



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research**

MEMORANDUM

Date: 28 March 2013

From: Wambui Chege, MD
Medical Officer, Therapeutics and Blood Safety Branch

Re: STN 125466\0

Through: Christopher Jankosky, MD, MPH
Branch Chief, Therapeutics and Blood Safety Branch

David Martin, MD, MPH
Director, Division of Epidemiology

Product: NovoEight (turoctocog alfa)

Subject: Biologics License Application

Sponsor: NovoNordisk

1. INTRODUCTION

On 15 October 2012, Novo Nordisk submitted an original Biologics License Application (BLA, 125466/0) to the Food and Drug Administration (FDA) for NovoEight (turoctocog alfa) – a B-domain deleted recombinant Factor VIII (BDDrFVIII) product synthesized in Chinese Hamster Ovary (CHO) cells and without the use of human serum or other animal-derived components. The product is purified using murine immunoglobulin G (IgG). Early in its development the product was called N8. For purposes of clarity it will be referred to in this memorandum by its current name – NovoEight.

The sponsor proposes the following indications for NovoEight:

- Control and prevention of bleeding episodes in adults, adolescents and children with hemophilia A
- Perioperative management of patients with hemophilia A
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults, adolescents and children

NovoEight will be supplied as a lyophilized powder in single-dose vials with a prefilled syringe of the diluent, 0.9% saline. The product will be supplied in six different strengths - 250, 500, 1000, 1500, 2000 or 3000 International Units (IU) per vial.

1.1 BDDrFVIII products – the newest subset of the class

BDDrFVIII products are the newest subset of Factor VIII (FVIII) products and are used in the treatment of hemophilia A. The B-domain is a large central region of the human FVIII glycoprotein which links two biologically active domains. In BDDrFVIII products, the B-domain is replaced with a short amino acid sequence that links the two biologically active 90-kd and 80-kd domains. An intact full length B-domain is thought to be non-essential for hemostatic effect as both recombinant and plasma-derived FVIII products lacking the B-domain have been shown to be effective in coagulation.¹ Deletion of the B-domain reduces the size of the glycoprotein resulting in greater ease of manufacturing. In addition, it is thought that deletion of the B-domain confers greater stability on the smaller molecule, eliminating the need for human albumin as a stabilizer and thus reducing the risk of transmission of viral pathogens.²

The first BDDrFVIII product – ReFacto, was produced by Wyeth and licensed by the FDA on 6 March 2000. Wyeth improved on ReFacto by eliminating human albumin from the manufacturing process and by using CHO cells grown in the absence of human or animal derivatives. This improved product was named Xyntha and was approved by the FDA on 21 February 2008. Following Xyntha's approval by the FDA, Wyeth reported their intention for Xyntha to replace ReFacto in the US market, while marketing a similar product ReFacto AF in Europe. Currently Xyntha is the only BDDrFVIII product marketed in the US. Should NovoEight be licensed by the FDA, it would be the second BDDrFVIII product marketed in the US. Unlike Xyntha, where the B-domain is truncated to a -----(b)(4)----- linker, in NovoEight the B-domain is replaced by a 21 amino acid sequence.

1.2 Known Safety Concerns and Historical Evolution to BDDrFVIII products

Known safety concerns for the class of FVIII products – particularly infectivity and immunogenicity – have led to changes in the manufacture of these products over time, culminating in the development of BDDrFVIII products, the newest products in the class. This evolution in the manufacture of FVIII products is summarized in Table 1 below and the safety concerns of infectivity and immunogenicity are described in sections 1.2.1 and 1.2.2 below respectively.

Table 1. Summary Timeline of Historical Evolution to BDDrFVIII products ^{1, 2, 3, 4}

Date	Event	
1960s	Plasma-derived FVIII concentrates become commercially available.	
1980s	HIV epidemic results in viral contamination of plasma-derived products and widespread infection of more than half of all hemophiliacs with HIV. ³	
1990s	Recombinant FVIII products become commercially available and are a popular alternative to plasma-derived concentrates due to the reduced risk of viral transmission. Each generation of recombinant products aims to further reduce the risk of transmission of viral pathogens as follows:	
	1 st Generation:	Recombinant product produced in hamster cells, use human albumin as a stabilizer
	2 nd Generation:	Recombinant product produced in hamster cells, eliminate human albumin as a stabilizer utilizing sterile laboratory-produced stabilizers such as a combination of sucrose and one or more amino acids
	3 rd Generation:	Recombinant product produced in hamster cells which are cultured in the absence of human and animal proteins, utilize sterile laboratory-produced stabilizers such as a combination of one or more sugars, amino acids and /or peptides.
2000	The first BDDrFVIII product ReFacto is licensed by FDA. Elimination of the B-domain results in ease of manufacturing and the production of a smaller stable molecule that is as effective in coagulation as full length products.	
2008	Xyntha – a BDDrFVIII albumin-free cell culture product is licensed by FDA and replaces ReFacto in the US market.	
2012	NovoNordisk submits an original BLA for NovoEight – a BDDrFVIII product	

1.2.1 Transmission of infectious pathogens

Successive generations of FVIII products have sought to reduce the risk of transmission of viral pathogens by moving from plasma-derived to recombinant products and by minimizing the use of human or animal proteins in the manufacturing process (Table 1).

As with other recombinant products, BDDrFVIII products seek to offer a lower risk of transmission of viral pathogens than plasma-derived products. Like Xyntha, the only BDDrFVIII product currently marketed in the US, Novo Eight will be a 3rd generation recombinant FVIII product – that is, a recombinant product manufactured in the absence of human and other animal derived-components to reduce the risk of transmission of infectious pathogens.

1.2.2 Immunogenicity – FVIII inhibitors and Antibodies to non-human proteins

A search of the published literature reveals no published studies evaluating the immunogenicity of NovoEight. However, published studies sponsored by Wyeth have evaluated the currently licensed Wyeth BDDrFVIII products for immunogenicity with regard to the development of both FVIII inhibitors and antibodies to non-human proteins. These studies are summarized in sections 1.2.2.1 and 1.2.2.2 below.

1.2.2.1 FVIII inhibitors

The development of FVIII inhibitors has long been recognized as a safety concern for the class of FVIII products. While the etiology of the development of inhibitors to FVIII has not been fully elucidated, it is thought to result from a host alloimmune response to infusions of FVIII.

Deletion of the B-domain results in a novel peptide sequence not found in plasma-derived FVIII. Early concerns that this novel sequence might function as an antigenic epitope and provoke increased production of antibodies to the BDDrFVIII molecule have not been borne out in clinical studies. An open-label observational study followed 113 severe hemophiliacs who were previously treated patients (PTPs) for a period ranging from 12 months up to 5 years and found

an incidence of inhibitor formation of 0.9% following the use of BDDrFVIII products, consistent with that reported for full-length recombinant and plasma derived FVIII products.⁵ A similar study evaluated previously untreated patients (PUPs). In an open-label multicenter study, 101 PUPS received prophylactic and/or treatment doses of BDDrFVIII products for a period ranging from 50 exposure days (ED) up to 5 years. Thirty-two percent of patients developed inhibitors, a rate comparable to that seen with full-length recombinant products.⁶

1.2.2.2 Antibodies to non-human proteins

Another more recent safety concern has been the detection of antibodies to non-human proteins in subjects treated with recombinant biologics. It appears for instance, that even minor amounts of CHO proteins in the final formulation of therapeutics can potentially stimulate an immune response. The clinical significance of the presence of these antibodies is unclear. It has however been suggested that any regions of these mammalian proteins that are homologous to human sequences may stimulate an immune response resulting in inhibition of the active pharmaceutical ingredient and perhaps diminish both the safety and efficacy of the final recombinant product.⁷

To evaluate this particular safety concern, a recent study has evaluated the development of both FVIII inhibitors and antibodies to specific molecules used in the manufacture of Xyntha, the BDDrFVIII product currently licensed in the US. In an open-label observational study, 94 PTPs with severe or moderately severe hemophilia were followed for 6 months with samples collected at 0, 1, 3 and 6 months for inhibitor testing. Only 2 of 94 participants (2.1%) developed low titer transient FVIII inhibitors with no clinical sequelae. In addition, testing of all participants was negative for the presence of antibodies to CHO proteins or TN8.2, a synthetic peptide ligand used in the manufacturing process.⁸

In summary, the available published literature suggests that evaluation of BDDrFVIII products for known safety concerns for the class of FVIII products, such as risk of infection and immunogenicity, indicate that the safety profile of BDDrFVIII products is comparable to or better than that of other products in the class. Safety related information specific to NovoEight, the particular BDDrFVIII product for which this BLA is submitted, is reviewed in detail in section 3 below.

2. OBJECTIVES

The purpose of this memorandum is to review the available safety related literature for NovoEight. In addition to the Pharmacovigilance Plan (PVP) submitted by the sponsor as part of the Risk Management Plan (RMP), study reports of 3 prelicensure clinical trials, a summary safety report and 2 protocols for planned future studies were also reviewed. A search of Pubmed.gov and Clinicaltrials.gov for published literature with safety related endpoints using the search terms “safety” and “NovoEight”, “N8” or “turoctocog” revealed no additional documents to review. Materials reviewed as part of this comprehensive safety review are listed in Table 2 below.

Table 2. Materials Reviewed

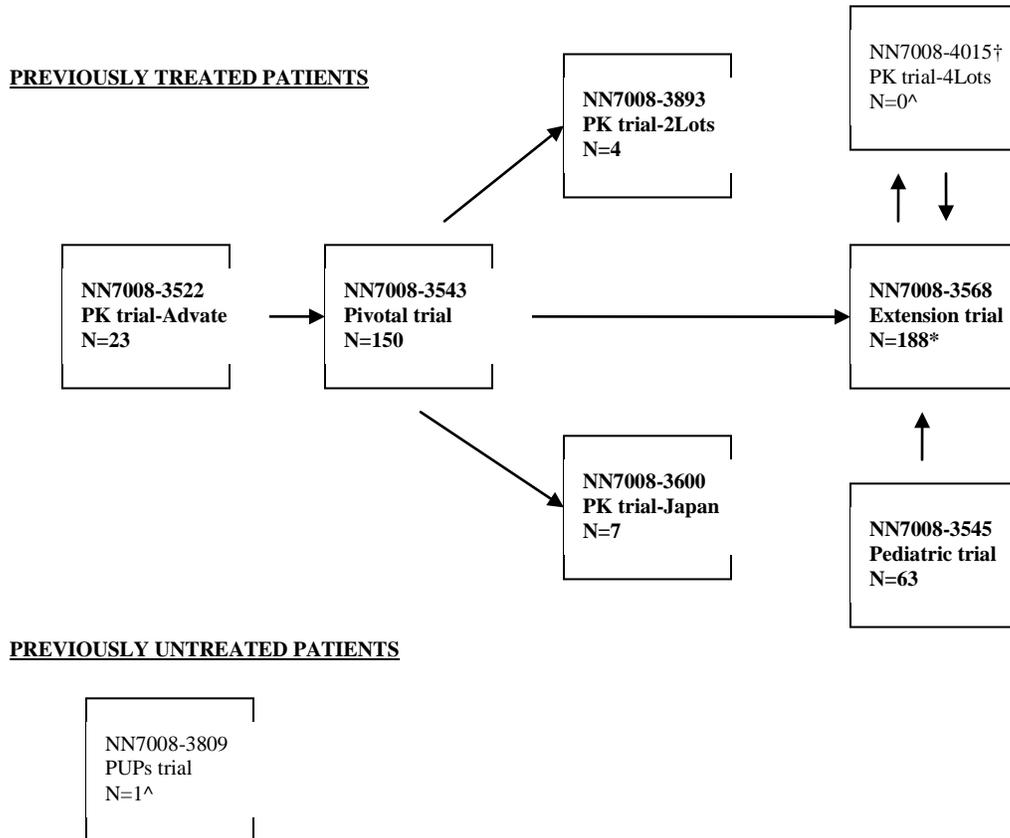
Document Date	Document Type	Document	Source
08 Feb 2012	Complete Study Report	Pivotal trial NN7008-3543 – A multi-centre, open-label, non-controlled trial on safety and efficacy of turoctocog alfa in prevention and treatment of bleeds in previously treated patients with haemophilia A.	Novo Nordisk, 125466/0
20 Mar 2012	Complete Study Report	Pediatric trial NN7008-3545 – A multi-centre, open-label, non-controlled trial on safety and efficacy of turoctocog alfa in previously treated pediatric patients with haemophilia A	Novo Nordisk, 125466/0
29 Jun 2012	Interim Study Report	Extension trial NN7008-3568 – Safety and efficacy of turoctocog alfa in prevention and on-demand treatment of bleeding episodes in patients with haemophilia A. Sub-trial: Efficacy and safety of turoctocog alfa in prevention and treatment of bleeding during surgical procedures in patients with haemophilia A.	Novo Nordisk, 125466/0
05 Oct 2012	Risk Management Plan	Risk Management Plan – Version 1, Turoctocog alfa (NovoEight®)	Novo Nordisk, 125466/0
13 Sep 2012	Summary Safety Report	Turoctocog alfa. Integrated summary of safety - Version 2.0 (as of 21 Nov 2011)	Novo Nordisk, 125466/0
07 Feb 2013	Summary Safety Report	Turoctocog alfa. 120 days safety update. (as of 1 Sep 2012)	Novo Nordisk, 125466/0.9
01 Oct 2012	Study Protocol	Observational trial NN7008-3553 Study Protocol – A Multi-centre Non-interventional Study of Safety and Efficacy of NNC 0155-0000-0004 turoctocog alfa (rFVIII) during Long-Term Treatment of Severe and Moderately Severe Haemophilia A (FVIII <2%)	Novo Nordisk, 125466/0
27 Aug 2012	Study Protocol	PUPs trial NN7008-3809 – Safety and Efficacy of NNC 0155-0000-0004 in Prevention and Treatment of Bleeds in Pediatric Previously Untreated Patients with Haemophilia A	Novo Nordisk, 125466/0

3. PHARMACOVIGILANCE PLAN REVIEW

3.1 Clinical Safety Database

The overall clinical development program submitted by the sponsor for NovoEight consists of a total of 8 clinical trials. Of these 8 trials, 6 have been conducted in the preclicensure phase and 2 are planned postlicensure. In addition, the sponsor plans to replace the Extension trial NN7008-3568 with a ninth trial, the Observational trial NN7008-3553, following licensure. Patient flow through the clinical development program is summarized in Figure 1 below.

Figure 1. Patient flow in the clinical development program for NovoEight



Bold = preclicensure study, ^as of 1Dec2012, *as of 1Sep2012, †New patients can enter trial

The 6 studies that have been conducted preclicensure have resulted in a total of 214 unique patients being exposed to NovoEight thus far. The patients who participated in the 6 preclicensure studies are listed in Table 3 below by age. Of note, a given patient may participate in more than one study (Figure 1). As a result the sum of the study subjects participating in these 6 trials is greater than 214.

Table 3. Study Subjects Enrolled in Prelicensure Studies of NovoEight

	NN7008-3522	NN7008-3543	NN7008-3545	NN7008-3600	NN7008-3893	NN7008-3568*
Study Type	PK trial – Advate	Pivotal trial	Pediatric trial	PK trial - Japan	PK trial - 2 Lots	Extension trial
Study Description	Comparison of PK of NovoEight and Advate	Evaluation of safety & efficacy of NovoEight in surgical patients	Evaluation of safety & efficacy of NovoEight in children <12 yo	Evaluation of PK of NovoEight in Japan	Evaluation of PK of 2 different lots of NovoEight	Extension trial of safety & efficacy of NovoEight
Subjects (n)						
Age: <18y	2	24	63	0	0	78
≥18y	21	126	0	7	4	110
Total	23	150	63	7	4	188

*Trial ongoing. Data provided as of 1Dec2012, PK = Pharmacokinetics

Of the 6 prelicensure trials, 3 have safety related endpoints – Pivotal trial NN7008-3543, Pediatric trial NN7008-3545 and Extension trial NN7008-3568. The Pivotal and Pediatric trials have been completed and study reports have been submitted with the BLA. The Extension trial NN7008-3568 is currently ongoing and an interim study report has been submitted by the sponsor. All 3 reports have been reviewed and are summarized in section 3.1.1 below.

Following licensure, the sponsor intends to launch a Phase III postmarketing study in PUPs. The sponsor also intends to end the Extension trial NN7008-3568 and replace it with a planned Phase IIIB Observational trial NN7008-3553. Both the PUPs trial and the Observational trial are listed in the PVP and are reviewed with the rest of the PVP in section 3.2 below. The sponsor also intends to launch a pharmacokinetics (PK) trial PK NN7008-4015 to evaluate PK in 4 lots of NovoEight. As of 1Dec2012 no study subjects have been enrolled in this trial.

3.1.1 Prelicensure Clinical Trial Safety Information

The sponsor has provided study reports for prelicensure clinical trials including 3 with safety related endpoints – Pivotal trial NN7008-3543, Pediatric trial NN7008-3545 and Extension trial NN7008-3568. The safety related data for these 3 trials is summarized in Sections 3.1.1.1, 3.1.1.2 and 3.1.1.3 below

3.1.1.1 Safety related data from Pivotal trial NN7008-3543

The prelicensure Pivotal trial NN7008-3543 has been completed by the sponsor. The final study report has been reviewed and safety related data is summarized in Table 4 below.

Table 4. Summary of Pivotal trial NN7008-3543

Study Title:	A multi-centre, open-label, non-controlled trial on safety and efficacy of turoctocog alfa in prevention and treatment of bleeds in previously treated patients with haemophilia A. Sub-Trial: Safety and efficacy of turoctocog alfa in prevention and treatment of bleeding during surgical procedures in patients with haemophilia A.				
Study Design:	Phase III multi-centre, multi-national, open-label, single-arm trial Part A: Patients who completed PK trial NN7008-3522 Part B: Patients who did not participate in PK trial NN7008-3522 Part C: Patients from Part A or B undergoing surgery				
Eligibility criteria:	Male severe (FVIII \leq 1%) hemophiliacs aged 12 to 65 years, No history of inhibitors (\geq 0.6 BU/mL), PTPs with \geq 150 ED to any FVIII product other than turoctocog, HIV negative or HIV positive with CD4# \geq 200 and viral load $<$ 400,000, No immunomodulators or severe hepatic dysfunction				
Study Duration:	07Apr2009 to 21Sep2011				
Study Status:	Complete. Final study report submitted.				
Objectives:	Primary: <ul style="list-style-type: none"> ○ To assess the incidence rate of FVIII inhibitors (\geq0.6 BU/mL) Secondary: <ul style="list-style-type: none"> ○ To evaluate safety and efficacy of prophylaxis and treatment in both surgical and routine care of patients with haemophilia A. ○ To assess changes in patient-reported outcomes ○ To evaluate the pharmacokinetic profile of turoctocog alfa 				
Safety related endpoints:	Adverse event (AE) and Physical examination (PE) monitoring, Laboratory parameters including FVIII inhibitor development				
Study Population:		Part A	Part B	Part C	Total (Part A+B)
	Total (n):	22	128	9	150
	Age (years):				
	Mean	24	29	25	28
	Range	13-54	12-60	14-36	12-60
	Race:				
	White	21	100	9	121
	Black/AfAm	0	3	0	3
Asian	1	19	0	20	
Other	0	6	0	6	
Study Results:	AE monitoring	9 serious AE were reported by 7 subjects – hypertension, sinus tachycardia, insomnia, transaminitis, accidental fall, car accident and 3 reports of GI bleed. 1 non-serious AE (fatigue) led to patient withdrawal. 3 AEs reported by surgical patients were mild or moderate. 1 patient with a history of depression attempted suicide. No deaths occurred during the trial			
	PE	No new PE findings reported for any subject at the last visit			
	Laboratory parameters	No FVIII inhibitors were detected. No subjects tested negative for α -murine IgG antibody (ab) at the first visit then seroconverted to positive during the trial. 2 subjects seroconverted to positive for α -CHO ab transiently during the trial. 3 of 58 patients with Hepatitis C had temporary exacerbation of transaminitis.			
Conclusion:	No clinically significant safety issues were identified				

3.1.1.1.2 Safety related data from Pivotal trial NN7008-3543 – α -murine IgG ab and α -CHO ab
 None of the study subjects seroconverted from negative to positive for α -murine IgG ab during the trial. Two subjects were negative for α -CHO ab at the first visit, seroconverted to positive

during the trial and were negative at the end of the study – subjects -----(b)(6)-----. The AE listings were searched for these 2 subjects.

---(b)(6)---: 23 yo male who completed the Pivotal trial and enrolled in the Extension trial. He reported no serious AEs in either trial and the following mild nonserious AEs all of which were thought unlikely to be related to the study drug – incorrect dose administered arthralgia, renal colic, hematuria, nephrolithiasis, toothache and dental caries.

---(b)(6)---: 14 yo male who completed the Pivotal trial. He reported no serious AEs and the following nonserious AEs all of which were mild in severity and thought unlikely to be related to the study drug – sinusitis, back pain, diarrhea, and nasopharyngitis.

3.1.1.2 Safety related data from Pediatric trial NN7008-3545

The prelicensure Pediatric trial NN7008-3545 has been completed by the sponsor. The final study report has been reviewed and safety related data is summarized in Table 5 below.

Table 5. Summary of Pediatric trial NN7008-3545

Study Title:	A multi-centre, open-label, non-controlled trial on safety and efficacy of turoctocog alfa in previously treated pediatric patients with haemophilia A.			
Study Design:	Phase III multi-centre, multi-national, non-controlled, open-label, safety, efficacy and pharmacokinetic trial			
Eligibility criteria:	Male severe (FVIII \leq 1%) hemophiliacs <12 yo, No history of inhibitors, PTPs with \geq 50 ED to any FVIII product other than turoctocog, HIV negative or HIV positive with CD4# \geq 200, No immunomodulators or severe renal or hepatic dysfunction.			
Study Duration:	18Jun2010 to 21Nov2011			
Study Status:	Complete. Final study report submitted.			
Objectives:	Primary: o To evaluate safety of turoctocog in PTPs <12 years of age with haemophilia A Secondary: o To evaluate efficacy and PK in PTPs <12 years of age with haemophilia A o To assess and compare patient-reported outcomes from baseline to end of trial			
Safety related endpoints:	AE and PE monitoring, Laboratory parameters including FVIII inhibitor development (\geq 0.6 BU)			
Study Population:		Small Children	Older Children	Total
	Total (n):	31	32	63
	Age (years):			
	Mean	3.65	8.44	6.08
	Range	1-5	6-11	1-11
	Race:			
	White	27	26	53
	Asian	2	4	6
	Other	2	2	4
Study Results:	AE monitoring	3 serious AE reported by 3 patients – soft tissue injury, viral gastroenteritis, device related infection. No withdrawal due to AE.		
	PE	Increasing height and weight consistent with a population of growing children.		
	Laboratory parameters	1 patient was positive for FVIII inhibitor (1.3 BU) but was negative on repeat testing so the definition of FVIII inhibitors was not met. No other patients tested positive for FVIII inhibitors. 2 patients seroconverted from negative to positive for α -CHO ab during the trial. 2 patients tested positive for α -murine IgG ab at the 2nd visit, but seroconverted to negative by the last visit.		
Conclusion:	No clinically significant safety issues were identified			

The report of a patient with a positive FVIII inhibitor test and the reports of seroconversion to α -CHO ab positive are reviewed in detail in sections 3.1.1.2.1 and 3.1.1.2.2 below.

3.1.1.2.1 Safety related data from Pediatric trial NN7008-3545 – FVIII inhibitor development

One study subject had a single positive test for FVIII inhibitor which was negative on repeat testing and therefore did not meet the study definition of FVIII inhibition. The subject was a 22 month old Brazilian boy with severe haemophilia A and a total of 50 prior ED to various plasma derived FVIII products. Prior to enrollment in the trial the patient had tested negative for FVIII inhibitor tests on 19Oct2010 and 19Jan2011. A summary timeline of the subject’s participation in the study is listed in Table 6 below.

Table 6. Summary timeline of Study Subject ---(b)(6)--- who had a single positive FVIII inhibitor test in Pediatric trial NN7008-3545

Date	Event
30Jun2011	Enrolled in Pediatric trial NN7008-3545. Screening inhibitor test negative.
18Jul2011	Started to receive the study drug for prophylaxis against bleeding.
20Jul2011	Inhibitor testing was negative.
22Aug2011	Patient tested positive for inhibitors with a level of 1.3 BU. FVIII recovery test performed 30 min post-dose on the same day showed significant FVIII activity of 0.539 and 0.807 IU/mL using one-stage clotting and chromogenic assay, respectively. No bleeds or AEs were reported.
31Aug2011	Investigator decided to withhold the study treatment.
02Sep2011	At a follow up visit a newly drawn inhibitor sample tested negative <0.6 BU.
12Sep2011	The patient was withdrawn from the trial per protocol due to treatment with a FVIII concentrate other than the study drug.
16Sep2011	Another negative (<0.6 BU) inhibitor sample was taken when the patient had his final visit following the decision to withdraw him from the trial.
27Sep2011	Investigator reported the outcome as recovered.

Since the study subject experienced a single finding of low titer FVIII inhibitor with significant FVIII activity and no clinical sequelae of bleeding, the significance of this finding is unclear.

3.1.1.2.2 Safety related data from Pediatric trial NN7008-3545 – α -CHO ab seroconversion

A total of 9 patients tested positive for α -CHO ab at some point during the trial. Of these 9 patients, 5 patients had a change in their α -CHO ab status after receiving a dose of NovoEight. Of these 5 patients, 3 converted from positive for α -CHO ab prior to NovoEight to negative after receipt of NovoEight. Thus only 2 patients seroconverted from negative to positive for α -CHO ab after receipt of NovoEight.

Since the pattern of seroconversion from negative to positive for α -CHO ab after receipt of NovoEight may indicate *de novo* seroconversion after administration of the study drug, the 2 patients who experienced this pattern of seroconversion were evaluated in detail. The adverse event listings were searched for these 2 patients – study subjects -(b)(6)- and -(b)(6)-. No adverse events were reported for study subject -(b)(6)-. Two adverse events were reported for study subject -(b)(6)-. The subject is a 5yo severe hemophiliac in Brazil who reported no serious AE and 2 mild nonserious AEs – underdose after taking less than the recommended dose and allergic rhinitis.

3.1.1.3 Safety related data from Extension trial NN7008-3568

The Extension trial NN7008-3568 is currently ongoing. The interim study report has been reviewed and safety related data is summarized in Table 7 below. The Extension trial NN7008-

3568 has been offered to subjects who completed the Pivotal and Pediatric trials as well as those who completed any of the 3 PK trials conducted in the prelicensure phase by the sponsor (Table 3 above).

Table 7. Summary of Extension trial NN7008-3568

Study Title:	Safety and efficacy of turoctocog alfa in prevention and on-demand treatment of bleeding episodes in patients with haemophilia A Sub-trial: Efficacy and safety of turoctocog alfa in prevention and treatment of bleeding during surgical procedures in patients with haemophilia A					
Study Design:	Phase IIIB open-label, multi-centre, multi-national, single-arm trial investigating long-term safety and efficacy in patients with severe haemophilia A without inhibitors. Sub-trial is designed to provide information on efficacy and safety of bolus or continuous infusion during surgery.					
Eligibility criteria:	Extension trial for patients completing Pivotal trial NN7008-3543, Pediatric trial NN7008-3545, or PK trials NN7008-3600 or NN7008-3893					
Study Duration:	27Oct2009 to current					
Study Status:	Ongoing. Interim study report submitted.					
Objectives:	Primary: ○ To assess safety in prevention and treatment of bleeds Secondary: ○ To assess efficacy in prevention and treatment of bleeds. Primary (Sub-trial): ○ To evaluate efficacy in surgery Secondary (Sub-trial): ○ To evaluate the hemostatic response in the postsurgery period ○ To evaluate safety in surgery.					
Safety related endpoints:	AE and PE monitoring, Laboratory parameters including FVIII inhibitor development (≥ 0.6 BU)					
Study Population (as of 1Dec2012):		Small Children (0-<6yo)	Older Children (6-<12yo)	Adolescents (12-<18yo)	Adults (≥ 18 yo)	Total
	Total (n):	27	28	23	110	188
	Age (y):					
	Mean	4.6	9.0	14.9	30.6	21.7
	Range	1-6	6-12	12-18	18-61	1-61
	Race (n):					
	White	24	22	16	94	156
	Black/AfAm	0	0	1	0	1
	Asian	2	4	2	13	21
	Other	1	2	4	3	10
	Number of prior turoctocog infusions (n):					
Mean	60.2	64.7	85.2	89.2	80.8	
Range	51-83	50-104	72-100	75-214	50-214	
Interim Study Results (as of 1Dec2012):	AE monitoring	11 serious AE were reported by 8 patients – cellulitis, fall, scrotal pain, psychosis, car accident, 2 hemorrhages, 2 injuries, and 2 fractures. 3 patients withdrew due to the AE psychosis, subdural hemorrhage and other. 1 death occurred during the trial due to subdural hemorrhage				
	PE	No trends over time with respect to abnormal PE findings				
	Laboratory parameters	No FVIII inhibitors were detected. Subjects were not tested for α -CHO or α -murine IgG ab. 14 reports of elevated hepatic parameters for 6 patients – 4 with HCV, 2 were HCV and HBV negative.				
Conclusion:	No clinically significant safety issues have been identified as of 1Dec2012					

The report of death is reviewed in detail in section 3.1.1.3.1 below. The patient who withdrew from the study for unclear reasons and the reports of elevated hepatic parameters in patients with no history of viral hepatitis were reviewed in detail in sections 3.1.1.3.2 and 3.1.1.3.3 below.

3.1.1.3.1 Safety related data from Extension trial NN7008-3568 – Death
As of the 1Dec2012 one death had occurred during the Extension trial.

121101: 27 yo male hemophiliac who was hospitalized with head trauma after an alleged assault. On presentation he was unconscious (Glasgow coma scale 7). Head CT revealed a right fronto-temporal parietal subdural haemorrhage with midline shift and cerebral edema. He underwent emergency decompressive craniotomy with evacuation of the haematoma but died on hospital day 2. He received trial medication both pre and post-operatively until the time of death.

This report of death is confounded by indication and thus does not represent new safety information.

3.1.1.3.2 Safety related data from Extension trial NN7008-3568 – Subject withdrawal
Of the 3 study subjects who withdrew from the Extension trial, 1 had a history of schizophrenia and withdrew due to psychosis and 1 was withdrawn due to a subdural hemorrhage which resulted in death. The third withdrew from the Extension trial on 22Jul2010 and listed “other” as the reason for withdrawal. This was study subject --(b)(6)-- who completed Part B of the Pivotal trial and enrolled in the Extension trial on 19Jul2010. The sponsor reports in the supplemental appendix that the subject developed AEs at the end of Pivotal trial NN2008-3543 which precluded his continued participation in the Extension trial. A search of the appendices of the Pivotal trial revealed that the patient is a 36 yo male with HIV and Hepatitis C. At the first clinic visit his laboratory findings were notable for a HIV viral load of 6900 copies/mL and a Hepatitis C viral load was 3,450,000 copies / μ L. On 19Jul2010, at the end of the Pivotal trial, he was diagnosed with abnormal liver function tests (LFTs), neutropenia and thrombocytopenia (Table 9 below) which may be a reflection of his known comorbidities.

Table 8. Adverse Events in Pivotal trial NN7008-3543 Precluding Continuation of Study Subject --(b)(6)-- in Extension trial NN7008-3568

Adverse Event		First visit	Last visit	Severity	Status*
Neutropenia	WBC (n)	6.8	2.9	Mild	Not recovered
	Neutrophils (%)	64	43		
Transaminitis	ALT	39	347	Moderate	Recovering
	AST	54	339		
	GGT	30	327		
Thrombocytopenia	Platelets (n)	253	82	Moderate	Recovering

WBC=White Blood Cell count in 1,000/mm³, Platelets=Platelet count in 1,000/mm³, ALT=Alanine aminotransferase in IU/L, AST=Aspartate aminotransferase in IU/L, *Status as of 22Jul2010

3.1.1.3.3 Safety related data from Extension trial NN7008-3568 – Elevated hepatic parameters
A total of 14 adverse events (including 3 linked events) of increased hepatic parameters were reported in 6 patients. Hepatic parameters are defined as alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin conjugated, blood alkaline phosphatase, blood bilirubin, hyperbilirubinemia, gamma-glutamyltransferase (GGT) and hepatic enzymes. Of the 6 subjects, 4 were positive for hepatitis C, which may have contributed to the increased values. However, 2 of the 6 patients were negative for both hepatitis B and C. The reports for these 2 study subjects – ---(b)(6)--- are reviewed in detail below.

---(b)(6)---: 14 yo Turkish boy had a pronounced increase of liver parameters in November 2010 compared to his first visit with a rise in ALT and AST from 24 to 1217 and 29 to 1083 IU/L respectively. Queried for the cause of this finding the investigator reported Hepatitis A as the primary AE and thought the elevated LFTs were unlikely to be related to the study drug. The patient recovered from all events and LFTs returned to normal.

---(b)(6)---: 22 yo patient had a rise in AST and ALT at the fourth visit compared to the first with ALT and AST rising from 69 to 99 and 22 to 139 respectively. The subject had persistently elevated GGT throughout the study and was also reported to have a high creatine phosphokinase (CPK) although values were not provided. The patient recovered and the cause of these elevated values was unknown to the investigator. However, the rise in CPK may indicate that the transaminitis is due to skeletal muscle rather than hepatic injury.

A search of the AE listings did not reveal any additional AEs reported for these 2 study subjects.

3.1.4 Limitations of the Clinical Safety Database

3.1.4.1 Predominance of male gender

A total of 214 unique patients have been evaluated in the clinical development program for NovoEight (Figure 1 above). All patients are male hemophiliacs. As a result, experience regarding the use of this product in female hemophiliacs and during pregnancy or lactation is limited. However, given the rarity of female hemophiliacs, the gender demographic of the clinical safety database likely reflects the target population in which this product will be used.

3.1.4.2 Relatively low risk population for development of FVIII inhibitors

The sponsor reports that no study subjects developed FVIII inhibitors. While the etiology of the development of FVIII inhibitors has not been fully elucidated, risk factors are thought to include a family history of inhibitors, nonwhite ethnicity and severe disease requiring intense replacement therapy.⁹ Although all patients in the clinical safety database are severe hemophiliacs, subjects with a history of inhibitors were excluded and the majority of patients reported their ethnicity as white. Thus, with regard to the development of FVIII inhibitors, the risk profile of the population in which the product has been used so far, may not be representative of the wider target population.

3.1.4.3 Evaluation of α -CHO and α -murine IgG ab

The significance of the presence of α -CHO and α -murine IgG ab is not clear. Patients who developed these antibodies during the Pivotal and Pediatric trials do not appear to share any particular AE suggestive of a common clinical manifestation of their seroconversion. Of note, patients in the Extension trial are not tested for these antibodies. Thus the natural history of these antibodies and any long term effects have not been fully evaluated.

3.1.4.4 Limited use in surgery

A total of 14 surgeries were performed in 14 patients – 13 major surgeries and 1 minor surgery. Of the 14 surgical patients, 13 were White and 1 patient was Asian. The mean age at the time of surgery was 28.4 years with ages ranging from 14 to 55. Thus the experience of use of NovoEight in surgical patients is limited by the small number of surgical patients, the predominance of white ethnicity and the absence of young children in this subset of study subjects.

3.1.4.5 Exclusive experience in PTPs

All study subjects in the clinical safety database are PTPs. There is currently no experience with the use of NovoEight in PUPs and information about the use of the product in this particular population will not be available until the planned postlicensure PUPs trial. This is however consistent with recommendations from the European Medicines Agency (EMA) and the International Society on Thrombosis and Hemostasis (ISTH) regarding the use of PTPs as study

subjects in prelicensure studies. PTPs, by virtue of not having developed an inhibitor, are generally considered to be tolerant of factor VIII and therefore at a relatively low risk for inhibitor development. The EMA therefore recommends that prelicensure trials to evaluate the immunogenicity of new products should include PTPs since excessive inhibitor formation in PTPs would suggest increased immunogenicity of the product.¹⁰ Because of the rarity of PUPs and the fact that PUPs have a certain – but not clearly defined – likelihood of inhibitor formation, the ISTH recommends that PUPs should be reserved for studies of the natural history of inhibitor development.¹¹

3.2 Pharmacovigilance Plan

The PVP submitted by the sponsor is summarized in Table 9 below.

Table 9. Pharmacovigilance Plan for NovoEight

SAFETY CONCERN	PLANNED ACTION(S)
Identified Risks	
None	
Important Potential Risks	
Inhibitor Development	<ul style="list-style-type: none"> ○ Routine pharmacovigilance including structured follow-up questions ○ Clinical trials - NN7008-3809, NN7008-3553
Allergic/Hypersensitivity Reactions	<ul style="list-style-type: none"> ○ Routine pharmacovigilance including structured follow-up questions ○ Clinical trial - NN7008-3553 ○ Hypersensitivity questionnaire
Important Missing Information	
Elderly patients (>65 years of age)	<ul style="list-style-type: none"> ○ Routine pharmacovigilance ○ Clinical trial - NN7008-3553
Previously Untreated Patients	<ul style="list-style-type: none"> ○ Routine pharmacovigilance ○ Clinical trial - NN7008-3809
Patients with HIV (CD4 <200 cells/μl) or HCV (viral load more than 200 particles/μl)	<ul style="list-style-type: none"> ○ Routine pharmacovigilance ○ Clinical trial - NN7008-3553 may include patients with HCV
Patients with Renal or Hepatic Insufficiency	<ul style="list-style-type: none"> ○ Routine pharmacovigilance ○ Clinical trial - NN7008-3553
Patients with mild or moderate hemophilia	<ul style="list-style-type: none"> ○ Routine pharmacovigilance ○ Clinical trial - NN7008-3553 may include patients with moderate hemophilia A (FVIII level <2%)

Routine pharmacovigilance is described by the sponsor as daily surveillance, literature surveillance, regular safety reporting, risk communication via reference safety information as well as periodic review of safety information and reporting rates of adverse events. Reports prepared by the sponsor will include development safety update reports and periodic safety update reports which will include specific sections for inhibitor development and hypersensitivity reactions. Additional information will be obtained on reports of inhibitor formation or allergic/hypersensitivity reactions via additional standard follow-up questions. The sponsor also plans to prepare biannual reports of suspected unexpected serious adverse reactions.

In addition to routine pharmacovigilance, the sponsor plans two post-marketing studies which are listed in the PVP – an Observational trial NN7008-3553 and a trial in PUPs NN7008-3809. The protocols for both trials have been submitted by the sponsor and have been reviewed and summarized in Tables 10 and 11 below respectively.

Table 10. Summary of Study Protocol for Observational Trial NN7008-3553

Study Title:	A Multi-centre Non-interventional Study of Safety and Efficacy of NNC 0155-0000-0004 turoctocog alfa (rFVIII) during Long-Term Treatment of Severe and Moderately Severe Haemophilia A (FVIII <2%)
Study Design:	Phase IV prospective, multinational, non-randomized, single-arm, non-interventional postauthorization safety study in patients with severe and moderately severe haemophilia A
Study Duration:	2014 to 2018
Study Population:	Goal recruitment of 50 to 70 subjects with at least 10 aged <12 yo at enrollment
Eligibility criteria:	Male patients with severe to moderately severe hemophilia A (FVIII <2%), No clinical suspicion of inhibitors or detectable inhibitors (≥ 0.6 BU/mL), No prior exposure to the study drug, HIV negative or HIV positive with CD4# ≥ 200 and viral load <400,000 within 6 months prior to enrollment, Treatment with any investigational drug 30 days prior to enrollment
Study Status:	Yet to launch. Final study report due 2019
Objectives:	Primary: To assess the incidence rate of FVIII inhibitors (≥ 0.6 BU/mL) during long-term prevention and treatment of bleeds with turoctocog alfa in patients with severe and moderately severe haemophilia A (FVIII <2%). Secondary: To further evaluate the general safety and clinical efficacy of turoctocog alfa in prevention and treatment of bleeds and prevention of bleeds during and after surgery.
Safety related endpoints:	Adverse event monitoring Physical examination and vital signs monitoring Monitoring of laboratory parameters Incidence of FVIII inhibitor development (≥ 0.6 BU)

Table 11. Summary of Study Protocol for Pediatric PUPs Trial NN7008-3809

Study Title:	Safety and Efficacy of NNC 0155-0000-0004 [turoctocog alfa] in Prevention and Treatment of Bleeds in Pediatric Previously Untreated Patients with Haemophilia A
Study Design:	Phase III multi-center, multinational, non-randomized, open-label safety and efficacy trial in PUPs with haemophilia A. The trial consists of two phases. In the main phase, at least 50 patients will receive preventive treatment for a minimum of 50ED (ED) or until they develop inhibitors. In the extension phase, the patient will be followed for approximately 3.5 years. The estimated total duration of the trial is approximately 5 years
Study Duration:	2011 to 2016
Study Population:	Goal recruitment of 60 subjects
Eligibility criteria:	Male <6 yo with severe hemophilia A (FVIII $\leq 1\%$), PUPs – no prior use of factor products, No known or suspected allergy to hamster protein or study drug, No detectable inhibitors (≥ 0.6 BU/mL), No additional congenital or acquired bleeding disorder, No immunomodulatory treatments such steroids during the trial period
Study Status:	Recruiting. Final study report due 2016
Objectives:	Primary: To evaluate safety in PUPs with haemophilia A Secondary: To evaluate efficacy in treatment of bleeds and to evaluate preventive effect on bleeds in pediatric PUP with haemophilia A
Safety related endpoints:	Adverse event monitoring Physical examination and vital signs Monitoring of laboratory parameters Incidence of clinically relevant FVIII inhibitors (FVIII inhibitor ≥ 0.6 BU and decreased recovery of FVIII activity level <66% of expected level) Incidence of any FVIII inhibitors (≥ 0.6 BU) and of high-titer inhibitors (≥ 5 BU)

4. INTEGRATED RISK ASSESSMENT

The available data submitted by the sponsor in support of this BLA have evaluated two of the known safety concerns for the class of FVIII products – infectivity and immunogenicity. As a 3rd generation recombinant FVIII product, NovoEight carries minimal risk of transmission of infectious agents such as Hepatitis viruses or HIV. In the clinical safety database, 2 of 214 subjects with no prior history of hepatitis experienced transaminitis after receiving NovoEight. However, review of both cases reveals possible alternative causes for transaminitis in both cases (Section 3.1.1.3.3).

With regard to immunogenicity, 1 of 214 subjects had a single low titer inhibitor test which was negative on repeat testing and the patient had no clinical evidence of bleeding (Section 3.1.1.2.1). Thus no study subjects met the study definition of FVIII inhibitor development. Although this finding is reassuring, the limitations of the clinical safety database with regard to development of FVIII inhibitors (Section 3.1.4.2) must be considered when interpreting these results.

Of the 214 patients in the clinical development program, 4 patients seroconverted from negative to positive for α -CHO ab following exposure to NovoEight. There does not appear to be shared clinical findings among these 4 subjects to suggest a common syndrome attributable to *de novo* seroconversion from negative to positive for α -CHO ab following exposure to NovoEight (Sections 3.1.1.1.2 and 3.1.1.2.2).

Seroconversions by study subjects from positive to negative, and vice versa, for both α -murine IgG ab and α -CHO ab have been documented in the clinical safety database with no clear or consistent pattern of seroconversion related to exposure to the study drug. Thus the clinical significance of these antibodies remains unclear. Additionally, while study subjects were tested for both α -murine IgG ab and α -CHO ab in both the Pivotal trial NN7008-3543 and the Pediatric trial NN7008-3545, patients in the Extension trial NN7008-3568 are not tested for these antibodies. Thus the natural history of these antibodies and any long term effects have not been fully evaluated.

Of note, the sponsor proposes that NovoEight be indicated for the perioperative management of hemophiliacs without clarification of patient age. However, the experience of use of NovoEight in surgical patients in the clinical safety database is limited by the small number of surgical patients, the predominance of white ethnicity and the absence of young children in this particular subset of study subjects (Section 3.1.4.4). Further evaluation of the use of NovoEight in pediatric surgical patients may be warranted. However, given the rarity of the disease and the additional rarity of pediatric surgeries the feasibility of a structured study may be limited.

5. RECOMMENDATIONS

At this time OBE agrees with routine pharmacovigilance as proposed by the sponsor in the PVP with adverse event reporting as required under 21 CFR 600.80. Periodic adverse event reports should include details of the potential risks and missing information identified in this safety review. The reviewed safety data do not substantiate a need for a post-marketing requirement (PMR) study or a Risk Evaluation and Mitigation Strategy (REMS). Interim study reports of the 2 planned post-marketing (PMC) studies listed in the PVP – an Observational trial NN7008-3553 and a PUPs trial NN7008-3809 – should be submitted periodically.

¹ Sandberg H, Almstedt A, Brandt J *et al.* Structural and Functional Characterization of B-Domain Deleted Recombinant FVIII. *Sem Hematol.* 2001;38(Suppl. 4):4-12.

² Fijnvandraat K, Berntorp E, ten Cate JW *et al.* Recombinant B-domain deleted FVIII (rVIII SQ): pharmacokinetics and initial safety aspects in hemophilia A patients. *Thromb Haemost* 1997; 77 (2):298-302

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- ³ National Hemophilia Foundation, Blood and Product Safety, HIV/AIDS. Available at: <http://www.hemophilia.org>
- ⁴ Hoots WK and Shapiro AD. Treatment of Hemophilia. *UpToDate* 2012. Available at <http://www.uptodate.com/contents/treatment-of-hemophilia>.
- ⁵ Courter SG and Bedrosian CL. Clinical Evaluation of B-Domain Deleted Recombinant FVIII in Previously Treated Patients. *Sem Hematol*. 2001;38 (Suppl. 4):44-51 (Protocol 3082A1-300-WW, Final study report, eCTD 103779/5089)
- ⁶ Courter SG and Bedrosian CL. Clinical Evaluation of B-Domain Deleted Recombinant FVIII in Previously Untreated Patients. *Sem Hematol*. 2001;38 (Suppl. 4):52-9. (Protocol 3082A1-301-WW, Final study report, eCTD 103779/5089)
- ⁷ Gutiérrez AH, Moise L and De Groot AS. Human Vaccines: News and Views. Of [hamsters] and men – A new perspective on host cell proteins. *Human Vaccines* 2012; 8:1172-1174; September 2012
- ⁸ Recht M, Nemes L, Matysiak M, *et al* Clinical evaluation of morctocog alfa (AF-CC), a new generation of B-domain deleted recombinant FVIII (BDDDrFVIII) for treatment of haemophilia A: demonstration of safety, efficacy, and pharmacokinetic equivalence to full-length recombinant FVIII *Haemophilia* 2009; 15:869-880 (Protocol 3082B2-310-WW, eCTD 1025264/0)
- ⁹ Hoots WK and Shapiro AD. Factor VIII and factor IX inhibitors in patients with hemophilia. *UpToDate* 2013. Available at <http://www.uptodate.com/contents/factor-viii-and-factor-ix-inhibitors-in-patients-with-hemophilia>
- ¹⁰ European Medicines Agency. Preauthorisation Evaluation of Medicines for Human Use, London 22 February 2007. Report on Expert Meeting on factor VIII products and inhibitor development. 28 February 2006-2 March 2006. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Report/2009/11/WC500015512.pdf
- ¹¹ White GC, DiMichele D, Mertens K *et al* Utilization of Previously Treated Patients (PTPs), Noninfected Patients (NIPs), and Previously Untreated Patients (PUPs) in the Evaluation of New Factor VIII and Factor IX Concentrates. Recommendation of the Scientific Subcommittee on Factor VIII and Factor IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost* (1999)81:462