Clinical trial results:
A Multi-Centre, Open-Label, Non-Controlled Trial on Safety and Efficacy of N8 in Previously Treated Paediatric Patients with Haemophilia A

Summary

EudraCT number	2009-016383-36
Trial protocol	IT LT
Global end of trial date	21 November 2011

Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	NN7008-3545

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01138501
WHO universal trial number (UTN)	U1111-1113-7182

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-000428-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	20 March 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 November 2011
Global end of trial reached?	Yes
Global end of trial date	21 November 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate safety of N8 (turoctocog alfa) in paediatric previously treated patients (PTPs) <12 years of age with haemophilia A

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996). The results presented reflect data available in the clinical database as of 13 -Dec-2011. The database was updated on 1-Feb-2012 in order to change the coding of one adverse event coded as 'anti-factor VIII antibody positive'. The results of a second separately drawn sample from this patient was negative, meaning that the definition of FVIII inhibitors was not met and the coding of the event was therefore changed to 'anti-factor VIII antibody test'.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	18 June 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	53 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 5
Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Serbia: 5
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	63
EEA total number of subjects	11

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)	4
Children (2-11 years)	59
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:

A total of 26 sites enrolled and dosed at least one patient. The country distribution was as follows (number of actively recruiting sites per country in parenthesis): Brazil (3), Italy (1), Lithuania (1), Macedonia (1), Malaysia (1), Poland (2), Russia (2), Serbia (1), Taiwan (1), Turkey (3) and the US (10)

Pre-assignment

Screening details:

Not Applicable

Period 1

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

Blinding implementation details:

Not applicable

Arms

Arm title	All subjects treated with Turoctocog Alfa

Arm description:

The patients received bleeding preventive treatment with a single dose of turoctocog alfa of 25-50 IU/kg every second day or 25-60 IU/kg three times weekly. Turoctocog alfa was administered as a slow bolus i.v. injection (approximately 1-2 mL/min). Pharmacokinetic assessments were performed in at least 13 patients from each age cohort. Each patient participating in the pharmacokinetic assessments received one dose of previous factor VIII (FVIII) and one dose of turoctocog alfa.

Arm type	Experimental
Investigational medicinal product name	N8
Investigational medicinal product code	
Other name	Turoctocog Alfa
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

A single dose of turoctocog alfa of 25-50 IU/kg every second day or 25-60 IU/kg three times weekly was administered as a slow bolus i.v. injection (approximately 1-2 mL/min). Each patient participating in the pharmacokinetic assessments received one dose of previous FVIII and one dose of turoctocog alfa.

Number of subjects in period 1	All subjects treated with Turoctocog Alfa
Started	63
Completed	60
Not completed	3
Consent withdrawn by subject	1
Treatment with FVIII concentrates other than N8	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	All subjects treated with Turoctocog Alfa

Reporting group description:

The patients received bleeding preventive treatment with a single dose of turoctocog alfa of 25-50 IU/kg every second day or 25-60 IU/kg three times weekly. Turoctocog alfa was administered as a slow bolus i.v. injection (approximately 1-2 mL/min). Pharmacokinetic assessments were performed in at least 13 patients from each age cohort. Each patient participating in the pharmacokinetic assessments received one dose of previous factor VIII (FVIII) and one dose of turoctocog alfa.

Reporting group values	All subjects treated with Turoctocog Alfa	Total	
Number of subjects	63	63	
Age categorical Units: Subjects			
Age continuous			
Male patients of age <12 years with severe (FVIII ≤1%) haemophilia A were enrolled in this trial.			
Units: years arithmetic mean standard deviation	 6.08 ± 2.91	 -	
Gender categorical			
Male patients of age <12 years with severe (FVIII ≤1%) haemophilia A were enrolled in this trial.			
Units: Subjects			
Female	0	0	
Male	63	63	

End points

End points reporting groups

Reporting group title	All subjects treated with Turoctocog Alfa

Reporting group description:

The patients received bleeding preventive treatment with a single dose of turoctocog alfa of 25-50 IU/kg every second day or 25-60 IU/kg three times weekly. Turoctocog alfa was administered as a slow bolus i.v. injection (approximately 1-2 mL/min). Pharmacokinetic assessments were performed in at least 13 patients from each age cohort. Each patient participating in the pharmacokinetic assessments received one dose of previous factor VIII (FVIII) and one dose of turoctocog alfa.

Primary: The incidence rate of FVIII inhibitors (≥0.6 BU/mL)

End point title	The incidence rate of FVIII inhibitors (≥0.6 BU/mL)[1]

End point description:

The incidence rate of FVIII inhibitors was calculated by having all patients with inhibitors in the nominator and including all patients with a minimum 50 exposure plus any patients with less than 50 exposures but with inhibitors in denominator.

End point type	Primary

End point timeframe:

The adverse events were collected throughout the trial which corresponded to an average of 138 days per subject.

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: A one-sided 97.5% upper confidence limit for the incidence rate of FVIII inhibitors was provided based on an exact calculation for a binomial distribution. Adequate safety with regard to inhibitors was concluded if the upper one-sided 97.5% confidence limit was below 10.7%.

Result : The one-sided 97.5% upper confidence limit for the inhibitor incidence rate of zero was 6.06%.

End point values	All subjects treated with Turoctocog Alfa			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: N with Inhibitors / N with ≥50 EDs	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events were collected throughout the trial, corresponding to an average of 138 days per subject.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	All subjects treated with Turoctocog Alfa

Reporting group description:

The patients received bleeding preventive treatment with a single dose of turoctocog alfa of 25-50 IU/kg every second day or 25-60 IU/kg three times weekly. Turoctocog alfa was administered as a slow bolus i.v. injection (approximately 1-2 mL/min). Pharmacokinetic assessments were performed in at least 13 patients from each age cohort. Each patient participating in the pharmacokinetic assessments received one dose of previous factor VIII (FVIII) and one dose of turoctocog alfa.

Serious adverse events	All subjects treated with Turoctocog Alfa		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 63 (4.76%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Soft tissue injury			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 63 (1.59%)		
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 %

Non-serious adverse events	All subjects treated with Turoctocog Alfa		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 63 (22.22%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	5		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	6		
Upper respiratory tract infection			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

Not applicable

Notes: