



## Clinical trial results:

### A Multi-Centre, Open-Label, Single-Arm and Multiple Dosing Trial on Efficacy and Safety of Monthly Replacement Therapy with Recombinant Factor XIII (rFXIII) in Subjects with Congenital Factor XIII Deficiency.

#### Summary

EudraCT number	2006-003148-51
Trial protocol	GB FR DE AT ES FI IT
Global end of trial date	15 April 2010

#### Results information

Result version number	v2 (current)
This version publication date	30 March 2016
First version publication date	21 July 2015
Version creation reason	<ul style="list-style-type: none"><li>• Correction of full data set</li><li>New AE data to be uploaded</li></ul>

#### Trial information

##### Trial identification

Sponsor protocol code	F13CD-1725
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00713648
WHO universal trial number (UTN)	-

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)	EMA-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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	17 November 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2010
Global end of trial reached?	Yes
Global end of trial date	15 April 2010
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

To evaluate the efficacy of monthly replacement therapy with rFXIII on prevention of bleeding episodes in subjects with congenital FXIII deficiency.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice.

Background therapy:

Subjects who had received regular replacement therapy before entering the trial, were to have initiated this treatment at least 6 months prior to screening.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	18 August 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	United States: 10
Country: Number of subjects enrolled	Switzerland: 2
Worldwide total number of subjects	41
EEA total number of subjects	18

Notes:

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**Subjects enrolled per age group**

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	9
Adolescents (12-17 years)	6
Adults (18-64 years)	26
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Of a total of 29 initiated trial sites, 23 sites enrolled and dosed at least one patient. The country distribution was (number of actively recruiting sites per country in parenthesis): Austria (1), Canada (1), Finland (1), France (1), Germany (3), Israel (2), Italy (1), Spain (1), Switzerland (1), UK (3) and United States of America (8).

### Pre-assignment

Screening details:

After screening, eligible subjects entered a 4-week run-in period followed by a 52-week recombinant factor XIII (rFXIII) treatment period. Subjects who before entering the trial were receiving regular replacement therapy with a FXIII-containing product were to receive their last standard replacement dose just before the screening visit.

### 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:

Not applicable.

### Arms

Arm title	rFXIII
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Arm description:

Subjects received 35 IU/kg rFXIII every 4th week (28±2 days) during a treatment period of 52 weeks. In case of acute bleeding episodes, any additional treatment as per investigator judgment was to be according to local standard practice. Additional doses of rFXIII could therefore not be used to treat such breakthrough bleedings.

Arm type	Experimental
Investigational medicinal product name	Recombinant Factor XIII
Investigational medicinal product code	F13CD
Other name	Coagulation factor XIII
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Monthly administration of recombinant factor XIII as preventative treatment of bleeding episodes. Dose: 35 IU/kg body weight intravenous (into the vein).

Number of subjects in period 1	rFXIII
Started	41
Completed	33
Not completed	8
Withdrawal Criteria	2
Adverse event, non-fatal	1
Other Reason	2
Non-Neutralising Antibodies	3



## Baseline characteristics

### Reporting groups

Reporting group title	rFXIII
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Reporting group description:

Subjects received 35 IU/kg rFXIII every 4th week ( $28 \pm 2$  days) during a treatment period of 52 weeks. In case of acute bleeding episodes, any additional treatment as per investigator judgment was to be according to local standard practice. Additional doses of rFXIII could therefore not be used to treat such breakthrough bleedings.

Reporting group values	rFXIII	Total	
Number of subjects	41	41	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	26.4 $\pm 15.9$	-	
Gender categorical Units: Subjects			
Female	18	18	
Male	23	23	
Race Units: Subjects			
Black or African American	2	2	
White	28	28	
Asian	5	5	
Other	5	5	
Unknown	1	1	

## End points

### End points reporting groups

Reporting group title	rFXIII
Reporting group description: Subjects received 35 IU/kg rFXIII every 4th week (28±2 days) during a treatment period of 52 weeks. In case of acute bleeding episodes, any additional treatment as per investigator judgment was to be according to local standard practice. Additional doses of rFXIII could therefore not be used to treat such breakthrough bleedings.	

### Primary: Rate (Number Per Subject Year) of Bleeding Episodes Requiring Treatment With a FXIII Containing Product During the Treatment Period

End point title	Rate (Number Per Subject Year) of Bleeding Episodes Requiring Treatment With a FXIII Containing Product During the Treatment Period <sup>[1]</sup>
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End point description:

The rate (Number Per Subject Year) of bleeding episodes represents the incidence of bleeding episodes requiring treatment with a FXIII-containing product.

End point type	Primary
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End point timeframe:

For a period of 322 days (approximately one year) comprised of a screening visit (Visit 1), treatment period (Visits 2-15), unscheduled visit and end-of-trial visit (Visit 16).

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 low bleeding incidence and frequency for patients currently on regular replacement therapy (on average approximately 0.3 bleeds/year) and the low number of patients diagnosed with congenital FXIII deficiency (400-700 patients worldwide) did not allow a statistical comparison of clinical outcome parameters (bleeding events) between rFXIII and any other type of regular replacement therapy with sufficient statistical power.

End point values	rFXIII			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: bleeding episodes per subject per year				
arithmetic mean (full range (min-max))	0.138 (0 to 2)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected and reported during the entire study period i.e. approximately one year (322 days)

Adverse event reporting additional description:

All AEs observed by the investigator or reported spontaneously by the subjects, were recorded by the investigator at each contact with the site (visit or telephone, excluding safety visits, where the subject was not seeing the Investigator or his staff (e.g.visits to the laboratory))

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.0
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### Reporting groups

Reporting group title	rFXIII
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Reporting group description:

Subjects received 35 IU/kg rFXIII every 4th week (28±2 days) during a treatment period of 52 weeks. In case of acute bleeding episodes, any additional treatment as per investigator judgment was to be according to local standard practice. Additional doses of rFXIII could therefore not be used to treat such breakthrough bleedings.

Serious adverse events	rFXIII		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 41 (14.63%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Antibody test positive			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			



subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	rFXIII		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 41 (60.98%)		
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Incorrect dose administered			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	11		
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 41 (26.83%)		
occurrences (all)	20		

General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	7 / 41 (17.07%) 7		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)  Toothache subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3  3 / 41 (7.32%) 5  3 / 41 (7.32%) 3		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Nasal congestion subjects affected / exposed occurrences (all)  Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 4  5 / 41 (12.20%) 6  4 / 41 (9.76%) 6		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)  Pain In Extremity subjects affected / exposed occurrences (all)	5 / 41 (12.20%) 5  4 / 41 (9.76%) 4		
Infections and infestations Influenza subjects affected / exposed occurrences (all)  Nasopharyngitis	4 / 41 (9.76%) 4		

subjects affected / exposed	8 / 41 (19.51%)		
occurrences (all)	11		
Urinary tract infection			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2008	The FXIII genotyping will not be made again for those patients if it can be confirmed that they have Congenital A-subunit deficiency and provided that the results can be made available to NN at screening or prior to administration of trial product. The text in the protocol and Subject Information / Informed Consent were updated accordingly. Regarding the participating countries the protocol will be updated according to the result for the country feasibility. The safety information in the protocol and SI/IC has been updated to include data from recently finalised trial F13CARD-1660. The remaining changes are editorial.
12 December 2008	A few subject selection criteria were slightly reworded or modified as described in Section 9.3. Furthermore, lack of efficacy of rFXIII (as judged by the investigator) was added as a withdrawal criterion. A sensitivity analysis for the primary endpoint excluding centres that contributed with more than 20% of the total number of subjects was specified.
27 January 2009	No major changes were implemented with this amendment, which specifies precautionary measures related to pregnancy.
10 June 2009	It was specified that if the Novo Nordisk Safety Committee decided to stop treatment of a subject with rFXIII for safety reasons, the subject could continue in the trial for continued blood and urine sampling for safety evaluation. In addition to recording of bleeding episode and adverse event details, sampling for haematology, biochemistry, urinalysis, FXIII laboratory parameters, immunology, coagulation parameters and clot solubility testing was to be performed prior to administration of standard replacement therapy.
25 November 2009	The subject information/informed consent form was slightly modified due to the fact that two additional subjects had developed non-neutralising antibodies after initiation of treatment with rFXIII.
02 December 2009	This amendment enabled further characterisation of anti-FXIII antibodies. Samples from any subjects in whom anti-FXIII antibodies had been observed following dosing with rFXIII were to be further characterised in order to determine the immunoglobulin isotype of the detected anti-rFXIII antibodies. Additionally, cross-reactivity of subject antibody to plasma-derived FXIII was to be assessed. These analyses were exploratory and were to be presented separately.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/22451421>

