EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2020
EMA/539227/2020
Committee for Medicinal Products for Human Use (CHMP)

CHMP group of variations including an extension of indication assessment report

Invented name: NovoThirteen

International non-proprietary name: catridecacog

Procedure No. EMEA/H/C/002284/II/0026/G

Marketing authorisation holder (MAH) Novo Nordisk A/S

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ABR	Annualised bleeding rate
ADR	Adverse drug reactions
AE	Adverse event
CI	Confidence interval
CRF	Case report form
ED	Exposure days
EU	European union
EMA	European medicines agency
FPFV	First patient first visit
FXIII CD	Factor XIII congenital deficiency
GVP	Good pharmacovigilance practice
HELLP	Haemolysis, elevated liver enzymes and low platelet count
LDH	Lactate dehydrogenase
LPLV	Last patient last visit
MESI	Medical event of special interest
NA	Not applicable
PASS	Post-authorisation safety Study
pdFXIII	Plasma-derived coagulation factor XIII
PK	Pharmacokinetics
PT	Preferred term
PRO-RBDD	Prospective rare bleeding disorder database
QRD	Quality review of documents
rFXIII	Recombinant factor XIII
RMP	Risk management plan
SAE	Serious adverse event
SOC	System organ class
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 19 December 2019 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB

Extension of indication to include treatment of bleeding episodes in patients with congenital factor XIII A-subunit deficiency as well as minor surgery based on the results of study NN1841-3868 and the PRO-RBDD registry. As a consequence, sections 4.1, 4.2, 4.4, 4.6, 5.1, 5.2 of the SmPC and the RMP version 15 has been submitted. Annex IID and the package leaflet have been updated accordingly. Furthermore, the PI is brought in line with the latest QRD template version. Minor editorial updates have also been made.

The group of variations requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

This request has been withdrawn by the MAH.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau

Timetable	Actual dates
Submission date	19 December 2019
Start of procedure:	1 February 2020
Rapporteur's preliminary assessment report circulated on:	1 April 2020
PRAC Rapporteur's preliminary assessment report circulated on:	1 April 2020
PRAC RMP advice and assessment overview adopted by PRAC	17 April 2020
CHMP members comments	20 April 2020
Joint Rapporteur's updated assessment report circulated on:	22 April 2020
Request for supplementary information and extension of timetable adopted by the CHMP on:	30 April 2020
MAH's responses submitted to the CHMP on:	22 May 2020
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	1 July 2020
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	1 July 2020
PRAC RMP advice and assessment overview adopted by PRAC	9 July 2020
CHMP members comments	13 July 2020
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	
CHMP opinion:	23 July 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Congenital coagulation factor XIII (FXIII) deficiency is a rare autosomal recessive bleeding disorder in which reduced plasma FXIII activity is caused by quantitative or rarely by qualitative defects in the FXIII A-subunit protein. Much less commonly, FXIII deficiency is caused by defects in the FXIII B-subunit protein. FXIII deficiency has an estimated worldwide prevalence of 1 per 2 to 5 million individuals. In patients with FXIII A-subunit deficiency the FXIII activity level is lower than 3 to 5% (or approximately 0.04 to 0.06 IU/mL), compared with a wide range of approximately 50% to 220% (0.60 to 2.60 IU/mL) in the normal population.

Diagnosis is based on quantitative FXIII activity measurement and antigen assays. Common clotting assays such as activated Partial Thromboplastin Time (aPTT) and Prothrombin Time (PT) are normal and cannot be used for the screening. The clot solubility test may also be used (clot is stable for more than 24 hours in case of FXIII deficiency). However, the assay is qualitative, and when performed correctly the test is positive only when the FXIII activity in the sample is close to zero. Molecular testing is available, but unnecessary for diagnosis. Differential diagnoses mainly include the other congenital coagulation factor deficiencies: fibrinogen, factors II, V, VII, X, XI, VIII, IX. Antenatal diagnosis is possible if the causal mutations have previously been identified in the family.

Congenital FXIII deficiency is characterised by haemorrhagic diathesis frequently associated with spontaneous abortions and defective wound healing. Congenital FXIII deficiency can manifest at any age, but diagnosis is often made during infancy. Umbilical stump bleeding manifests in up to 80% of patients. Other common signs include intracranial haemorrhage (25-30%), soft tissue bleeding, bruising, hemarthroses (20%), and recurrent spontaneous abortions. In most cases, haemorrhages are delayed (12-36hr) after trauma or surgery. Patients may have poor wound healing.

Given that intracranial bleeding is common in FXIII deficiency and may be a presenting feature later in childhood, most cases receive long-term prophylaxis with FXIII concentrate. Current treatment options in FXIII deficiency include cryoprecipitate, fresh frozen plasma, plasma-derived FXIII (pdFXIII) concentrate (Fibrogammin / Corifact) and recombinant FXIII subunit-A (rFXIII, NovoThirteen).

2.1.2. About the product

NovoThirteen is not FXIII. Its active substance, catridecacog, is the A subunit dimer [A2] of human coagulation FXIII produced in yeast cells (Saccharomyces cerevisiae) by recombinant DNA technology. NovoThirteen (A-subunit) binds to free human FXIII B-subunit resulting in a heterotetramer [rA2B2] with a similar half-life to endogenous [A2B2].

One vial of NovoThirteen contains catridecacog (recombinant coagulation factor XIII) (rDNA): 2500 IU per 3 ml, after reconstitution corresponding to a concentration of 833 IU/ml. As compared to NovoThirteen, pdFXIII concentrate contains approximately 62.5 IU/ml, such that larger volumes need to be administrated.

The recommended dose is 35 IU/kg body weight approximately once monthly, administered as an intravenous bolus injection. This will result in a maximum plasma concentration of 5 µg/ml and is not expected to exceed the available free FXIII– B2 subunit.

NovoThirteen was approved by European Medicines Agency (EMA) on 03 September 2012 and was first launched in Denmark on 10 December 2012. It is currently indicated for the long-term prophylactic treatment of bleeding in patients with congenital factor XIII A-subunit deficiency.

As per currently approved labelling of NovoThirteen, it has been indicated for long-term prophylaxis of bleeding in patients with congenital FXIII A-subunit deficiency. The use of rFXIII other than for prophylactic treatment in patients with congenital FXIII A-subunit deficiency was collected as one of the secondary endpoints in the post-authorisation safety study (PASS) (NN1841-3868, MentorTM6). The results of this secondary endpoint suggest that rFXIII can also be used as a treatment of bleeds during the prophylactic regimen in these patients. Supportive results were also reported in a pivotal extension trial (F13CD-3720, mentorTM2) and a paper by Arokszallasi et al.

Additionally, in F13CD-3720 and NN1841-3868 it was demonstrated that prophylaxis with rFXIII would alone be sufficient to avoid bleeding episodes during minor elective surgeries during prophylaxis in patients with congenital FXIII A-subunit deficiency.

As a consequence of the above, this group of variations requests to include addition of treatment of bleeding episodes in patients with congenital factor XIII A-subunit deficiency in the indication as well as a posology-update related to minor surgeries.

In support of this application, the MAH submitted the final results of the PASS NN1841-3868 as part of commitment on post-authorisation measure MEA-003.1. This final study report also includes final data from the global Prospective Rare Bleeding Disorder Database (PRO-RBDD) registry. Two interim reports of PASS NN1841-3868 have been submitted previously. The second interim report covering the period from FPFV until 17th May 2017 with the enrolment of 30 patients were assessed under the procedure EMEA/H/C/2284/MEA-15.1.

The MAH has also updated the SmPC of NovoThirteen to align with the most recent QRD template, version 10.1. The RMP is updated to version 15.0 based on the study results from the PASS NN1841-3868 and PRO-RBDD registry.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

- Tabular overview of clinical studies

The clinical development program of NovoThirteen consists of 12 completed Novo Nordisk sponsored clinical

trials with rFXIII as the investigational drug. Of these, 5 trials with a total of 82 subjects were conducted on the patient population with congenital factor XIII A-subunit deficiency. White (59%) and Asian (17%) racial groups represented the largest populations among these patients.

2.3.2. Pharmacokinetics

No new pharmacokinetics data were submitted in this application.

The half-life of NovoThirteen was assessed in the F13CD-1725 trial from a limited blood sampling scheme at 1 hour, 14 and 28 days post-dose. Based on FXIII activity measured by the Berichrom assay in patients with congenital FXIII deficiency, a geometric mean half-life of 11.8 days was estimated. This is in agreement with the elimination pharmacokinetics estimated from a clinical pharmacology trial in healthy subjects, which determined the half-life to be 11.8 days. In this trial the mean volume of distribution at steady state was 47 ml/kg, mean residence time was 15.5 days and mean clearance was 0.13 ml/kg.

Paediatric population: in a pharmacokinetic trial 6 children (age 1 to less than 6 years old) with congenital FXIII A-subunit deficiency were exposed to one single i.v. dose of NovoThirteen 35 IU/kg. The mean t½ of FXIII was approximately 15 days (range: 10 to 25 days) and the mean clearance in children was 0.15 ml/h/kg.

2.3.3. Pharmacodynamics

Mechanism of action

In plasma, FXIII circulates as a heterotetramer [A2B2] composed of 2 FXIII A-subunits and 2 FXIII B-subunits held together by strong non-covalent interactions. The FXIII B-subunit acts as a carrier molecule for the FXIII A-subunit in circulation and is present in excess in plasma. When the FXIII A-subunit is bound to the FXIII B-subunit [A2B2], the half-life of the FXIII A-subunit [A2] is prolonged.

FXIII is a pro-enzyme (pro-transglutaminase), which is activated by thrombin in the presence of Ca2+. The enzymatic activity resides with the FXIII A-subunit. Upon activation, the FXIII A-subunit dissociates from the FXIII B-subunit and thereby exposes the active site of the FXIII A-subunit. The active transglutaminase cross-links fibrin and other proteins resulting in increased mechanical strength and resistance to fibrinolysis of the fibrin clot and contributes to enhanced platelet and clot adhesion to the injured tissue.

NovoThirteen is a recombinant FXIII A-subunit is structurally identical to the human FXIII A-subunit [A2]. NovoThirteen (A-subunit) binds to free human FXIII B-subunit resulting in a heterotetramer [rA2B2] with a similar half-life to endogenous [A2B2].

Primary and secondary pharmacology

No new pharmacodynamic data were submitted in this application.

At present there are no markers that can quantitatively assess the *in vivo* pharmacodynamics of FXIII. The results of standard coagulation tests are normal, as it is the quality of the clot that is affected. A clot solubility assay is widely used as an indicator of FXIII deficiency, but the assay is qualitative, and when performed correctly the test is positive only when the FXIII activity in the sample is close to zero.

NovoThirteen has been shown to have the same pharmacodynamic properties in plasma as endogenous FXIII.

2.3.4. Discussion on clinical pharmacology

The currently approved SmPC Section 5.2 reflects pharmacokinetic data obtained in healthy subjects (NN1841-3788), patients (≥ 6 years old) in the pivotal phase 3 pivotal trial F13CD-1725 and paediatric patients (1-4 years) with congenital FXIII A-subunit deficiency (Study F13CD-3760).

In the application, the MAH updated SmPC Section 5.2 by replacing the PK data from healthy subjects (NN1841-3788) by PK data from full PK profiles 23 patients with congenital FXIII A-subunit deficiency (age 7-58 years) in Study F13CD-3720 (PK sub-study), so that the proposed SmPC Section 5.2 only reflects pharmacokinetics obtained from patients as this is considered mostly relevant in clinical use.

The Study F13CD-3720 was a safety extension study of the pivotal study F13CD-1725. In this multi-centre, open-label, single-arm, and repeat dose phase 3b trial on safety of monthly replacement therapy with rFXIII in subjects with congenital FXIII A-subunit deficiency, a total of 60 subjects were enrolled and exposed to trial drug which includes 34 subjects from trial F13CD-1725 and 26 new subjects. Of these 60 subjects, 16 were paediatric and adolescents received NovoThirteen at a monthly dose of 35UI/Kg.

The final results of Study F13CD-3720 including "Detailed PK report for patients included in trial F13CD-3720" have been previously submitted in procedures EMEA/H/C/002284/P46/016 and EMEA/H/C/002284/II/0018, however, no assessment of PK data have been found in the AR.

For reminder, the summary of PK results presented in "Detailed PK report for patients included in trial F13CD-3720" (cut-off date for PK: 3 December 2012) are displayed as following:

Table 2: Summary of FVIII activity and PK parameters

	rFXIII 35 IU/kg		
	FDA	Non FDA	All
Number of subjects	8	15	23
Cmax (IU/mL)			
N (%)	8 (100)	15 (100)	23 (100)
Mean (SD)	0.847 (0.243)	0.917 (0.168)	0.893 (0.195)
Median	0.810	0.862	0.862
Min ; Max	0.565 ; 1.240	0.685 ; 1.160	0.565 ; 1.240
Geometrical mean	0.817	0.902	0.872
Ctrough - Day 28 (IU/mL)			
N (%)	6 (100)	15 (100)	21 (100)
Mean (SD)	0.156 (0.083)	0.179 (0.056)	0.173 (0.064)
Median	0.153	0.157	0.154
Min ; Max	0.025 ; 0.277	0.124 ; 0.324	0.025 ; 0.324
Geometrical mean	0.127	0.172	0.158
AUC_0-t (IU*h/mL)			
N (%)	8 (100)	15 (100)	23 (100)
Mean (SD)	245.1 (108.0)	258.5 (54.5)	253.8 (75.1)
Median	205.0	238.4	236.5
Min ; Max	131.2 ; 429.6	204.3 ; 390.5	131.2 ; 429.6
Geometrical mean	225.6	253.8	243.6
AUC_0-28 (IU*h/mL)			
N (%)	6 (75)	13 (86.7)	19 (82.6)
Mean (SD)	234.2 (70.9)	243.3 (38.5)	240.4 (49.0)
Median	211.4	234.0	234.0
Min ; Max	168.6 ; 327.2	201.1 ; 355.9	168.6 ; 355.9
Geometrical mean	225.7	240.9	236.0
AUC_0-inf (IU*h/mL)			
N (%)	7 (87.5)	13 (86.7)	20 (87)
Mean (SD)	302.7 (103.8)	339.5 (81.3)	326.6 (88.9)
Median	237.6	310.7	304.3
Min ; Max	223.1 ; 462.6	268.2 ; 515.2	223.1 ; 515.2
Geometrical mean	289.1	331.6	316.1
MRT (h)			
N (%)	6 (75)	13 (86.7)	19 (82.6)
Mean (SD)	458.2 (46.5)	501.7 (163.6)	488.0 (153.3)
Median	448.4	436.2	444.0
Min ; Max	388.7 ; 518.9	344.3 ; 1028	344.3 ; 1028
Geometrical mean	456.3	478.9	471.6
t½ (h)			
N (%)	7 (87.5)	13 (86.7)	20 (87)
Mean (SD)	332.5 (51.4)	335.4 (97.8)	334.4 (82.9)
Median	321.4	306.1	315.8
Min ; Max	267.3 ; 430.9	243.1 ; 590.2	243.1 ; 590.2
Geometrical mean	329.3	324.4	326.1
Terminal Rate (1/h)			
N (%)	7 (87.5)	13 (86.7)	20 (87)
Mean (SD)	0.002 (0.000)	0.002 (0.001)	0.002 (0.000)
Median	0.002	0.002	0.002
Min ; Max	0.002 ; 0.003	0.001 ; 0.003	0.001 ; 0.003
Geometrical mean	0.002	0.002	0.002

- PK parameters represent steady state parameters based on unadjusted profile values.
- t½ is calculated from profile data in the interval from Day 3 to Day 28.
- FXIII activity values reaching LLOQ are set equal ½*LLOQ for descriptive statistics, but are not included in calculation of t½ (or AUC_0_inf).
- Clearance is calculated using a nominal dose of 35 IU/kg.

	rFXIII 35 IU/kg		
	FDA	Non FDA	All
CL (mL/h/kg)			
N (%)	6 (75)	13 (86.7)	19 (82.6)
Mean (SD)	0.16 (0.04)	0.15 (0.02)	0.15 (0.03)
Median	0.17	0.15	0.15
Min ; Max	0.11 ; 0.21	0.10 ; 0.17	0.10 ; 0.21
Geometrical mean	0.16	0.15	0.15
Vss (mL/kg)			
N (%)	6 (75)	13 (86.7)	19 (82.6)
Mean (SD)	73.2 (20.7)	73.2 (27.3)	73.2 (24.8)
Median	69.3	64.1	65.9
Min ; Max	49.6 ; 101.1	44.0 ; 150.3	44.0 ; 150.3
Geometrical mean	70.8	69.6	69.9

Table 3: observed and estimated PK parameters (based on the FVIII activity assay) for the F13CD-1725 and the F13CD-3720 trail

	F13CD-1725		F13CD-3720[1]		F13CD-1725[2]		F13CD-3720[1,3]	
	C_{max}[4] (IU/mL)	C_{trough} (IU/mL)	C_{max}[5] (IU/mL)	C_{trough} (IU/mL)	$t_{½}$ (days)	$AUC_{0\text{-}28days}$ (IU*h/mL)	$t_{½}$ (days)	$AUC_{0\text{-}28days}$ (IU*h/mL)
N	41	41	23	21	41	41	20	19
Mean (SD)	0.77 (0.20)	0.19 (0.05)	0.89 (0.20)	0.17 (0.06)	12.05 (2.50)	248.2 (56.9)	13.93 (3.45)	240.4 (49.0)
Geo. Mean	0.75	0.18	0.87	0.16	11.80	242.2	13.59	236.0

To summarise,

- Of all enrolled patients in Study F13CD-3720, 23 agreed to participate in the PK part. These patients are not considered different regarding baseline demographics compared to those not participating in the PK session and the mean PK results could therefore be considered as representative for the entire FXIII A-subunit congenital deficiency population. Of note, in FDA approved label of rFXIII (Tretten in US), the section 12.3 Pharmacokinetics in US Prescription Information reflects the results (baseline corrected) obtained from this PK study (n=23).
- The FXIII steady-state PK results, obtained from a total of 23 patients with congenital deficiency of FXIII are in good agreement with PK data from pivotal trial F13CD-1725 (repeat monthly dose of 35 IU/kg see Table 6-1), as well as paediatric Study F13CD-3760 (a single dose of 35 IU/kg, cf AR procedure EMEA/H/C/002284/II-02)
- The mean Cmax and Ctrough levels were constant over time, when compared to data obtained from the pivotal F13CD-1725 trial, supportive of a steady-state condition with no accumulation and clearly indicating that the clearance of rFXIII is not affected by any extrinsic or intrinsic factors. This is further supported by the comparable exposures, mean AUC0-28days obtained in the F13CD-3720 trial versus the mean AUC0-28days results obtained in the F13CD-1725 trial, 240.4 IU*h/mL and 248.2 IU*h/mL, respectively.
- The overall mean half-life of 13.9 days for the 23 patients participating in the PK session is comparable with the half-life reported in the F13CD-3760 trial (mean t1/2: 15.8 days), as well as the half-life reported in the F13CD-1725 trial (mean t1/2: 12.1 days). Also mean Cmax levels are in the same range for the three trials; 0.89 IU/mL, 0.69 IU/mL and 0.77 IU/mL for trials F13CD-3720, F13CD-3760 and F13CD-1725, respectively, as well as mean Ctrough values (0.17 IU/mL, 0.21 IU/mL and 0.19 IU/mL, respectively).

Based on these results, the MAH presents the pharmacokinetic data from three clinical trials (F13CD-3760, F13CD-1725 and F13CD-3720) in proposed Section 5.2 of the SmPC. in the following table 3-1 to give a better overview of PK data in patients with congenital FXIII A-subunit deficiency.

Table 4: Pharmacokinetic parameters after dosing 35 IU/kg NovoThirteen® based on FXIII activity measured by Berichrom assay

PK parameter Geometric mean (range)	F13CD-1725 Patients[1]	F13CD-3720 Patients[1]	F13CD-3760 Paediatric patients[1]
Number of subjects	41	23	6
Age (years)	26.4 (7-60)	30.7 (7-58)	2.7 (1-4)
Gender	18F+23M	5F+18M	3F+3M
C_{max} (IU/ml)	0.74 (0.17) #,[3]	0.87[3] (0.57-1.24)	0.67[2] (0.49-0.91)
C_{28days} (IU/ml)	0.18 (0.07) #	0.16 (0.03-0.32)	0.21 (0.05) #,[4]
AUC_{0-inf} (IU*h/ml)	NA	318.1 (223.1-515.1)	355.1 (285.3-425.6)
CL (ml/h/kg)	NA	0.15 (0.10-0.21)	0.15 (0.13-0.17)
$t_{½}$ (days)	11.8[5] (7.5-18.5)	13.7 (10.1-24.6)	15.0 (9.8-24.8)

Mean (SD); NA Not available
1: patients with congenital FXIII A-subunit deficiency;
2: 30 min post-dose
3: 1-hour post-dose
4: 30 days post-dose
5: the half-life is based on 3 blood samples drawn 1h, 14- and 28-days post-dosing

2.3.5. Conclusions on clinical pharmacology

There are no updates related to pharmacokinetics and pharmacodynamics of the product that might affect efficacy and/or safety of the marketed formulation of NovoThirteen.

2.4. Clinical efficacy

The grouped variations are based on results from PASS NN1841-3868, safety extension Study F13CD-3720, PRO-RBDD registry and some relevant literature.

Only the study report of PASS NN1841-3868 including PRO-RBDD has been submitted in this application. For Study F13CD-3720, no new data are found in the submission package. The final study report and the response submitted in 2016 have been assessed in procedures EMEA/H/C/2284/P46 016 and variation II/0018.

Hence, the assessment is focusing on PASS NN1841-3868.

2.4.1. Main study

PASS NN1841-3868: "Use of rFXIII in treatment of congenital FXIII deficiency, a prospective multi-centre observational study."

Methods

This is a prospective, single-arm, multi-centre, multinational observational non-interventional post-authorisation safety study (PASS) of safety related to treatment with rFXIII in patients with congenital FXIII A-subunit deficiency. No controls or blinding procedures are applied.

The study report also includes results from the global prospective rare bleeding disorder database PRO-RBDD registry. The PRO-RBDD is an international database collecting prospective clinical and laboratory data of patients with rare bleeding disorders in order to gather information on the incidence of bleeding episodes and consumption of treatment products. A contractual collaboration (02 February 2012 to 11 November 2018) with the registry had been established to collect data on patients with congenital FXIII A-subunit deficiency.

Data was collected at:

- Baseline: clinical history reported at patient's enrolment.

- Follow-up: prospective data collection on any clinical event (bleeding, pregnancy, surgery), treatment, adverse events or complications, every 6 months for a duration of three years, later extended to five years.

Study participants

Inclusion criteria

1. Informed consent obtained before any study-related activities.

2. Able and willing to provide signed informed consent

3. Congenital FXIII A-subunit deficiency. The diagnosis was as per patients' medical records which also included underlying gene defect if known (FXIII subunit A, FXIII subunit B, other)

4. Actual or planned exposure to the rFXIII.

Exclusion criteria

Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.

Treatments

The study medication used is the commercially available rFXIII, solely at the discretion of the physician in accordance with usual care and the approved EU SmPC or US/local Proscribing Information.

Objectives

Primary objective:

The aim of this non-interventional study is to investigate the incidence of specific ADRs associated with the use of rFXIII in patients with congenital FXIII A-subunit deficiency, comprising anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of therapeutic effect.

Secondary objectives:

- To further explore the overall safety and effectiveness of rFXIII under conditions of routine clinical care in patients with congenital FXIII A-subunit deficiency, including special population (i.e., children, elderly, pregnant and lactating women, and patients with renal insufficiency).
- *To assess the use of rFXIII in patients with congenital FXIII A-subunit deficiency, also other than for prophylactic use.*
- To better understand the use of rFXIII and practice patterns in the usual care of patients.

Outcomes/endpoints

Primary endpoint

- The incidence of specific adverse drug reactions (ADRs) in patients with congenital FXIII A-subunit deficiency treated with rFXIII, comprising anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of effect, collected during a study period of up to 6 years.

Secondary endpoints

- All serious adverse events collected during a study period of up to 6 years (which will be presented by all patients as well as by special populations comprising children, elderly, pregnant and lactating women, and patients with renal insufficiency)
- All medical events of special interest collected during a study period of up to 6 years
- All medication errors and near medication errors collected during a study period of up to 6 years
- Use of rFXIII in patients with congenital FXIII A-subunit deficiency, also for other uses than for prophylactic treatment collected during a study period of up to 6 years
- Annualised bleeding rate collected during a study period of up to 6 years.

Sample size

Due to the rarity of the disease and very limited data with regards to adverse events, no formal calculation of sample size was conducted. It was determined by the market update of rFXIII for prophylactic treatment of patients with congenital FXIII A-subunit deficiency.

Randomisation

Not Applicable

Blinding (masking)

Not Applicable

Statistical methods

This was a purely descriptive study and the statistical analyses and presentations did not include any testing of pre-specified hypotheses. All analyses and presentations were based on the full analysis set, which was identical to the safety analysis set.

The descriptions of main secondary endpoint related to this variation as well as bleeding assessments are listed below:

- The use of rFXIII in patients with congenital FXIII A subunit deficiency, other than for prophylactic treatment included on demand treatment (patients who do not receive regular treatment but are only treated when needed). This also included an additional product dosage for patients on prophylactic treatment to treat breakthrough bleeds in relation to traumas, surgeries, and spontaneous bleeds referred to as "treatment of bleeds".
- Definition of severity of bleeds:
    - Mild/Moderate: Minor uncomplicated bleeds.
    - Severe: Major bleeds which require hospitalisation. All head, CNS and neck bleeds were categorised as severe.
- Definition of haemostatic response:
    - Excellent: abrupt pain relief and/or substantial improvement in signs of bleeding within approximately 8 hours after a single infusion.
    - Good/Effective: some pain relief and/or improvement in signs of bleeding within approximately 8 hours after infusion of product, but not requiring more than one infusion for complete bleeding arrest.
    - Moderate/partly effective: slight beneficial effect on pain relief and/or minimal improvement in signs of bleeding within approximately 8 hours after the first product infusion, but not requiring more than one infusion for complete bleeding arrest.
    - None: no improvement or worsening of symptoms or use of other FXIII products.
- Definition of major and minor surgery

Major surgery is any invasive operative procedure where any one or more of the following occur:

- A body cavity is entered.
- A mesenchymal barrier (e.g., pleura, peritoneum or dura) is crossed.
- A fascial plane is opened.
- An organ is removed.
- Normal anatomy is operatively altered.

Minor surgery is any invasive operative procedure in which only skin, mucous membranes, or superficial connective tissue is manipulated. Examples of minor surgery include vascular cut down for catheter placement, implanting pumps or ports in subcutaneous tissue, biopsies or placement of probes, leads, or catheters requiring the entry into a body cavity only through a needle/guidewire.

Dental surgery will be classified as minor or major based on above definitions.

- Haemostatic response during surgery
    - Excellent: blood loss less than expected.

- Good: blood loss as expected.
- Moderate: blood loss more than expected.
- None: uncontrolled bleeding.

- Haemostatic response after surgery:
  - Excellent: better than expected in this type of patient and procedure.
  - Good: as expected in this type of patient and procedure.
  - Moderate: less than optimal for the type of procedure, maintained without change of treatment regimen.
  - None: bleeding due to inadequate therapeutic effect with adequate dosing, change of regimen required.

All bleeding episodes including bleeding during prophylaxis, on-demand therapy and in relation to surgery, were further listed including information about cause, severity, location, date and time of onset, date and time of arrest, product name, dose, haemostatic response, related concomitant illness and related concomitant medication. Both treatment-requiring (i.e. rFXIII or Fibrogammin) and non treatment-requiring bleeding episodes was calculated for Annualised Bleeding rate (ABR)

Results

Recruitment

Start of data collection (FPFV): 17 May 2013; End of data collection for final report (LPLV): 29 June 2019.

A total of 30 patients were enrolled at 17 sites in 7 countries: Denmark (4), Canada (3), Spain (3), USA (13), United Kingdom (1), Hungary (1) and Italy (5), all were exposed to rFXIII in this study. 25 patients completed the study defined as minimum 2 years participation or 24 exposure days and 5 patients were withdrawn from the study:

- 1 withdrawal by the investigator for noncompliant reason.
- 4 withdrawals by patients for personal reasons including change of Haemophilia treatment centre.

Conduct of the study

PRO-RBDD registry

As of the cut-off date of 11 November 2018, there were 4 patients of European origin who were registered in the PRO-RBDD registry and who were on prophylaxis with rFXIII, all with endogenous FXIII:C levels < 2%. The age of the patients ranged from 20 to 41 years.

All the patients had a history of severe bleeding, such as haemarthrosis, haematoma, and umbilical cord bleeding, in addition to mucocutaneous bleeding, before prophylaxis. Out of the 4 patients, 1 patient had a post-traumatic cutaneous bleeding and 1 patient experienced epistaxis during prophylaxis with rFXIII, with no need for further treatment.
No AEs or treatment-requiring bleeding episodes were reported. One patient reported 2 events of pregnancy and had one spontaneous abortion, all of which occurred before the patient entered into the registry. There were no spontaneous bleeding episodes, no pregnancies and no major surgeries reported during the registry period.

No patients had major surgery during the study. No pregnant and lactating women or patients with renal insufficiency were enrolled in this study. Consequently, no results are presented for these two special populations.

Baseline data

Table 6: Baseline demographics – full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15		30
Age at baseline (years)				
N	13	15		30
Mean (SD)	9.2 (4.9)	33.9 (11.9)		25.5 (18.8)
Median	9.0	33.0		21.0
Min ; Max	2 ; 17	19 ; 62		2 ; 68
Gender, N (%)				
N	13 (100.0)	15 (100.0)		30 (100.0)

N: Number of patients, %: Percentage of patients, SD: Standard deviation, NA: not applicable
f13-3868/freeze_20191022_er - 22OCT2019 - t_1410_demo/14100010_demo.txt

The mean age of the patients was 25.5 years, and there were slightly more males (n=17, 57%) than females (n=13, 43%). The majority (n=22, 73%) of the patients were White.

Concomitant medications and illness/medical history at baseline

17 of 30 patients reported concomitant illness/medical history at baseline, in particular 6 patients had allergic reactions to pharmaceutical drug and 2 patients had a history of embolic/thrombotic events.

At baseline, 25 patients were on prophylaxis, 4 patients were on supplemental doses of rFXIII or plasma derived FXIII products (2 for each) while on prophylaxis and 1 patient was on-demand without routine prophylaxis. For patients on prophylaxis, within the last 24 months prior to entry into the study, the mean of the number of bleeding episodes for treatment-requiring bleeds and for non treatment-requiring bleeds was 0.17 and 1.00 respectively. In the patient requiring on-demand treatment, neither treatment-requiring nor non treatment-requiring bleeding episodes were reported within the last 24 months prior to entry into the study.

Table 7: treatment history – full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15		
Current treatment prior to study, N (%)				
Prophylaxis	12 (92.3)	11 (73.3)		
On-demand	-	1 (6.7)		
Supplemental on-demand				

Bleeding episodes within the 24 months				
Treatment requiring				
N	9	13	2	24
Mean (SD)	0.11 (0.33)	0.15 (0.38)	0.50 (0.71)	0.17 (0.38)
Median	0.00	0.00	0.50	0.00
Min ; Max	0 ; 1	0 ; 1	0 ; 1	0 ; 1
Non-treatment requiring				
N	8	12	1	21
Mean (SD)	2.13 (4.52)	0.33 (0.78)	0.00 (-)	1.00 (2.88)
Median	0.00	0.00	0.00	0.00
Min ; Max	0 ; 13	0 ; 2	0 ; 0	0 ; 13

Numbers analysed

All analyses and presentations were based on the full analysis set (n=30), which was identical to the safety analysis set. No patients were excluded from the full analysis set.

Outcomes and estimation

Use of rFXIII other than for prophylactic treatment

All the 30 patients in the study were on prophylactic treatment. No spontaneous treatment-requiring bleeding episodes were reported. A total of 5 traumatic bleeding episodes in 4 patients were treated with an additional dose of rFXIII in the study. All the patients showed a good to excellent haemostatic response. In PRO-RBDD registry, no spontaneous or traumatic bleeding episodes were reported in any of 4 registered patients.

A young adult patient had bleeding on the left knee, 10 days after the last prophylactic dose. He was treated with 36 IU/kg of rFXIII on 02 November 2015 and showed a good haemostatic response. The FXIII activity recorded on 22 October 2015 prior to the bleeding episode was 0.04 IU/mL.

A teenager fell on the face and had a head injury, 7 days after the last prophylactic dose. She was treated with 53.3 IU/kg of rFXIII on 28 March 2016 and showed an excellent haemostatic response. The FXIII activity recorded on 12 May 2015, prior to the bleeding episode was 0.16 IU/mL.

A child had bleeding when she fell directly on the knee, 23 days after the last prophylactic dose. She was treated with 37.6 IU/kg of rFXIII on 22 March 2017 and showed an excellent haemostatic response. The FXIII activity recorded on 23 February 2017 prior to the bleeding episode was 0.06 IU/mL.

The same patient experienced distortion of the ankle, 16 days after the last prophylactic dose. She was treated with 36.3 IU/kg of rFXIII on 20 June 2018 and showed an excellent haemostatic response. The FXIII activity recorded on 04 June 2018 prior to the bleeding episode was 0.09 IU/mL.

A baby received a prophylactic dose of rFXIII and underwent revision of circumcision on the same day. After 18 days of this prophylactic dose, the patient fell on his abdomen and had haematoma to penile shaft. The patient's haematoma was treated with 41.7 IU/kg of rFXIII and had an excellent haemostatic response.

Annualised bleeding rate (ABR)

A total of 65 bleeding episodes were reported by 14 of 30 patients (47%) in the study including:

- 6 bleeding episodes required treatment with a FXIII containing product: 5 traumatic bleeding episodes were treated with an additional dose of rFXIII with good to excellent haemostatic (see above), the 6th traumatic bleed was treated with Fibrogammin.

- 59 non FXIII treatment-requiring bleeding episodes, of which 41 bleeds were reported by a 6-year-old girl (Patient ID 321001) who repeatedly had nose bleeds. Aminocaproic acid was given to 2 patients for 4 bleeding events.

There were no spontaneous treatment-requiring bleeding episodes. None of patient was withdrawn from the study due to the lack of efficacy treatment.

Table 9: Annualised bleeding rate of all bleeding episodes – full analysis set

	Treatment requiring	Non Treatment requiring	All
Number of patients	30	30	30
Number of patients with bleed	5	10	14
Total number of bleeds	6	59	65
Range of bleedings	0 ; 2	0 ; 41	0 ; 41
Mean bleedings per patient	0.200	1.967	2.167
Mean observation period (days)	916.5	916.5	916.5
Total observation period (years)	75.3	75.3	75.3
Poisson analysis*			
Annualised bleeding rate	0.066	0.784	0.850
95% CI	0.029 ; 0.150	0.204 ; 3.011	0.246 ; 2.940
Cause of bleed			
N	6	50**	56
Spontaneous	-	30	30
Traumatic	6	18	24
Not known	-	2	2
Haemostatic response			
N	6	-	6
Excellent	4	-	4
Good	2	-	2

* A 95% CI for the annualised bleeding rate is estimated from a Poisson analysis with over-dispersion if the number of bleeds is greater than 1, otherwise only the Poisson estimate is provided assuming no over-dispersion
** The cause of bleed for 9 non-treatment requiring episodes was missing in the CRF.
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The overall estimated (mean, 95% CI) ABR for all bleeding episodes and ABR for treatment with FXIII-requiring bleeding episode was 0.850 [0.246; 2.940] and 0.066 [0.029; 0.150] bleeds/patient/year respectively. The mean duration of bleeds was 32.1 hours (SD: 48.0).

Surgery

There were no major surgeries during the study. A total of 6 patients underwent 9 minor elective surgeries during the study. Out of these, 5 patients had minor surgeries, 0-3 days after the last prophylactic dose. One patient had 2 minor surgeries, 12 and 15 days after the last prophylactic dose and received an extra dose of rFXIII of 23.2 IU/kg and 21.4 IU/kg prior to both surgeries respectively. The haemostatic response during and after the surgeries was good to excellent (the haemostatic response was missing for one surgery).

Supportive study

Study F13CD-3720: Safety Extension Trial to pivotal phase 3 study F13CD-1725

Title: A Multi-Centre, Open-Label, Single-Arm, and Multiple Dosing Trial on Safety of Monthly Replacement Therapy with rFXIII in Subjects with Congenital Factor XIII Deficiency,

Additional dose for breakthrough bleeds during prophylaxis

In Study F13CD-3720 (long-term extension of phase 3 Study F13CD-1725), haemostatic response to rFXIII after a single dose of 35 IU/kg for treatment of breakthrough bleeds was assessed about 8 hours after prophylactic rFXIII administration.

Only one rFXIII-treated bleed was reported. This subject experienced a trauma-induced muscular bleed 24 days after the latest prophylactic rFXIII dose. Approximately 34.7 IU/kg were administered as a single dose, and the haemostatic response was rated as 'excellent'. No additional FXIII-containing products were necessary to treat the bleed.

Surgery

In F13CD-3720, 12 minor surgeries were performed in 9 patients within 1 to 21 days of the last scheduled rFXIII dose (35 IU/kg). The longest period between a rFXIII dose and minor surgery was 3 weeks; based on PK modelling, it was estimated that the patient would have had a FXIII activity level of 0.19 IU/mL.

In all 12 procedures, there were no reports of unexpected blood loss or requirements for transfusion with blood or blood products; no surgical complications related to congenital FXIII A-subunit deficiency or treatment were reported, yet a good haemostatic outcome was observed in all these 12 instances.

Literature:

"The use of recombinant factor XIII in a major bleeding episode of a patient with congenital factor XIII deficiency – the first experience" Arokszallasi A. et al Haemophilia (2015), 21, e70--e121

On-demand treatment without routine prophylaxis

Only one individual case was reported in the article of Arokszallasi et al (2015). A male patient with severe congenital FXIII A-subunit deficiency experienced an intramuscular haematoma while not being on FXIII prophylaxis. This major bleeding episode was treated with a single dose of 35 IU/kg rFXIII and within the first 24 h after injection, pain, swelling and stiffness of the thigh decreased. The patient was fully mobilized on the fourth day after infusion of rFXIII. Thus, a single dose of rFXIII was effective in the management of this major bleeding episode in a patient with severe congenital FXIII A-subunit deficiency, who was not previously treated with rFXIII.

Minor elective surgery

Two dental procedures were carried out under rFXIII cover in a patient:

- On the 6th post infusion day after the first dose of rFXIII, a patient developed acute pulpitis of a tooth. As FXIII activity was 32%, tooth-extraction was performed without additional FXIII support.
- A second dental manipulation was scheduled for the same patient on the day of the first prophylactic infusion after tooth extraction. This was carried out with a FXIII activity of 68%.
- No bleeding complication followed in either of the procedures.

2.4.2. Discussion on clinical efficacy

Study design of PASS NN1841-3868

Title: Use of rFXIII in treatment of congenital FXIII deficiency, a prospective multi-centre observational study

This is a prospective, single-arm, multi-centre, multinational observational non-interventional post-authorisation safety study (PASS) of safety related to treatment with rFXIII in patients with congenital FXIII A-subunit deficiency. No controls or blinding procedures are applied. The study report also includes results from the global prospective rare bleeding disorder database (PRO-RBDD) registry.

The PASS NN1841-3868 was designed to address the question in a real-world setting "What is the long-term safety and effectiveness of rFXIII in patients with congenital FXIII A-subunit deficiency and what are the current clinical treatment practices for rFXIII use?". All study visits are to be performed according to normal local clinical practice and no additional visits are to be conducted due to the participation in this study.

For this observational PASS, a number of bias and limitation would occur due to potential confounding factors (e.g. selection bias) and data collect in a real-life setting (e.g. incorrectness of dose and bleeding evaluation by patient). The very few inclusion and no exclusion criteria would reduce selection bias.

The total study duration was 6 years, all patients should have either a minimum of 2 years' participation or 24 exposure days whichever came first, unless the patient had dropped out. Such long-term follow-up is

considered reasonable and appropriate for expansion of knowledge of safety and efficacy of rFXIII for the treatment of patients with congenital FXIII A-subunit deficiency.

As one of the secondary endpoint, data of "use of rFXIII other than for prophylactic treatment in patients with congenital FXIII A-subunit deficiency" were collected; and based on the results of this secondary endpoint, the MAH requests to include addition of "treatment of bleeding episodes" in patients with congenital FXIII A-subunit deficiency in the indication as well as a posology-update related to minor surgeries in this group variations.

This was a purely descriptive study and the statistical analyses and presentations did not include any comparison or testing of pre-specified hypotheses.

Results

A total of 30 patients were enrolled at 17 sites in 7 countries, all were exposed to rFXIII in this study. Considering the rarity of congenital FXIII deficiency, the enrolment of 30 patients before the planned end of recruitment date is highly appreciated, and the sample size is satisfactory. Of them, 25 patients completed the study (i.e. $\geqslant$ 2 years participation or 24 ED) and 5 were withdrawn for incompliant or personnel reason. No patients had major surgery, no pregnant or lactating women and no patients with renal insufficiency were enrolled.

All the 30 patients in the study were on prophylactic treatment. No spontaneous treatment-requiring bleeding episodes were reported. A total of 5 traumatic bleeding episodes were treated in 4 young patients during prophylaxis, all were mild/moderate and showed a good to excellent haemostatic response. The FXIII activity recorded prior to bleedings ranged from 0.04 IU/ml to 0.16 IU/ml.

Based on these results, the MAH claimed the extension of indication, by adding "treatment bleeding episodes".

As a reminder, the study protocol defined that the use of rFXIII in patients with congenital FXIII A subunit deficiency, other than for prophylactic treatment included two sub-groups:

1/ on demand treatment (patients who do not receive regular treatment but are only treated when needed).

2/ an additional product dosage for patients on prophylactic treatment to treat breakthrough bleeds in relation to traumas, surgeries, and spontaneous bleeds.

None of patients was in on demand sub-group 1. All of 4 patients who treated for their traumatic bleeds were currently on long-term prophylactic regimen with rFXIII (Prophylaxis sub-group 2) and all of 5 episodes of breakthrough bleeds occurred during their regular prophylaxis.

Hence, the MAH was requested to modify the updates in section 4.1 "Therapeutic indications" of the SmPC of NovoThirteen as following in order to clearly reflect the real recorded data:

"4.1 Therapeutic indications

Long term prophylaxis of bleeding in patients with congenital factor XIII A-subunit deficiency.

As supplementary treatment to management of breakthrough bleeding episodes during regular prophylactic treatment regimen.

NovoThirteen can be used for all age groups." (SmPC, MO)

In the response to 1st RSI, the MAH acknowledges that all patients in the PASS NN1841-3868 were on monthly prophylaxis regimen and none of patients were treated on-demand. However, the MAH continues to consider that treatment of a bleeding episode with NovoThirteen in a patient NOT on monthly prophylaxis is a relevant treatment option and proposes to add "treatment of episodic bleedings in patients not covered by prophylaxis" in the section 4.1 "Therapeutic indications" of the SmPC of NovoThirteen, on the basis of the

supportive information such as single dose PK data, mechanism of action of NovoThirteen (endogenous FXIII A-subunit) and clinical experiences for pdFXIII products over 20 years of on-demand treatment in patients with FXIII A-subunit deficiency when not on prophylaxis.

The provided rationale is not considered substantial enough to support the extension of indication of on-demand treatment. Indeed, although the therapeutic effect of NovoThirteen may be expected when it is administrated to treat bleeding episodes in patients not covered by prophylaxis; no clinical trial has confirmed this potential effect neither with pd FXIII nor with rFXIII. No relevant supportive information has been found in the references 4, 5, 6 indicated by the MAH in the response.

Hence, it was agreed that the indication wording should remain as requested in RSI as follows:

"Long term prophylaxis of bleeding in patients with congenital factor XIII A-subunit deficiency.

Treatment of breakthrough bleeding episodes during regular prophylactic treatment regimen.

NovoThirteen can be used for all age groups."

By supplementary responses on 3rd and 13th July 2020, the MAH agreed with revising the indication (MO) on SmPC 4.1 extension of indication as well as comments on 4.2.

Of note, the MAH withdrew the request for extended marketing protection period of NovoThirteen.

Furthermore, the deletion of all information on "On-demand treatment" in the section 4.4 Special warning and precautions of the SmPC was not considered acceptable. The information regarding very limitation of "on-demand treatment" was maintained as follows:

"On-demand treatment was not studied in clinical development programme. Until further results are available, alternative treatment should be considered in such situations." (SmPC, OC)

In the response to 1st RSI, the MAH has accepted to keep section "On-demand treatment" in SmPC Section 4.4. as requested and proposed the following wording which is considered acceptable:

"On-demand treatment of patients not on prophylactic treatment was not studied in clinical development programme".

It is noted that the FXIII trough level was relatively low in these 4 patients under long-term prophylaxis by rFXIII (mean Ctrough 0.087 ± 0.045 IU/ml), as compared to the geometric mean FXIII Ctrough reported in pivotal children and adult studies (0.21±0.05 and 0.18±0.07 IU/ml respectively), suggesting therapeutic response decreased in these patients and insufficient FXIII trough level for preventing breakthrough bleeding. The MAH was requested to provide an estimation of FXIII trough level in all patients participating in the PASS NN1841-3868 with available PK data.

The requested PK data have been provided and compared to Study F13CD-3720 (PK sub-study: geometric mean C28days = 0.16 IU/mL range 0.03-0.32 at steady-state). In PASS NN1841-3868, only 11 out of 30 patients had FXIII trough assessed at the central laboratory within 28 ± 2 days and contributed with 40 FXIII trough assessments. The geometric mean C28 ± 2 days was 0.16 IU/mL (range 0.05−0.32), so comparable to the trough value reported for PK sub-study F13CD-3720, i.e. geometric mean C28days = 0.16 IU/mL (range 0.03-0.32).

Two of 4 patients having bleeds under prophylaxis have received an additional dose of rFXIII at 53.3 IU/kg and 41.7 IU/kg respectively for the treatment bleeding episodes. Such doses were much higher than the recommended dose (35 UI/kg), but they corresponded to the stable prophylactic doses received by these patients prior to their bleed.

The MAH was requested to clarify the following issues:

- A teenager was treated with an additional dose of rFXIII for breakthrough bleeding on 28 March 2016, i.e. 7 days after the last regular monthly prophylaxis on 21 March 2016. While the FXIII activity prior to the bleeding episode was recorded on 12 May 2015 (10 months ago). Please clarify.

In the response to 1st RSI, the MAH acknowledges the error in reporting the wrong date and clarifies that in this PASS NN1841-3868 the blood samples for evaluation of FXIII activity were drawn at the discretion of the investigator and there was no systematic evaluation of FXIII activity values due to the non-interventional nature of the study.

- A child received a prophylactic dose on 23 February 2017 (38th month). She was treated with "an additional" dose of rFXIII for bleeding episode on 22 March 2017 (39th month), i.e. one month later, not "23 days after the last prophylactic dose" as mentioned on page 33 of study report. Please clarify or correct. This patient received her next monthly prophylactic dose was on 19 April 2017 (40th). Please clarify, why the 39th month-dose was accounted as "an additional dose" but not a regular prophylactic dose.

In the response to 1st RSI, the MAH clarified that the additional dose (22 March 2017) was administered for the treatment of the bleeding episode as confirmed and reported by site. Although close in time for the next regular prophylaxis dose, Novo Nordisk accounts the 39th month-dose as an additional dose and not a regular prophylactic dose.

In NN1841-3868, no differences in the treatment responses were observed between the paediatric and adult population. 3 of 4 patients were children (2, 12 and 13 years old), it is agreed that no dose adjustment is required when NovoThirteen is used in paediatric patients and the dose of 35 IU/kg body weight should be used for both prophylaxis and treatment of bleeding episodes.

Annualised bleeding rate (ABR)

The mean rate of bleeding episodes requiring treatment with rFXIII was 0.066 bleeds/patient/year, which is very low as compared to that reported in pivotal phase 3 study F13CD-1725 (0.138 bleeds/patient/year). This PASS proved that regular prophylaxis with rFXIII prevents breakthrough bleeding in congenital FXIII deficient patient and thus confirmed haemostatic efficacy of NovoThirteen for long-term routine prophylactic treatment of congenital FXIII A-subunit deficiency.

Minor elective surgery

There were no major surgeries during the study. A total of 6 patients underwent 9 minor elective surgeries during the study. No bleeding complication followed in minor surgical procedures. The haemostatic response during and after the surgeries was good to excellent (the haemostatic response was missing for one surgery).

2.4.3. Conclusions on the clinical efficacy

Based on the above discussions, NovoThirteen has shown to be effective in treatment of breakthrough bleeding episodes as well as minor surgeries during long-term regular prophylaxis during in patients with congenital FXIII A-subunit deficiency. Further efficacy conclusions are as follows:

- A total of 7 bleeding episodes in 6 patients with congenital FXIII A-subunit deficiency were reported. The haemostatic outcome in all the bleeds treated with rFXIII was good or excellent. Based on these results, Sections 4.1, 4.2, 4.4 and 5.1 of SmPC, Sections 2 and 3 of package leaflet were updated.
- A total of 23 minor surgeries were performed in 16 patients with congenital FXIII A-subunit deficiency. Of these, 21 surgeries were covered by a single prophylactic dose of rFXIII for each surgery.
- One patient from NN1841-3868 who underwent 2 surgeries received an additional vial (2500 IU) of rFXIII prior to each surgery.
- All the patients who underwent minor surgeries (in F13CD-3720 and NN1841-3868) had a successful

haemostatic outcome of good or excellent, except for 1 patient whose haemostatic outcome was missing. Based on these results, posology of rFXIII during minor surgeries is updated in Sections 4.2 and 5.1 of SmPC.

- In NN1841-3868, no differences in the treatment responses were observed between the paediatric and adult population. The same has been updated in Section 5.1 of SmPC and reflected accordingly in Section 3 of package leaflet.

Taken together, the use of rFXIII other than for prophylactic treatment in patients with congenital FXIII A-subunit deficiency was collected as one of the secondary endpoints in the PASS NN1841-3868, and recorded results demonstrates that rFXIII can also be used as a treatment of bleeds during the prophylactic regimen in these patients. Additionally, in the pivotal extension study F13CD-3720 and NN1841-3868, it was demonstrated that prophylaxis with rFXIII would alone be sufficient to avoid bleeding episodes during minor elective surgeries in patients with congenital FXIII A-subunit deficiency.

2.5. Clinical safety

Introduction

The safety profile of rFXIII have been evaluated in the clinical programme which consists of 12 completed MAH-sponsored clinical trials as well as post-marketing experiences. The most frequent adverse reaction is headache reported in 37% of patients.

Blood and lymphatic system disorders Common (≥ 1/100 to < 1/10)	Leucopenia and aggravated neutropenia
Nervous system disorders Common (≥ 1/100 to < 1/10)	Headache
Musculoskeletal and connective tissue disorders Common (≥ 1/100 to < 1/10)	Pain in extremity
General disorders and administration site conditions Common (≥ 1/100 to < 1/10)	Injection site pain
Investigations Common (≥ 1/100 to < 1/10) Common (≥ 1/100 to < 1/10)	Non-neutralising antibodies Fibrin D-dimer increased

Patient exposure

The consumption of rFXIII are summarised in Table 10-5. The consumption of rFXIII used for the treatment (including all doses given for prophylaxis and treatment of bleed) per year per patient was 395.9 IU/kg/year (SD: 155.23) and the average rFXIII dose given for prophylaxis was 37.2 IU/kg (SD: 12.16).

Table 13: Consumption of rFVIII during the study – full analysis set

	Children < 18 years	Adults (18 to 65 years)	Elderly > 65 years	Total
Number of patients	13	15	2	30
Consumption used for treatment* per year per patient** (IU/kg/year)				
N	13	15		
Mean (SD)	470.2 (195.79)	337.8 (89.41)		
Median	452.5	348.4		
Min ; Max	154.2 ; 982.3	173.7 ; 456.6		
Average prophylaxis dose*** (IU/kg)				
N	420	364		
Mean (SD)	43.7 (12.57)	31.3 (7.71)	26.9 (0.84)	37.2 (12.16)
Median	38.9	31.2	26.7	35.7
Min ; Max	30.3 ; 89.7	18.2 ; 50.7	26.0 ; 28.7	18.2 ; 89.7
Average dose for treatment of bleed from start to stop of bleed+ (IU/kg/bleed)				
N	4	1	0	5
Mean (SD)	42.2 (7.73)	36.0 (-)	- (-)	41.0 (7.24)
Median	39.6	36.0	-	37.6
Min ; Max	36.3 ; 53.3	36.0 ; 36.0	- ; -	36.0 ; 53.3

*Consumption used for treatment includes all doses given (prophylaxis, treatment of bleed)
The contribution from the last prophylactic dose given is adjusted to the remaining relative part of planned dosing interval of 28 days up to the cut-off date
**N is number of patients
***N is number of doses
+N is number of bleeds

Adverse events

Table 14: Overview of adverse events -safety analysis set

	Children < 18 years N (%) E [R]	Adults (18 - 65 years) N (%) E [R]	Elderly > 65 years N (%) E [R]	Total N (%) E [R]
Number of patients	13	15		
Total time in study (years)	37.00	34.44		
Total number of exposure days	431	404		
All adverse events	9 (69.2) 16 [0.43]	7 (46.7) 23 [0.67]		
Serious adverse events	2 (15.4) 2 [0.05]	4 (26.7) 7 [0.20]		
Adverse events by severity				
Mild	7 (53.8) 12 [0.32]	5 (33.3) 16 [0.46]		
Moderate	3 (23.1) 4 [0.11]	5 (33.3) 6 [0.17]		
Severe	-	1 (6.7) 1 [0.03]		
Adverse events by relationship				
Probably or possibly related	2 (15.4) 3 [0.08]	3 (20.0) 5 [0.15]		
Unlikely related	7 (53.8) 13 [0.35]	6 (40.0) 18 [0.52]		
Adverse events				
Leading to withdrawal	-	-	-	-

All adverse events in this table are treatment emergent.
N: Number of patients with adverse event, %: Percentage of patients with adverse event,
E: Number of adverse events
[R]: Number of adverse events per patient years of exposure (E/total time in study)
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A total of 18 patients had 44 adverse events (60.0%). The 44 adverse events were mainly within the MedDRA SOCs of "Infections and infestations" (11 events reported in 7 patients, PTs included nasopharyngitis, sepsis, conjunctivitis, gastroenteritis viral, influenza, sialoadenitis, tonsillitis and upper respiratory tract infection), "Nervous system disorders" (7 events reported in 4 patients, PTs included dizziness, post-traumatic headache, dysarthria and headache), "General disorders and administration site conditions" (6 events reported in 4 patients, PTs included chest discomfort, fatigue, influenza like illness and therapeutic response decreased), and "Injury, poisoning and procedural complications" (5 events reported in 4 patients, PTs included contusion, accidental overdose, ligament sprain and limb injury).

30 of 44 AEs were mild in 13 patients (43.3%). There was 1 severe AE of sepsis reported. A total of 13 moderate AEs were reported in 10 patients (33.3%). None of the patients were withdrawn from the study due to AEs.

Table 15: Overview of adverse events in NN1841-3868

Safety parameter		Children		Adults		Elderly		Total	
		N	**E**	**N**	**E**	**N**	**E**	**N**	**E**
Treatment emergent adverse events	Mild	7	12	5	16	1	2	13	30
	Moderate	3	4	5	6	2	3	10	13
	Severe	0	0	1	1	0	0	1	1
	Total	9	16	7	23	2	5	18	44
Adverse events with positive relation to rFXIII		2	3	3	5	2	3	7	11
Serious adverse events		2	2	4	7	1	1	7	10
Medical events of special interest (MESI)		3	3	1	1	0	0	4	4

N- No. of patients experiencing adverse events

E- No. of events experienced

Adverse events with possible or probable relation to study product

A total of 11 events reported by 7 patients (23.3%) were evaluated to be possibly or probably related to the rFXIII by the investigator. None of these events were SAE and the patients recovered from all the events.

Medical events of special interest

There were 4 medical events of special interest reported in this study.

Primary endpoint: specific adverse drug reactions

The specific ADRs included anti-FXIII antibodies, allergic reaction, embolic and thrombotic events and lack of therapeutic effect.

A total of 3 specific ADRs in 2 patients were reported in this study; 2 incidences of positive non-neutralising anti-rFXIII antibody in one patient at 2 time-points (12 May 2015 and 22 June 2015) and a suspected lack of therapeutic effect in another patient.

The incidence of non-neutralising anti-rFXIII antibody concerned a 6-year-old female patient who tested positive at two visits for a total period of 2.5 years. The patient developed low-titre transient non-neutralising anti-rFXIII antibodies after several years of treatment with NovoThirteen. No clinical findings were associated with these antibodies and there was no evidence of lack of effect.

The event of suspected lack of therapeutic effect concerned a young child. The patient was on rFXIII since 24 February 2015. The patient repeatedly had nose bleeds (41 episodes) which occurred when she got hit on the nose while playing. The patient had received the prophylactic dose on 31 October 2018. On 14 November 2018, the investigator reported decreased therapeutic response. The FXIII activity recorded on 20 November 2018 was 0.4 IU/mL. The next prophylactic dose was on 30 November 2018. Since FXIII activity was 0.4 IU/mL on 20 November 2018, the FXIII activity would be >0.4 IU/mL on 14 November 2018, when the investigator reported the suspected lack of therapeutic response. Hence, the patient had normal FXIII in-vitro activity levels and also had no anti-rFXIII antibodies. The patient recovered from the event of suspected lack of therapeutic effect in December 2018.

None of the patients withdrew from the study due to lack of efficacy of the rFXIII product.

There were no neutralising antibodies reported during the study period. There were no allergic reactions and no embolic and thrombotic events assessed as related to rFXIII reported in this study.

Medical errors

There was one case of accidental overdose reported: The case concerned a teenager who had an accidental overdose of rFXIII (63.3 IU/kg; a whole vial of the product was administered instead of half vial); the patient did not have any clinical consequences due to this event.

Serious adverse event/deaths/other significant events

A total of 10 SAEs were reported in 7 patients. A brief summary of the SAEs is provided below:

Case: a young adult reported haemarthrosis of moderate severity for which he was hospitalised. Ultrasound of the knee revealed haematoma. The patient received an extra dose of rFXIII to treat the event and recovered. The event was unlikely related to the product as assessed by investigator.

Case: a young adult experienced pain in the right leg and was admitted to the hospital. A CT scan revealed a ruptured ovarian follicle without bleeding. The patient was discharged from the hospital and recovered from the event. The event was unlikely related to the product as assessed by investigator.

This patient also had a medical history of tightness of chest and reported 3 non-serious events of chest discomfort. The first 2 events were possibly related to the product and the third event was probably related to the product as assessed by the investigator. All the 3 events recovered.

Case: a teenager reported post-traumatic headache of moderate severity. Patient was hospitalised, and a CT scan was performed which did not reveal any abnormality and the patient recovered from the event. The event was unlikely related to the product as assessed by investigator.

Case: a middle aged patient reported dizziness of mild severity during an appointment for receiving rFXIII prophylaxis; the event occurred before the dosage. The patient had received medications due to tooth pain prior to the visit; he was hospitalised for observation following symptoms of dizziness, recovered from the event. The event was unlikely related to the product as assessed by investigator. This patient also presented with influenza of moderate severity in September 2017. He had symptoms of tenderness in the left side of the chest and dry cough which developed into increased pain in thorax and fever. Five days later, the patient received the regular rFXIII prophylaxis dose. The patient had headache, dizziness, slightly sensitive to light, shortness of breath and radiation of pain to the left upper arm. The patient also presented with ventricular extrasystoles and palpitation. The patient was hospitalised for deep vein thrombosis which started with a phlebitis at a peripheral vein catheter on the hand during the first day of an influenza-hospitalization. Peripheral vein catheter site was changed to the elbow flexion where the patient developed another phlebitis. After discontinuation of these, continuous ongoing redness and tenderness was observed. Ultrasound of the right upper extremity described a thrombosis. A pulmonary ventilation-perfusion scan was performed which excluded pulmonary embolism. The patient recovered and was discharged beginning of October 2017. According to the investigator, the condition was due to a combination of a systemic inflammation due to influenza together with a local tissue irritation and endothelia activation due to ongoing peripheral venous catheter phlebitis which had caused the patient's superficial venous thrombosis. Both the events of influenza and deep vein thrombosis were unlikely related to the product as assessed by investigator.

Case: In 2018, 9 days after receiving the rFXIII prophylaxis dose, the patient (a very young child) experienced swelling of the salivary glands and lymph nodes of the neck. An ultrasound scan revealed sialoadenitis and the patient was hospitalised and treated with oral antibiotics. The patient was recovered from the event 4 days later. The event was unlikely related to the product as assessed by investigator.

Case: In 2017, a young adult presented to the hospital with chills, abdominal pain with the concern for a urinary tract infection (UTI). A urinalysis performed was negative for UTI. A CT scan of the abdomen and chest x-ray did not reveal any findings. Four days later, the patient was discharged with a diagnosis of sepsis due to an unclear source. In January 2018, the patient presented to the emergency room with symptoms similar to the previous episode of sepsis. The patient was treated with antibiotics, recovered and was discharged 3 days later. Both the events of sepsis were unlikely related to the product as assessed by investigator.

Case: an elderly patient with medical history of osteoarthritis of the hip, who reported arthralgia (hip pain) of moderate severity. The patient was hospitalised and magnetic resonance imaging (MRI) scan of the right hip was performed which revealed a small right hip effusion with some early osteoarthritic changes. After treatment with analgesics, the patient recovered. The event was unlikely related to the product as assessed by investigator.

Death

There were no deaths reported in this study.

Safety in special populations

Safety of rFXIII during pregnancy

Pregnancies in women with FXIII deficiency have a significant risk of miscarriage, bleeding, placental abruption and post-partum haemorrhage if not on prophylaxis treatment. The combined guideline from the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) and the Royal College of Obstetricians and Gynaecologists (RCOG) recommends increased intensity prophylaxis during pregnancy using FXIII plasma concentrate or rFXIII (if A-subunit deficiency). Dosing frequency should be increased from every 28 days to every 14–21 days to maintain a FXIII activity level of more than 0.2 IU/mL. For delivery, consider additional FXIII concentrate 10-40 IU/kg once during established labour or before caesarean section, depending on the interval since last prophylaxis**.** Coagulation factors are large molecules unlikely to cross the placental barrier. Replacement therapy with rFXIII is not expected to affect pregnancy or offspring negatively.

The table below provides an overview of cases form F13CD-1725, F13CD-3720, relevant literature and post-marketing surveillance, where patients with congenital FXIII A-subunit deficiency were treated with rFXIII during pregnancy.

Table 19: Overview of rFXIII use in pregnant women and outcomes

Patient's age /time of rFXIII exposure	Action taken with rFXIII	Outcome	Narrative
Clinical trials (F13CD-1725 and F13CD-3720)			
20 years/ 7 weeks	Discontinued	Pregnancy terminated	A young adult with congenital FXIII A-subunit deficiency unintentionally became pregnant. and was treated with rFXIII for 7 months when the pregnancy was discovered. The foetus was exposed to rFXIII for 7 weeks when the mother was withdrawn from the clinical trial and the pregnancy was terminated as per the patient's wishes. No contraceptive was used at the time of conception.
36 years/ 1st trimester	Discontinued	Normal child	This case concerned a young adult with congenital FXIII A-subunit deficiency who had been treated with rFXIII for 10 months. During the 1st trimester of pregnancy, the foetus was

Patient's age /time of rFXIII exposure	Action taken with rFXIII	Outcome	Narrative
			exposed to rFXIII and the patient was withdrawn from the clinical trial. The pregnancy went well with no complications and a healthy baby was born. The pregnancy occurred while the patient was using contraception (Meliane).
27 years/ 1st trimester	Discontinued	Pregnancy terminated	This case concerned a young adult with congenital FXIII A-subunit deficiency who became pregnant after being treated with rFXIII for 1 month. The patient had previously given birth to 2 healthy infants and was not interested in more children; therefore, the pregnancy was terminated.
26 years/ 1st trimester	Discontinued	Normal child	A young adult with congenital FXIII A-subunit deficiency who had been treated with rFXIII for 19 months became pregnant while using contraception. The pregnancy resulted in a male child born after being exposed to rFXIII in utero in the beginning of the pregnancy (mother received no dosing after the last menstrual cycle). After birth, an echocardiogram of the baby revealed a minor septal defect and a patent ductus arteriosus; the events were assessed by the investigator as unlikely related to rFXIII.
34 years/ 1st trimester	Discontinued	Spontaneous abortion	This young adult with congenital FXIII A-subunit deficiency reported a pregnancy and subsequently experienced a spontaneous abortion. The patient had previously been pregnant 5 times and had given birth to 3 healthy children. The patient was withdrawn from the study after being treated with rFXIII for 4.5 years. No contraception was used at the time of conception.
30 years/ 1st trimester	Discontinued	Pregnancy terminated	This case concerned a young adult with congenital FXIII A-subunit deficiency who had been treated with rFXIII for 4 years. The foetus was exposed to rFXIII during the 1st trimester. A routine ultrasound at gestational week 7 revealed that the pregnancy was ectopic. The pregnancy was terminated, and the patient was withdrawn from the study; the event was assessed as unlikely related to rFXIII. Patient's history includes 1 child born at week 25 who died 21 days later.
32 years/ 3 weeks	Discontinued	Normal child	This case concerned a young adult with congenital FXIII A-subunit deficiency treated with rFXIII for 4 years for congenital factor XIII deficiency. The pregnancy was discovered via urine testing at the patient's end-of-trial visit (oral contraceptive was used). The child was exposed to rFXIII for 3 weeks. According to the information available, no complications were reported in the pregnancy. The pregnancy resulted in a healthy baby boy. After delivery, the patient developed postpartum haemorrhage due to uterine atony; the outcome of the event was reported as recovered.
Abdel-Samad N et al[26]			
37 years/ 1st trimester	Continued during breastfeeding	Normal child	This case concerned a young adult with congenital FXIII A-subunit deficiency. The patient was treated with 2500 units of Tretten® (rFXIII) monthly. Eight (8) days after the last dose of rFXIII, the patient presented with H1N1 influenza and was diagnosed with HELLP syndrome. As a consequence of the HELLP syndrome, a caesarean section was performed. The pregnancy resulted in the birth of a normal male child and the outcome of the events was reported as recovered. A causal relationship with rFXIII was assessed as unlikely.
Al-Khabori M et al[27]			
26 years/ 1st trimester	Not reported	Normal child	A young adult with congenital FXIII A-subunit deficiency was treated with rFXIII when she was 2 months into her pregnancy.

Patient's age /time of rFXIII exposure	Action taken with rFXIII	Outcome	Narrative
			She was administered with 31 IU/kg of rFXIII every 4 weeks and her FXIII trough levels were closely monitored. The patient did not experience any complications of pregnancy, had a normal spontaneous vaginal delivery at week 36 (+ 5 days) of gestation, and delivered a normal healthy baby. The patient did not experience any postpartum haemorrhage and her FXIII level 2 months postpartum was < 0.055 IU/mL (while she was not receiving therapy).
Post-marketing surveillance			
39 years[a]/ NA	Not reported	Outcome not reported	A heterozygous pregnant patient with congenital FXIII A-subunit deficiency was treated with a single dose of Tretten® (rFXIII) prophylactically prior to her caesarean section (C-section). The patient's C-section was performed in a controlled environment to avoid any complications during the surgery. She had never received FXIII replacement therapy prior to this event. Attempts have been made to follow up, but no further information is available.

Source: PSUR Table 15-1, Abdel-Samad N et al,[26] Al-Khabori M et al[27]

HELLP- haemolysis, elevated liver enzymes and low platelet count

LDH- lactate dehydrogenase

NA- Not Applicable

[a]- Reason for no prior dose in the heterozygous pregnant woman: In general, heterozygous patients with congenital FXIII A-subunit deficiency do not require prophylaxis as they do not experience severe haemorrhage.[28] However, some heterozygous women with FXIII deficiency may require FXIII prophylaxis due to the well-described decrease of FXIII levels during pregnancy.[29, 30]

Safety of rFXIII in paediatric population

The Table below provides an overview of the AEs from PASS NN1841-3868 by age groups.

Table 20: Overview of adverse events in NN1841-3868

Safety parameter		Children		Adults		Elderly		Total	
		N	**E**	**N**	**E**	**N**	**E**	**N**	**E**
Treatment emergent adverse events	Mild	7	12	5	16	1	2	13	30
	Moderate	3	4	5	6	2	3	10	13
	Severe	0	0	1	1	0	0	1	1
	Total	9	16	7	23	2	5	18	44
Adverse events with positive relation to rFXIII		2	3	3	5	2	3	7	11
Serious adverse events		2	2	4	7	1	1	7	10
Medical events of special interest (MESI)		3	3	1	1	0	0	4	4

N- No. of patients experiencing adverse events

E- No. of events experienced

Post marketing experience

No post-marketing data was submitted in this variation. Please refer to the last PRAC PSUR assessment report dated on 29 January 2020 for details.

2.5.1. Discussion on clinical safety

Main study PASS NN1841-3868: Primary endpoint: specific ADRs

A total of 3 specific ADRs in 2 patients were reported in this study; 2 incidences of positive non-neutralising anti-rFXIII antibody in one patient at 2 time-points and a suspected lack of therapeutic effect in another patient.

There were no allergic reactions or embolic and thrombotic events assessed as related to rFXIII or neutralising antibodies against rFXIII reported during the study.

Secondary safety endpoints

Of the 30 patients, a total of 18 patients reported 44 adverse events of which 11 events in 7 patients were evaluated to be possibly or probably related to the rFXIII. All the related AEs recovered.

In total, there were 10 SAEs reported by 7 patients during the study; all the SAEs were unlikely related to the rFXIII as assessed by the investigator and all the SAEs recovered.

There were 4 medical events of special interest reported during the study and all the events recovered.

PRO-RBDD results

As of the cut-off date of 11 November 2018, there were 4 patients of European origin who were registered in the PRO-RBDD registry and who were on prophylaxis with rFXIII, all with endogenous FXIII:C levels < 2%. The age of the patients ranged from 20 to 41 years. No adverse events or treatment-requiring bleeding episodes were reported as of the cut-off date.

Taken together and regarding the safety updates proposed by the MAH in this variation:

- NovoThirteen prophylaxis during pregnancy in patients with congenital FXIII A-subunit deficiency did not show any particular safety concerns. As a result, the MAH proposed to update Section 4.6 of SmPC accordingly.
- In NN1841-3868, no differences in the safety profile was observed in the paediatric population when compared to the adult population. As a result, the MAH proposed to update Section 5.1 of SmPC and Section 3 of package leaflet accordingly.
- No allergic reactions or embolic and thrombotic events assessed as related to rFXIII were reported in NN1841-3868.
- In PRO-RBDD registry, no pregnancies and no adverse events were reported as of the cut-off date of 11 November 2018.

2.5.2. Conclusions on clinical safety

Based on results assessed above and since the last PRAC PSUR AR, no safety concerns were observed with the use of NovoThirteen prophylaxis in congenital FXIII A-subunit deficiency.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 15.1 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update, as follows: "and treatment of episodic bleedings in patients not covered by prophylaxis" should be omitted and the proposals be changed to the facts throughout the RMP, incl. part 1 and section 2.5.2.2 "Post-authorisation off-label use".

The CHMP endorsed the Risk Management Plan version 15.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

Not applicable, given the lack of safety concerns.

Risk minimisation measures

Not applicable, given the lack of safety concerns.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.6, 5.1, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The MAH is seeking an extension of indication for NovoThirteen to include treatment of bleeding episodes in patients with congenital factor XIII A-subunit deficiency as well as minor surgery. Updates of PK proprieties based on the results of study NN1841-3868, F13CD-3720 and the PRO-RBDD registry are also proposed.

3.1.1. Disease or condition

Congenital coagulation factor XIII (FXIII) deficiency is a rare autosomal recessive bleeding disorder in which reduced plasma FXIII activity is caused by quantitative or rarely by qualitative defects in the FXIII A-subunit protein. Much less commonly, FXIII deficiency is caused by defects in the FXIII B-subunit protein. FXIII deficiency has an estimated worldwide prevalence of 1 per 2 to 5 million individuals. In patients with FXIII A-subunit deficiency the FXIII activity level is lower than 3 to 5% (or approximately 0.04 to 0.06 IU/mL), compared with a wide range of approximately 50% to 220% (0.60 to 2.60 IU/mL) in the normal population.

3.1.2. Available therapies and unmet medical need

Given that intracranial bleeding is common in FXIII deficiency and may be a presenting feature later in childhood, most cases receive long-term prophylaxis with FXIII concentrate. Current treatment options in FXIII deficiency include cryoprecipitate, fresh frozen plasma, plasma-derived FXIII (pdFXIII) concentrate (Fibrogammin / Corifact) and recombinant FXIII subunit-A (rFXIII, NovoThirteen).

3.1.3. Main clinical studies

In support of this application, the MAH submitted the final results of the PASS NN1841-3868 as part of commitment on post-authorisation measure MEA-003.1. This final study report also includes final data from the global Prospective Rare Bleeding Disorder Database (PRO-RBDD) registry. Two interim reports of PASS NN1841-3868 have been submitted previously. The second interim report covering the period from FPFV until 17th May 2017 with the enrolment of 30 patients were assessed under the procedure EMEA/H/C/2284/MEA-15.1.

PASS NN1841-3868 was a prospective, single-arm, multi-centre, multinational observational non-interventional post-authorisation safety study (PASS) of safety related to treatment with rFXIII in patients with congenital FXIII A-subunit deficiency. No controls or blinding procedures were applied.

3.2. Favourable effects

A total of 7 bleeding episodes in 6 patients with congenital FXIII A-subunit deficiency were reported. The haemostatic outcome in all the bleeds treated with rFXIII was good or excellent.

A total of 23 minor surgeries were performed in 16 patients with congenital FXIII A-subunit deficiency. Of these, 21 surgeries were covered by a single prophylactic dose of rFXIII for each surgery.

One patient from NN1841-3868 who underwent 2 surgeries received an additional vial (2500 IU) of rFXIII prior to each surgery.

All the patients who underwent minor surgeries (in F13CD-3720 and NN1841-3868) had a successful haemostatic outcome of good or excellent, except for 1 patient whose haemostatic outcome was missing.

Based on these results, posology of rFXIII during minor surgeries is updated in Sections 4.2 and 5.1 of SmPC.

In NN1841-3868, no differences in the treatment responses were observed between the paediatric and adult population.

Taken together, the use of rFXIII other than for prophylactic treatment in patients with congenital FXIII A-subunit deficiency was collected as one of the secondary endpoints in the PASS NN1841-3868, and recorded results demonstrates that rFXIII can also be used as a treatment of bleeds during the prophylactic regimen in these patients. Additionally, in the pivotal extension study F13CD-3720 and NN1841-3868, it was demonstrated that prophylaxis with rFXIII would alone be sufficient to avoid bleeding episodes during minor elective surgeries in patients with congenital FXIII A-subunit deficiency.

3.3. Uncertainties and limitations about favourable effects

In PASS NN1841-3868, none of patients was on demand treatment defined as patients who do not receive regular treatment but are only treated when needed per protocol. All of 4 patients who treated for their traumatic bleeds were currently on long-term prophylactic regimen with rFXIII and all of 5 episodes of breakthrough bleeds occurred during their regular prophylaxis.

3.4. Unfavourable effects

The primary endpoint of study PASS NN1841-3868 was the incidence of specific adverse drug reactions (ADRs) in patients with congenital FXIII A-subunit deficiency treated with rFXIII, comprising anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of effect, collected during a study period of up to 6 years.

A total of 3 specific ADRs in 2 patients were reported in study PASS NN1841-3868; 2 incidences of positive non-neutralising anti-rFXIII antibody in one patient at 2 time-points and a suspected lack of therapeutic effect in another patient.

Secondary safety endpoints

Of the 30 patients, a total of 18 patients reported 44 adverse events of which 11 events in 7 patients were evaluated to be possibly or probably related to the rFXIII. All the related AEs recovered.

In total, there were 10 SAEs reported by 7 patients during the study; all the SAEs were unlikely related to the rFXIII as assessed by the investigator and all the SAEs recovered.

There were 4 medical events of special interest reported during the study and all the events recovered.

PRO-RBDD results

As of the cut-off date of 11 November 2018, there were 4 patients (3 males and one female) of European origin who were registered in the PRO-RBDD registry and who were on prophylaxis with rFXIII, all with endogenous FXIII:C levels < 2%. The age of the patients ranged from 20 to 41 years. No adverse events or treatment-requiring bleeding episodes were reported as of the cut-off date.

3.5. Uncertainties and limitations about unfavourable effects

Based on the provided data and since the last PRAC PSUR AR, no safety concerns were observed with the use of NovoThirteen prophylaxis in congenital FXIII A-subunit deficiency.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

A long-term non-interventional post-authorisation safety study PASS NN1841-3868 has been conducted in a real-world setting in patients with congenital FXIII A-subunit deficiency, who received rFXIII. This prospective single-arm, multi-national PASS addressed the long-term safety and effectiveness of rFXIII in patients with congenital FXIII A-subunit deficiency and the current clinical treatment practices for rFXIII use in all age groups.

A total of 30 patients were enrolled, of which 13 were children and adolescents, 15 adults and 2 elderlies. No spontaneous treatment requiring bleeds occurred during 6-year study period. None of the patients withdrew from the study due to the lack of efficacy. Six traumatic bleeding episodes were managed with additional dose of rFXIII during regular prophylaxis regimen and all had excellent or good response. Haemostatic responses observed during and after minor surgeries were favourable.

No safety concerns were raised.

The real-world data from this PASS showed that rFXIII prophylaxis every 4 weeks is effective and well tolerated for treatment and preventing bleeds in patients with congenital FXIII-A subunit deficiency.

3.6.2. Balance of benefits and risks

The benefit-risk balance for rFXIII remains overall favourable and unchanged.

3.6.3. Additional considerations on the benefit-risk balance

3.7. Conclusions

The overall B/R of Novothirteen is positive. In PASS NN1841-3868, none of patients was on demand treatment. Therefore, no clear conclusion could be drawn in the treatment of episodic bleedings in patients not covered by prophylaxis. As a consequence, Novothirteen can only be recommended for the long term prophylactic treatment of bleeding in patients with congenital factor XIII A-subunit deficiency, and as supplementary treatment to management of breakthrough bleeding episodes during regular prophylactic treatment regimen. By supplementary responses on 3rd and 13th July 2020, the MAH agreed with this conclusion and updated the SmPC (4.1 and 4.2) as requested.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition	Type II	I, IIIA and

	of a new therapeutic indication or modification of an approved one		IIIB

Extension of indication to include long term prophylactic treatment of bleeding in patients with congenital factor XIII A-subunit deficiency, and as supplementary treatment to management of breakthrough bleeding episodes during regular prophylactic treatment regimen in patients with congenital factor XIII A-subunit deficiency as well as minor surgery based on the results of study NN1841-3868 and the PRO-RBDD registry. As a consequence, sections 4.1, 4.2, 4.4, 4.6, 5.1, 5.2 of the SmPC and the RMP version 15 has been submitted. Annex IID and the package leaflet have been updated accordingly.
Furthermore, the PI is brought in line with the latest QRD template version. Minor editorial updates have also been made.

The group of variations leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'NovoThirteen H-C-2284-II-26-G'