Clinical trial results:
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 : Safety Extension Trial to F13CD-1725.

Summary

EudraCT number	2008-007883-41
Trial protocol	FI DE GB FR ES IT AT
Global end of trial date	20 October 2015

Results information

Result version number	v1 (current)
This version publication date	05 May 2016
First version publication date	05 May 2016

Trial information

Trial identification

Sponsor protocol code	F13CD-3720 (Mentor™2)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00978380
WHO universal trial number (UTN)	U1111-1111-9289

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé,, Bagsvaerd,, Denmark, 2880
Public contact	Global Clinical Registry (GCR, 1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Global Clinical Registry (GCR, 1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000185-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 October 2015
Global end of trial reached?	Yes
Global end of trial date	20 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long term safety of monthly replacement therapy with recombinant factor XIII (rFXIII) when used for prevention of bleeding episodes in subjects with congenital factor XIII (FXIII) deficiency.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki[World medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects - Last amended by the 59th WMA General Assembly, Seoul. 2008. 2015.], ICH GCP [International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Good Clinical Practice. 01 May 1996. 2015.] and FDA 21 CFR 312, 50 and 56.

Background therapy:

Previous participation (means up to and including end-of-trial visit) in F13CD-1725 (EudraCT no: 2006-003148-51).

Evidence for comparator:

Not applicable

Actual start date of recruitment	21 September 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	63
EEA total number of subjects	26

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	8
Adolescents (12-17 years)	8
Adults (18-64 years)	46
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 34 sites in 12 countries as follows: Austria: 1 site; Canada: 1 site; Finland: 1 site; France: 4 sites; Germany: 4 sites; Israel: 1 site; Italy: 1 site: Japan: 2 sites; Spain: 2 sites; Switzerland: 1 site; United Kingdom: 4 sites; United States: 12 sites.

Pre-assignment

Screening details:

Subjects who completed F13CD-1725 (EudraCT no: 2006-003148-51) end of trial visit were eligible to enroll in this trial. Also, new subjects diagnosed with congenital FXIII A-subunit deficiency (confirmed by genotyping at screening visit or documented results from previously performed genotyping) were enrolled to expand the safety population.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The trial was an open-label phase 3b trial.

Arms

Arm title	Recombinant factor XIII (rFXIII)

Arm description:

All subjects received 35 IU/kg bodyweight of rFXIII every 4 weeks (28 days±2 days) until the end of trial for a minimum period of 52 weeks. The dose was identical to the dose administered in the F13CD-1725 trial. Additional haemostatic rescue medication as per local standard of care was to be intiated in subjects with the consent of the investigator, where haemostatic control could not be achieved with a single dose of rFXIII 35 IU/kg. A total of 60 unique subjects were enrolled and exposed in the trial, but 3 of these subjects were later withdrawn and subsequently re-enrolled with new subject IDs, giving rise to a total of N=63 subjects. The unique subjects (N=60) were presented as full analysis set while summarising adverse events to avoid double-counting.

Arm type	Experimental
Investigational medicinal product name	Recombinant factor XIII (rFXIII)
Investigational medicinal product code	
Other name	Catridecacog
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Monthly administration of recombinant factor XIII (rFXIII) as preventative treatment of bleeding episodes of dose: 35 IU/kg body weight intravenous (into the vein). Sterile, freeze-dried powder rFXIII was reconstituted with 3.2 mL of sterile water for injection at room temperature. The solution was administered by syringe as a slow bolus injection at a rate not higher than 1−2 mL/minute within 6 hours after reconstitution. The correct dosing was calculated and adjusted based on the actual weight of the subject.

Number of subjects in period 1	Recombinant factor XIII (rFXIII)
Started	63
Completed	44
Not completed	19
withdrawal criteria	9
Unclassified	8
Protocol deviation	2

Baseline characteristics

Reporting groups

Reporting group title	Recombinant factor XIII (rFXIII)

Reporting group description:

All subjects received 35 IU/kg bodyweight of rFXIII every 4 weeks (28 days±2 days) until the end of trial for a minimum period of 52 weeks. The dose was identical to the dose administered in the F13CD-1725 trial. Additional haemostatic rescue medication as per local standard of care was to be intiated in subjects with the consent of the investigator, where haemostatic control could not be achieved with a single dose of rFXIII 35 IU/kg. A total of 60 unique subjects were enrolled and exposed in the trial, but 3 of these subjects were later withdrawn and subsequently re-enrolled with new subject IDs, giving rise to a total of N=63 subjects. The unique subjects (N=60) were presented as full analysis set while summarising adverse events to avoid double-counting.

Reporting group values	Recombinant factor XIII (rFXIII)	Total	
Number of subjects	63	63	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	8	8	
Adolescents (12-17 years)	8	8	
Adults (18-64 years)	46	46	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	31		
standard deviation	± 16.8	-	
Gender categorical Units: Subjects			
Female	23	23	
Male	40	40	
Ethnicity Units: Subjects			
Hispanic or Latino	7	7	
Not Hispanic or Latino	52	52	
Unknown	4	4	
Race Units: Subjects			
Black or African American	6	6	
American Indian or Alaska Native	1	1	
White	37	37	
Asian	9	9	
Other	6	6	
Unknown	4	4	

End points

End points reporting groups

Reporting group title	Recombinant factor XIII (rFXIII)

Reporting group description:

All subjects received 35 IU/kg bodyweight of rFXIII every 4 weeks (28 days±2 days) until the end of trial for a minimum period of 52 weeks. The dose was identical to the dose administered in the F13CD-1725 trial. Additional haemostatic rescue medication as per local standard of care was to be intiated in subjects with the consent of the investigator, where haemostatic control could not be achieved with a single dose of rFXIII 35 IU/kg. A total of 60 unique subjects were enrolled and exposed in the trial, but 3 of these subjects were later withdrawn and subsequently re-enrolled with new subject IDs, giving rise to a total of N=63 subjects. The unique subjects (N=60) were presented as full analysis set while summarising adverse events to avoid double-counting.

Primary: Adverse events (serious and non-serious) occurring from first trial related activity after signing the informed consent to the end of subject's participation in the trial

End point title	Adverse events (serious and non-serious) occurring from first trial related activity after signing the informed consent to the end of subject's participation in the trial[1]

End point description:

An adverse events (AEs) was defined as any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Trial AEs included any event that occurred from the time of informed consent until the post-treatment followup period as specified in the protocol.

End point type	Primary

End point timeframe:

All adverse events were collected and reported from screening (visit 1) and until the end of trial visit for a minimum period of 52 weeks.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoint investigated safety and was analysed using descriptive statistics, and thus no statistical analysis was performed.

End point values	Recombinant factor XIII (rFXIII)			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: Events				
All adverse events	920			
Serious adverse events	19			
Non-serious adverse events	901			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) were collected and reported from screening (visit 1) and until the end of trial visit for a minimum period of 52 weeks.

Adverse event reporting additional description:

All AEs either observed by the investigator or reported spontaneously by the subjects were recorded by the investigator and evaluated at each contact with the trial site (visit or telephone). The full analysis set included all subjects who received at least one dose of the trial product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	rFXIII Novo Nordisk

Reporting group description:

Subjects in this arm received identical dose of 35 IU/kg bodyweight of rFXIII every 4 weeks (28 days±2 days) until the end of trial for a minimum period of 52 weeks. In the early stage of the trial, a contract manufacturing facility (Avecia) produced the rFXIII drug substance (rFXIII Avecia) and subsequently, Novo Nordisk took over production of the rFXIII drug substance (rFXIII Novo Nordisk). Characterisation testing between the two products confirmed that rFXIII Novo Nordisk and rFXIII Avecia had identical structures, and similar physico-chemical properties. The recombinant factor XIII (rFXIII) reporting group was segregated as rFXIII Novo Nordisk and rFXIII Avecia while reporting endpoints and AEs.

Reporting group title	rFXIII Avecia

Reporting group description:

Subjects in this arm received 35 IU/kg bodyweight of rFXIII every 4 weeks (28 days±2 days) until the end of trial for a minimum period of 52 weeks. Early on in the trial, a contract manufacturing facility (Avecia) produced the rFXIII drug substance (rFXIII Avecia). Subsequently, Novo Nordisk took over production of the rFXIII drug substance (substance referred to as rFXIII Novo Nordisk). Characterisation testing between two products confirmed that rFXIII Novo Nordisk and rFXIII Avecia had identical structures and similar physico-chemical properties. The recombinant factor XIII (rFXIII) reporting group was segregated as rFXIII Novo Nordisk and rFXIII Avecia while reporting endpoints and AEs.

Serious adverse events	rFXIII Novo Nordisk	rFXIII Avecia	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 59 (20.34%)	0 / 26 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	1 / 59 (1.69%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	2 / 59 (3.39%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	2 / 59 (3.39%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 59 (1.69%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 59 (1.69%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	2 / 59 (3.39%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord injury			
subjects affected / exposed	1 / 59 (1.69%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 59 (1.69%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patent ductus arteriosus			
subjects affected / exposed	1 / 59 (1.69%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Cerebral ischaemia			
subjects affected / exposed	1 / 59 (1.69%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 59 (1.69%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			
subjects affected / exposed	1 / 59 (1.69%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 59 (1.69%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 59 (1.69%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			
subjects affected / exposed	1 / 59 (1.69%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	rFXIII Novo Nordisk	rFXIII Avecia	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 59 (91.53%)	15 / 26 (57.69%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Pain			
subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Pyrexia			
subjects affected / exposed	6 / 59 (10.17%)	0 / 26 (0.00%)	
occurrences (all)	11	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 59 (20.34%)	0 / 26 (0.00%)	
occurrences (all)	29	0	
Nasal congestion			
subjects affected / exposed	7 / 59 (11.86%)	0 / 26 (0.00%)	
occurrences (all)	20	0	
Oropharyngeal pain			
subjects affected / exposed	11 / 59 (18.64%)	0 / 26 (0.00%)	
occurrences (all)	31	0	
Rhinorrhoea			
subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Investigations			

White blood cells urine positive			
subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	4 / 59 (6.78%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Contusion			
subjects affected / exposed	11 / 59 (18.64%)	2 / 26 (7.69%)	
occurrences (all)	18	2	
Fall			
subjects affected / exposed	8 / 59 (13.56%)	1 / 26 (3.85%)	
occurrences (all)	10	1	
Head injury			
subjects affected / exposed	3 / 59 (5.08%)	1 / 26 (3.85%)	
occurrences (all)	4	1	
Incorrect dose administered			
subjects affected / exposed	6 / 59 (10.17%)	1 / 26 (3.85%)	
occurrences (all)	9	1	
Injury			
subjects affected / exposed	4 / 59 (6.78%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Joint injury			
subjects affected / exposed	4 / 59 (6.78%)	0 / 26 (0.00%)	
occurrences (all)	6	0	
Laceration			
subjects affected / exposed	4 / 59 (6.78%)	1 / 26 (3.85%)	
occurrences (all)	4	1	
Ligament sprain			
subjects affected / exposed	6 / 59 (10.17%)	2 / 26 (7.69%)	
occurrences (all)	9	2	
Limb injury			
subjects affected / exposed	5 / 59 (8.47%)	3 / 26 (11.54%)	
occurrences (all)	8	3	
Post-traumatic pain			

subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Procedural pain			
subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Road traffic accident			
subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Skin abrasion			
subjects affected / exposed	3 / 59 (5.08%)	1 / 26 (3.85%)	
occurrences (all)	4	1	
Thermal burn			
subjects affected / exposed	6 / 59 (10.17%)	2 / 26 (7.69%)	
occurrences (all)	6	2	
Wound			
subjects affected / exposed	2 / 59 (3.39%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 59 (32.20%)	2 / 26 (7.69%)	
occurrences (all)	72	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 59 (6.78%)	0 / 26 (0.00%)	
occurrences (all)	6	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	4 / 59 (6.78%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 59 (8.47%)	0 / 26 (0.00%)	
occurrences (all)	6	0	
Constipation			
subjects affected / exposed	5 / 59 (8.47%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
Dental caries			

subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Diarrhoea			
subjects affected / exposed	3 / 59 (5.08%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Dyspepsia			
subjects affected / exposed	6 / 59 (10.17%)	0 / 26 (0.00%)	
occurrences (all)	14	0	
Nausea			
subjects affected / exposed	7 / 59 (11.86%)	0 / 26 (0.00%)	
occurrences (all)	8	0	
Toothache			
subjects affected / exposed	4 / 59 (6.78%)	0 / 26 (0.00%)	
occurrences (all)	6	0	
Vomiting			
subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	4 / 59 (6.78%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
Dermatitis contact			
subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Pruritus			
subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
Rash			
subjects affected / exposed	5 / 59 (8.47%)	0 / 26 (0.00%)	
occurrences (all)	8	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	3 / 59 (5.08%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	11 / 59 (18.64%)	1 / 26 (3.85%)	
occurrences (all)	24	1	
Back pain			
subjects affected / exposed	9 / 59 (15.25%)	2 / 26 (7.69%)	
occurrences (all)	12	2	
Musculoskeletal pain			
subjects affected / exposed	6 / 59 (10.17%)	0 / 26 (0.00%)	
occurrences (all)	7	0	
Musculoskeletal stiffness			
subjects affected / exposed	4 / 59 (6.78%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Myalgia			
subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
Neck pain			
subjects affected / exposed	3 / 59 (5.08%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Pain in extremity			
subjects affected / exposed	12 / 59 (20.34%)	1 / 26 (3.85%)	
occurrences (all)	32	1	
Infections and infestations			
Folliculitis			
subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Gastroenteritis			
subjects affected / exposed	8 / 59 (13.56%)	0 / 26 (0.00%)	
occurrences (all)	10	0	
Influenza			
subjects affected / exposed	7 / 59 (11.86%)	0 / 26 (0.00%)	
occurrences (all)	8	0	
Nasopharyngitis			
subjects affected / exposed	19 / 59 (32.20%)	2 / 26 (7.69%)	
occurrences (all)	48	2	
Sinusitis			

subjects affected / exposed	11 / 59 (18.64%)	1 / 26 (3.85%)	
occurrences (all)	17	1	
Tonsillitis			
subjects affected / exposed	5 / 59 (8.47%)	0 / 26 (0.00%)	
occurrences (all)	8	0	
Upper respiratory tract infection			
subjects affected / exposed	14 / 59 (23.73%)	0 / 26 (0.00%)	
occurrences (all)	25	0	
Viral infection			
subjects affected / exposed	3 / 59 (5.08%)	0 / 26 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2009	The number of subjects who had developed non-neutralising antirFXIII antibodies in trial F13CD-1725 was modified from two to 'a few'. As an exception, the United States (US) was excluded from this protocol amendment.
21 October 2009	Evaluation of subjects for exclusion to use platelet count from visit 15 in F13CD-1725. Added requirement that subjects who develop antibodies must visit the clinic for administration of trial product. Additional blood sampling for antibody analysis will be performed at these visits to further characterise the antibodies.
09 November 2009	Subject Information/Informed Consent updated according to the changes implemented in the protocol following Substantial Amendment no. 4, dated 21-October-2009.
02 December 2009	Allowance for additional laboratory testing when the Novo Nordisk produced rFXIII is administrated to subjects in the trial.
16 February 2010	Introduced additional blood sampling prior to all monthly rFXIII administrations (and cessation of home treatments). Instituted that interim analyses were to be performed after 3 and 6 months of exposure data with Novo Nordisk-produced rFXIII had been obtained. For Canada only: post-reconstitution in-use shelf life period of rFXIII was changed from 6 hours at room temperature and 24 hours at 2-8°C (as currently written in consolidated protocol no. 2) to 3 hours at room temperature.
08 September 2010	Allowed all subjects who had participated in Trial F13CD-1725 (not only those who completed the study) and additional subjects with FXIII A-subunit deficiency into the extension Trial if eligible. Recruitment period was extended and the total number of subjects for inclusion increased.
02 September 2011	Allowed the central laboratory to report to the investigator additional analyses not required by the protocol but produced in connection with the requested analyses.
22 February 2012	Withdrawal criterion no. 6 "Routine treatment with any antithrombotic drug" was rephrased to allow use of antithrombotic drugs. Japan added to the list of participating countries and text related to Japan's participation updated. Number of visits until end-of-trial increased from 16 to 24.
14 May 2012	Steady-state PK assessment added as well as offer to treat with rFXIII in case of treatment-requiring breakthrough bleeding. The conditions for treatment with rFXIII in relation to treatment requiring bleeding episodes were specified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Limitations of the trial include small number of children and adolescents (16 subjects), and the sensitivity of the Berichrome® FXIII activity assay. However, mean FXIII activity levels were consistent with few bleeds requiring haemostatic treatment.

Notes: