Clinical trial results:
A Multi-Centre, Open-Label, Non-Controlled Trial on Safety and Efficacy of N8 (turoctocog alfa) in Prevention and Treatment of Bleeds in Previously Treated Subjects with Haemophilia A
Sub-Trial:
Safety and Efficacy of N8 (turoctocog alfa) in Prevention and Treatment of Bleeding during Surgical Procedures in Subjects with Haemophilia A

Summary

EudraCT number	2008-003960-20
Trial protocol	DE GB ES IT DK
Global end of trial date	21 September 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	NN7008-3543

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00840086
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)	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	08 February 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 September 2011
Global end of trial reached?	Yes
Global end of trial date	21 September 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A and Part B: To evaluate the efficacy of N8 in bleeding prevention in subjects with haemophilia A. To evaluate the efficacy of N8 in on-demand treatment of bleeding episodes in subjects with haemophilia A. Additional Objective for Part A To describe the steady-state PK profile of N8 in the subjects who participated in the phase 1 trial NN7008-3522, 3 months after initial dose of N8. Part C: To evaluate the efficacy of N8 in bleeding prevention during surgical procedures in subjects with haemophilia A. To evaluate the haemostatic effect of N8 during surgical procedures and in the early postoperative period (Day 1 to Day 6) for subjects 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).

Background therapy:

In accordance with the EMA guidelines on development of new FVIII products the clinical programme for turoctocog alfa was initiated with a pharmacokinetic trial (NN7008-3522) to document the essential pharmacokinetic characteristics of the product and to achieve initial safety information. The initial pharmacokinetic trial was designed as a comparative trial to the rFVIII product, Advate which is one of the commercially available rFVIII products. The pharmacokinetic parameters were based on FVIII coagulation activity measurements. This parameter is known to correlate to clinical efficacy of FVIII products. In the present trial, a pharmacokinetic session was performed 3-6 months after the first pharmacokinetic session with turoctocog alfa in NN7008-3522 using the same dose as the first pharmacokinetic session with turoctocog alfa, which is in accordance with the EMA guideline on development of new FVIII products. The main purpose of the second pharmacokinetic assessment was to evaluate changes in pharmacokinetic parameters as indicators of inhibitor information. This pharmacokinetic session was included in the present trial (NN7008-3543) for patients who completed the pharmacokinetic trial (NN7008-3522) mentioned above.
The present trial consisted of three parts (part A, part B and part C). The only difference between part A and part B is the above described pharmacokinetic session. In the surgery sub-trial part C, the patients had the option to undergo surgery. The surgery part was also designed in accordance with the EMA guideline on development of new FVIII products.

Evidence for comparator:

Not applicable

Actual start date of recruitment	07 April 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	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Croatia: 11
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Japan: 9
Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Serbia: 19
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	United States: 29
Country: Number of subjects enrolled	Brazil: 16
Worldwide total number of subjects	150
EEA total number of subjects	35

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)	0
Adolescents (12-17 years)	24
Adults (18-64 years)	126
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at 48 sites in 15 countries: Brazil (2 sites), Croatia (2 sites), Germany (4 sites), Israel (1 site), Italy (2 sites), Japan (8 sites), Malaysia (1 site), Russian Federation (1 site), Republic of Serbia (5 sites), Spain (2 sites), Switzerland (1 site), Taiwan (1 site), Turkey (5 sites), the UK (3 sites) and US (10 sites).

Pre-assignment

Screening details:

Not applicable

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	All Subjects treated with turoctocog alfa

Arm description:

All subjects participating in the study (Part A + Part B + Part C).

Arm type	Experimental
Investigational medicinal product name	N8
Investigational medicinal product code	NN7008
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects will receive bleeding preventive treatment (home treatment with self-injection i.v.) with turoctocog alfa at a dose of 20-40 IU/kg body weight every second day or 20-50 IU/kg body weight three times per week at the investigator's discretion

Number of subjects in period 1	All Subjects treated with turoctocog alfa
Started	150
Completed	146
Not completed	4
Protocol violation	2
Adverse event	1
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	All Subjects treated with turoctocog alfa

Reporting group description:

All subjects participating in the study (Part A + Part B + Part C).

Reporting group values	All Subjects treated with turoctocog alfa	Total	
Number of subjects	150	150	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	28		
standard deviation	± 11.79	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	150	150	
Region of Enrollment Units: Subjects			
Brazil	16	16	
Croatia	11	11	
Germany	10	10	
Israel	12	12	
Italy	7	7	
Japan	9	9	
Malaysia	5	5	
Russia	5	5	
Serbia	19	19	
Spain	4	4	
Switzerland	5	5	
Taiwan	4	4	
Turkey	11	11	
United Kingdom	3	3	
United States	29	29	

Subject analysis sets

Subject analysis set title	Total (Part A+ Part B)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Preventive treatment and treatment of bleeds: The doses were individualised based on the trough FVIII activity level. The doses could be adjusted by the investigator. The dose level chosen was 20-40 IU/kg every second day or 20-50 IU/kg three times per week (Part A + Part B). Subjects previously treated with turoctocog alpha were included in Part A.

Subject analysis set title	Part C

Subject analysis set type	Safety analysis

Subject analysis set description:

Surgery sub-trial: This part of the trial included any of the patients from Part A and Part B that during the course of the trial needed to undergo a major or minor surgical procedure requiring at least 7 days of daily FVIII treatment, including the day of surgery. Patients received a preoperative loading dose of turoctocog alfa immediately prior to the surgical procedure. On the day of surgery and until Day 7 (included) turoctocog alfa was dose adjusted aiming for a trough level above 0.50 IU/mL. Day 8 to last day of the surgical recovery period (if relevant) turoctocog alfa was dosed according to local guidelines

Reporting group values	Total (Part A+ Part B)	Part C	
Number of subjects	150	9	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	28	25	
standard deviation	± 11.79	± 6.53	
Gender categorical Units: Subjects			
Female			
Male			
Region of Enrollment Units: Subjects			
Brazil			
Croatia			
Germany			
Israel			
Italy			
Japan			
Malaysia			
Russia			
Serbia			
Spain			
Switzerland			
Taiwan			
Turkey			
United Kingdom			
United States			

End points

End points reporting groups

Reporting group title	All Subjects treated with turoctocog alfa

Reporting group description:

All subjects participating in the study (Part A + Part B + Part C).

Subject analysis set title	Total (Part A+ Part B)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Preventive treatment and treatment of bleeds: The doses were individualised based on the trough FVIII activity level. The doses could be adjusted by the investigator. The dose level chosen was 20-40 IU/kg every second day or 20-50 IU/kg three times per week (Part A + Part B). Subjects previously treated with turoctocog alpha were included in Part A.

Subject analysis set title	Part C
Subject analysis set type	Safety analysis

Subject analysis set description:

Surgery sub-trial: This part of the trial included any of the patients from Part A and Part B that during the course of the trial needed to undergo a major or minor surgical procedure requiring at least 7 days of daily FVIII treatment, including the day of surgery. Patients received a preoperative loading dose of turoctocog alfa immediately prior to the surgical procedure. On the day of surgery and until Day 7 (included) turoctocog alfa was dose adjusted aiming for a trough level above 0.50 IU/mL. Day 8 to last day of the surgical recovery period (if relevant) turoctocog alfa was dosed according to local guidelines

Primary: The incidence rate of FVIII inhibitors (greater than or equal to 0.6 Bethesda Units (BU))

End point title	The incidence rate of FVIII inhibitors (greater than or equal to 0.6 Bethesda Units (BU))[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, corresponding to an average of 188 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: The trial was one-armed, so there were no comparison arms in the trial. The primary endpoint was incidence rate of FVIII inhibitors (≥0.6 BU). No FVIII inhibitors were detected during the trial. Furthermore, the 1-sided 97.5% upper confidence limit for the inhibitor incidence rate of zero was 2.46%, thus the primary test of adequate safety (upper confidence limit below 6.8%) succeeded. No further statistical analysis was done.

End point values	All Subjects treated with turoctocog alfa	Part C		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	150	9		
Units: N with Inhibitors / N with ≥50 EDs	150	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Adverse Events (AEs)

End point title	Frequency of Adverse Events (AEs)

End point description:

Adverse event was defined as events occurring after administration of trial product. Severe AEs: considerable interference with subject's daily activities, unacceptable. Moderate AEs: Marked symptoms, moderate interference with the patient's daily activities. Mild AEs: No or transient symptoms, no interference with the patient's daily activities. Serious AEs: AE that at any dose results in any of the following: death, a life-threatening experience, in-subject hospitalization/prolongation of existing hospitalization, persistent/significant disability/incapacity/congenital anomaly/birth defect.

End point type	Secondary

End point timeframe:

The adverse events were collected throughout the trial, corresponding to an average of 188 days per subject

End point values	All Subjects treated with turoctocog alfa	Total (Part A+ Part B)	Part C	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	150[2]	150	9	
Units: events				
All AEs	225	222	3	
Severe AEs	8	8	0	
Moderate AEs	52	51	1	
Mild AEs	165	163	2	
Serious AEs	9	9	0	
Probably or Possibly Related	17	17	0	

Notes:

[2] - Adverse events reported during surgeries are listed in Part C. those outside are reported in A and B

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 188 days per subject.

Adverse event reporting additional description:

Safety analysis set includes all subjects who received at least one dose of the investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	All Subjects Treated With Turoctocog Alfa

Reporting group description:

All subjects participating in the study (Part A + Part B + Part C).

Serious adverse events	All Subjects Treated With Turoctocog Alfa		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 150 (4.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Melaena			
subjects affected / exposed	2 / 150 (1.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 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	36 / 150 (24.00%)		
Injury, poisoning and procedural complications			
Incorrect dose administered			
subjects affected / exposed	15 / 150 (10.00%)		
occurrences (all)	19		
Nervous system disorders			
Headache			

subjects affected / exposed occurrences (all)	14 / 150 (9.33%) 18		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 12 / 150 (8.00%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2009	Substantial amendment 9. The substantial amendment 9 to the NN7008-3543 protocol version 3.0 (dated 28-Aug-2008) and Subject Information/Informed Consent Form version 2.0 dated 28-Aug-2008: The purpose of this amendment is to clarify further the description of the protocol procedures which includes the addition of Appendix D, Surgery Guideline. Also the trial title was updated. This amendment is applicable to all countries.
02 February 2010	Substantial amendment 14. The current document is a substantial amendment to protocol NN7008-3543 version 3.0 (dated 28-Aug-2008) and Subject Information/Informed Consent Form version 5.0 (dated 18-May-2009). Changes are made to this protocol in response to comments from the FDA dated August 14, 2009 and to harmonize the protocol with EMEA guidelines on investigation of FVIII products, issued July 2009. This amendment is applicable to all countries. The most significant change is revision to the objectives and endpoints where safety (incidence of inhibitor development) is now the primary endpoint, and efficacy is secondary. As part of the new primary endpoint, a new hypothesis test is set, and inhibitor tests are added at visits 5, 6b, and 8 to ensure adequate safety follow-up. The requirement that subjects should be HCV negative and/or lupus anticoagulant negative if no other condition precludes trial participation has been removed in agreement with EMEA guidelines on investigation of FVIII products, issued July 2009. In addition, other minor changes have been made to further improve the clinical protocol. Explanations of the changes are outlined below: • Revision of order of objectives and endpoints: safety (incidence of inhibitor development) is now the primary endpoint, and efficacy endpoints are secondary. In development of FVIII products, PK is an accepted surrogate endpoint for efficacy, and is demonstrated in phase 1. In general, safety is the primary objective to address in phase 3 trials. • Revision of title and re-ordering of sections addressing safety and efficacy, respectively. • Addition of inhibitor tests at visits 5, 6b, and 8 to ensure adequate safety follow-up in accordance with the changed primary endpoint every 4-5 weeks during study participation. • Introduction of hypothesis test for inhibitor development with upper limit of 6.8%, resulting in acceptance of max. 3 inhibitors in the trial. This change is in line with observed inhibitor

02 February 2010	Substantial amendment 15. The current document is a Substantial amendment to protocol NN7008-3543 version 3.0 (dated 28-Aug-2008) and Subject Information/Informed Consent Form version 5.0 (dated 18-May-2009). Changes are made to this protocol in response to obtained results from the completed phase 1 trial, NN7008-3522, and to accommodate requests and comments from participating investigators. This amendment is applicable to all countries. The most significant changes are an increase of the maximum allowed dose from 100 IU/kg BW to 200 IU/kg BW and the limit of 14 days on maximum dose has been removed. The changes are made to accommodate sufficient haemostasis and to allow for a FVIII level above 0,5 IU/ml during surgery and post surgery. These changes are supported by CMC documentation. Non-planned surgery is now allowed in Part C. Therefore emergency surgery is removed as withdrawal criterion. The required assessments from day 8 to End of Recovery in Part C have been reduced in agreement with EMEA guidelines. Viral safety assessment has been clarified and removed from visit 2b to avoid duplicate blood sampling. For Switzerland Amendment 9 the section about birth control was rewritten excluding a requirement for a medically acceptable birth control. By mistake this was not excluded from the protocol at the same time. This has been corrected now.
22 April 2010	Substantial amendment 17. This global substantial amendment has primarily been prepared to adjust the definition of inhibitor history. Due to historical laboratory cut-off values ≤ 1BU/mL for inhibitor testing in some countries we have decided to change our inclusion criterion #6 in Section 6.2.2 and Section 8.6.2.2 in order to clarify the inclusion requirement for the sites with above mentioned past practice. Clarification of required registration of data during the Recovery Period has been added. Furthermore, the wording 'bleeding resolution' will be changed to 'stop of bleeding' to be in alignment with the Case Record Form (CRF) and also minor mistakes will be corrected to be in alignment with the wording introduced with the previous global substantial amendment no.15. Substantial Protocol Amendment no. 17 will be forwarded to Health Authorities and IRBs/Ethics Committees for approval. The consolidated Protocol NN7008-3543 version 11.0 incorporates all changes.

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/23647704