Clinical trial results:
Safety, tolerability, and pharmacokinetics study of single and multiple subcutaneous doses of turoctocog alfa pegol in patients with haemophilia A

Summary

EudraCT number	2016-002396-99
Trial protocol	AT DE BG FR GB
Global end of trial date	15 October 2018

Results information

Result version number	v1 (current)
This version publication date	26 April 2019
First version publication date	26 April 2019

Trial information

Trial identification

Sponsor protocol code	NN7170-4213

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02994407
WHO universal trial number (UTN)	U1111-1183-5111
Other trial identifiers	Japanese trial registration: JapicCTI-173683

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk, 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	02 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 October 2018
Global end of trial reached?	Yes
Global end of trial date	15 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of s.c. administration of turoctocog alfa pegol (SC N8-GP) in patients with severe haemophilia A

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) and ICH Good Clinical Practice, including archiving of essential documents (2009) and 21 CFR 312.120.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	30 January 2017
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	Austria: 4
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	Serbia: 5
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	36
EEA total number of subjects	20

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)	3
Adults (18-64 years)	33
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 25 sites in 9 countries as follows: Austria: 2 sites; Bulgaria: 1 site; France: 1 site; Germany: 3 sites; Japan: 2 sites; Serbia: 5 sites; Turkey: 1 site; United Kingdom: 3 sites; United States: 7 sites.

Pre-assignment

Screening details:

The study consisted of two parts: one single dose, dose escalation part (part A) and one multiple dose part (part B) with daily administrations of SC N8-GP for a period of 3 months. Subjects having completed part A and who had wanted to continue to part B treated themselves with their regular FVIII product in the period between part A and B.

Period 1

Period 1 title	Part A
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Carer, Subject

Blinding implementation details:

Double blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A - SC N8-GP (12.5 IU/kg)

Arm description:

Subjects received a single dose (12.5 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.

Arm type	Experimental
Investigational medicinal product name	SC turoctocog alfa pegol A 2000
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received a single dose of SC N8-GP 12.5 IU/kg and placebo as subcutaneous injection with a syringe. The two treatments (SC N8-GP and placebo) were administered immediately after one another (one in the abdomen above the umbilicus and one below the umbilicus) in a blinded randomised manner.

Arm title	Part A - SC N8-GP (25 IU/kg)

Arm description:

Subjects received a single dose (25 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.

Arm type	Experimental
Investigational medicinal product name	SC turoctocog alfa pegol A 2000
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received a single dose of SC N8-GP 25 IU/kg and placebo as subcutaneous injection with a syringe. The two treatments (SC N8-GP and placebo) were administered immediately after one another (one in the abdomen above the umbilicus and one below the umbilicus) in a blinded randomised manner.

Arm title	Part A - SC N8-GP (50 IU/kg)

Arm description:

Subjects received a single dose (50 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.

Arm type	Experimental
Investigational medicinal product name	SC turoctocog alfa pegol A 2000
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received a single dose of SC N8-GP 50 IU/kg and placebo as subcutaneous injection with a syringe. The two treatments (SC N8-GP and placebo) were administered immediately after one another (one in the abdomen above the umbilicus and one below the umbilicus) in a blinded randomised manner.

Arm title	Part A - SC N8-GP (100 IU/kg)

Arm description:

Subjects received a single dose (100 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.

Arm type	Experimental
Investigational medicinal product name	SC turoctocog alfa pegol A 2000
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received a single dose of SC N8-GP 100 IU/kg and placebo as subcutaneous injection with a syringe. The two treatments (SC N8-GP and placebo) were administered immediately after one another (one in the abdomen above the umbilicus and one below the umbilicus) in a blinded randomised manner.

Number of subjects in period 1[1]	Part A - SC N8-GP (12.5 IU/kg)	Part A - SC N8-GP (25 IU/kg)	Part A - SC N8-GP (50 IU/kg)
Started	6	6	6
Completed	6	6	6

Number of subjects in period 1[1]	Part A - SC N8-GP (100 IU/kg)
Started	6
Completed	6

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Only one period can be selected for baseline period. Therefore the baseline characteristics of the second period (part B) is explained by means of subject analysis set.

Period 2

Period 2 title	Part B
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	SC N8-GP

Arm description:

Subjects received daily subcutaneous administrations of SC N8-GP for a period of 3 months (13 weeks). In addition to 12 new subjects, fourteen subjects having completed part A continued to part B and treated himself with his regular FVIII product in the period between part A and B.

Arm type	Experimental
Investigational medicinal product name	SC turoctocog alfa pegol A 2000
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received daily subcutaneous administrations of SC N8-GP for a period of 3 months (13 weeks). The starting dose for all patients depended on their individual body weight. Based on available safety data from part A, SC N8-GP doses of up to 100 IU/kg per day were considered safe also for repeated daily dosing.

Number of subjects in period 2[2]	SC N8-GP
Started	12
Completed	12

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The number of subjects mentioned here (12) are the new subjects enrolled in part B, in addition to the 14 subjects who continued from the previous period.

Baseline characteristics

Reporting groups	
Reporting group title	Part A - SC N8-GP (12.5 IU/kg)
Reporting group description:	
Subjects received a single dose (12.5 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.	
Reporting group title	Part A - SC N8-GP (25 IU/kg)
Reporting group description:	
Subjects received a single dose (25 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.	
Reporting group title	Part A - SC N8-GP (50 IU/kg)
Reporting group description:	
Subjects received a single dose (50 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.	
Reporting group title	Part A - SC N8-GP (100 IU/kg)
Reporting group description:	
Subjects received a single dose (100 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.	

Reporting group values	Part A - SC N8-GP (12.5 IU/kg)	Part A - SC N8-GP (25 IU/kg)	Part A - SC N8-GP (50 IU/kg)
Number of subjects	6	6	6
Age Categorical			
Number of subjects in each age category.			
Units: Subjects			
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	6	6
From 65-84 years	0	0	0
Age Continuous			
Units: years			
arithmetic mean	36.0	37.8	34.7
standard deviation	± 10.5	± 15.8	± 16.7
Gender Categorical			
Units: Subjects			
Female	0	0	0
Male	6	6	6

Reporting group values	Part A - SC N8-GP (100 IU/kg)	Total	
Number of subjects	6	24	
Age Categorical			
Number of subjects in each age category.			
Units: Subjects			
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	6	24	
From 65-84 years	0	0	
Age Continuous			
Units: years			
arithmetic mean	38.7		
standard deviation	± 16.1	-	

Gender Categorical Units: Subjects			
Female	0	0	
Male	6	24	

Subject analysis sets

Subject analysis set title	Part B SC-N8-GP
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received daily subcutaneous administrations of SC N8-GP for a period of 3 months (13 weeks). In addition to 12 new subjects, fourteen subjects having completed part A continued to part B and treated themselves with their regular FVIII product in the period between part A and B. Thus the subject analysis set included 26 subjects.

Reporting group values	Part B SC-N8-GP		
Number of subjects	26		
Age Categorical			
Number of subjects in each age category.			
Units: Subjects			
Adolescents (12-17 years)	3		
Adults (18-64 years)	22		
From 65-84 years	1		
Age Continuous Units: years			
arithmetic mean	33.9		
standard deviation	± 15.4		
Gender Categorical Units: Subjects			
Female	0		
Male	26		

End points

End points reporting groups

Reporting group title	Part A - SC N8-GP (12.5 IU/kg)
Reporting group description:	
Subjects received a single dose (12.5 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.	
Reporting group title	Part A - SC N8-GP (25 IU/kg)
Reporting group description:	
Subjects received a single dose (25 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.	
Reporting group title	Part A - SC N8-GP (50 IU/kg)
Reporting group description:	
Subjects received a single dose (50 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.	
Reporting group title	Part A - SC N8-GP (100 IU/kg)
Reporting group description:	
Subjects received a single dose (100 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.	
Reporting group title	SC N8-GP
Reporting group description:	
Subjects received daily subcutaneous administrations of SC N8-GP for a period of 3 months (13 weeks). In addition to 12 new subjects, fourteen subjects having completed part A continued to part B and treated himself with his regular FVIII product in the period between part A and B.	
Subject analysis set title	Part B SC-N8-GP
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received daily subcutaneous administrations of SC N8-GP for a period of 3 months (13 weeks). In addition to 12 new subjects, fourteen subjects having completed part A continued to part B and treated themselves with their regular FVIII product in the period between part A and B. Thus the subject analysis set included 26 subjects.	

Primary: Number of adverse events reported after exposure to SC N8-GP

End point title	Number of adverse events reported after exposure to SC N8-GP[1]
End point description:	
Number of treatment emergent adverse events reported after exposure to SC N8-GP until 7 days after last exposure.The reporting period of adverse events was changed to until 7 days after last exposure due to the half-time of SC N8-GP.	
End point type	Primary
End point timeframe:	
Until 7 days after last exposure	

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 investigates safety and is analysed using descriptive statistics, and thus no statistical analysis is performed.

End point values	Part A - SC N8-GP (12.5 IU/kg)	Part A - SC N8-GP (25 IU/kg)	Part A - SC N8-GP (50 IU/kg)	Part A - SC N8-GP (100 IU/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: number of events	7	4	1	3

End point values	Part B SC-N8-GP			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: number of events	40			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter Cmax (up to 144 hours after dose)

End point title	Pharmacokinetic parameter Cmax (up to 144 hours after dose)

End point description:

The maximal FVIII activity measured after single dose administration.

End point type	Secondary

End point timeframe:

After single dose administration (part A)

End point values	Part A - SC N8-GP (12.5 IU/kg)	Part A - SC N8-GP (25 IU/kg)	Part A - SC N8-GP (50 IU/kg)	Part A - SC N8-GP (100 IU/kg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: IU/dL				
arithmetic mean (standard deviation)	1.3 (± 106.9)	2.5 (± 62.8)	4.6 (± 32.6)	15.2 (± 75.6)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After the first day of trial product administration until 7 days after last exposure i.e. total duration of visit 2 for part A and from visit 2 to 7 days after visit 8 in part B.

Adverse event reporting additional description:

Adverse events were reported tor the safety analysis set which included all patients exposed to the trial product. The reporting period of adverse events was changed from 28 days to 'until 7 days after last exposure' due to the half-time of SC N8-GP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Part A - SC N8-GP (12.5 IU/kg)

Reporting group description:

Subjects received a single dose (12.5 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.

Reporting group title	Part A - SC N8-GP (25 IU/kg)

Reporting group description:

Subjects received a single dose (25 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.

Reporting group title	Part A - SC N8-GP (50 IU/kg)

Reporting group description:

Subjects received a single dose (50 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.

Reporting group title	Part A - SC N8-GP (100 IU/kg)

Reporting group description:

Subjects received a single dose (100 IU/kg) of SC N8-GP and a single subcutaneous injection of placebo.

Reporting group title	Part B - SC-N8-GP (once daily)

Reporting group description:

Subjects received daily subcutaneous administrations of SC N8-GP for a period of 3 months (13 weeks). In addition to 12 new subjects, fourteen subjects having completed part A continued to part B and treated himself with his regular FVIII product in the period between part A and B. Thus the subject analysis set included 26 subjects

Serious adverse events	Part A - SC N8-GP (12.5 IU/kg)	Part A - SC N8-GP (25 IU/kg)	Part A - SC N8-GP (50 IU/kg)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Factor VIII inhibition			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part A - SC N8-GP (100 IU/kg)	Part B - SC-N8-GP (once daily)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	2 / 26 (7.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Factor VIII inhibition			
subjects affected / exposed	0 / 6 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part A - SC N8-GP (12.5 IU/kg)	Part A - SC N8-GP (25 IU/kg)	Part A - SC N8-GP (50 IU/kg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	2 / 6 (33.33%)	1 / 6 (16.67%)
Injury, poisoning and procedural complications			
Scratch			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration			

site conditions			
Injection site bruising			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Injection site erythema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Injection site haematoma			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Injection site pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Injection site swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site bruise			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part A - SC N8-GP (100 IU/kg)	Part B - SC-N8-GP (once daily)	
Total subjects affected by non-serious			

adverse events			
subjects affected / exposed	3 / 6 (50.00%)	7 / 26 (26.92%)	
Injury, poisoning and procedural complications			
Scratch			
subjects affected / exposed	0 / 6 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	6	
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	0 / 6 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Injection site erythema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Injection site haematoma			
subjects affected / exposed	0 / 6 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	2	
Injection site pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Injection site swelling			
subjects affected / exposed	1 / 6 (16.67%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Vessel puncture site bruise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 6 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	

Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1	 0 / 26 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 0 / 6 (0.00%) 0	 3 / 26 (11.54%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2016	Text regarding stopping rules and SUSAR reporting have been updated
27 December 2017	To specify the dose for part B and updates based on authority commitments prior to the start of part B.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported