



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

MEMORANDUM

Date: November 6, 2013

From: Firoozeh Alvandi, MD
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Epidemiology (DE), Office of Biostatistics and Epidemiology
(OBE)

Re: STN 125398

To: Zuben Sauna, PhD
Visiting Scientist, OMPT,CBER,OBRR,DH,LH

Through: Christopher Jankosky, MD, MPH
Branch Chief, PVB, DE, OBE

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Product: NovoThirteen* (Catridecacog)
*Proprietary name: Tretten

Indication: Routine prophylaxis of bleeding in patients with congenital Factor
XIII A-subunit deficiency

Sponsor: NovoNordisk

Submission Date: 27 December, 2012

Memo Due Date: 6 December 2013

Action Due Date: 25 December 2013

1. INTRODUCTION

a. Product Description

Tretten is the proprietary name for Coagulation Factor XIII A-Subunit (Recombinant). It was submitted as “NovoThirteen” in the Biologics License Application (BLA). It is the A- subunit dimer [A₂] of human coagulation Factor XIII produced from genetically modified yeast (*Saccharomyces cerevisiae*), and supplied as a sterile lyophilized powder. After reconstitution and intravenous injection, the A subunit dimer combines with free B subunits in the plasma to form a heterotetramer [A₂B₂] with properties similar to those of human coagulation Factor XIII, and has transglutaminase activity similar to Factor XIII. Tretten will be referred to throughout this review as NovoThirteen, the product name as it appeared in the BLA submission.

FXIII Congenital Deficiency is a potentially life-threatening autosomal recessive bleeding disorder that occurs in approximately 1 in 2 million individuals, with no predisposition for gender or race. It is characterized by recurrent spontaneous hemorrhages including subcutaneous hematomas, superficial ecchymoses, bleeding into muscles after strenuous exercise, epistaxis, gastrointestinal bleeding, central nervous system bleeds, especially in young children, and delayed bleeding from sites of trauma; delayed wound healing and heavy menses can also be signs of the condition. Patients may bleed around joints after trauma, although spontaneous hemarthrosis is less common than in hemophilia patients.

The World Federation of Haemophilia (WFH) Global Survey 2011 presents data that has been reported from WFH members for their countries. Although these reports are not independently verified by the WFH, they provide an estimate of the intended patient population for this product. The survey reports that there are 115 individuals with FXIII deficiency in the US, and 1,054 globally.¹

b. Regulatory History

The original Biologics License Application (BLA 125398/0) for NovoThirteen (proprietary name Tretten) for the indication of routine prophylaxis of bleeding in patients with congenital Factor XIII A-subunit deficiency was submitted by the sponsor, NovoNordisk, on February 23, 2011. A Complete Response Letter (CRL) was issued on December 23, 2011 based on inspectional deficiencies, CMC deficiencies, and clinical deficiencies. These deficiencies were not based on issues specific to the pharmacovigilance plan. The sponsor submitted responses to the Agency’s CR Letter and resubmitted the BLA on December 27, 2012.

A CR letter was issued by the Agency on June 27, 2013, based on CMC, and not clinical, deficiencies. The Agency stated that further review of the submission was pending review of the (b) (4) inspection of the facility located in Denmark. The Agency also cited a lack of demonstration of an acceptable, validated 100% Visual Inspection Program, requesting that the sponsor submit a validation protocol and pertinent corresponding study results using an “*updated visual inspection test defect kit*,” and acceptance limits for the defect categories (critical, major, and minor subgroupings),

¹ Available at <http://www1.wfh.org/publications/files/pdf-1488.pdf> accessed March 20, 2013.

as appropriate for the product. (Source: FDA Complete Response Letter, dated June 27, 2013 – 09bcaea6812638d0.pdf). The sponsor’s response to the CMC-based June 27, 2013 CR was received by the FDA on October 25, 2013, and there were no clinical issues to be addressed.

c. Objectives

The purpose of this memorandum is to review the available safety information related to NovoThirteen and to review the Pharmacovigilance Plan (PVP) submitted by the sponsor as part of the Risk Management Plan (RMP) and determine the need for postmarketing surveillance and other postmarketing studies.

2. MATERIALS REVIEWED

Materials reviewed as part of this comprehensive safety review are the following:

June 27, 2013 OBRR/DH Complete Response Letter for BLA 125398/00

December 22, 2011 OBRR/DH Clinical Review of initial BLA submission

November 14, 2011 OBE MO (Alan C. Ou, MD, MPH) Pharmacovigilance Plan Review Memo

Response to Clinical Deficiencies - 1.12.11

Draft Labeling -1.14

Risk Management Plan– 1.16

Tabular Listing of Clinical Studies – 5.2

Clinical Trials: F13CD-3835 – module 2, 2.7.6

F13CD-1725 – module 5, 5.3.5.1

F13CD-3720 – module 5, 5.3.5.2

F13CD-3760 – module 5, 5.3.3.2

NN1841-3788 – module 5, 5.3.5.3

Literature Search: A search of PubMed performed on October 1, 2013, for safety related endpoints using the search terms “Factor XIII and antibodies,” “Fibrogammin and antibodies,” “Corifact and antibodies,” and “safety and NovoThirteen,” retrieved four publications with safety related endpoints.

One publication describes the results of the pivotal clinical trial (F13CD-1725).² The material pertinent to this publication and the clinical trial is discussed in this memo in section 3.

² Aida Inbal, Johannes Oldenburg, Manuel Carcao, Anders Rosholm, Ramin Tehrani, Diane Nugent. Recombinant factor XIII: a safe and novel treatment for congenital factor XIII deficiency. *Blood*.2012; 119: 5111-7 (doi: 10.1182/blood-2011-10-386045. Epub 2012 Mar 26)

The second publication is a case report of auto-anti FXIII antibody in a 66 year old female with no personal history or family history of a bleeding disorder.³ The patient was not treated with any exogenous rFXIII, but she presented with bleeding and after an extensive work up was found to have low FXIII activity. The authors describe this as an idiopathic autoantibody to FXIII, likely associated with the patient's underlying condition of neurosyphilis and hepatitis C virus (HCV), and the medication the patient received for the treatment of neurosyphilis (ceftriaxone).

Reviewer comment: This case report reinforces the complexities of inhibitory antibody formation, and the difficulty in both predicting their formation in individual patients, as well as ascribing causation when such antibodies are found.

The third publication is a case report of 65 year old male with no history of abnormal bleeding, who was hospitalized for an ankle fracture and hematoma of the right thigh.⁴ His hemoglobin was found to be low and remained low despite red cell transfusions. Although the patient had no prior history of abnormal bleeding, he “*suddenly developed massive hemorrhages associated with strong and isolated FXIII inhibitor*” at the time he was hospitalized for an ankle fracture. He was found to have severe FXIII deficiency (FXIII-A 0% and FXIII-B 64.8%). FXIII auto-antibody was detected which persisted at low titers despite immunosuppressive therapy including prednisone, rituximab, cyclophosphamide, immunoadsorption. No cause for the development of FXIII could be found. The patient was treated with Fibrogammin (a purified concentrate of blood coagulation factor XIII) and continued various immunosuppressive therapies, and occasional short-term rFVIIa as needed. He subsequently experienced deep vein thrombosis and pulmonary embolism (the time of AE relative to Fibrogammin treatment is not specified in the publication). The Fibrogammin P administration was decreased from 15U/kg every other day to three times per week, and the DVT improved. The inhibitor levels persisted. Various changes were made to the Fibrogammin P therapy schedule (increased in frequency to treat bleeding episodes and decreased to maintain low level of FXIII activity) and the authors reported that, “*Although the patient has had no major bleedings for more than one year now, the inhibitor is still present.*”

Reviewer comment: Although this publication pertains to auto-anti-FXIII (not antibody to exogenous FXIII), it depicts complexities of treatment of bleeding in the presence of antibodies and also highlights possible thrombotic complications associated with factor replacement. The publication focuses on treatment strategies for patients with auto-anti-FXIII, suggesting a combination of therapies including immunosuppression and FXIII replacement (to maintain at least low levels of FXIII activity, which the authors state is sufficient for prevention of bleeding).

³ Hiroyuki Sugiyama et al. Aggressive fatal case of autoimmune hemorrhaphilia resulting from anti-Factor XIII antibodies. *Blood Coagulation and Fibrinolysis* 2013; 24:85-89.

⁴ Françoise Boehlen et al. Acquired factor XIII deficiency: a therapeutic challenge. *Thromb Haemost.* 2013;109:479-87. doi: 10.1160/TH12-08-0604

The fourth publication is a review of autoantibodies to clotting factors, including Factor XIII, in patients with no previous bleeding diathesis.⁵ Although this publication does not directly pertain to antibodies to exogenous clotting factor replacement, it discusses the complexities of diagnosis and treatment of the auto-antibodies to clotting factors which can neutralize clotting factor activation or function or promote rapid clearance of a specific clotting factor from the blood, leading potentially to varying degrees of hemorrhage depending on the factor and amount of activity of the factor affected.

Four publications were cited by the sponsor in the BLA regarding the potential of formation of antibodies which may result in decreased effectiveness of FXIII. These are reviewed below. They discuss cases associated with non-recombinant sources of FXIII (plasma, Factor VIII concentrate, and cryoprecipitate) and *in vitro* tests.

1. Henriksson P, McDonagh J, Villa M. Type I autoimmune inhibitor of factor XIII in a patient with congenital factor XIII deficiency. *Thrombosis and Haemostasis* 1983; 50:272.

Abstract discussing a 12 year old patient with congenital factor XIII deficiency in a family with factor XIII deficiency. She had been treated successfully with prophylactic plasma infusions until the age of eleven when “the treatment suddenly failed,” per the author. The authors do not provide additional clinical information and do not discuss the clinical outcome of treatment failure. The authors state that an inhibitory antibody was found and two methods of treatment were suggested, including removal of the antibodies by extracorporeal Protein-A-Sepharose chromatography and administration of activated factor XIII. No further clinical information is available in this publication.

Reviewer comment: Provides an example of a Factor XIII inhibitory antibody that resulted in clinical ineffectiveness of prophylactic infusions of plasma. This supports the theoretical potential for development of Factor XIII inhibitory antibodies in patients with Novothirteen, whereupon Novothirteen infusions may no longer be effective (both an efficacy and safety concern).

2. Lorand L, Urayama T, De Kiewiet JW, Nossel HL. Diagnostic and genetic studies on fibrin stabilizing factor with a new assay based on amine incorporation. *J Clin Invest* 1969; 48(6):1054-1064.

Discusses mainly an *in vitro* laboratory assay for antibody detection. This publication does not contain adequate detailed clinical information, and, while it suggests that “Futility of the last transfusion could be ascribed to the appearance of a neutralizing antibody directed against the precursor stabilizing factor,” it does not definitively establish the presence of neutralizing antibodies nor does it discuss any clinical adverse event in association with the decreased “corrective power of the transfusion.”

Reviewer comment: This 1969 article reinforces that neutralizing antibodies have been a concern in the scientific community for many years.

⁵ Massimo Cugno et al. Autoantibodies to coagulation factors: From pathophysiology to diagnosis and therapy. *Autoimmun Rev.* 2013; S1568-9972:146-8. 10.1016/j.autrev.2013.08.001.

3. Rivard GE, St LJ, Lacroix S, Champagne M, Rock G. Immunoabsorption for coagulation factor inhibitors: a retrospective critical appraisal of 10 consecutive cases from a single institution. *Haemophilia*. 2003; 9(6):711-716.
Discusses immunoabsorption for management of coagulation factor inhibitors and, of the 10 cases discussed, contains only one case of anti-FXIII antibody in a patient receiving cryoprecipitate. This patient, diagnosed at 40 months of age with severe factor XIII deficiency, was receiving cryoprecipitate from paternal and maternal grandmothers. 18 months post diagnosis she had an intracranial bleed and was found to have FXIII inhibitor (6 BU). Over the years immunoabsorption/ plasma exchanges were attempted, and the patient subsequently received Fibrogammin. The publication states that immunoabsorption was not effective in producing immune tolerance, and that the patient is “still on daily FXIII (20 IU/kg)” Fibrogammin. There is no evidence of lack of response to Fibrogammin in this publication.

Reviewer comments: (1) Despite inhibitory antibodies, a patient with FXIII deficiency continued to receive FXIII infusions. (2) Intracranial bleed may have been associated with a lack of effectiveness of the cryoprecipitate due to FXIII inhibitory antibodies, reinforcing the efficacy-safety link associated with prophylactic infusions of factor products.

4. Seiving B, Henriksson P, Stenberg P, Nilsson IM. A reversed activity staining procedure for detection of an acquired antibody against factor XIII in a girl with factor XIII deficiency. *Br J Haematol* 1992; 82(2):414-416.
Focuses on adsorption of anti FXIII antibodies and discusses the case of a 10 year old patient with factor XIII deficiency successfully treated with tranexamic acid and with transfusion of whole blood and plasma for the first 5 years. Upon suffering trauma to the forehead the patient experienced intracranial hemorrhage and AHF-Kabi (a brand of virus inactivated factor VIII concentrate) containing “substantial amounts of factor XIII” was administered perioperatively (1100 U factor XIII) six times on alternate weeks. Two weeks later no factor XIII activity was demonstrable and anti-factor XIII antibody was found. She subsequently received AHF Kabi again for a serious bleed several years later and her FXIII activity again increased to normal.

Reviewer comments: (1) It appears that in this case the inhibitory antibodies to FXIII were transient. (2) This publication discussed the use of a factor VIII concentrate which also contained FXIII .

3. PHARMACOVIGILANCE PLAN REVIEW

a. Clinical Safety Database

NovoThirteen Clinical Trials

The sponsor has reported a total of 518 subjects exposed to rFXIII (corresponding to a total of 2,540 person exposures). Of these, 80 patients had congenital factor XIII deficiency (and may have participated in more than 1 trial) as of September 30 2012. Of the 80 patients with congenital deficiency, 41 participated in the pivotal trial F13CD-1725. The remainder of the rFXIII exposures were in trials of (b) (4) (316

persons corresponding to 316 person exposures) and in trials with healthy subjects (122 persons corresponding to 2,540 person exposures). Cumulative exposures to rFXIII in patients with congenital deficiency (80 patients) ranged from 1 month to 53 months, totaling 1,990 exposures (all 80 patients were exposed for 1 month and 1 patient was exposed for 53 months).

Of the 80 patients with congenital factor XIII deficiency, 62 were exposed to rFXIII drug substance manufactured by NovoNordisk (rFXIII_{NN}) and 18 were exposed to rFXIII drug substance prior to introduction of rFXIII_{NN} which was produced by (b) (4) (rFXIII (b) (4)). Cumulative exposures to rFXIII_{NN} in patients with congenital deficiency ranged from 1 month to 34 months, totaling 1,386 exposures (all 62 patients were exposed for 1 month and 2 patients were exposed for 34 months). Recombinant FXIII (b) (4) (rFXIII (b) (4)) was used in early phase of trials and subsequently upon Novo Nordisk production of rFXIII, rFXIII_{NN} was introduced. Drug substances rFXIII (b) (4) and rFXIII_{NN} were found to be PK-bioequivalent. (Source: 12/27/2012 sponsor submission 125398/0.33 *Module 5, 5.3.5.3, Clinical study report, PK-Cross Trial Evaluation Report, Pharmacokinetic Cross Trial Evaluation of Recombinant Factor XIII (rFXIII) in Healthy Volunteers and in Patients with Congenital Factor XIII Deficiency*, page 24 of 32).

Completed and Ongoing Trials on rFXIII (as of 30 September 2012)

NN Trial ID	Phase	Trial status	Trial description
Congenital deficiency			
F13-1663 (CD1.3)	Phase 1	Final	Single dose exposure in patients with congenital FXIII deficiency.
F13CD-1725	Phase 3a	Final	Evaluation of efficacy and safety of monthly replacement therapy with rFXIII on prevention of bleeding episodes in subjects with congenital FXIII deficiency.
F13CD-3720	Phase 3b	Ongoing until Q4 2016	Evaluation of safety of monthly replacement therapy with rFXIII in subjects with congenital FXIII deficiency.
F13CD-3760	Phase 3b	Final	A phase 3b trial investigating the pharmacokinetics and safety profile of a single i.v. dose of rFXIII in paediatric (1 to less than 6 years old) subjects with congenital FXIII A-subunit deficiency.
F13CD-3835	Phase 3b	Ongoing until Q2 2014	Evaluation of safety of monthly replacement therapy with rFXIII in paediatric subjects with congenital FXIII A-subunit deficiency (Extension to F13CD-3760).

(b) (4)

Healthy subjects			
F13-1661 (UKHV-1)	Phase 1	Final	Single dose exposure in healthy subjects.
F13-1662 (112C01.0)	Phase 1	Final	Multiple dose (5 consecutive days) exposure in healthy subjects.
NN1841-3788	Phase 1	Final	Investigation of bioequivalence and pharmacokinetics of rFXIII _{(b) (4)} to rFXIII _{NN} in healthy male subjects.
NN1810-3733	Phase 1	Final	Evaluation of safety and pharmacokinetics of rFXIII in healthy Japanese subjects.

Source: Sponsor submission *Risk Management Plan* page 25 of 779

Exposure to rFXIII was summarized by age group by the sponsor in the table below:

Age group (years)	Persons		Person exposures	
	Male	Female	Male	Female
Congenital deficiency (F13-1663, F13CD-1725, F13CD-3720, F13CD-3760 and F13CD-3835)				
0–5	3	3	44	48
6–12	7	5	243	155
13–17	7	2	148	14
18–65	30	21	786	544
66+	1	1	1	7
Subtotal	48	32	1,222	768
(b) (4)				
18–65	81	13	81	13
66+	181	41	181	41
Subtotal	262	54	262	54
Healthy subjects (F13-1661, F13-1662, NN1841-3788 and NN1810-3733)				
18–65	96	26	176	58
Subtotal	96	26	176	58
Total	406	112	1,660	880

Source: Sponsor submission *Risk Management Plan* page 28 of 779

No treatment-related antibodies were reported in the (b) (4) trials.

b. Safety Concerns

Antibody formation (MedDRA preferred terms *non-neutralizing antibodies positive*, *antibody test positive*, *drug-specific antibody present*):

There was one case of low-level antibody development reported in a healthy subject trial (NN1841-3788) following the first exposure to rFXIII (b) (4). However, no adverse events were reported in association with this finding and the patient was not re-exposed to rFXIII (discontinued treatment with rFXIII), and a follow up sample taken after 6 months for re-evaluation of anti-rFXIII antibodies was negative.

In the pivotal trial (F13CD-1725), 4 patients were found to have developed anti-rFXIII antibodies. These transient, low-titer antibodies (titers of 2.3-2.6, with lowest quantification level being 2.0 in log scale) were considered by the sponsor to be non-neutralizing antibodies given the apparent lack of impact on treatment effectiveness and because no neutralizing activity was identified by functional inhibitory assay at any time point. Two of the 4 patients were (b) (4) (14 year old male and 16 year old female) and were reported to have developed anti-rFXIII antibodies after the first exposure to rFXIII. NovoThirteen was discontinued in the trial as the risk of development of neutralizing antibody (inhibitor) development was unknown. These 2 patients continued to receive local standard treatment and were monitored throughout the trial and the antibody titer was found to decline below detection limits at 4 and 8 months after rFXIII initiation. One patient, an 8 year old male, developed antibodies after the first exposure. Antibody levels had decreased to below level of detection by the time for the second dose. Parents withdrew consent and the patient discontinued trial participation. Another patient, also

an 8 year old male, continued receiving monthly rFXIII treatment and the antibody titer decreased to below detection limits 4 months later. The sponsor reported no adverse events (including no treatment-requiring bleeding episodes) observed in any of these 4 patients during presence of antibodies or during the follow-up. The sponsor further reported that there was no change in FXIII activity (peak and trough levels) after dosing with rFXIII following the detection of anti-rFXIII antibodies in any of the four patients. All 4 patients had received at least 2 doses of rFXIII, including at least one dose of rFXIII subsequent to antibody formation. Because an actual case of neutralizing antibody formation has not been identified based on the results of the clinical safety database this is not considered an identified risk for this rFXIII A subunit product at this time. It is considered a potential risk.

The following summary pertaining to the 4 cases of antibody development in the pivotal clinical trial (F13CD-1725) was provided by the sponsor:

Parameter	Subject			
	(b) (6)			
Age (at baseline), gender and country	16-year-old female USA	14-year-old male USA	8-year-old male Canada	8-year-old male Spain
Genetic defect	Homozygous for a splice site mutation in intron 5	Homozygous for a splice site mutation in intron 5	Compound heterozygous for 2 missense mutations (exon 5 and exon 10)	Compound heterozygous for 2 missense mutations (in exon 3 and in exon 7)
Previously used FXIII product	Cryoprecipitate	Cryoprecipitate	Fibrogammin® P	Fibrogammin® P
Antibodies detected	Non-neutralising specific binding antibodies to rFXIII			
Isotype of antibody	IgM	IgM	IgM	Not measurable
Number of doses at detection	1	1	1	2
Total exposures to rFXIII	2	2	3	33 and treatment with rFXIII continues
Exposure to rFXIII after detection of antibodies	1	1	2	31 and treatment with rFXIII continues
Action taken	Patient discontinued treatment with rFXIII. Prophylaxis continued with cryoprecipitate	Patient discontinued treatment with rFXIII. Prophylaxis continued with cryoprecipitate	Patient discontinued treatment with rFXIII at request of parents. Prophylaxis continued with Fibrogammin® P.	Patient continued treatment with rFXIII
Outcome	Transient	Transient	Transient while still receiving rFXIII	Transient while still receiving rFXIII
Comment	All patients received at least 2 doses of rFXIII and there has been neither increase nor isotype switching upon the second administration of rFXIII. No allergic reactions or bleeding episodes were reported during the period that antibodies were detectable or in the follow-up period in these patients.			

Source: Sponsor submission *Risk Management Plan* page 39 of 779

No treatment-related antibodies were reported in the (b) (4) trials (b) (4)

Hypersensitivity reactions: There have been allergic reactions reported in the development program for rFXIII in patients with congenital deficiency. These included 2 events of eye swelling in one subject in trial F13CD-1725 with the investigator's assessment that causality was unlikely, 1 serious event of anaphylactic reaction in 1 subject in trial (b) (4), investigating use of rFXIII following (b) (4) (the patient was also receiving concomitant protamine with known associated risk of anaphylactic reaction), and 1 non-serious event of anaphylactic shock in trial (b) (4) in which causality was deemed unlikely.

No allergic reactions were reported in healthy subjects.

No allergic or hypersensitivity reactions were reported in association with anti-rFXIII and no allergic reactions reported during the period in which antibodies were detectable or in the follow-up period in the 4 patients in whom anti-rFXIII was detected.

Thrombotic events: No thrombotic or embolic events were reported in study patients with congenital factor XIII deficiency

Lack of therapeutic effect: Per the sponsor, rFXIII requires endogenous FXIII B-subunit to be effective in providing prophylaxis against bleeding for a 1-month period and that as such, severe hepatic impairment may result in B-subunit deficiency, resulting in lack or decreased efficacy of rFXIII.

Viral transmission: Viral and other infectious disease transmission: rFXIII is recombinant and the risk of viral/infectious agent transmission is considered virtually eliminated.

Missing Information: Patients who were pregnant/lactating, patients with renal insufficiency, and elderly patients were excluded from the rFXIII development program and will be covered by routine pharmacovigilance activities and risk minimization activities, and the post marketing study (NN1841-3868) and the Prospective Rare Bleeding Disorder Database Registry.

c. Sponsor's proposed actions and timelines:

The sponsor anticipates the completion of the proposed phase IV study by 2018 (study duration of 5 years).

The sponsor proposes the following action plan for the non-neutralizing antibodies to determine clinical significance:

- Continued analysis of safety data from clinical trials and safety data collected during post-marketing period including PASS NN1841-3868.
- Structured follow-up of reports where clinical findings or laboratory findings may indicate a lack of expected effect in order to determine the cause.
- Analysis of blood samples for formation of antibodies when there is lack of effect indicated by clinical signs or laboratory findings reported in the post-marketing period from both spontaneous sources and also from non-interventional studies.
- Cases of antibodies to rFXIII will be reported on an expedited basis regardless of case type (seriousness and expectedness).

The sponsor recognizes and states that if non-neutralizing antibodies are demonstrated to be associated with adverse events, the known safety profile of rFXIII would change, thus requiring changes in labeling and risk minimization activities.

The sponsor, in order to detect, assess, and characterize theoretical risk of neutralizing antibodies to rFXIII, proposes the following action plan in the event of identification of neutralizing antibodies:

- Continued analysis of safety data from clinical trials and safety data collected during post-marketing period including post-authorization safety study (PASS) NN1841-3868 and Prospective Rare Bleeding Disorder Database (PRO-RBDD) registry.
- Structured follow-up in the post-marketing period of reports of suspected neutralizing antibodies and also reports where clinical findings or laboratory findings may indicate a lack of expected effect from both spontaneously reported and non-interventional studies.
- Analysis of blood samples for formation of antibodies when there is lack of effect indicated by clinical signs or laboratory findings or there is suspicion of neutralizing antibodies reported in the post-marketing period from both spontaneous sources and non-interventional studies.
- Cases of neutralizing antibodies to rFXIII will be reported on an expedited basis regardless of case type (seriousness and expectedness).

Per the sponsor, the detection of anti-rFXIII specific antibodies will be reported to the FDA on an expedited basis regardless of seriousness, source of report and country of origin. In addition, as part of the pharmacovigilance plan Novo Nordisk has described a process for antibody assessment for all patients that are treated with rFXIII regardless of their inclusion in an observational study. This process will be initiated in the event that Novo Nordisk receives any reports of a suspicion of antibodies or reports that are assessed by Novo Nordisk to indicate antibody formation.

The sponsor recognizes and states that if neutralizing antibodies are detected and found to be associated with adverse events, this would change the benefit to risk profile of rFXIII, requiring changes in labeling and risk minimization activities. Neutralizing antibodies with inhibitory action would result in priority update of product labeling and possible risk minimization activities such as a direct health care communication.

Allergic Reactions

The sponsor, in order to assess and characterize risk of allergic reactions associated with rFXIII, proposes the following action plan in the event of identification of allergic reactions:

- Continued analysis of safety data from clinical trials and safety data collected during post-marketing period including PASS NN1841-3868 and PRO-RBDD registry.
- Structured follow-up in the post-marketing period of reports indicating a possible allergic reaction from both spontaneous reports and reports from non-interventional studies.

- Cases of allergic reaction to rFXIII will be reported on an expedited basis regardless of seriousness and expectedness.

The sponsor recognizes and states that demonstration of causal relationship between rFXIII and allergic reactions will result in an update to the label and appropriate pharmacovigilance activities.

Embotic/Thrombotic Events

The sponsor, in order to assess and characterize theoretical risk of embolic and thrombotic events, proposes the following action plan in the event of identification of thrombotic/embolic events (given that rFXIII is expected to have an effect on the coagulation system):

- Continued analysis of safety data from clinical trials and safety data collected during post-marketing period including PASS NN1841-3868 and PRO-RBDD registry.
- Structured follow-up in the post-marketing period of reports that indicate embolic or thrombotic events from spontaneous reports and reports from non-interventional studies.

The sponsor recognizes and states that demonstration of a definite causal relationship between rFXIII and embolic and thrombotic events will result in an update to the label and appropriate pharmacovigilance activities.

Lack of Efficacy

The sponsor, in order to assess and characterize potential of lack of efficacy, proposes the following action plan to assess and characterize risk of antibodies that may present with lack of efficacy:

- Continued analysis of safety data from clinical trials and safety data collected during post-marketing period including PASS NN1841-3868 and PRO-RBDD registry.
- Structured follow-up in the post-marketing period of reports that indicate lack of expected response from spontaneous reports and reports from non-interventional studies.
- Analysis of blood samples if related to immunogenicity

The sponsor recognizes and states that demonstration of lack of efficacy demonstrated to be due to immunogenicity would, in the same manner that neutralizing antibodies would, require changes in labeling and risk minimization activities given that neutralizing antibodies with inhibitory action would result in priority update of product labeling and possible risk minimization activities such as a direct health care communication.

The table below, from the sponsor's risk management plan submission summarizes the planned actions to identify and characterize identified risks:

Safety concern	Planned actions to identify and characterise risk
Identified risks	
Non-neutralising antibodies	<ul style="list-style-type: none"> • Routine pharmacovigilance, including: <ul style="list-style-type: none"> – Structured follow-up form – Analysis of blood samples – Expanded reporting • PASS NN1841-3868
Important potential risks	
Neutralising antibodies	<ul style="list-style-type: none"> • Routine pharmacovigilance, including: <ul style="list-style-type: none"> – Structured follow-up form – Analysis of blood samples – Expanded reporting • All clinical trials • PASS NN1841-3868 • PRO-RBDD registry
Allergic reactions	<ul style="list-style-type: none"> • Routine pharmacovigilance, including: <ul style="list-style-type: none"> – Structured follow-up form – Expanded reporting • All clinical trials • PASS NN1841-3868 • PRO-RBDD registry

Source: Sponsor Submission *Module 1.16 Risk Management Plan* page 60 of 779

Reviewer comment: The above proposed monitoring and action plan for addressing non-neutralizing antibody formation, allergic reactions, the theoretical risks of neutralizing antibodies/lack of efficacy, and thrombotic/embolic events, is adequate.

d. Review of the sponsor's post marketing study

The sponsor has proposed a Phase IV Post-Marketing Study, the summary excerpt of which is included below as appears as part of the sponsor's response to one of the CR letter questions:

“Phase 4 Post-marketing Study

Novo Nordisk is committed to continuing to further understand the safety profile of rFXIII in the post-marketing period and has proposed to conduct a post-marketing observational study (NN1841-3868) and a pharmacovigilance plan to continue this assessment. NN1841-3868 will investigate the incidence of specific adverse drug reactions associated with the use of rFXIII in patients with congenital Factor XIII A-subunit deficiency. Specific adverse drug reactions to be investigated include anti-FXIII antibodies, allergic reactions, thromboembolic events and lack of therapeutic effect. An updated protocol is included in the updated version of the Risk Management Plan. In the post-marketing observational study NN1841-3868 physicians are encouraged to perform testing for FXIII antibodies at the initiation of treatment with rFXIII and as routine practice during visits to the clinic. Physicians are also strongly encouraged to perform clinical evaluation and blood testing for FXIII antibodies in the presence of lack of therapeutic effect in accordance with the product labeling. If a patient is monitored at the initiation of treatment with rFXIII, the treating physician is

asked to collect blood samples for FXIII antibody assessment. If anti-rFXIII antibodies are detected at any time it is highly recommended that an additional sample is drawn and analyzed, including a monitoring of the peak and trough level of FXIII activity according to clinical practice. Novo Nordisk offers to perform, analyze and report the antibody assessment and will cover the associated expenses. The antibody assessment is a stepwise tiered analytical process involving antibody screening, confirmation of specificity, titer, isotyping and evaluation of inhibitory activity. Safety data from the observational study will be reported in the Periodic Safety Update Report (PSUR) which will be submitted to FDA according to the regulations.

In addition, as part of the pharmacovigilance plan Novo Nordisk has described a process for antibody assessment for all patients that are treated with rFXIII regardless of their inclusion in an observational study. This process will be initiated in the event that Novo Nordisk receives any reports of a suspicion of antibodies or reports that are assessed by Novo Nordisk to indicate antibody formation. The detection of anti-rFXIII specific antibodies will be reported to the FDA on an expedited basis regardless of seriousness, source of report and country of origin.

In addition, the proposed post-marketing study will continue to collect safety data in this ultraorphan condition and ensure a continuously favorable benefit risk profile.”

The sponsor also commits to “Cooperation with other existing local FXIII or rare bleeding disorders registries in EU, US and other countries is being sought in order to collect data on all patients with FXIII CD regardless of treatment. Especially contractual collaboration with the currently global Prospective Rare Bleeding Disorder Database (PRO-RBDD) is being investigated. A comparison between the results from this observational PASS (NN1841-3868) and PRO-RBDD will be included in the final observational study report.” (Source: Sponsor Submission Module 1.16 Risk Management Plan page 328 of 779)

Reviewer Summary of Sponsor's Proposed Observational Study Protocol (NN1841-3868)

The sponsor has submitted a proposal for a phase IV post-marketing prospective multi-center observational study which aims to observe all patients exposed to rFXIII in the EU and “selected” non-EU countries, including the US, over a period of 5 years, for adverse events and antibody formation, including special focus on FXIII antibodies, lack of therapeutic effect, allergic reactions, embolic and thrombotic events as its primary objective.

The population eligible for participation will be any patient with FXIIIA-subunit deficiency for whom a decision to treat with rFXIII has been made and who has provided signed informed consent, upon screening and meeting inclusion criteria for participation in this observational study. The inclusion criteria are informed consent obtained before any study-related activities (all study-related activities are any procedure related to recording of data according to the protocol); ability and willingness to provide signed informed consent (or patient's legally acceptable representative (LAR) consent, if applicable), as required by local ethics committee, governmental or regulatory authorities; congenital FXIII A-subunit deficiency; actual or planned exposure to the rFXIII; no specific exclusion criteria are proposed. The lack of specific exclusion criteria, as proposed by the sponsor is adequate in this setting, given that the trial is to include all patients who have been previously determined to require NovoThirteen administration for their congenital FXIII A-subunit deficiency (as long as the patient consents to inclusion in the observational post marketing study).

The primary endpoint is adverse drug reactions in patients with congenital FXIII A-subunit deficiency treated with rFXIII, specifically FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of effect, collected during study period up to 5 years. The secondary endpoints are all serious adverse events collected during study period up to 5 years, all medical events of special interest collected during study period up to 5 years, and all medication errors and near medication errors collected during study period up to 5 years, where these three secondary endpoint results will be presented by all patients and by special populations (children, elderly, pregnant and lactating, and renal insufficiency). Also included as secondary endpoints are use of rFXIII in patients with congenital FXIII A-subunit deficiency also for other uses than for prophylactic treatment collected during study period up to 5 years (which comprise events of special interest, per the sponsor), and frequency of bleeding episodes collected during study period up to 5 years.

The proposed assessments, included in the table below, submitted by the sponsor, are adequate in obtaining the information sought. In this observational study physicians are directed to submit samples to investigate antibodies in the event of lack of therapeutic effect. Per the sponsor, *“Laboratory analysis and reporting will be performed by a central laboratory designated by Novo Nordisk. Laboratory data from the central laboratories will be reported to the site and Novo Nordisk. Laboratory data will be reported to Novo Nordisk with an identifier in a manner that anonymity of patients will be maintained. All central laboratory analyses will be paid for by the sponsor.”*

The quality control of the central laboratory test results will be performed according to the regulations and specifications set by the authorities at the location of the central laboratory used for this study. Laboratory kits with tubes will be provided to the sites for the optional collection of blood samples.” The sponsor plans to provide sample collection tubes and states that NovoThirteen is to be acquired through usual post licensure commercial means and will not be supplied by Novo Nordisk, stating further that all direction for medication use is solely at the discretion of the physicians in accordance with usual care guided by provided product information (US PI EUmPC, or corresponding local prescribing information).

Reviewer comment: The sponsor also proposes collection of information pertaining to exposure and follow-up on adverse reaction reports associated with off-label use, through both study NN1841-3868 and the PRO RBDD Registry. The PASS NN1841-3868 study and PRO-RBDD registry do not require any testing for non-neutralizing antibody formation. Therefore the sponsor should include at least yearly evaluation of anti-rFXIII antibody status of patients enrolled in the study PASS NN1841-3868, and should revise the protocol and consents to reflect this change, accordingly.

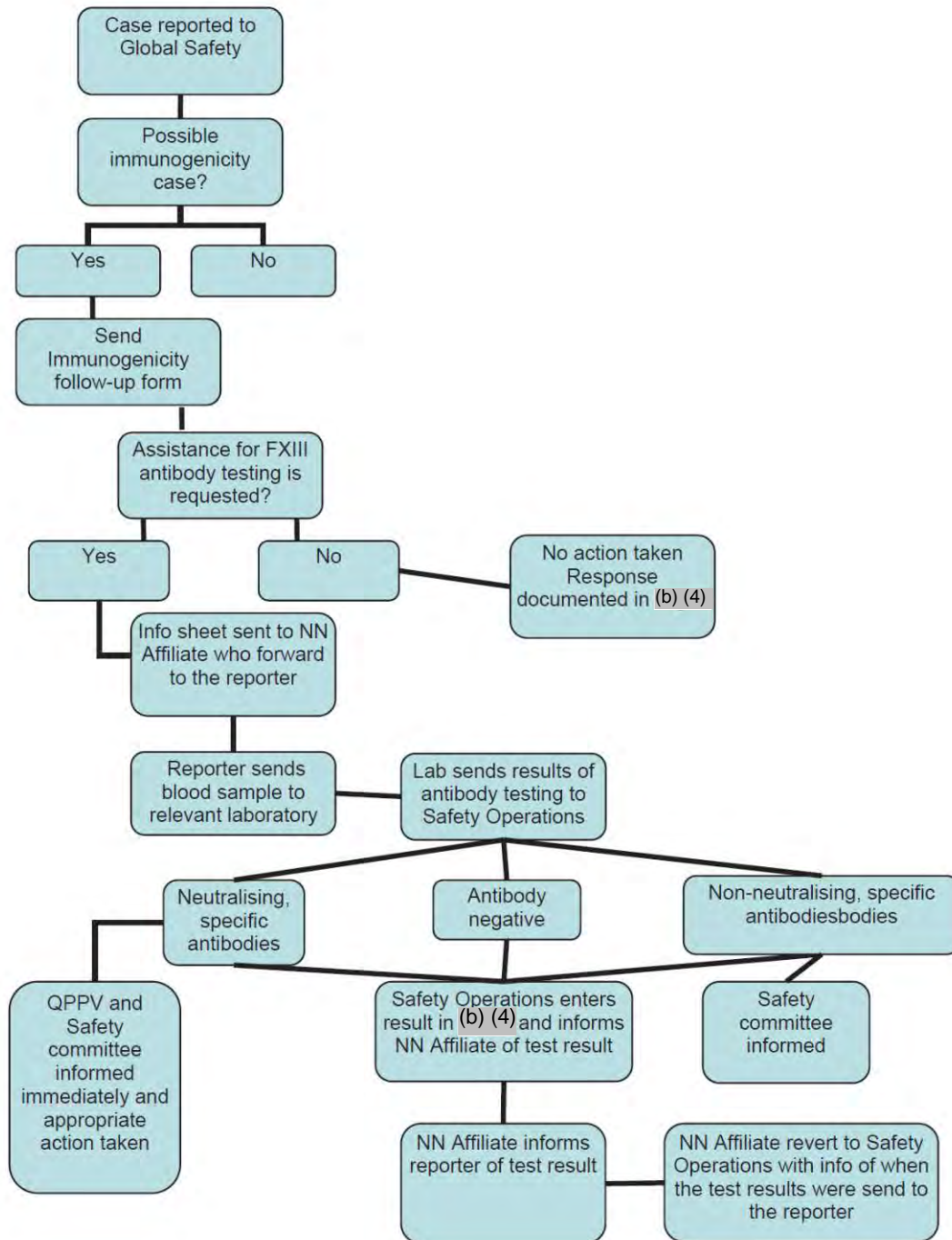
The following, provided by the sponsor, is a summary of the assessment and monitoring plan for the proposed study:

Assessment/Monitoring

Study periods	Baseline (visit 1)	Assessment visits (visit 2.1, 2.2, 2.3 ...)	End of study visit (visit 3)
Visit type	Baseline visit	In conjunction with regular	
Visit window/days	Day 0	Visits with recommended 1-6 months	
PATIENT RELATED ASSESSMENTS			
Informed consent	X		
In/exclusion criteria	X		
Withdrawal criteria		X	
Demography	X		
Bleeding treatment history/history of bleeding episodes	X		
Pre-defined complications	X		
Medical history/concomitant illness	X		
Details of diagnosis of FXIII deficiency (FXIII activity and FXIII antibodies)	X		
Concomitant medication	X	X	X
Concomitant illness		X	X
Body measurements	X	X ₂	X ₂
Vital signs	X		X
Participation in registries	X	X	X
SAFETY ASSESSMENTS			
Adverse drug reaction assessment		X	X
Specific adverse drug reaction assessment			
Optional blood samples for FXIII antibodies ¹	X ³	X	X
Embolic and thrombotic events		X	X
Lack of therapeutic effect		X	X
Allergic reactions		X	X
Optional blood samples for FXIII activity ¹	X ³	X	X
Serious adverse event		X	X
Medical event of special interest		X	X
Medication errors and near medication errors		X	X
BLEEDING ASSESSMENTS			
Bleeding episode description		X	X
Bleeding episodes since last visit		X	X
OTHER ASSESSMENTS			
Diary (instruction/evaluation)	X	X	X
o Prophylactic treatment regimes			
o Bleeding episode description			
o Prophylactic treatment related to surgery			
Documentation of pregnancy		X	X
Footnote	Description		
¹	Blood samples to be drawn prior to any planned rFXIII injection		
²	Body weight only		
³	Performed as part of routine clinical care established by the physician, or in case of lack of therapeutic effect.		

Source: Sponsor Submission *Module 1.16 Annex 5C Protocol* pages 10-11 of 57

The sponsor states that Novo Nordisk will conduct the proposed requisite antibody tests (at no charge). FXIII neutralizing antibody assay has been developed and validated. The assay principle is based on a (b) (4) assay. The effect of FXIII neutralizing antibodies is to be evaluated through rFXIII spiking of study samples. The algorithm below will be used:



Source: Sponsor submission Module 1.16 Annex 5C, *Process for rFXIII Antibody Testing in the Post-Marketing Period*, page 5 of 9

The study design is an open label uncontrolled registry which will limit epidemiologic inferences. However, given the rarity of the condition, it has the potential to be a useful addition to other pharmacovigilance activities. OBE recommends that the sponsor alter the study design so that patients enrolled in this trial should, in addition to baseline anti-rFXIII antibody testing, have samples drawn at least yearly for anti-rFXIII antibody evaluation in order to serve as comparison and better inform the clinical significance of presence of any antibodies that may alter the effectiveness of treatment, if these develop. It would be important to know the anti-rFXIII antibody status of all patients in order to be able to better evaluate the clinical significance of such antibodies. This would allow evaluation of number of patients found to be antibody positive and without any clinically significant consequence (no decrease in effectiveness of treatment) and compare it to the number of patients, if any, who develop antibodies that impact effectiveness of the product. The protocol and informed consents should be revised accordingly.

The following is the planned study schedule specified by the sponsor and details the key milestones for the sponsor's postmarketing commitment:

Planned duration of recruitment period is 3 years after first patient first visit (FPFV) in the study.

Planned date for FPFV: Q1 2013

Planned date for last patient first visit (LPFV): Q1 2016

Planned date for last patient last assessment visit: Q2 2018

The end of the observational study is defined as termination of study, after this date the patients' next visit to the clinic will be their end of study visit.

Planned completion of the last patient (LPLV): Q2 2018

Planned completion of observational study report: Q3-4 2018

The study will include patients exposed to rFXIII. The study duration is 5 years.

Source: Sponsor Submission *Module 1.16 Risk Management Plan* 313 of 779

In addition, the sponsor has 2 ongoing trials (F13CD-3720 and F13CD-3835), with safety endpoints, summarized below:

- Study F13CD-3720 consists of a phase 3b multicenter, multinational, open label, single arm, multiple dosing trial evaluating safety of monthly rFXIII replacement in patients with congenital factor XIII deficiency. It is a safety extension study to F13CD-1725 (pivotal trial in patients ages ≥ 6 years with diagnosis of congenital FXIII A subunit deficiency confirmed by genotyping). All 33 patients (ages 7-60, mean age 28.8 years) who completed F13CD-1725, entered F13-CD3720, and are to continue treatment for 52 weeks. The study was conducted in centers in Canada, US, UK, Austria, Finland, France, Germany, Israel, Italy, Spain, and Switzerland, for total of 19 study sites, 6 of which are in the US). Trial participation was ongoing at the time of the sponsor's submission (cutoff of November 30, 2010) with preliminary results consisting of the following:
 - In total, 98 treatment-emergent adverse events were reported. The most commonly reported events were headache and nasopharyngitis. The

overall rates of adverse events were reported as similar for the two drug substances (rFXIII(b) (4): 31.1 adverse events per 100 exposures; rFXIII_{NN}: 25.5 adverse events per 100 exposures) and no differences in rate of any adverse event was apparent between the two drug substances. Two events (limb injury and overdose) were evaluated by the investigator to be possibly or probably related to trial product.

- No anti-rFXIII antibodies were detected.
 - No thromboembolic events, fatal adverse events or adverse events leading to withdrawal were reported.
 - Results on safety laboratory parameters and other safety-related examinations did not indicate clinically significant changes as a result of rFXIII administration, and no differences in these parameters were noted between the two drug substances (rFXIII(b) (4) and rFXIII_{NN}).
- Study F13CD-3835 consists of a multicenter, multinational, open label, single arm, multiple dosing trial evaluating the safety and efficacy of monthly rFXIII replacement therapy in pediatric patients (ages 1 to less than 6 years) with congenital factor XIII A-subunit deficiency who completed pharmacokinetic (PK) trial F13CD-3760. It is a safety extension study to PK trial F13CD-3760* (a phase 3b trial investigating the pharmacokinetics and safety profile of a single intravenous dose of rFXIII in pediatric patients with congenital FXIII A-subunit deficiency, ages 1 to less than 6 years old, which enrolled 6 patients ages 1-4 years, with a mean age of 2.7 years). All six patients are planned to participate in this extension study for a minimum of 52 weeks upon completion of trial F13CD-3760 participation. As of the time of this submission by the sponsor, 1 subject (3 year old female) had received two doses of study drug (cutoff of February 11, 2011). The study drug substance is rFXIII_{NN}.
 - As of the cutoff date (February 11, 2011), no adverse events were reported.
 - *The safety results for trial F13CD-3760 are as follows:
 - No deaths, other serious adverse events, adverse event withdrawals or MESIs were reported after exposure to one single intravenous dose of rFXIII 35 IU/kg in young children with congenital FXIII A-subunit deficiency.
 - There were no treatment-requiring bleeds.
 - Two adverse events (pyrexia and pain in extremity/arm) were reported after exposure. Both events were mild in severity and considered unlikely related to trial product. Both children recovered from their adverse events.
 - No anti-rFXIII antibodies were detected in any of the patients.
 - No clinically relevant changes in safety laboratory parameters or other safety-related examinations were observed.

The table below, submitted by the sponsor summarizes the overview of study protocols of the discussed ongoing and planned clinical trials

Indication Study ID Phase	Study title	Protocol status	Planned date for submission of final data
Congenital deficiency			
F13CD-3720 phase 3b	A multi-centre, open-label, single-arm and multiple dosing trial on safety of monthly replacement therapy with recombinant factor XIII (rFXIII) in subjects with congenital factor XIII deficiency	Final	2016
F13CD-3835 phase 3b	A multi-centre, multinational, open-label, single-arm and multiple dosing trial on safety and efficacy of monthly replacement therapy with recombinant factor XIII (rFXIII) in paediatric subjects with congenital factor XIII A-subunit deficiency (safety extension trial to F13CD-3760)	Final	2014
NN1841-3868 phase 4	Treatment of congenital FXIII deficiency, a prospective multi-centre observational study	Draft	2018

Source: Sponsor Submission *Module 1.16 Risk Management Plan* pages 70-71 of 779

The following table, submitted the sponsor, summarizes outstanding actions:

Actions	Population Planned exposure	Milestones/exposure	Study status
Clinical trials			
F13CD-3720	Extension to F13CD-1725 Planned subjects: 47	PPFV 21 Sep 2009 LPLV (planned) 31 Dec 2015	Ongoing Amendment to the protocol will be effective when protocol is approved by competent authorities and ethics committees.
F13CD-3835	Extension to F13CD-3760 Planned subjects completed: 7	PPFV 07 Jan 2011 LPLV (planned) 25 Dec 2013	Ongoing
Observational studies			
NN1841-3868	Subjects with congenital FXIII A-subunit deficiency treated with rFXIII. No limits established.	PPFV (planned) 04 Mar 2013 LPLV (planned) 01 Jun 2018 Interim analysis planned for 2015.	Proposed protocol
Registries			
PRO-RBDD	Subjects with congenital FXIII deficiency. No limits established.	Starting in 2012 and lasting for 3 years	Ongoing
Reporting			
RMP	Not applicable	Update as appropriate in case of safety issues	Not applicable
DSUR and PSUR	Not applicable	Based on international birth date of 31 Jul 2012	Not applicable

DSUR = development safety update report; PPFV = first patient first visit; FXIII = factor XIII; CTR = clinical trial report; LPLV = last patient last visit; PSUR = periodic safety update report; rFXIII = recombinant factor XIII; RMP = risk management plan

Source: Sponsor Submission *Module 1.16 Risk Management Plan* page 72 of 779

The following is a summary of the risk management plan submitted by the sponsor:

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified risks		
Non-neutralising antibodies	<ul style="list-style-type: none"> Continued analysis of safety data from clinical trials and safety data collected during post-marketing period including PASS NN1841-3868 Structured follow-up of reports where clinical findings or laboratory findings may indicate a lack of expected effect in order to determine the cause Analysis of blood samples for formation of antibodies when there is lack of effect indicated by clinical signs or laboratory findings reported Case reporting on an expedited basis regardless of case type (seriousness and expectedness) 	<p>The CCDS Sections 4.2 and 4.8 state:</p> <ul style="list-style-type: none"> “Treatment should be initiated under the supervision of a doctor experienced in the treatment of rare bleeding disorders.” That frequency of non-neutralising antibodies is common ($\geq 1/100$ to $< 1/10$).
Important potential risks		
Neutralising antibodies	<ul style="list-style-type: none"> Continued analysis of safety data from clinical trials and safety data collected during post-marketing period including PASS NN1841-3868 and PRO-RBDD registry Structured follow-up of reports of suspected neutralising antibodies and also reports where clinical findings or laboratory findings may indicate a lack of expected effect Analysis of blood samples for formation of antibodies when there is lack of effect indicated by clinical signs or laboratory findings or there is suspicion of neutralising antibodies reported Case reporting on an expedited basis regardless of case type (seriousness and expectedness) 	<p>The CCDS Sections 4.2 and 4.4 state:</p> <ul style="list-style-type: none"> “Treatment should be initiated under the supervision of a doctor experienced in the treatment of rare bleeding disorders.” “Inhibitor formation to NovoThirteen® therapy has not been detected in clinical trials. Inhibitors may be suspected in the event of lack of therapeutic response which is observed as bleeding or demonstrated by laboratory findings including FXIII activity that fails to reach expected levels. In the event that inhibitors are suspected analysis for antibodies should be performed. Patients known to have neutralising antibodies to FXIII should not be treated with NovoThirteen® without close monitoring.”
Allergic reactions	<ul style="list-style-type: none"> Continued analysis of safety data from clinical trials and safety data collected during post-marketing period including PASS NN1841-3868 and PRO-RBDD registry Structured follow-up of reports indicating a possible allergic reaction Case reporting on an expedited basis regardless of seriousness and expectedness 	<p>The CCDS Sections 4.2 and 4.4 state:</p> <ul style="list-style-type: none"> “Treatment should be initiated under the supervision of a doctor experienced in the treatment of rare bleeding disorders.” “As NovoThirteen® contains a recombinant protein it may cause allergic reactions including anaphylactic reaction. Patients should be informed of the early signs of hypersensitivity reactions (including hives, generalised urticaria, tightness of the chest, wheezing, hypotension) and anaphylaxis. If allergic or anaphylactic-type reactions occur, the administration should be immediately discontinued and further treatment with NovoThirteen® should not be given.”

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Embolic and thrombotic events	<ul style="list-style-type: none"> Continued analysis of safety data from clinical trials and safety data collected during post-marketing period including PASS NN1841-3868 and PRO-RBDD registry Structured follow-up of reports indicating embolic and thrombotic events 	<p>The CCDS Sections 4.2 and 4.4 state:</p> <ul style="list-style-type: none"> “Treatment should be initiated under the supervision of a doctor experienced in the treatment of rare bleeding disorders.” “In case of predisposition to conditions of thrombosis, caution should be exercised due to the fibrin-stabilising effect of rFXIII. A stabilisation of the thrombus might occur, resulting in increased risk of vessel occlusions.” “Incorrect storage of the product after reconstitution must be avoided as it may result in loss of sterility and in increased levels of activated NovoThirteen®. Increased levels of activated NovoThirteen® may increase the risk of thrombosis.” <p>Patient educational material and physician information brochure are being prepared to decrease the risk of toxicity in connection with incorrect storage (draft in Annex 10 and Annex 11 in Table 49).</p>
Lack of efficacy	<ul style="list-style-type: none"> Continued analysis of safety data from clinical trials and safety data collected during post-marketing period including PASS NN1841-3868 and PRO-RBDD registry Structured follow-up of reports indicating lack of efficacy Analysis of blood samples if related to immunogenicity 	<p>The CCDS Sections 4.1, 4.2 and 4.4 state:</p> <ul style="list-style-type: none"> “rFXIII is indicated for long-term prophylactic treatment of bleeding in patients with congenital factor XIII A-subunit deficiency.” “In patients with FXIII deficiency, NovoThirteen® is not effective if used for monthly prophylactic treatment of bleeding in patients with congenital FXIII B-subunit deficiency. FXIII B-subunit deficiency is associated with a much reduced half life of the administered pharmacologically active A-subunit. The subunit deficiency of patients should be determined prior to treatment by appropriate diagnostic procedures.” “Treatment should be initiated under the supervision of a doctor experienced in the treatment of rare bleeding disorders. The congenital factor XIII A-subunit deficiency should be confirmed by appropriate diagnostics procedures.” “Patients with hepatic impairment have not been studied. NovoThirteen® may not be effective in patients with hepatic impairment if the hepatic impairment is severe enough to result in decreased levels of FXIII B-subunits. FXIII activity levels should be monitored in patients with severe hepatic impairment.”

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Drug interaction of rFXIII with rFVIIa when used outside of the approved indication	<ul style="list-style-type: none"> Collect exposure and follow-up on adverse reaction reports associated with off-label use during post-marketing period including PASS NN1841-3868 and PRO-RBDD registry. 	<p>Mandatory training for all relevant Novo Nordisk A/S employees in SOPs concerning off-label information is anticipated to improve communication and decrease potential off-label use.</p> <p>The CCDS Sections 4.1, 4.2 and 4.5 state:</p> <ul style="list-style-type: none"> “rFXIII is indicated for long-term prophylactic treatment of bleeding in patients with congenital factor XIII A-subunit deficiency.” “Treatment should be initiated under the supervision of a doctor experienced in the treatment of rare bleeding disorders. The congenital factor XIII A-subunit deficiency should be confirmed by appropriate diagnostics procedures.” <p>“There are no clinical data available on interaction between NovoThirteen® and other medicinal products. A potential synergistic effect of combined treatment with NovoThirteen® and rFVIIa in an advanced cardiovascular model in (b) (4) monkey was seen resulting in exaggerated pharmacology (thrombosis and death) at a lower dose level than when administering the individual compounds. Based on the non-clinical study it is not recommended to combine NovoThirteen® and rFVIIa.”</p>
Medication error related to reconstitution and administration	<ul style="list-style-type: none"> Continued analysis of safety data from clinical trials and safety data collected during post-marketing period including PASS NN1841-3868 and PRO-RBDD registry Structured follow-up forms in cases of embolic and thrombotic events 	<p>The CCDS Section 4.4 states:</p> <p>“Incorrect storage of the product after reconstitution must be avoided as it may result in loss of sterility and in increased levels of activated NovoThirteen®. Increased levels of activated NovoThirteen® may increase the risk of thrombosis.”</p> <p>Patient educational material and a physician information brochure are being prepared to avoid medication error related to reconstitution and administration (draft in Annex 10 and Annex 11 in Table 49).</p>
Off-label use for management of bleedings	<ul style="list-style-type: none"> An amendment to F13CD-3720 has been made to allow the collection of efficacy and safety data for the management of breakthrough bleeds with rFXIII. Continued analysis of safety data from clinical trials (F13CD-3720) and safety data during the post-marketing period including PASS NN1841-3868 and PRO-RBDD registry. Collection of drug utilisation data during the post-marketing period including PASS NN1841-3868 and PRO-RBDD registry. 	<p>As a routine risk minimisation, the CCDS Sections 4.1 and 4.4 state:</p> <ul style="list-style-type: none"> “rFXIII is indicated for long-term prophylactic treatment of bleeding in patients with congenital factor XIII A-subunit deficiency.” “The on-demand treatment of acute bleeds or breakthrough bleeds with NovoThirteen® has not been studied in clinical trials. An alternative treatment could be considered in such situations.” <p>A physician information brochure is being prepared to create awareness among physicians about the indications of the product (draft in Annex 11 in Table 49).</p>

Important missing information		
Elderly	<ul style="list-style-type: none"> Continued analysis of safety data from clinical trials (F13CD-3720) and safety data collected during post-marketing period including PASS NN1841-3868 and PRO-RBDD registry 	The CCDS Section 4.4 states: “There is limited clinical experience in administering rFXIII to elderly patients with congenital FXIII deficiency.”
Pregnant and lactating women	<ul style="list-style-type: none"> Continued analysis of safety data collected during post-marketing period including PASS NN1841-3868 and PRO-RBDD registry 	<p>The CCDS Section 4.6 states:</p> <ul style="list-style-type: none"> “There are no clinical data on the use of NovoThirteen® in pregnant women. Animal studies are insufficient with respect to reproductive toxicity as NovoThirteen® has not been studied in pregnant animals. The risk to humans is not known. However, based on the therapeutic need the use of NovoThirteen®
Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		<p>as a replacement therapy may be considered during pregnancy. It is unknown whether rFXIII is excreted in human breast milk. The excretion of rFXIII drug substance in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with NovoThirteen® should be made taking into account the benefit of breast-feeding to the child and the benefit of NovoThirteen® therapy to the mother.”</p> <ul style="list-style-type: none"> “No effects on reproductive organs have been seen in nonclinical studies. There are no human data on potential effects on fertility.”
Patients with renal insufficiency	<ul style="list-style-type: none"> Continued analysis of safety data collected during post-marketing period including PASS NN1841-3868 and PRO-RBDD registry 	The CCDS Section 4.4 states: “Patients with renal insufficiency requiring dialysis have not been studied in clinical trials.”

CCDS = company core data sheet; FXIII = factor XIII; rFVIIa = activated recombinant factor VII; rFXIII = recombinant factor XIII; PASS = post-authorisation safety study; PRO-RBDD = Prospective Rare Bleeding Disorder Database; SOP = standard operating procedure.

Source: Sponsor Submission *Module 1.16 Risk Management Plan* pages 84-88 of 779

4. REVIEW OF OTHER INFORMATION FROM THE MANAGED REVIEW PROCESS

Final determination of the safety profile of the product used in the studies submitted to this BLA is pending final clinical and statistical reviews which are not complete at this time.

5. INTEGRATED RISK ASSESSMENT

No new safety signals were identified during this review. The available data pertaining to the risk of antibody formation submitted by the sponsor in support of this BLA indicates a risk of anti-rFXIII antibody formation (4/41) in association with NovoThirteen. Antibodies described were of low titers and transient. These antibodies did not appear to adversely affect treatment outcome or increase the incidence of adverse reactions (specifically of concern is a lack of drug efficacy, or bleeding requiring treatment). No neutralizing antibodies were reported and the titers of the antibodies were found, over time, to have decreased to below detection limits. Review of the scientific literature did not provide additional data to assist us in determining the probability of these antibodies persisting or developing neutralizing activity. Based on the findings in the clinical trials discussed in section 3, despite having no neutralizing antibodies identified in these clinical trials, there remains the potential for neutralizing antibody formation to NovoThirteen. This potential for antibody formation is well known for many (perhaps all) factor products, will be mentioned in the label, and will be addressed in the post marketing study proposed by the sponsor. This review did not substantiate a need for a post marketing requirement or Risk Evaluation and Mitigation Strategies (REMS).

The proposed pharmacovigilance plan, which includes enhanced pharmacovigilance, the discussed post marketing safety study (NN1841-3868), and a registry or contractual collaboration established with the Prospective Rare Bleeding Disorder Database to ensure access to all patients treated with rFXIII, is adequate to monitor the safety of NovoThirteen, if the sponsor agrees to add at least yearly evaluation of anti-rFXIII antibody status of patients enrolled in the study PASS NN1841-3868.

The prevalence of the FXIII congenital deficiency is low and as such an observational study is a reasonable method for obtaining additional safety information in the post marketing setting. In the post marketing setting additional numbers of patients would have access to rFXIII, further informing the safety profile of the drug, particularly as pertains to the incidence and effects of antibodies.

The sponsor has in place an acceptable plan and mechanism for identifying/reporting and following up adverse events, including possible effects of antibodies on the treatment outcome (reduced efficacy), that would further inform the risk/benefit assessment and the safety profile of NovoThirteen. If the sponsor adds the requirement of yearly testing for anti-rFXIII antibodies to the assessments and monitoring plan, the proposed observational clinical trial will be adequate.

6. RECOMMENDATIONS

Routine pharmacovigilance along with the sponsor's Pharmacovigilance Plan (Edition 9, Version 1, dated 12/12/2012) including post marketing safety study (NN1841-3868), and a registry or contractual collaboration established with the Prospective Rare Bleeding Disorder Database to ensure access to all patients treated with rFXIII, is acceptable at this time.

The sponsor's enhanced pharmacovigilance plan consists of

- i. Continued analysis of safety data from clinical trials, and safety data collected during the post-marketing period, including PASS NN1841-3868.
- ii. Structured follow-up of reports where clinical findings or laboratory findings may indicate a lack of expected effect in order to determine the cause.
- iii. Analysis of blood samples for formation of antibodies when there is lack of effect indicated by clinical signs or laboratory findings reported in the post-marketing period from both spontaneous sources and also from non-interventional studies.
- iv. Reporting of cases of antibodies to rFXIII on an expedited basis regardless of case type (seriousness and expectedness).

In addition, patients enrolled in the Phase IV observational study (NN1841-3868) should, in addition to baseline anti-rFXIII antibody testing, have samples drawn at least yearly for anti-rFXIII antibody evaluation in order to serve as comparison and better inform any clinical significance of presence of any antibodies that may affect effectiveness of treatment. The protocol and consents should be accordingly modified to reflect this change.