

**Clinical trial results:****A Multi-Centre, Multinational, Open-Label, Single-Arm and Multiple Dosing Trial on Safety and Efficacy of Monthly Replacement Therapy with Recombinant Factor XIII (rFXIII) in Paediatric Subjects with Congenital Factor XIII A-subunit Deficiency - Safety Extension Trial to F13CD-3760.****Summary**

EudraCT number	2010-020192-23
Trial protocol	GB
Global end of trial date	29 March 2015

Results information

Result version number	v1 (current)
This version publication date	14 April 2016
First version publication date	14 April 2016

Trial information**Trial identification**

Sponsor protocol code	F13CD-3835
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01253811
WHO universal trial number (UTN)	U1111-1117-1063

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)	No
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	11 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 March 2015
Global end of trial reached?	Yes
Global end of trial date	29 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long term safety of monthly replacement therapy with rFXIII when used for prevention of bleeding episodes in paediatric subjects with congenital FXIII A-subunit deficiency.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996) and 21 Code of Federal Regulations parts 321, 50, and 56.

Background therapy:

Previous participation (means up to and including end of trial visit) in F13CD-3760 (EudraCT no: 2009-016869-28).

Evidence for comparator:

Not applicable.

Actual start date of recruitment	07 January 2011
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	United Kingdom: 3
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	6
EEA total number of subjects	3

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)	1

Children (2-11 years)	5
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 5 sites in 3 countries as follows: Israel (IS): 1 site; United Kingdom (UK): 2 sites; and United States (US): 2 sites.

Pre-assignment

Screening details:

Subjects who completed the F13CD-3760 trial were eligible to enroll in this trial.

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
------------------	-------------------------

Arm description:

Each subject received one single dose of 35 IU/kg rFXIII was administered as a slow intravenous (i.v.) injection preventive treatment of bleeding episodes. The dose was identical to the dose administered in F13CD-3760. The correct dosing was calculated based on subject's body weight and the trial dose was scheduled at visit 1 and for every 4th week (28 ± 2 days).

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:

Each single dose included intravenous injection of recombinant factor XIII, 35 IU/kg bodyweight. The rFXIII was reconstituted and diluted with saline, administered as a slow i.v. injection at a rate not exceeding 1-2 mL min⁻¹.

Number of subjects in period 1	Recombinant factor XIII
Started	6
Completed	5
Not completed	1
Withdrawal criteria	1

Baseline characteristics

Reporting groups

Reporting group title	Overall study
-----------------------	---------------

Reporting group description:

Each subject received one single dose of 35 IU/kg rFXIII was administered as a slow intravenous (i.v.) injection preventive treatment of bleeding episodes. The dose was identical to the dose administered in F13CD-3760. The correct dosing was calculated based on subject's body weight and the trial dose was scheduled at visit 1 and for every 4th week (28 ± 2 days).

Reporting group values	Overall study	Total	
Number of subjects	6	6	
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)	1	1	
Children (2-11 years)	5	5	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	3	-	
standard deviation	± 1.3	-	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	3	3	
Ethnicity			
Units: Subjects			
Not hispanic or latino	6	6	
Race			
Units: Subjects			
Asian	3	3	
Black or african american	1	1	
White	2	2	

End points

End points reporting groups

Reporting group title	Recombinant factor XIII
Reporting group description: Each subject received one single dose of 35 IU/kg rFXIII was administered as a slow intravenous (i.v.) injection preventive treatment of bleeding episodes. The dose was identical to the dose administered in F13CD-3760. The correct dosing was calculated based on subject's body weight and the trial dose was scheduled at visit 1 and for every 4th week (28 ± 2 days).	

Primary: Treatment emergent adverse events (serious and non-serious), defined as adverse events occurring from first trial product administration to the end of the subject's participation in the trial.

End point title	Treatment emergent adverse events (serious and non-serious), defined as adverse events occurring from first trial product administration to the end of the subject's participation in the trial. ^[1]
-----------------	---

End point description:

An adverse event was described as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. Treatment emergent adverse events (serious and non-serious), defined as adverse events occurring from first trial product administration to the end of the subject's participation in the trial. The safety analysis set (SAS) included all subjects exposed to trial drug (rFXIII).

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			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Events				
All adverse events	100			
Serious adverse events	2			
Non-serious adverse events	98			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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.

Adverse event reporting additional description:

The SAS included all subjects who received at least one dose of the trial product.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	16.1
--------------------	------

Reporting groups

Reporting group title	Recombinant factor XIII (rFXIII) 35 IU/kg
-----------------------	---

Reporting group description:

Each subject received one single dose of 35 IU/kg rFXIII was administered as a slow intravenous (i.v.) injection preventive treatment of bleeding episodes. The dose was identical to the dose administered in F13CD-3760. The correct dosing was calculated based on subject's body weight and the trial dose was scheduled at visit 1 and for every 4th week (28 ± 2 days).

Serious adverse events	Recombinant factor XIII (rFXIII) 35 IU/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Recombinant factor XIII (rFXIII) 35 IU/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Investigations			

Bacterial test positive subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Injury, poisoning and procedural complications			
Arthropod bite subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Contusion subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 3		
Fall subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 7		
Incorrect dose administered subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Joint injury subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Laceration subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2		
Limb injury subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Skin abrasion subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2		
Thermal burn subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Traumatic haematoma subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Traumatic haemorrhage			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Vascular disorders Haematoma subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 3		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Infusion site extravasation subjects affected / exposed occurrences (all) Infusion site rash subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1 2 / 6 (33.33%) 2 1 / 6 (16.67%) 1 2 / 6 (33.33%) 2 4 / 6 (66.67%) 6		
Blood and lymphatic system disorders Lymphopenia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea	1 / 6 (16.67%) 1		

subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 5		
Nausea subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2		
Tooth loss subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Vomiting subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 4		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 3		
Epistaxis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Nasal congestion subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2		
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Respiratory disorder subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 7		
Sneezing			

<p>subjects affected / exposed occurrences (all)</p> <p>Snoring subjects affected / exposed occurrences (all)</p>	<p>2 / 6 (33.33%) 3</p> <p>1 / 6 (16.67%) 1</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>Dry skin subjects affected / exposed occurrences (all)</p> <p>Rash subjects affected / exposed occurrences (all)</p>	<p>1 / 6 (16.67%) 1</p> <p>1 / 6 (16.67%) 3</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia subjects affected / exposed occurrences (all)</p>	<p>1 / 6 (16.67%) 1</p>		
<p>Infections and infestations</p> <p>Acute tonsillitis subjects affected / exposed occurrences (all)</p> <p>Gastroenteritis subjects affected / exposed occurrences (all)</p> <p>Gastroenteritis viral subjects affected / exposed occurrences (all)</p> <p>Influenza subjects affected / exposed occurrences (all)</p> <p>Nasopharyngitis subjects affected / exposed occurrences (all)</p> <p>Otitis media acute subjects affected / exposed occurrences (all)</p> <p>Pharyngitis streptococcal</p>	<p>1 / 6 (16.67%) 1</p> <p>2 / 6 (33.33%) 3</p> <p>1 / 6 (16.67%) 1</p> <p>1 / 6 (16.67%) 1</p> <p>1 / 6 (16.67%) 1</p> <p>1 / 6 (16.67%) 1</p> <p>1 / 6 (16.67%) 2</p>		

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 7		
Varicella subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Viral infection subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2010	Additions made to data collection in relation to bleeding episodes and in case of surgery; revision of an exclusion criteria; clarification of water and sodium supply; change in trial title.
13 April 2011	Date for LSLV was moved up; additional analyses were permitted to be reported to the investigator by the local laboratory.
10 October 2013	Date for LSLV was postponed
01 April 2014	Date for LSLV was postponed.

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 included the small number of subjects analysed and the sensitivity of the Berichrom® FXIII activity assay. However, congenital FXIII deficiency is a rare disease and there were no bleeds requiring haemostatic treatment.

Notes: