Clinical trial results:
A multi-centre, comparative, double blind, randomised cross-over trial investigating single dose pharmacokinetics and safety of turoctocog alfa pegol from the pivotal process and turoctocog alfa pegol from the commercial process in patients with severe haemophilia A

Summary

EudraCT number	2015-005327-63
Trial protocol	NL DK DE ES FR
Global end of trial date	07 April 2017

Results information

Result version number	v1 (current)
This version publication date	12 April 2018
First version publication date	12 April 2018

Trial information

Trial identification

Sponsor protocol code	NN7088-4033

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02920398
WHO universal trial number (UTN)	U1111-1176-9253

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (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	28 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 April 2017
Global end of trial reached?	Yes
Global end of trial date	07 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate and compare the single-dose pharmacokinetic of N8-GP (turoctocog alfa pegol) from the pivotal process with N8-GP from the commercial process, each given as intravenous administrations of 50 U/kg to patients with severe haemophilia A.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2008), International Conference on Harmonisation (ICH) Good Clinical Practice (1996) and United States Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) 312.120.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	04 October 2016
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	Denmark: 3
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	21
EEA total number of subjects	10

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	19
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 11 sites in 6 countries, as follows: Denmark: 1 site; France: 1 site; Germany: 1 site; Netherlands: 1 site; Spain: 2 sites; United States: 5 sites.

Pre-assignment

Screening details:

Study Design: Subjects were recruited from trial NN7088-3859 (EudraCT number: 2011-001142-15) and returned to trial NN7088-3859 upon completion of this trial. This cross over trial included two identical pharmacokinetic (PK) visits (each consisting of 5 days) with a wash-out period of at least 7 days prior to each PK visit.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

N8-GP was packed blinded and allocated via the interactive web response system (IWRS) to ensure the blinding of the trial product. The N8-GP from the pivotal manufacturing process and N8-GP from the commercial manufacturing process were visually identical.

Arms

Arm title	Overall population

Arm description:

This was a two period cross-over study. All subjects were randomised in a 1:1 manner to receive one of the two possible treatment sequences of trial products, turoctocog alfa pegol (N8-GP) from the commercial process and N8-GP from the pivotal process. Subjects, who received N8-GP from the commercial process in treatment period 1, received N8-GP from the pivotal process in treatment period 2. And subjects, who received N8-GP from the pivotal process in treatment period 1, received N8-GP from the commercial process in treatment period 2. There was a wash-out period of at least 7 days prior to dosing in both the periods.

Arm type	Cross-over
Investigational medicinal product name	Turoctocog alfa pegol
Investigational medicinal product code	
Other name	N8-GP
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered with a single-dose of N8-GP 50±5 IU/kg from the commercial process on day 1 of both the treatment periods. N8-GP was supplied as a sterile, freeze-dried powder in a 2–8°C (36–46°F) stable formulation single use vial with a nominal content of 2000 IU/vial was reconstituted with 4.3 mL 0.9% isotonic sodium chloride solution for intravenous (i.v.) injection. After reconstitution each vial contained 500 IU/mL N8-GP.

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IU/mL N8-GP.

Number of subjects in period 1	Overall population
Started	21
Completed	21

Baseline characteristics

Reporting groups	
Reporting group title	Overall population

Reporting group description:

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Reporting group values	Overall population	Total	
Number of subjects	21	21	
Age Categorical Units: Subjects			
Adults (18-64 years)	19	19	
From 65-84 years	2	2	
Age Continuous Units: years			
arithmetic mean	42.4		
standard deviation	± 14.2	-	
Gender Categorical Units: Subjects			
Male	21	21	

Subject analysis sets	
Subject analysis set title	Turoctocog alfa pegol commercial process
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received N8-GP from the commercial process in treatment period 1 (from treatment sequence, N8-GP commercial process/N8-GP pivotal process) and in treatment period 2 (from treatment sequence, N8-GP pivotal process/N8-GP commercial process).

Subject analysis set title	Turoctocog alfa pegol pivotal process
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received N8-GP from the pivotal process in treatment period 1 (from treatment sequence, N8-GP pivotal process/N8-GP commercial process) and in treatment period 2 (from treatment sequence, N8-GP commercial process/N8-GP pivotal process).

Reporting group values	Turoctocog alfa pegol commercial process	Turoctocog alfa pegol pivotal process	
Number of subjects	21	21	
Age Categorical Units: Subjects			
Adults (18-64 years)	19	19	
From 65-84 years	2	2	

Age Continuous Units: years arithmetic mean standard deviation	 42.4 ± 14.2	 42.4 ± 14.2	
Gender Categorical Units: Subjects			
Male	21	21	

End points

End points reporting groups

Reporting group title	Overall population

Reporting group description:

This was a two period cross-over study. All subjects were randomised in a 1:1 manner to receive one of the two possible treatment sequences of trial products, turoctocog alfa pegol (N8-GP) from the commercial process and N8-GP from the pivotal process. Subjects, who received N8-GP from the commercial process in treatment period 1, received N8-GP from the pivotal process in treatment period 2. And subjects, who received N8-GP from the pivotal process in treatment period 1, received N8-GP from the commercial process in treatment period 2. There was a wash-out period of at least 7 days prior to dosing in both the periods.

Subject analysis set title	Turoctocog alfa pegol commercial process
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received N8-GP from the commercial process in treatment period 1 (from treatment sequence, N8-GP commercial process/N8-GP pivotal process) and in treatment period 2 (from treatment sequence, N8-GP pivotal process/N8-GP commercial process).

Subject analysis set title	Turoctocog alfa pegol pivotal process
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received N8-GP from the pivotal process in treatment period 1 (from treatment sequence, N8-GP pivotal process/N8-GP commercial process) and in treatment period 2 (from treatment sequence, N8-GP commercial process/N8-GP pivotal process).

Primary: Area under the FVIII activity-time curve - dose normalised to 50 U/kg (AUC0-96h, norm)

End point title	Area under the FVIII activity-time curve - dose normalised to 50 U/kg (AUC0-96h, norm)

End point description:

Area under the FVIII plasma activity versus time profile from time zero to 96h normalised to 50 U/kg (AUC0-96h, norm). i.e., Measure of FVIII plasma exposure in the time interval 0 to 96h. Blood samples were analysed using both chromogenic and one-stage clotting assays. The results are based on the full analysis set (FAS), which included all subjects with at least one evaluable PK profile. Number of subjects analysed = number of subjects contributed to the analysis. The following mentioned 'Measure Type' should be read as 'Geometric Mean (Coefficient of Variation in Percentage)'.

End point type	Primary

End point timeframe:

From 0 to 96 h post injection

End point values	Turoctocog alfa pegol commercial process	Turoctocog alfa pegol pivotal process		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: IU*h/mL				
geometric mean (geometric coefficient of variation)				
Chromogenic assay	34.250 (± 32.091)	34.064 (± 28.715)		
One-stage clotting assay	40.965 (± 29.241)	41.731 (± 19.964)		

Statistical analyses

Statistical analysis title	N8-GP commercial process vs N8-GP pivotal process

Statistical analysis description:

The primary endpoint was log-transformed and analysed using an analysis of variance (ANOVA) model with product, period, sequence and patient within sequence as factors. The following ‘comparison groups’ should be read as 'N8-GP commercial process versus (vs) N8-GP pivotal process'. Due to cross-over design of the trial, the following ‘number of subjects included in analysis’ is being erroneously displayed as 40. Actual ‘number of subjects included in analysis’ is 20.

Comparison groups	Turoctocog alfa pegol commercial process v Turoctocog alfa pegol pivotal process
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment ratio
Point estimate	1.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.97
upper limit	1.04

Secondary: FVIII activity 30 min post administration - dose normalised to 50 U/kg

End point title	FVIII activity 30 min post administration - dose normalised to 50 U/kg

End point description:

The FVIII activity recorded 30 minutes after end of injection normalised to 50 U/kg. Blood samples were analysed using both chromogenic and one-stage clotting assays. The following timeframe should be read as ‘from time of trial product administration to 30 minutes post-dose’. The results are based on the FAS. Number of subjects analysed = number of subjects contributed to the analysis. The following mentioned ‘Measure Type’ should be read as ‘Geometric Mean (Coefficient of Variation in Percentage)’.

End point type	Secondary

End point timeframe:

From time of trial product administration to 96 hours post-dose

End point values	Turoctocog alfa pegol commercial process	Turoctocog alfa pegol pivotal process		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: IU/mL				
geometric mean (geometric coefficient of variation)				

Chromogenic assay	1.183 (± 16.568)	1.157 (± 18.982)		
One-stage clotting assay	1.420 (± 22.105)	1.320 (± 19.032)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the FVIII activity-time curve from 0 to infinity

End point title	Area under the FVIII activity-time curve from 0 to infinity

End point description:

Area under the FVIII activity versus time profile from time zero to infinity (AUC0-inf). i.e., Measure of total FVIII plasma exposure. Blood samples were analysed using both chromogenic and one-stage clotting assays. The following timeframe should be read as 'from time of trial product administration to infinity'. The results are based on the FAS. Number of subjects analysed = number of subjects contributed to the analysis. The following mentioned 'Measure Type' should be read as 'Geometric Mean (Coefficient of Variation in Percentage)'.

End point type	Secondary

End point timeframe:

From time of trial product administration to 96 hours post-dose

End point values	Turoctocog alfa pegol commercial process	Turoctocog alfa pegol pivotal process		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: IU*h/mL				
geometric mean (geometric coefficient of variation)				
Chromogenic assay	40.305 (± 32.112)	40.987 (± 27.532)		
One-stage clotting assay	49.598 (± 28.704)	50.594 (± 22.384)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance

End point title	Clearance

End point description:

Total plasma clearance (CL) of drug after intravenous administration. Blood samples were analysed using both chromogenic and one-stage clotting assays. The following timeframe should be read as 'from time of trial product administration to infinity'. The results are based on the FAS. Number of subjects analysed = number of subjects contributed to the analysis. The following mentioned 'Measure Type' should be read as 'Geometric Mean (Coefficient of Variation in Percentage)'.

End point type	Secondary

End point timeframe:

From time of trial product administration to 96 hours post-dose

End point values	Turoctocog alfa pegol commercial process	Turoctocog alfa pegol pivotal process		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: mL/h/kg				
geometric mean (geometric coefficient of variation)				
Chromogenic assay	1.340 (± 31.753)	1.340 (± 27.141)		
One-stage clotting assay	1.089 (± 28.218)	1.085 (± 22.120)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental recovery

End point title	Incremental recovery

End point description:

Dose-normalised FVIII activity recorded 30 min after end of injection and reported as [U/mL]/[U/kg]. Expected to be the highest dose-normalised activity observed. Blood samples were analysed using both chromogenic and one-stage clotting assays. The following timeframe should be read as 'from time of trial product administration to 30 min post-dose'. The results are based on the FAS. Number of subjects analysed = number of subjects contributed to the analysis. The following mentioned 'Measure Type' should be read as 'Geometric Mean (Coefficient of Variation in Percentage)'.

End point type	Secondary

End point timeframe:

From time of trial product administration to 96 hours post-dose

End point values	Turoctocog alfa pegol commercial process	Turoctocog alfa pegol pivotal process		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: (IU/mL) / (U/kg)				
geometric mean (geometric coefficient of variation)				
Chromogenic assay	0.023 (± 17.284)	0.023 (± 19.909)		
One-stage clotting assay	0.028 (± 24.325)	0.026 (± 20.728)		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal half-life

End point title	Terminal half-life

End point description:

Terminal half-life (t½) = ln(2) / λz, where λz was the terminal elimination rate estimated using linear regression on the terminal part of the log(activity) versus time profile. Blood samples were analysed using both chromogenic and one-stage clotting assays. The following timeframe should be read as 'from 24 hours post-dose to 96 hours post-dose'. The results are based on the FAS. Number of subjects analysed = number of subjects contributed to the analysis. The following mentioned 'Measure Type' should be read as 'Geometric Mean (Coefficient of Variation in Percentage)'.

End point type	Secondary

End point timeframe:

From time of trial product administration to 96 hours post-dose

End point values	Turoctocog alfa pegol commercial process	Turoctocog alfa pegol pivotal process		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: hour (h)				
geometric mean (geometric coefficient of variation)				
Chromogenic assay	19.469 (± 37.648)	20.648 (± 30.984)		
One-stage clotting assay	22.908 (± 37.168)	23.405 (± 35.313)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All AEs reported after exposed to N8-GP were defined as TEAEs. Since all patients were transferred from trial NN7088-3859, all AEs reported in this trial were considered as treatment emergent even if the AE occurred prior to the first dosing in this trial

Adverse event reporting additional description:

Analysis population: Safety analysis set, which included all subjects transferring from trial NN7088-3859 into this trial. All reported adverse events in this trial were treatment emergent adverse events (TEAEs).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events with a prevalence of 5% are available for this trial. In total, 2 subjects in the turoctocog alfa pegol pivotal process arm had non-serious adverse events and no subject in the turoctocog alfa pegol commercial process arm had non-serious adverse events. Additionally 3 AEs were reported outside the PK visits

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2016	Changes were done in exclusion criteria. A criterion on hypersensitivity was added. The wording of the criterion is identical to the exclusion criterion in trial NN7088-3859's protocol from where all patients were recruited.
23 March 2017	This protocol amendment was prepared to clarify the assays used for assessment of coagulation factor VIII (FVIII) activity in trial NN7088-4033 in order to align with updates in the assay strategy for all pathfinder™ trials.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported