries.*

6.2.11.3 Subpopulation Analyses

N/A

6.2.11.4 Dropouts and/or Discontinuations

One subject of the total of 34 subjects enrolled in the trial withdrew due to cancelation of the surgery.

6.2.11.5 Exploratory and Post Hoc Analyses

N/A

6.2.12 Safety Analyses

6.2.12.1 Methods

The 33 subjects who underwent a total of 45 surgeries were exposed to ESPEROCT. All safety evaluations were based on the safety analysis set, including all 34 dosed subjects. The safety analysis set was identical to the full analysis set.

6.2.12.2 Overview of Adverse Events

Total of 118 AEs were reported in 37 out of 48 planned surgeries. The most common AEs were constipation (11 surgeries [23%]) and nausea (6 surgeries [12%]). A total of 19 AEs in 5 surgeries were evaluated to be possibly or probably related to ESPEROCT by the investigator. Most of these events (17 out of 19 events) were non-SAEs.

Most AEs were evaluated as mild or moderate in severity. One non-SAE (bone pain) was rated as severe and judged as possibly related to the trial product.

Reviewer comment: *One subject was exposed to ESPEROCT manufactured with the commercial process but did not develop any AEs. See section 5.3 for details regarding the PK study, Study 4033, which evaluated PK parameters following dosing with ESPEROCT manufactured with the commercial process.*

6.2.12.3 Deaths

No deaths occurred during the trial.

6.2.12.4 Nonfatal Serious Adverse Events

Five SAEs were reported. Two of these events (hemorrhage and ischemia) were reported in the same surgery and were judged as possibly related to the trial product. The other SAEs were judged as unlikely related to the trial product.

6.2.12.5 Adverse Events of Special Interest (AESI)

No FVIII inhibitors were detected and no thromboembolic events occurred.

6.2.12.6 Clinical Test Results

Results of safety laboratory parameters and other safety-related evaluations did not indicate clinically relevant changes as a result of administration of ESPEROCT.

6.2.12.7 Dropouts and/or Discontinuations

No subjects were withdrawn from the trial due to adverse events.

6.2.13 Study Summary and Conclusions

The hemostatic effect of ESPEROCT during surgery was demonstrated. The hemostatic effect was rated as ‘excellent’ or ‘good’ in 96% of surgeries and as ‘moderate’ in 4% of surgeries. The hemostatic effect of ESPEROCT during the post-operative period was also demonstrated. During these periods, the hemostatic effect was rated as ‘excellent’ or ‘good’ in 3 of the 4 bleeding episodes and the effect was not rated in one bleeding episode. No inhibitory FVIII antibodies were detected, no thromboembolic events occurred, and no other clinically significant safety issues were identified.

6.3 Trial #3: Study NN7088-3885 (or 3885)

Clinical Trials Identifier: NCT01731600
Initiated: 20 February 2013. Completed: 17 November 2014

Title: A Multinational, Open-Label, Non-Controlled Trial on Safety, Efficacy and PK of ESPEROCT in Previously Treated Pediatric Patients with Severe HA (pathfinder™5)

6.3.1 Objectives (Primary, Secondary, etc)

Primary objective:

- To evaluate immunogenicity of ESPEROCT

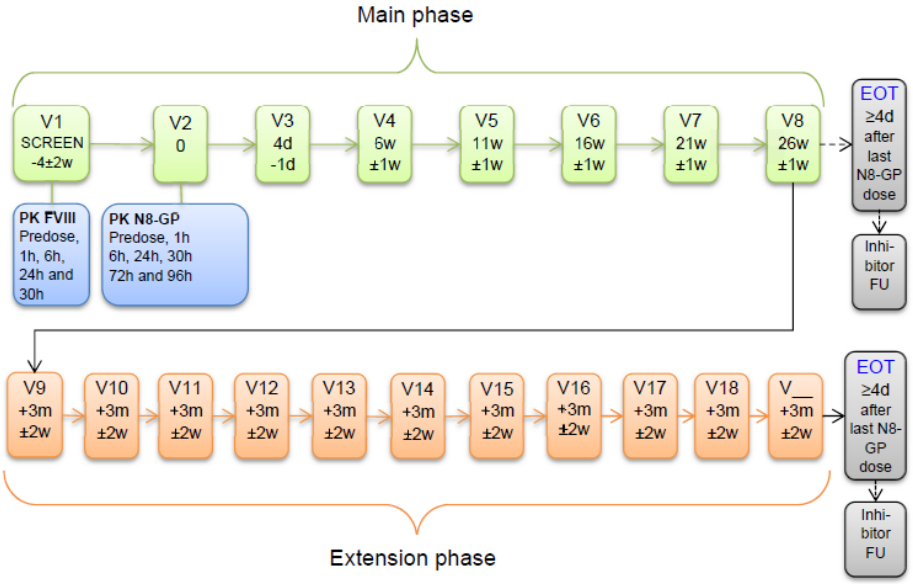
Secondary objectives:

- To evaluate safety other than immunogenicity of ESPEROCT
- To evaluate efficacy of ESPEROCT in prophylaxis and treatment of bleeding episodes
- To evaluate PK properties of ESPEROCT and compare to previous FVIII product (only PK assessments)
- To support a population based PK model for ESPEROCT (only PK assessments)
- To evaluate patient reported outcomes (PRO)

6.3.2 Design Overview

This was a phase 3, multi-national, open-label single-arm, non-controlled trial designed to assess the safety including immunogenicity, efficacy, and PK of ESPEROCT in pediatric subjects. The trial product was given for prophylaxis and treatment of bleeding episodes to subjects below 12 years of age with severe HA where >50 EDs in the 0–5 age group and >150 EDs in the 6–11 age-group in whom previous FVIII products were required. The trial consisted of a main phase and an extension phase. The duration of the main phase for each subject was approximately 26 weeks (corresponding to 50 EDs). After completion of the main phase, the subjects could continue in an extension phase lasting until ESPEROCT was commercially available or the study was terminated. During the Main and Extension phases, subjects treated with FVIII products other than ESPEROCT had to be withdrawn from the trial. The PK assessments with previous FVIII product were performed at Visit 1. The main parameters assessed were incremental recovery, area under the curve, terminal half-life and clearance. The PK assessments with ESPEROCT were performed at Visit 2. PRO data were collected to assess change in health related, disease, and age-specific quality of life (HAEMO-QOL) as well as treatment satisfaction (HEMO-SAT) of subjects from the screening visit (Visit 1) to the EOT Visit. Figure 9 below presents an overview of the study visits in the main and extension phases.

Figure 9: Visits Overview



Source: BLA 125671 Study 3885 CSR Figure 9-2 Page 50/830
W: week, d: day, h: hour, EOT: end-of-trial, FU: follow-up

6.3.3 Population

This trial enrolled male patients less than 12 years of age with severe HA. A weight limit of ≥10 kg was set to ensure sufficient blood sampling volume could be drawn without jeopardizing subject safety.

Key inclusion criteria:

- Male patients with severe congenital HA (FVIII activity level below 1%)
- Weight above or equal to 10 kg
- Documented history of > 150 EDs to FVIII products for subjects aged 6-11 years and > 50 ED to FVIII products for subjects aged 0-5 years

Key exclusion criteria:

- Any history of FVIII inhibitors
- Known or suspected hypersensitivity to trial product including allergy to hamster protein or to related products.
- Congenital or acquired coagulation disorders other than haemophilia A
- ALT > 3 times ULN
- Cr ≥ 1.5 ULN
- Previous significant thromboembolic event
- HIV positive
- Surgery planned to occur during the main phase of the trial (except: port placement, dental extractions, and minor, uncomplicated emergent procedures).

Reviewer comment: *The eligibility criteria were in line with previously studied recombinant FVIII products.*

6.3.4 Study Treatments or Agents Mandated by the Protocol

The study drug was supplied as a sterile, freeze-dried powder in a 2-8°C (36-46°F) stable formulation single use vial with a nominal content of 500 IU/vial or 2000 IU/vial to be reconstituted with (b) (4) 0.9% Sodium chloride (NaCl) solution for *i.v.* injection. After reconstitution each vial contains 125 U/mL or 500 U/mL ESPEROCT, respectively.

6.3.5 Directions for Use

One single dose of approximately 60 IU/kg BW of ESPEROCT was administered intravenously every 3–4 days (twice weekly). A dose range of 50-75 IU/kg BW was permitted for prophylaxis. Treatment requiring bleeding episodes were treated with doses of ESPEROCT ranging from 20-75 IU/kg BW, according to the severity and location of the bleeding episode. Single doses were not to exceed 75 IU/kg BW and total daily dose was not to exceed 200 IU/kg BW.

Minor surgeries, dental extractions and placement of central venous access ports could be performed while participating in this trial by administering an extra dose of ESPEROCT. It was considered unethical to assign subjects already on prophylaxis to on-demand treatment, and therefore there was no on-demand arm in the study.

Table 24: Treatment Overview

Phase	Dose	Frequency
PK assessments (12 subjects from each age-group	50 IU/Kg BW	Visit 1 and 2
Main: Prophylaxis**	50-75 IU/Kg BW Approximately 60 IU/kg BW	Every 3-4 days
Main: Treatment of bleeds**	20-75 IU/Kg BW	Investigator's discretion

Source: FDA analysis
PK= pharmacokinetics, BW=body weight.
* An increase in dose frequency from twice weekly to every third day was permitted at the investigators discretion (based on bleeding pattern).
**Treatment in the extension phase was identical to the main phase

Reviewer comment: *Per protocol; joints bleeds were recommended to be treated with a dose of 20-60 IU/Kg and central nervous system (CNS) and gastrointestinal (GI) bleeds with a dose of 40-75 IU/kg. However, the Applicant's proposed dosing in the label is to administer 10-20 IU/kg body weight for minor bleeds and 15-30 IU/kg body weight for moderate bleeds, and 30-50 IU/kg body weight for major bleeds. The dose recommendation in the label needs to represent data obtained from the clinical trials. Therefore, recommendation regarding modifying the proposed dosing will be communicated to the Applicant during labeling negotiations.*

6.3.6 Sites and Centers

The trial was conducted at 35 sites in 15 countries as follows: Canada: (1), France: (1), Germany: (1), Greece: (2), Israel: (1), Italy: (1), Japan: (2), Lithuania: (1), Malaysia: (1), Portugal: (1), Switzerland: (3), Turkey: (3), Ukraine: (2), UK: (3), and US: (12).

6.3.7 Surveillance/Monitoring

The sponsor constituted an internal safety committee to perform ongoing safety surveillance of ESPEROCT. The committee had the responsibility of overseeing the safety of the enrolled subjects in the trial.

6.3.8 Endpoints and Criteria for Study Success

Primary endpoint:

- Incidence of inhibitory antibodies against FVIII ≥0.6 BU during the main phase of the trial (from 0-26 weeks of treatment)

Secondary endpoints:
Criteria for efficacy evaluation: Efficacy (from 0-26 weeks of treatment):

- Hemostatic effect of ESPEROCT when used for treatment of bleeding episodes
- Number of bleeding episodes during prophylactic treatment with ESPEROCT (ABR)
- Consumption of ESPEROCT per bleeding episode (number of injections and IU/kg)
- Consumption of ESPEROCT during prophylaxis (number of injections and IU/kg per month and year)
- Changes in PRO scores from baseline to the end of main phase

PK endpoints on previous FVIII product and ESPEROCT

- Incremental recovery (IR_{60min}: peak FVIII level recorded 60 min after end of injection)
- Area under the curve (AUC; h×U/mL)
- Terminal half-life (t½; h)
- Clearance (CL; mL/h/kg)

Criteria for safety evaluation:

- Incidence of inhibitory antibodies against FVIII ≥0.6 BU during the extension phase of the trial (from 26 weeks to the last subject completion of the trial)
- Frequency of AEs and SAEs

Success of hemostatic effect of ESPEROCT was defined as a response of Good or Excellent, while failure was defined as moderate, none or missing. ABR of treatment requiring bleeding episodes was estimated by a Poisson regression model with log (prophylaxis duration) as offset and estimating over-dispersion by Pearson's scale. The estimated ABR was presented together with a 2-sided 95% confidence interval.

Definition of analysis sets:

- Full analysis set (FAS) – All trial subjects allocated to treatment for which at least one of the PK or efficacy endpoints was assessed.
- Safety analysis set (SAS) – All subjects exposed to at least one dose of ESPEROCT.

Reviewer comment: *The full analysis set (FAS) and safety analysis set (SAS) were identical and consisted of all dosed subjects. No subjects were excluded from any analyses.*

6.3.9 Statistical Considerations & Statistical Analysis Plan

The analyses of the safety endpoints were based on the safety analysis set and all available information until the last visit.

Power calculation:

- No formal sample size calculations were performed. The sample size was based on current EMA guidelines for hemophilia products.

Statistical analyses

- The FVIII inhibitor rate was calculated by dividing number of subjects with neutralizing inhibitors by the number of subjects with at least 50 EDs. A one-sided, upper 97.5% confidence limit was provided based on an exact calculation for a binomial distribution.
- All efficacy endpoints were summarized in total and by age-group (children 0-5 years old at screening and children 6-11 years old at screening). Summaries for continuous endpoints included total number (N), mean (SD), median and min/max and for pharmacokinetic endpoints also geometric mean and CV%. Summaries for discrete endpoints included N, number (n) and percentages (%) for each outcome category.

Imputation: The primary analysis of ABR was repeated to investigate the potential impact of early withdrawals by imputing number of bleeding episodes for withdrawals. For subjects who withdrew prematurely, the number of bleeding episodes included in the analysis was imputed up to what they could be expected to have had if they had completed the trial.

Reviewer comment: *In addition to the mean ABR (±SD), the Poisson regression model was used to estimate ABRs and was presented with a 2-sided 95% CI. This method estimates ABR based on the observed bleeding episodes while accounting for outliers;, however, it does not represent the true observed ABRs. The efficacy analysis performed by the clinical reviewer is based on the mean ABR (SD) because it represents the true observed ABRs rather than an estimated ABR.*

This clinical trial report is based on a partial data base lock and includes data from the main phase of the trial (i.e. up to and including Visit 8). Three subjects (b) (6) and (b) (6) had data from their Visit 9 included as well.

6.3.10 Study Population and Disposition

The study population consisted of pediatric males less than 12 years of age with severe HA.

Protocol deviations: A total of 138 important protocol deviations were reported in the main phase of this trial: none were at trial level, one was at country level (Germany), 13 were at trial site level, and 124 were at subject level. These deviations were mainly related to the informed consent procedure, monitoring intervals outside the intervals described in the protocol, drug handling procedures, assessment of deviations, missing source data, and laboratory procedures. All subjects were eligible once the data and laboratory reports were reviewed. There were no safety concerns reported by the Applicant in association with these deviations.

Table 25: Summary of Important Protocol Deviations at Subject Level

Protocol deviation category	Number of deviations
Informed consent	19
Inclusion/exclusion criteria	4
Withdrawal criteria	8
Trial drug handling*	10
Treatment compliance	27
Assessment deviations including laboratory samples	42
Other	14

Source: FDA analysis and adapted form BLA 125671 CSR 3885 Table 10-8 Page 93/830
*Subject (b) (6) received four “2000 U/vial” of the study drug instead of four “500 IU/vial”. After issue identification, the trial manager was informed, and site staff were re-trained on trial product dispensing and accountability. No MESI was needed to be completed for this deviation.

Reviewer comment: *None of the important protocol deviations were considered to have an overall impact on trial conduct, subject safety or data interpretation.*

6.3.10.1 Populations Enrolled/Analyzed

A total of 72 subjects were screened and 68 of these were exposed to ESPEROCT, thereby comprising the FAS which was evenly distributed between the 0-5 year age-group and the 6-11 year age-group (34 subjects in each). The remaining four subjects were screening failures and were not exposed to the study drug. A total of 27 subjects (40% of FAS) were enrolled for PK assessments:15 subjects in the 0-5 year age-group and 12 subjects in the 6-11 year age-group.

The FAS and SAS were identical and consisted of all dosed subjects. No subjects were excluded from any analyses.

Reviewer comment: *Four subjects failed the screening:*

- *Subjects* (b) (6) *(age 3 and 2 years, respectively): FVIII inhibitors ≥0.6 BU measured at screening.*
- *Subject* (b) (6) *(age 1 year): Unwillingness, language or other barriers precluding adequate understanding and/or cooperation from parents or child.*
- *Subject* (b) (6) *(age 11 years): History of FVIII inhibitors.*

6.3.10.1.1 Demographics

The trial population consisted of male pediatric subjects with severe HA recruited from 15 countries worldwide. The majority of the subjects were 'White' (81%) followed by 'Asian' (7%). The remaining part of the trial population was categorized either as 'Black or African American' (4%), 'Other' (3%), or not reported. At baseline, the subjects in the 0–5 year age-group where characterized by a mean (range) age of 3.0 (1–5) years, and body weight: 16.1 (10.9–23.0) kg. For comparison, the subjects in the 6–11 year age-group were of mean (range) age: 8.9 (6–11) years, and body weight: 34.1 (17.0-60.4) kg. Prior to enrollment in the trial, 65 subjects (96% of FAS) were on prophylactic treatment (61 subjects on recombinant FVIII products and four subjects on plasma-derived FVIII products). The remaining three subjects (4%; all in the 0-5 year age-group) were on on-demand treatment. At baseline, 6 (8.8%) subjects (3 in each age-group) had clinically significant abnormal findings in the musculoskeletal system, likely associated with their HA condition. All subjects were negative for HIV and hepatitis C at baseline. See Table 26 for details.

Table 26: Demographics and Baseline Characteristics

Characteristics	Statistics	0-5 years	6-11 years	All Age
Sex [n (%)]	M	34 (100%)	34 (100%)	68 (100%)
Race [n (%)]	Asian	1 (3%)	4 (12%)	5 (7%)
	Black or African American	2 (6%)	1 (3%)	3 (4%)
	NA	0 (0%)	3 (9%)	3 (4%)
	Other	1 (3%)	1 (3%)	2 (3%)
	White	30 (88%)	25 (74%)	55 (81%)
Ethnicity [n (%)]	Hispanic or Latino	0 (0%)	3 (9%)	3 (4%)
	NA	0 (0%)	1 (3%)	1 (2%)
	Not Hispanic or Latino	34 (100%)	30 (88%)	64 (94%)
Country [n (%)]	Canada	0 (0%)	2 (6%)	2 (3%)
	France	4 (12%)	3 (9%)	7 (10%)
	Germany	1 (3%)	0 (0%)	1 (2%)

	Greece	0 (0%)	1 (3%)	1 (2%)
	Israel	0 (0%)	2 (6%)	2 (3%)
	Italy	0 (0%)	1 (3%)	1 (2%)
	Japan	0 (0%)	2 (6%)	2 (3%)
	Lithuania	1 (3%)	4 (12%)	5 (7%)
	Malaysia	1 (3%)	1 (3%)	2 (3%)
	Portugal	0 (0%)	2 (6%)	2 (3%)
	Switzerland	2 (6%)	2 (6%)	4 (6%)
	Turkey	2 (6%)	4 (12%)	6 (9%)
	Ukraine	6 (18%)	0 (0%)	6 (9%)
	United Kingdom	5 (15%)	1 (3%)	6 (9%)
	United States	12 (35%)	9 (26%)	21 (31%)
All subjects		**34 (100%)**	**34 (100%)**	**68 (100%)**

Source: FDA analysis

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The trial population consisted of male patients with severe HA. A total of 30 subjects (44%) reported history of hemophilia A among relatives. Prior to enrollment in the trial, 65 (96%) of the subjects were on prophylactic treatment (61 on rFVIII and 4 on plasma-derived FVIII products). The remaining three (4%) subjects were on on-demand treatment. The most common underlying *F8* gene defect was an inversion in Intron 22 (34%), followed by substitution nonsense mutations (13%), and missense mutations (10%). A total of 15 subjects had target joints (six subjects in the 0-5 year age-group and nine subjects in the 6-11 year age-group).

6.3.10.1.3 Subject Disposition
An overview of subjects' disposition is provided in Table 27.

Table 27: Subjects Disposition

Characteristics		**0-5 years N (%)**	**6-11 years N (%)**	**All Age N (%)**
Safety population		34 (100%)	34 (100%)	68 (100.0%)
Full analysis set population		34 (100%)	34 (100%)	68 (100.0%)
PK Analysis population		15 (44%)	12 (35%)	27 (39.7%)
Subjects disposition	Completed	29 (85%)	34 (100%)	63 (93%)
	Discontinued	5 (15%)	0 (0%)	5 (7%)
Reason for Discontinuation	Adverse event	2 (6%)	0 (0%)	2 (3%)
	Other	2 (6%)	0 (0%)	2 (3%)
	Withdrawal criteria	1 (3%)	0 (0%)	1 (2%)
Total Subjects		**34 (100%)**	**34 (100%)**	**68 (100.0%)**

Source: FDA analysis

The FAS was evenly distributed between the 0-5 year age-group and the 6-11 year age-group (34 subjects in each). Four subjects were screening failures and were not exposed to the study drug. A total of 27 (40%) subjects of the FAS were enrolled for PK assessments, of which 15 were 0-5 years and 12 were 6-11 years of age. At the end of the main phase of the study, a total of five subjects, all in the 0-5 year age-group, had withdrawn from the study as follows:

- Two subjects due to AEs of decreased efficacy:
  - Subject (b) (6) was a 4 year old male who experienced increased joint bleeding and low FVIII activity post treatment with the study drug.
  - Subject (b) (6) was a 4 year old who experienced failure of the study drug in preventing bleeding.
- One subject due to withdrawal criteria: allergic reaction related to trial product after 4 EDs
- Two subjects due to 'other' reasons as outlined below:
  - Subject (b) (6) was a 4 year old male who withdrew from the study after 2 ED due to receiving high dose treatment for synovitis. The subject had prior problems with the same joint which was not documented initially in his medical record.
  - Subject (b) (6): was a 5 year old and discontinued from the trial after 27 EDs. The subject was wrongly enrolled in the trial due to presence of FVIII inhibitor prior to receiving the study drug. The inhibitor test was negative at the screening visit but was transiently positive subsequently. This was considered a late screening failure.

A total of four subjects underwent one minor surgical procedure each during this trial.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

The primary endpoint: incidence of inhibitory antibodies against FVIII ≥0.6 BU during the main phase of the trial (from 0-26 weeks of treatment) was a safety endpoint and reported in the safety section below. No FVIII inhibitors were observed.

6.3.11.2 Analyses of Secondary Endpoints

Number of bleeding episodes during prophylactic treatment (ABR): A total of 70 bleeds were treated in 39 subjects (57%) during the trial. The majority of the bleeds (71%) were traumatic, 27% were spontaneous bleeds, and a one bleed (1%) was due to minor surgery. The most frequent location of bleeds was in a joint, which accounted for 34 (49%). Ten joint bleeds occurred in the 0-5 years age-group and 24 joint bleeds in the 6-11 year age-group. All bleeds were classified as mild or moderate, and no re-bleeds during the trial were reported. The most predominant location of bleeds was joints (48%) followed by skin (19%) and muscular (15%) bleedings. The mean (range) duration of bleeds among the 0-5 years age-group was 53.0 (0.4–209.6) hours compared to 35.2 (1.0–136.2) hours in the 6-11 year age-group.

Reviewer comment: *It is noted that the duration of bleeding episodes was longer among the younger age group (0-5 years) as compared to the older age group (6-11). However, none of these bleeds was considered severe.*

Of the 15 (22%) subjects who reported 19 target joints at baseline, 11 (73%) subjects did not report any target joint bleeds during the trial, the remaining four subjects reported 6 bleeding episodes involving a target joint: two bleeding episodes in the 0-5 year age-group (both spontaneous) and four bleeding episodes in the 6-11 year age-group (two spontaneous and two traumatic).

Reviewer comment: *Similar to the efficacy analyses in Study 3859, non-treatment requiring bleeding episodes that coincided with regular prophylaxis doses were not included in this ABR analysis. The additional efficacy analyses by including the non-treatment required bleeds are included below and are summarized in Table 28.*

The Applicant's primary analysis was based on imputed ABRs as discussed in section 6.3.9 of this memo. Sensitivity analysis was repeated based on observed data without imputation. Additionally, the Applicant performed sensitivity analyses by applying a negative binomial regression model, the results of all analyses based on this model were consistent with those obtained based on the Poisson model.

The median ABR was 1.95 (IQR: 0.00; 2.79) and was comparable between the two age-groups. The mean (SD) ABR was 3.08 (7.13). Mean ABR was 3.87 (9.68) for the 0-5 age group and 2.29 (2.86) for the 6-11 age group.

Reviewer comment: *It was noted that the maximum individual ABR (45.66) was driven by one subject* (b) (6) *in the 0-5 year age-group who was discontinued early from the trial after eight EDs due to an adverse event of decreased efficacy.*

Among the five subjects who discontinued from the study, four of them had less than 30 EDs to the study drug. The Poisson estimated ABR was 2.13 (95% CI :1.48; 3.06), 1.94 (95% CI :1.10; 3.42) in the 0-5 year age-group, and 2.30 (95% CI :1.40; 3.75) in the 6-11 year age-group when no imputation was performed for withdrawn subjects.

When including all bleeds (treated and non-treated); the mean ABR (SD) across all age groups increases to 4.38 (8.71); 5.00 (11.85) in the 0-5 year age-group, and 3.76 (3.59) in the 6-11 year age-group.

Table 28 summarizes the efficacy of the prophylaxis regimen in Study 3885.

Table 28: Efficacy in Pediatric Prophylaxis, Median and Mean ABRs by Age and Bleed Type (For All bleeds and Treated Bleeds)

	Prophylaxis Regimen 65 IU/kg twice weekly		
	0-5 years N=34	**6-11 years N=34**	**0-11 years N=68**
Mean treatment duration (years)	0.46	0.51	0.48
Treated bleeds			
# of subjects (%)	19 (56)	20 (59)	39 (57)
# of subjects with 0 bleed (%)	15 (44)	14 (41)	29 (43)
# of bleeds	30	40	70
Median ABR (IQR)	1.94 (0.00;2.08)	1.97 (0.00;3.91)	1.95 (0.00;2.79)
Mean ABR (SD)	3.87 (9.68)	2.29 (2.86)	3.08 (7.13)
Mean ABR (95% CI)**	1.94 (1.10; 3.42)	2.30 (1.40;3.75)	2.13 (1.48;3.06)
All Bleeds*			
# of subjects (%)	20 (59)	26 (77)	46 (68)
# of subjects with 0 bleed (%)	14 (41)	8 (24)	22 (32)
# of bleeds	41	65	106
Median ABR (IQR)	1.97 (0.00;3.99)	2.02 (1.93;5.99)	2.00 (0.00;4.15)
Mean ABR (SD)	5.00 (11.85)	3.76 (3.59)	4.38 (8.71)
Mean ABR (95% CI)**	2.65 (1.57;4.46)	3.73 (2.46;5.64)	3.22 (2.36;4.40)

Treated spontaneous bleeds			
# of subjects (%)	6 (18)	7 (21)	13 (19)
# of subjects with 0 bleed (%)	28 (82)	27 (79)	55 (81)
# of bleeds	9	10	19
Median ABR (IQR)	0.00 (0.00;0.00)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)
Mean ABR (SD)	0.58 (0.16;2.12)	0.58 (0.16;2.12)	0.58 (0.16;2.12)
Mean ABR(95% CI)**	0.58 (0.16;2.12)	0.57 (0.17;1.96)	0.58 (0.24;1.40)
Treated traumatic bleeds			
# of subjects (%)	15 (44)	17 (50)	32 (47)
# of subjects with 0 bleed (%)	19 (56)	17 (50)	36 (53)
# of bleeds	20	30	50
Median ABR (IQR)	0.00 (0.00; 2.03)	0.88 (0.00;2.04)	0.00 (0.00;2.03)
Mean ABR (SD)	1.29 (0.74;2.26)	1.72 (1.09;2.71)	1.52 (1.07;2.17)
Mean ABR(95% CI)**	1.29 (0.74;2.26)	1.72 (1.09;2.71)	1.52 (1.07;2.17)
Treated joint bleeds			
# of subjects (%)	7 (21)	12 (35)	19 (28)
# of subjects with 0 bleed (%)	27 (79)	22 (65)	49 (72)
# of bleeds	10	24	34
Median ABR (IQR)	0.00 (0.00;0.00)	0.00 (0.00;2.00)	0.00 (0.00;1.95)
Mean ABR (SD)	0.65 (0.21;1.95)	1.38 (0.67;2.81)	1.03 (0.59;1.81)
Mean ABR(95% CI)**	0.65 (0.21;1.95)	1.38 (0.67;2.81)	1.03 (0.59;1.81)

Source: FDA analysis
*Post-hoc analysis was performed to include non-treatment required bleeds
**Based on Poisson regression model that allows for over-dispersion. Values were provided by the Applicant and confirmed by the statistical reviewer

Reviewer comment: *As expected, the mean ABRs are increased when the analysis includes non-treatment requiring bleeds (4.38 vs. 3.08). The younger age group had the highest mean ABR of 5.00. Although the increases are noticeable, they are within the acceptable range and are comparable with other FDA approved FVIII products; which ranged from 4.9 (6.8) to 7.2 (7.5). (in subset of subjects who were treated twice weekly and were ineligible to be randomized to receive a less frequent treatment regimen). Therefore, the clinical reviewer recommends including the prophylactic dose of 65 IU/kg twice weekly for pediatric subjects in the label.*

Additionally, ABRs during Study 3885 were compared to the historical ABRs for the 12 months prior to inclusion for subjects previously on prophylaxis and on-demand treatment. Overall, the ABRs reported in this study were lower than the historical ABRs measured while on previous FVIII products for the older age group who were on prophylaxis and for the three subjects in the 0-5 years age group who were on on-demand treatment.

Hemostatic effect for treatment of bleeding episodes: A summary of hemostatic responses and success rates for all subjects is presented in Table 29. Out of the 70 bleeding episodes in 39 subjects during the trial, 67 bleeds were rated, while rating of 3 bleeds was missing. The estimated success rate using the logistic regression model for all bleeds (including missing responses as failure) was 82.1% (95% CI: 70.2; 89.9). The observed success rate for all bleeds (including missing responses as failure) was 78.6%. The observed success rate appeared similar in the two age groups. Twenty-nine (43%) subjects reported no bleeding. The total success rate was slightly lower for spontaneous compared with traumatic bleeds. The proportion of successfully treated bleeds that resolved with one injection of ESPEROCT was 63%, and with two injections was 17%. No subject had a re-bleed.

Table 29: Efficacy in Control of Bleeding Episodes by Age group

Age group		< 6 years N=34	6 to < 12 years N=34	0 to < 12 years N=68
# of subjects		34	34	68
# of subjects with bleeds (%)		19 (56)	20 (60)	39 (57)
# of subjects with 0 bleeds (%)		15 (44)	14 (40)	29 (43)
# of bleeds*		30	40	70
# of injections	1-2	76.7%	82.5%	80%
	>2	23.3%	17.5%	20%
Hemostatic response**	Failure	6 (20)	9 (23)	15 (79)
	Success	24 (80)	31 (78)	55 (21)
	Success rate	**82.4%**	**81.5%**	**82.1%**

Source: FDA analysis
* Including treated bleeds only since hemostatic control cannot be assessed for untreated bleeds.
** Including three missing ratings as failure. Success was defined as a response of Excellent or Good.

Reviewer comment: *Hemostatic response using logistic regression accounting for repeated measures within-subject assuming compound symmetry working correlation was performed by the Applicant and was verified by the statistical reviewer.*

Consumption of ESPEROCT per bleeding episode: Overall, 56 out of 70 (80%) bleeding episodes were treated with ≤ 2 injections of ESPEROCT. Two bleeding episodes required six injections:

- Subject (b) (6): 2 years old who was treated for a spontaneous bleeding episode in a target joint (right elbow). The subject was treated with a total of 435 IU/kg during 9 days. The investigator classified the bleeding episode as mild/moderate with a good treatment outcome.
- Subject (b) (6): 5 years old who was treated for a traumatic bleeding episode in the left knee. The subject received 422 IU/kg during 8 days. The investigator classified the bleeding episode as mild/moderate with a moderate treatment outcome.

The per protocol dose level to be used for treatment of a bleeding episode was 20-75 IU/kg. The median dose used to treat a bleed was 61 IU/kg in the 0-5 age group and 67 IU/kg in the 0-5 age group, and 62 IU/kg across all ages. The mean dose used to stop bleeding from start to stop of a bleed was 123 (range: 44.9-436) IU/kg in the 0-5 year age-group and 99 (range: 49.9-296.4) IU/kg in the 6-11 year age-group and 109.3 IU/Kg for all bleeds.

Reviewer comment*: Five subjects (two from 0-5 years age group* (b) (6) *and three from 6-11 age groups (*(b) (6) *received a dose that was more than the per-protocol maximum dose of 75 IU/kg for treatment of bleeding. Doses ranged from 83-99 IU/Kg, excluding Subject* (b) (6) *who was reported in the safety section as having an AE of accidental overdose of 115 IU/kg.*

Reviewer comment: *The Applicant proposes including dosing recommendations for the treatment of bleeds in the label based on the WFH guidelines. In general, labelling recommendations for dosing should be based on clinical trial data. Since the majority of the subjects in the trial did not receive the lower range of the Applicant's proposed dose, the dose range proposed does not represent trial data. Thus, the proposed dose for on-demand treatment will need to be revised to provide a range in dosing based on the median that was observed during the pediatric study. Dose based on WFH or other guidelines should be deferred to the prescriber.*

Consumption of ESPEROCT during prophylaxis: The mean consumption per subject, including prophylaxis, treatment of bleeds, minor surgeries, and PK doses was comparable between the two age-groups, and the total number of prophylaxis injections was 3391, with an average dose of 63.7 IU/kg, which is slightly higher than the per protocol specified dose of 60 U/kg.

Reviewer comment*: Because the average mean dose per subject was 64 IU/Kg in the trial, the clinical reviewer recommends revising the Applicant's proposed dosing of 60 IU/Kg to 65 IU/Kg. This will be reflected in the label.*

PK: Incremental recovery (IR_{60min}) for ESPEROCT was slightly lower in the 0-5 year age-group (0.023 IU/mL) than in the 6-11 year age-group (0.027 IU/mL). The area under the curve (AUC_{0-inf}) measured as IU×h/mL was approximately three-fold higher for ESPEROCT than for previous FVIII product in both age-groups. Additionally, using the population-based method, estimates of t½ were 7.4h for previous FVIII product compared with 14.6h for ESPEROCT. Furthermore, clearance measured as (mL/h/kg) was approximately 2.5-fold higher for previous FVIII product compared with ESPEROCT in both age-groups.

PRO: PROs indicated modest improvement in quality of life as well as in treatment satisfaction.

Reviewer comment: *The significance of the results reported by the Applicant are difficult to interpret as these PROs were not specific for this context of use. Moreover, the quality of life assessment information was not prespecified/validated nor agreed upon with the Agency prior to the BLA submission. Therefore, PROs information will not be included in the label.*

6.3.11.3 Subpopulation Analyses

Although there were notable differences in the ABRs amongst countries, the small number of subjects in some countries makes it challenging to draw any conclusions. Furthermore, the ABR was investigated by race, ethnicity, weight and by body mass index. No apparent differences in the ABRs were observed for these subgroups.

6.3.11.4 Dropouts and/or Discontinuations

At the end of the main phase of the study, a total of five subjects, all in the 0-5 year age-group, had withdrawn: two due to AEs (decrease efficacy), one due to allergic reaction, one due to presence of synovitis (prior to enrollment, but missed at time of screening), and one due to late screen failure (presence of inhibitor prior to enrollment).

6.3.11.5 Exploratory and Post Hoc Analyses

N/A

6.3.12 Safety Analyses

6.3.12.1 Methods

All safety evaluations were based on the safety analysis set, including all 68 dosed subjects; the number of subjects in the safety analysis set was equal to the FAS. Subjects had a total of 3475 EDs during the study. Per subject number of EDs, prophylaxis doses and doses used to treat bleeding episodes were comparable between the two age-groups.

6.3.12.2 Overview of Adverse Events

The primary endpoint was incidence of inhibitory antibodies against FVIII ≥0.6 BU during the main phase of the trial (from 0-26 weeks of treatment). No confirmed FVIII inhibitors were observed during the main phase of the trial.

Adverse events occurring after first ESPEROCT administration were defined as treatment- emergent AEs (TEAEs). Total of 160 AEs were reported in 50 (74%) subjects. The most frequent AEs were upper respiratory tract infections in 7 (10%) subjects and gastroenteritis in 6 (9%) subjects, followed by headache, nasopharyngitis, and cough in 4 (6%) subjects each. See Table 30 for details of TEAEs. The majority of all AEs were evaluated as mild (134 AEs) or moderate (23 AEs). The remaining three AEs were reported as severe for 3 (4%) subjects.

Table 30: Most Common Treatment-Emergent Adverse Events (>1%)

Adverse Events	Subjects N (%)
Upper respiratory tract infection	7 (10%)
Gastroenteritis	6 (9%)
Headache	4 (6%)
Rhinitis	4 (6%)
Nasopharyngitis	4 (6%)
Oropharyngeal pain	4 (6%)
Cough	4 (6%)
Influenza	3 (4%)
Vomiting	3 (4%)
Rhinorrhea	3 (4%)
Eczema	3 (4%)
Nasal congestion	3 (4%)
Pain in extremity	3 (4%)
Contusion	3 (4%)
Varicella	2 (3%)
Pyrexia	2 (3%)
Pneumonia	2 (3%)
Otitis media	2 (3%)
Acute tonsillitis	2 (3%)
Constipation	2 (3%)

Adverse Events	Subjects N (%)
Arthropod sting	2 (3%)
Joint swelling	2 (3%)
Abdominal pain upper	2 (3%)
Hyperthermia	2 (3%)
Erythema	2 (3%)
Ear infection	2 (3%)
Total subjects with AEs	**50 (74%)**
Safety population	**68 (100%)**

Source: FDA analysis

In all, 13 out of 160 AEs (8%) were evaluated by the investigator to be possibly or probably related to trial product. These AEs were predominantly in the 0-5 year age-group (11 AEs reported in 8 subjects) compared with two AEs reported in 2 subjects in the 6-11 year age- group. All of these AEs had resolved by the end of the trial. In three subjects, AEs led to a dose change as follows:

- Subject (b) (6) experienced two AEs after four EDs to ESPEROCT (contusion and hemorrhage) where the dose was first increased and the trial product was subsequently withdrawn permanently. As a consequence, this patient was withdrawn from the trial. Notably, this subject had increased titers of pre-existing anti-PEG antibodies at one visit.
- Subject (b) (6) experienced an AE after three EDs to ESPEROCT (injection site swelling) upon which the dose was reduced. This subject continued in the trial.
- Subject (b) (6) experienced one SAE of hypersensitivity (rash and vomiting without anaphylaxis, which resolved without intervention) after four EDs to ESPEROCT, upon which the trial product was withdrawn permanently. This subject was withdrawn from the trial.

Adverse events occurring before first ESPEROCT administration were defined as non-treatment- emergent events. A total of 28 non-treatment emergent AEs were reported for 20 (29%) subjects. All of these AEs were non-serious and mild or moderate in severity. One non-treatment emergent AE was reported as a MESI for Subject (b) (6) (increased level of FVIII inhibitor prior to ESPEROCT exposure. The subject was a late screening failure).

A total of 4 subjects underwent one minor surgical procedure each during the trial. Two were in the 0-5 year age-group (tooth extraction and emergency circumcision), and two were in the 6-11 year age-group (surgery-suture and port-a-cath removal). One AE was related to the surgery-suture procedure (preferred term: face injury) after 49 EDs and lasted for 8 days. The AE was non-serious and moderate in severity.

6.3.12.3 Deaths

No deaths occurred during the trial.

6.3.12.4 Nonfatal Serious Adverse Events

A total of five SAEs were reported in four (6%) subjects, of which two SAEs ('severe allergic reaction' in Subject (b) (6), and 'increasing hemorrhagic symptoms' in Subject (b) (6) were evaluated as probably related to trial product by the investigator. The

other two subjects experienced SAEs of 'acquired phimosis and encephalitis' in one subject and 'acute tonsillitis' in the other subject.

Reviewer comment: *SAE of hypersensitivity although described as severe by the investigator, the subject only developed vomiting and mild rash in his arms both of which resolved within minutes without intervention. The subject didn't experience any hypotension, angioedema or respiratory symptoms. Hypersensitivity as a potential AE will be included in the W&P section of the label. SAEs of phimosis, encephalitis and tonsillitis were clearly attributable and had competing causes. Therefore, these AEs will not be included in the label.*

6.3.12.5 Adverse Events of Special Interest (AESI)

FVIII inhibitors, allergic reactions (including anaphylactic reactions), thromboembolic events, and medication errors were defined as medical events of special interest (MESIs) in this trial. A total of 13 MESIs were reported for 9 (13%) of the subjects. One of these MESIs was reported as probably related to trial product ('severe allergic reaction' also categorized as an SAE). No thromboembolic events occurred during the trial. Table 31 lists all MESIs.

Table 31: Medical Events of Special Interest

Adverse Event	Subjects N (%)
Accidental overdose	1 (1%)
Anti factor VIII antibody positive	1 (1%)
Anti factor VIII antibody test	1 (1%)
Drug administration error	1 (1%)
Eye allergy	1 (1%)
Eye pruritus	1 (1%)
Hemorrhage	1 (1%)
Hypersensitivity	1 (1%)
Medication error	1 (1%)
Rash	1 (1%)
Total subjects	**9 (13%)**

Source: FDA analysis

Antibodies:

FVIII inhibitors: No confirmed FVIII inhibitors (FVIII inhibitor ≥0.6 BU) were observed during the main phase of the trial. Any subject with a minimum 50 EDs plus any subject with acquired inhibitors was included in the denominator. The 1-sided 97.5% upper confidence limit for the inhibitor incidence rate of zero was 6.7%.

Reviewer comment: *Subject* (b) (6) *was not included as the inhibitor status was positive at inclusion. Furthermore, Subject* (b) (6) *had a positive FVIII inhibitor test at Visit 4 but was negative at the confirmatory inhibitor test. This subject also tested positive for lupus anti-coagulant at subsequent visits.*

N8-GP Binding Antibodies (Non-neutralizing): Three subjects tested positive for binding antibodies:

- Subject (b) (6) was positive for anti-N8-GP binding antibodies before the first ESPEROCT exposure and throughout his trial participation with a titer of 4. This subject was a late screening failure.
- Subject (b) (6) was positive for anti-N8-GP binding antibodies before the first ESPEROCT exposure and throughout the trial with a titer of 1.
- Subject (b) (6) was positive with a titer of 1 for binding antibodies only at Visit 5 after 27 EDs.

Reviewer comment: *All confirmed anti-N8-GP binding antibodies were found to cross-react with recombinant FVIII. Subjects* (b) (6) *and* (b) (6) *both had adequate and expected FVIII activity levels 30 min post dosing, confirming that the anti-N8-GP binding antibodies were non-neutralizing.*

Anti-PEG antibodies: A total of 21 (31%) subjects were positive for anti-PEG antibodies prior to first ESPEROCT exposure. Of the 21 subjects with pre-existing anti-PEG antibodies 18 were measured with titers at or below 2. The remaining 3 subjects had titers between 4 and 8. Three subjects (b) (6) developed low-titer (≤2) anti-PEG antibodies after ESPEROCT exposure. In addition, subject (b) (6) had one positive anti-PEG antibody test (titer of 4) at an unscheduled visit. This subject had positive pre-existing low-titer antibodies (titer <1) at baseline and was discontinued from the trial due to an adverse event of increased bleeding.

Reviewer comment*: In order to investigate the impact of anti-PEG antibodies on PK profiles, subjects who underwent PK sessions at Visit 1 and 2 were categorized in two sub-groups according to their anti-PEG antibody status (positive / negative) prior to ESPEROCT dosing. No apparent differences in PK profiles were observed for ESPEROCT as well as for previous product.*

Two subjects in the 0-5 year age-group had low FVIII activity after 20h post dosing: One was a subject ((b) (6) *who was a late screening failure. The other was a subject (*(b) (6) *who was not included in the analysis due to low exposure at Visit 2 but normal at all other visits.*

6.3.12.6 Clinical Test Results

Standard laboratory panels for hematology, biochemistry and coagulation-related parameters were measured over time.

No clinically relevant abnormalities in laboratory parameters that had an impact on the results and conclusions of the trial were observed. The two reported AEs related to elevated anti factor VIII antibodies are presented in Table 31.

Reviewer comment*: Overall, none of the observed abnormalities were considered clinically relevant and were expected for the patient population.*

6.3.12.7 Dropouts and/or Discontinuations

A total of Five subjects, all in the 0-5 year age-group, had withdrawn from the study as follows:

- Two subjects due to AEs
  - Subject (b) (6) was a 4 year old male who experienced increased joint bleeding and low FVIII activity post treatment with the study drug. He received 8 EDs before he discontinued from the study. FVIII level was <1% at 24hrs post dosing, but no FVIII inhibitors and anti- N8-GP binding antibodies were identified. Low titer anti-PEG antibodies were measured before starting treatment with ESPEROCT as well as after exposure (titer increased to 4). Potential reasons such as increased clearance or incomplete trial product administration could not be ruled out.
  - Subject (b) (6) was a 4 year old who experienced lower extremity joint bleeding and swelling and was withdrawn from the trial after 7 weeks (8 EDs for prophylaxis, including 2 EDs related to treatment of bleeds), as ESPEROCT was not considered as adequately preventing bleeds. FVIII inhibitors and anti-N8-GP binding antibodies were negative. Pre-existing, low-titer anti-PEG antibodies were measured (titer <1 at both Visit 1 and 2) prior to exposure with ESPEROCT.
- One subject (b) (6) withdrew due to allergic reaction. The subject was a 3 year old who experienced mild followed by severe allergic reactions (vomiting and mild rash) after four EDs.
- Two subjects due to 'other' reasons as outlined below:
  - Subject (b) (6) was a 4 year old male who withdrew from the study after two ED due to receiving high dose treatment for synovitis. The subject had prior problems with the same joint which was not documented initially in his medical record.
  - Subject (b) (6): was a 5 year old who discontinued from the trial after 27 EDs. The subject was erroneously enrolled in the trial due to presence of FVIII inhibitor prior to receiving the study drug. The inhibitor test was negative at the screening visit but was transiently positive subsequently. This was considered a late screening failure.

6.3.13 Study Summary and Conclusions

The hemostatic effect of ESPEROCT used for treatment of bleeding episodes was confirmed by a success rate of 82.1%. Prophylactic protection of ESPEROCT was demonstrated by a median ABR (IQR) of 2.99 (0.00, 4.15) and a mean (SD) ABR of 4.38 (8.71) for all bleeds, and median ABR (IQR) of 1.95 (0.00, 2.79) and a mean (SD) ABR of 3.08 (7.13) for treated bleeds. Population-based estimates of terminal half-life were 7.4h for previous FVIII product compared with 14.6h for ESPEROCT.

Most AEs were mild or moderate. No confirmed inhibitory antibodies were observed during the trial. Two subjects discontinued from the study due to AEs of increased bleeding due to ineffective therapy with ESPEROCT. One of these subjects was positive for anti-PEG antibodies. An allergic reaction occurred in one subject in the trial and will be included in the W&P section of the label. There was no apparent association between PEG-antibodies, allergic reaction and loss of efficacy. Overall, no specific safety signal was identified.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication # Routine prophylaxis

7.1.1 Methods of Integration

Integration of the pediatric study data with the adult and adolescent data was not done because of the different study design and treatment regimen in the two studies. Integration is challenging, therefore, the data are summarized and presented separately for each study, the goal being that the data from the different studies for the same indication are presented in the same section. The studies discussed below are Study 3859 and Study 3885.

7.1.2 Demographics and Baseline Characteristics

Across all clinical studies, all subjects were male. The median age in the adult/adolescent studies was 29 years of age. The median age in the pediatric study was 6 years of age. The predominant races represented were White and Asian. See Table 1 in Section 1.1 for details.

Reviewer comment: *no relevant differences were noted in baseline characteristics between adults and children except for age.*

7.1.3 Subject Disposition

A total of 254 PTPs were included in the integrated efficacy analysis. Of these, 228 (90%) subjects completed the main part of the trials. When including data from ongoing extension studies, a total of 56 (22%) subjects discontinued; 7 (3%) due to AEs, 5 (2%) due to lack of efficacy, and 29 (11%) due to meeting the withdrawal criteria. Some subjects withdrew due to logistical reasons. Of the 7 withdrawals due to AEs, three AEs were judged to be probably related to treatment which included FVIII inhibitor in one subject and increased bleeding and loss of efficacy in another subject. One death in a 67 years old subject with pancreatic cancer was reported and was judged to be unlikely related to ESPEROCT.

7.1.4 Analysis of Primary Endpoint(s)

Summary of efficacy for routine prophylaxis is presented in Table 32 across the different age groups. Data are only summarized side by side and are not integrated due to different dosing regimen that were used in the two different studies. A markedly lower ABR was noticed for all prophylaxis regimens in comparison to the on-demand group. The median ABR for treated bleeds was 1.18 for the 12-70 years old age group and 1.95 for subjects 0-11 years of age, and was comparable to the ABR when non-treated bleeds were included. The mean ABR was 3.00 in subjects 12-70 years old, and 3.08 for 0-11 years old subjects. The mean ABR increased to 3.26 and 4.38, respectively when all bleeds were included in the calculation (treated and non-treated). Forty one percent (41%) of 243 prophylaxis subjects did not experience any bleeds that required treatment with ESPEROCT and 37% did not experience any bleeds.

Table 32: Summary of Efficacy for Prophylaxis in Studies 3859 and 3885

	Prophylaxis*				On-demand
Age Range	**0-6 years**	**6-11 years**	**0-11 years**	**12–70 years**	**18–70 years**
# of subjects	**N=34**	**N=34**	**N=68**	**N=175**	**N=12**
Mean treatment duration (years)	0.46	0.51	0.48	0.82	1.33
Treated bleeds					
# of subjects (%)	19 (56)	20 (59)	39 (57)	105 (60)	12 (100)
# of subjects with 0 bleed (%)	15 (44)	14 (41)	29 (43)	70 (40)	0
# of bleeds	30	40	70	436	532
Median ABR (IQR)	1.94 (0.00;2.08)	1.97 (0.00;3.91)	1.95 (0.00;2.79)	1.18 (0.00;4.25)	30.87 (18.64;38.51)
Mean ABR (SD)	3.87 (9.68)	2.29 (2.86)	3.08 (7.13)	3.00 (4.66)	31.90 (19.08)
All bleeds (treated & non-treated)					
# of subjects (%)	20 (59)	26 (77)	46 (68)	107 (61)	12 (100)
# of subjects with 0 bleed (%)	14 (41)	8 (24)	22 (32)	68 (39)	0
# of bleeds	41	65	106	458	536
Median ABR (IQR)	1.97 (0.00;3.99)	2.02 (1.93;5.99)	2.00 (0.00;4.15)	1.20 (0.00;4.73)	31.25 (18.64;38.90)
Mean ABR (SD)	5.00 (11.85)	3.76 (3.59)	4.38 (8.71)	3.26 (4.92)	32.15 (19.12)

Source: FDA analysis
*Prophylaxis regimen was 50-75 IU/Kg twice weekly for the pediatric age group <12 and 50 IU/Kg Q4D for subjects ≥12 years of age.

7.1.5 Analysis of Secondary Endpoint(s)

N/A

7.1.6 Other Endpoints

N/A

7.1.7 Subpopulations

See discussion above regarding the pediatric subjects.

7.1.8 Persistence of Efficacy

The persistence of efficacy over time is anticipated with the study drug and has been demonstrated in the extension studies.

7.1.9 Product-Product Interactions

N/A

7.1.10 Additional Efficacy Issues/Analyses

N/A

7.1.11 Efficacy Conclusions

Overall, prophylactic infusion with ESPEROCT was effective for prevention of bleeds at dose intervals of every 4 days, as compared with a non-randomized control group of subjects receiving on-demand treatment. ESPEROCT was efficacious across all age groups (pediatric and adults). All pediatric subjects were treated with a prophylaxis regimen and had an overall slightly higher ABR (particularly subjects less than 6 years of age) compared to adults subjects. However, ABRs for all age groups were comparable to other FDA approved FVIII products.

7.2 Indication #2: Perioperative management

Trial #2 Section 6.2 discusses perioperative management. There were no other studies assessing perioperative management, as such integration is not applicable.

7.2.1 Methods of Integration

N/A

7.2.2 Demographics and Baseline Characteristics

N/A

7.2.3 Subject Disposition

N/A

7.2.4 Analysis of Primary Endpoint(s)

N/A

7.2.5 Analysis of Secondary Endpoint(s)

N/A

7.2.6 Other Endpoints

N/A

7.2.7 Subpopulations

N/A

7.2.8 Persistence of Efficacy

N/A

7.2.9 Product-Product Interactions

N/A

7.2.10 Additional Efficacy Issues/Analyses

N/A

7.2.11 Efficacy Conclusions

See above.

7.3 Indication #3: On-demand treatment and control of bleeding episodes

Method of integration, study population and disposition are the same as described in the routine prophylaxis indication in section 7.1

7.3.1 Methods of Integration

See above.

7.3.2 Demographics and Baseline Characteristics

See above.

7.3.3 Subject Disposition

See above.

7.3.4 Analysis of Primary Endpoint(s)

There were 1506 bleeds reported in 171 of 254 subjects across the completed clinical trials (3859 Main and Ext 1 and 3885 Mani). The most common bleed types were joint (65.2%), muscle (14.5%), and subcutaneous (8.9%). Of the 1506 bleeds, 1314 (87.2%) were rated excellent or good in their response to ESPEROCT, 167 (11.1%) were moderate, six (0.4%) were rated as having no improvement, and for 19 (1.3%) the response to treatment was missing. Doses used for treatment of bleeding episodes depended on the severity of the bleed. The median dose to treat a bleeding episode was 52.1 IU/kg across all age groups; 94% of the bleeds were resolved with 1-2 injections of ESPEROCT and 80% were resolved with one injection.

See Table 33 for details.

Table 33: Summary of Efficacy in Control of Bleeding Episodes by Age for Studies: 3859 Main + Ext 1 and Study 3885 main:

Age range # of subjects		**0-5 years N=34**	**6-11 years N=34**	**12-17 years N=25**	**≥ 18 years N=161**
# of bleeds		30	40	112	1324
# of injections	1–2	76.7%	82.5%	88.4%	95.5%
	> 2	23.3%	17.5%	11.6%	4.5%
Response to first treatment	Excellent/ Good	80.0%	77.5%	75%	88.7%
	Moderate	13.3%	17.5%	17.9%	10.3%
	None	3.3%	0.0%	0.0%	0.4%
	Missing	3.3%	5.0%	7.1%	0.6%

Source: FDA analysis Adapted from BLA 125671; Module 2.7.3 Summary of clinical efficacy

When including data from all clinical trials (including the ongoing extension studies), there were 2,766 bleeds reported in 203 of 254 subjects. The most common bleed types were joint (63%), muscle (13%), and subcutaneous (12%). Of the 2,766 bleeds, 2,427 (88%) were rated excellent or good in their response to ESPEROCT, 278 (10%) were moderate, 12 (1%) were rated as having no improvement, and for 49 (2%) the response to treatment was missing.

See Table 34 for details.

Table 34: Summary of Efficacy in Control of Bleeding Episodes by Age Across All studies (Including Ongoing Extensions)

Age range # of subjects		**0-5 years N=34**	**6-11 years N=34**	**12-17 years N=25**	**≥ 18 years N=161**
# of bleeds		90	192	168	2316
# of injections	1 – 2	86.7%	89.1%	90.5%	95.4%
	> 2	13.3%	10.9%	9.5%	4.6%
Response to first treatment	Excellent/ Good	86.7%	76.6%	76.8%	89.5%
	Moderate	8.9%	19.3%	17.9%	8.8%
	None	2.2%	1.0%	0.0%	0.3%
	Missing	2.2%	3.1%	5.4%	1.4%

Source: FDA analysis Adapted from BLA 125671/0; Module 2.7.3 Summary of clinical efficacy

Reviewer comment: *Because the extension studies are not completed yet, Table 33 includes data from the completed studies only.*

7.3.5 Analysis of Secondary Endpoint(s)

N/A

7.3.6 Other Endpoints

N/A

7.3.7 Subpopulations

N/A

7.3.8 Persistence of Efficacy

N/A

7.3.9 Product-Product Interactions

N/A

7.3.10 Additional Efficacy Issues/Analyses

N/A

7.3.11 Efficacy Conclusions

The submitted data demonstrate that on-demand treatment with ESPEROCT was effective for treatment of bleeds at dose regimens of 20-75 IU/Kg. Pediatric subjects required higher doses as compared to adults.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The safety was evaluated in 270 subjects (202 adults/adolescents and 68 children).

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Safety was evaluated in five prospective, multi-center clinical studies in PTPs with severe HA and no history of inhibitors. All subjects received at least one dose of ESPEROCT. Total exposure to ESPEROCT was 80,425 exposure days corresponding to 889 subjects years of treatment.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

No relevant differences were noted in baseline characteristics of the safety population between adults and children except for age.

8.2.3 Categorization of Adverse Events

N/A

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Although the results across all studies were pooled, the study designs were different.

8.4 Safety Results

8.4.1 Deaths

One adult subject died of pancreatic carcinoma, which was unlikely related to ESPEROCT.

8.4.2 Nonfatal Serious Adverse Events

SAEs occurred in 47 (17%) of subjects.

8.4.3 Study Dropouts/Discontinuations

Five subjects were withdrawn from Study 3859 and two subjects were withdrawn from Study 3885 due to AEs. In addition, two subjects were withdrawn because they met a withdrawal criterion related to safety; one subjects due to high titer FVIII inhibitor and one subject due to allergic reaction related to ESPEROCT.

8.4.4 Common Adverse Events

Data were pooled across the non-surgical studies: 3776, 3859, 4033 and 3885. A total of 2307 AEs were reported in 239 (89%) subjects. The most commonly reported AEs were viral upper respiratory tract infection (130 events in 78 [29%] subjects), upper respiratory tract infection (105 events in 57 [21%] subjects), headache (118 events in 56 [21%] subjects), arthralgia (66 events in 43 [16%] subjects), cough (53 events in

37 [14%] subjects), diarrhea (39 events in 31 [12%] subjects) and influenza (42 events in 29 [11%] subjects). Adverse reactions occurred at a rate of 0.10 events per subject year of exposure. The most frequently reported adverse reactions were rash in 14 (5.2%) subjects, injection site reaction in seven (2.6%) subjects, erythema in five (1.9%) subjects, and pruritus in four (1.5%) subjects, which will be included in the label.

Reviewer comment: *Overall, the AE pattern was considered typical for PTPs, and adverse reactions were also considered expected in the patient population. Injection site reactions include the preferred terms: infusion site reaction, injection site reaction, injection site erythema, injection site rash, vessel puncture site hematoma, vessel puncture site pain and injection site swelling.*

8.4.5 Clinical Test Results

Overall, no clinically relevant changes associated with exposure to ESPEROCT have been observed for laboratory parameters. Several subjects had elevated hepatic enzymes, and some of these were reported as AEs. However, the findings did not give rise to any safety concern because the majority of these AEs were low grade and transient and occurred in subjects with pre-existing hepatitis B or C. Estimated glomerular filtration rate was calculated in connection with safety assessments related to PEG. No safety concern was identified.

8.4.6 Systemic Adverse Events

N/A.

8.4.7 Local Reactogenicity

See section 8.4.4.

8.4.8 Adverse Events of Special Interest

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. See Table 35 for details regarding immunogenicity. No thromboembolic event occurred during the clinical trials.

Table 35: Immunogenicity

	3776 N=26	**3859 N=186**	**3885 N=68**	**All studies N=270**
Confirmatory Anti-CHO HCP antibodies	0 (0%)	7 (4%)	4 (6%)	11 (4%)
Confirmatory anti-PEG antibodies	0 (0%)	23 (12%)	22 (32%)	45 (17%)
Confirmatory binding anti N8-GP	1 (4%)	5 (3%)	3 (4%)	9 (3%)
Cross-reacting anti N8	1 (4%)	5 (3%)	3 (4%)	9 (3%)
FVIII Inhibitor (BU)	1 (4%)	1 (1%)*	3 (4%)	5 (2%)
Total Subjects	**1 (4%)**	**34 (18%)**	**28 (41%)**	**270 (100%)**

Source: FDA analysis
* Confirmed FVIII High titer inhibitor.

***Reviewer comments**: Four subjects ((b) (6) , and (b) (6) had low titer inhibitors. Two subjects had one single positive result that disappeared within 2 weeks with no clinical consequences and they stayed in the trial:*

- (b) (6) *(1.0 BU* (b) (6) *and negative since* (b) (6) *)*
- (b) (6) *(1.1 BU* (b) (6) *and negative since* (b) (6)

Two subjects had pre-existing low positive titers (i.e., they were late screening failures) and they were withdrawn from the trials: (b) (6)

When considering the number of subjects at risk (denominator) for FVIII inhibitors, subjects who have a minimum of 50 EDs to ESPEROCT or who have confirmed FVIII inhibitors regardless the number of EDs, the incidence of FVIII inhibitors remains low at 0.4%. Except for the confirmed high titer FVIII inhibitory antibody, all other antibodies had no clinical consequence and no AEs were reported at the time of the positive results.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

N/A

8.5.2 Time Dependency for Adverse Events

N/A

8.5.3 Product-Demographic Interactions

N/A

8.5.4 Product-Disease Interactions

N/A

8.5.5 Product-Product Interactions

N/A

8.5.6 Human Carcinogenicity

N/A

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

During the clinical trials, overdoses up to 114 IU/kg have been reported, resulting in a FVIII activity level of 285% post overdose. No symptoms associated with overdoses have been reported, thus not considered a safety concern. While no specific studies have been conducted, ESPEROCT is not expected to have abuse potential. No cases of abuse have been reported.

8.5.8 Immunogenicity (Safety)

See Section 8.4.8 above. In the 120 Day safety follow-up report, no subjects were reported to have developed FVIII inhibitors (≥0.6 BU) since the data cut-off date for the original BLA in studies 3859, 3885 and 3860.

8.5.9 Person-to-Person Transmission, Shedding

N/A

8.6 Safety Conclusions

Factor VIII inhibitor development was observed in the safety evaluable population. No deaths related to ESPEROCT occurred. One adult subject died of pancreatic cancer which is considered by the reviewer as unlikely related to ESPEROCT. No anaphylactic allergic reactions were observed, and no clinical consequence of PEG antibodies were noted. Pre-clinical studies do not raise concerns related to PEG accumulation in the brain or renal tissues. The safety profile of ESPEROCT for the proposed indications is favorable.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Animal reproduction studies have not been conducted with ESPEROCT. Based on the rare occurrence of HA in women, experience regarding the use of FVIII during pregnancy and breastfeeding is not available.

9.1.2 Use During Lactation

It is not known if ESPEROCT is excreted in human milk.

9.1.3 Pediatric Use and PREA Considerations

The applicant completed efficacy and safety evaluations in pediatric studies across all age groups: 34 subjects 0-5 years, 34 subjects 6-11 years and 25 subjects 12-17 years of age. The indication will include adult and pediatric age groups. No deferrals or waivers are being granted and are not warranted as the studies were already conducted.

9.1.4 Immunocompromised Patients

N/A

9.1.5 Geriatric Use

N/A

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

N/A

10. CONCLUSIONS

Overall, ESPEROCT demonstrated efficacy in adults and children for on-demand treatment to control bleeding episodes, perioperative management of bleeding and routine prophylaxis. Due to the potential for selection bias in subjects who were randomized to the 7-day dosing regimen and increased bleeding requiring increasing dose of frequency in 9 of 38 subjects, this dosing regimen is not recommended. Treatment related FVIII inhibitor developed in one (0.4%) subject and allergic reactions occurred. No treatment related deaths were observed. No safety signals were observed in the safety evaluable pediatric, adolescent and adult subjects.

FVIII inhibitors and allergic reactions will be communicated in the Warnings and Precautions Sections of the label.

ESPEROCT is being approved for the following indications in adults and children:

- On demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Insert table number and title here

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hemophilia A is a rare hereditary bleeding disorder characterized by recurrent bleeding which if untreated leads to synovitis, chronic arthropathy, muscular atrophy and deformities. • Treatment of bleeds may delay these complications but does not prevent them. • Primary prophylaxis with regular factor VIII (FVIII) injections initiated at an early age is now the standard of care for patients with severe hemophilia A. • The frequency of bleeding in hemophilia A is generally inversely correlated with the FVIII activity level.	• Hemophilia A is a hereditary, serious and life-threatening disease. • Hemophilia A can have a debilitating impact on physical and psychosocial well-being.
Unmet Medical Need	• There are several FVIII products licensed by FDA, both recombinant and plasma-derived. Two of these are extended half-life FVIII products and one is pegylated. • Plasma-derived products carry a potential risk of transmission of infection; all products carry the risks of inhibitor formation leading to ineffective therapy and hypersensitivity.	• Development of products with greater incremental recovery, good hemostatic coverage and extended half-life is desirable. • Less frequent injections may reduce the burden of treatment.
Clinical Benefit	• ESPEROCT has demonstrated a half-life 1.6 times longer than nonmodified FVIII products; the PEG moiety confers this extended half-life. • Three trials to evaluate the efficacy of ESPEROCT in 254 adults and children were provided. The efficacy ESPEROCT was demonstrated for treatment of and prevention of spontaneous or traumatic bleeding in patients with Hemophilia A. • ESPEROCT was effective in the perioperative setting for reduction of bleeding during surgery.	• The evidence for clinical benefit is shown in reduction of bleeds.
Risk	• The identified risks of FVIII replacement therapy are the development of FVIII inhibitors and allergic reactions. • In the ESPEROCT clinical trials, one previously treated patient developed FVIII inhibitors. • Allergic reactions were recorded. Of 270 subjects evaluated for safety, the following adverse drug reactions occurred: rash (5.2%), erythema (1.9%), pruritus (1.5%) and hypersensitivity (0.7%). • Injection site reactions were reported in 2.6% of the subjects. All events were of mild or moderate severity and resolved without sequelae.	• The risk of inhibitor development and allergic reactions is comparable to other FVIII products. • ESPEROCT was well tolerated with no unexpected safety issues. • No clinical or non-clinical indication of PEG-related side effects was observed.
Risk Management	• The most substantial risks of treatment with ESPEROCT are the development of FVIII inhibitors and hypersensitivity. • A study in previously untreated patients (PUP) is ongoing.	• The package insert and routine pharmacovigilance activities are adequate to manage risk. • The PUP study will provide information in another patient population.

11.2 Risk-Benefit Summary and Assessment

The benefits of ESPEROCT include:

- On-demand ESPEROCT is effective for treatment of and prevention of spontaneous or traumatic bleeding in patients with Hemophilia A
- ESPEROCT is effective in the perioperative setting for reduction of bleeding during surgery.
- ESPEROCT demonstrated clinical benefit in all age groups.

The risks of ESPEROCT include:

- FVIII inhibitory antibodies development. The risk of development of inhibitory antibodies is considered an expected adverse event.

The results from the phase 3 trials demonstrated that ESPEROCT is safe and effective in adults and children with hemophilia A. The median and mean ABRs were acceptable for the patient population and were comparable to other FDA approved FVIII products. Effective treatment of bleeds was achieved, and surgical bleeding was well controlled. However, given the number of subjects who required rescue treatment and change to a more frequent dosing and the potential for selection bias for subjects who were selected for randomization, the every 7 day prophylaxis regimen is not recommended. Finally, the safety profile of ESPEROCT was similar to what is known and expected for this class of product. Thus, the benefit risk profile of ESPEROCT is considered favorable.

11.3 Discussion of Regulatory Options

The available data support approval of the indication for on-demand treatment and control of bleeding episodes, peri-operative management, and routine prophylaxis for adults and children with hemophilia A.

11.4 Recommendations on Regulatory Actions

Traditional approval for the on-demand treatment and control of bleeding episodes, peri-operative management, and routine prophylaxis indication is recommended for adults and children.

11.5 Labeling Review and Recommendations

The revised package insert (PI) was reviewed, commented, and revised by the appropriate discipline reviewers. APLB conducted its review from a promotional and comprehension perspective. Labeling issues have successfully been resolved with the Applicant.

11.6 Recommendations on Postmarketing Actions

The Applicant has proposed a phase 4 interventional, open label, non-controlled study of at least 25 previously treated male patients $\geq$12 years of age with severe hemophilia A. This study is being undertaken to meet the target of 200 patients achieving 100 exposure days, as required by the EMA, but not FDA. No PMR or PMC studies are requested at this time.

INSERT FIRST **APPENDIX HEADING HERE**

Insert text here

Do Not Change Anything Below This Line