Clinical trial results:
Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Prophylaxis and Treatment of Bleeds in Previously N8-GP Treated Patients with Severe Haemophilia A

Summary

EudraCT number	2017-003788-36
Trial protocol	LT GB PT GR NO DK HU FR NL DE ES HR IT
Global end of trial date	03 December 2020

Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021

Trial information

Trial identification

Sponsor protocol code	NN7088-4410

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03528551
WHO universal trial number (UTN)	U1111-1202-2780
Other trial identifiers	Japanese trial registration number: JapicCTI-183952

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Transparency Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Transparency 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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001174-PIP02-12
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2020
Global end of trial reached?	Yes
Global end of trial date	03 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the safety of turoctocog alfa pegol during continuous use for prevention and treatment of bleeding episodes of previously turoctocog alfa pegol treated severe haemophilia A patients.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (64th World Medical Association (WMA) 2013) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, including archiving of essential documents, (2016) and 21 CFR 312.120.

Background therapy:

Not Applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	30 April 2018
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	Australia: 2
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Switzerland: 8
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Lithuania: 4

Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Turkey: 13
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Ukraine: 5
Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	160
EEA total number of subjects	48

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)	29
Adolescents (12-17 years)	29
Adults (18-64 years)	98
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 66 sites in 25 countries: Australia(2), Brazil(1), Canada(1), Croatia(1), Denmark(1), France(2), Germany(2), Greece(1), Hungary(2), Israel(1), Italy(2), Japan(3), Korea(1), Lithuania(1), Malaysia(1), Netherlands(2), Norway(1), Portugal(1), Spain(2), Switzerland(4), Taiwan(1), Turkey(5), Ukraine(1), UK(8), USA(19).

Pre-assignment

Screening details:

Out of 160 subjects enrolled in this study, 102 came from trial NN7088-3859 and 58 came from trial NN7088-3885. The subjects received turoctocog alfa pegol (N8-GP) injections either as once-weekly, twice weekly or thrice weekly during the 104 weeks treatment period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	N8-GP, Once weekly

Arm description:

Subjects received once weekly (dosing every 7 day) prophylaxis doses of N8-GP, 75 IU/kg intravenous injections for 104 weeks. Subjects treated with N8-GP once weekly or were on the on demand regimen in the previous trial NN7088-3859 (pathfinder2) were included in this arm. At the investigator's discretion an intensification of the dosing regimen to twice weekly was allowed if the subject experienced more than 2 bleeds within an 8 week period or experienced a severe bleed requiring hospitalization.

Arm type	Experimental
Investigational medicinal product name	N8-GP 3000 IU/vial
Investigational medicinal product code	
Other name	Turoctocog alfa pegol
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The recommended prophylaxis dose was 75 IU/kg BW. The individual dose levels were decided by the investigator based on recommendations from the World Federation of Haemophilia. For prevention of bleeding during surgery and for treatment of bleeding episodes, the recommended doses were 20-75 IU/kg BW, depending on the surgical procedure and location and severity of the bleed, respectively. Depending on the body weight of the subject at the last scheduled visit, the strength of the product was chosen and continued the same throughout the trial: for <80 kg BW - 2000 IU vials and for ≥ 80 kg BW - 3000 IU vials.

Arm title	N8-GP, Twice weekly

Arm description:

Subjects received twice weekly (dosing every 3 and 4 days) prophylaxis doses of N8-GP intravenous injections for 104 weeks: N8-GP, 50 IU/kg for subjects aged ≥ 12 years and N8-GP, 60 IU/kg for subjects aged < 12 years. Subjects treated with N8-GP in the previous trials NN7088-3859 (pathfinder2) and NN7088-3885 (pathfinder5) were included in this arm. At the investigator's discretion, an intensification of the dosing regimen to thrice weekly was allowed if the subject experienced spontaneous bleeding episodes. Subjects in this arm were permitted to switch to three times weekly at any time if clinically justified. Otherwise any treatment regimen was preferably be kept for a minimum of 6 months.

Arm type	Experimental

Investigational medicinal product name	N8-GP 3000 IU/vial
Investigational medicinal product code	
Other name	Turoctocog alfa pegol
Pharmaceutical forms	Powder and solvent for solution for injection
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Arm title	N8-GP, Three times weekly

Arm description:

Subjects received three times weekly (dosing every 2, 2 and 3 days) prophylaxis doses of N8-GP, 50 IU/kg as intravenous injections for a duration of 104 weeks. Subjects treated with N8-GP in the previous trials NN7088-3859 (pathfinder2) and NN7088-3885 (pathfinder5) were included in this arm. Subjects in this arm were permitted to switch to twice weekly at any time if clinically justified. Otherwise any treatment regimen was preferably be kept for a minimum of 6 months.

Arm type	Experimental
Investigational medicinal product name	N8-GP 3000 IU/vial
Investigational medicinal product code	
Other name	Turoctocog alfa pegol
Pharmaceutical forms	Powder and solvent for solution for injection
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Dosage and administration details:

The recommended prophylaxis doses were 50 IU/kg BW. The individual dose levels were decided by the investigator based on recommendations from the World Federation of Haemophilia. For prevention of bleeding during surgery and for treatment of bleeding episodes, the recommended doses were 20-75 IU/kg BW, depending on the surgical procedure and location and severity of the bleed, respectively. Depending on the body weight of the subject at the last scheduled visit, the strength of the product was chosen and continued the same throughout the trial: for <80 kg - 2000 IU vials and for ≥80 kg 3000 IU vials.

Number of subjects in period 1[1]	N8-GP, Once weekly	N8-GP, Twice weekly	N8-GP, Three times weekly
Started	25	133	2
Completed	23	114	2
Not completed	2	19	0
Consent withdrawn by subject	-	16	-
Transferred to other arm/group	2	3	-

Notes:

[1] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.
Justification: Despite 133 and 2 subjects have started the trial with twice weekly and three times weekly regimen respectively, 2 subjects switched from once weekly to twice weekly and 5 subjects switched from twice weekly to three times weekly regimen. Due to the system limitation, the totals after subject switches are presented under 'Endpoints' section.

Baseline characteristics

Reporting groups	
Reporting group title	N8-GP, Once weekly

Reporting group description:

Subjects received once weekly (dosing every 7 day) prophylaxis doses of N8-GP, 75 IU/kg intravenous injections for 104 weeks. Subjects treated with N8-GP once weekly or were on the on demand regimen in the previous trial NN7088-3859 (pathfinder2) were included in this arm. At the investigator's discretion an intensification of the dosing regimen to twice weekly was allowed if the subject experienced more than 2 bleeds within an 8 week period or experienced a severe bleed requiring hospitalization.

Reporting group title	N8-GP, Twice weekly

Reporting group description:

Subjects received twice weekly (dosing every 3 and 4 days) prophylaxis doses of N8-GP intravenous injections for 104 weeks: N8-GP, 50 IU/kg for subjects aged ≥ 12 years and N8-GP, 60 IU/kg for subjects aged < 12 years. Subjects treated with N8-GP in the previous trials NN7088-3859 (pathfinder2) and NN7088-3885 (pathfinder5) were included in this arm. At the investigator's discretion, an intensification of the dosing regimen to thrice weekly was allowed if the subject experienced spontaneous bleeding episodes. Subjects in this arm were permitted to switch to three times weekly at any time if clinically justified. Otherwise any treatment regimen was preferably be kept for a minimum of 6 months.

Reporting group title	N8-GP, Three times weekly

Reporting group description:

Subjects received three times weekly (dosing every 2, 2 and 3 days) prophylaxis doses of N8-GP, 50 IU/kg as intravenous injections for a duration of 104 weeks. Subjects treated with N8-GP in the previous trials NN7088-3859 (pathfinder2) and NN7088-3885 (pathfinder5) were included in this arm. Subjects in this arm were permitted to switch to twice weekly at any time if clinically justified. Otherwise any treatment regimen was preferably be kept for a minimum of 6 months.

Reporting group values	N8-GP, Once weekly	N8-GP, Twice weekly	N8-GP, Three times weekly
Number of subjects	25	133	2
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	35.1	27.3	25.3
standard deviation	± 12.7	± 16.8	± 17.8
Gender Categorical Units: Subjects			
Male	25	133	2
Female	0	0	0

Reporting group values	Total		
Number of subjects	160		
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		

Gender Categorical Units: Subjects			
Male	160		
Female	0		

End points

End points reporting groups

Reporting group title	N8-GP, Once weekly

Reporting group description:

Subjects received once weekly (dosing every 7 day) prophylaxis doses of N8-GP, 75 IU/kg intravenous injections for 104 weeks. Subjects treated with N8-GP once weekly or were on the on demand regimen in the previous trial NN7088-3859 (pathfinder2) were included in this arm. At the investigator's discretion an intensification of the dosing regimen to twice weekly was allowed if the subject experienced more than 2 bleeds within an 8 week period or experienced a severe bleed requiring hospitalization.

Reporting group title	N8-GP, Twice weekly

Reporting group description:

Subjects received twice weekly (dosing every 3 and 4 days) prophylaxis doses of N8-GP intravenous injections for 104 weeks: N8-GP, 50 IU/kg for subjects aged ≥ 12 years and N8-GP, 60 IU/kg for subjects aged < 12 years. Subjects treated with N8-GP in the previous trials NN7088-3859 (pathfinder2) and NN7088-3885 (pathfinder5) were included in this arm. At the investigator's discretion, an intensification of the dosing regimen to thrice weekly was allowed if the subject experienced spontaneous bleeding episodes. Subjects in this arm were permitted to switch to three times weekly at any time if clinically justified. Otherwise any treatment regimen was preferably be kept for a minimum of 6 months.

Reporting group title	N8-GP, Three times weekly

Reporting group description:

Subjects received three times weekly (dosing every 2, 2 and 3 days) prophylaxis doses of N8-GP, 50 IU/kg as intravenous injections for a duration of 104 weeks. Subjects treated with N8-GP in the previous trials NN7088-3859 (pathfinder2) and NN7088-3885 (pathfinder5) were included in this arm. Subjects in this arm were permitted to switch to twice weekly at any time if clinically justified. Otherwise any treatment regimen was preferably be kept for a minimum of 6 months.

Subject analysis set title	N8-GP, Once weekly
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received once weekly (dosing every 7 day) prophylaxis doses of N8-GP, 75 IU/kg intravenous injections for 104 weeks.

Subject analysis set title	N8-GP, Twice weekly (subjects transferred from other arm)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received twice weekly (dosing every 3 and 4 days) prophylaxis doses of N8-GP intravenous injections for 104 weeks. During the trial, 2 subjects switched from once weekly to twice weekly regimen for treatment intensification. Thus, though 133 subjects have started the trial with twice weekly regimen, results of this arm is presented for 135 subjects in this arm (i.e. 133+2 = 135).

Subject analysis set title	N8-GP,Three times weekly (subjects transferred from other arm)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received three times weekly (dosing every 2, 2 and 3 days) prophylaxis doses of N8-GP, 50 IU/kg as intravenous injections for a duration of 104 weeks. During the trial, 5 subjects switched from twice weekly to three times weekly regimen for treatment intensification. Thus, though 2 subjects have started the trial with three times regimen, results for this arm is presented for 7 subjects in this arm (i.e. 2+5 = 7).

Primary: Number of adverse events reported

End point title	Number of adverse events reported[1]

End point description:

All presented adverse events are treatment emergent (TEAEs). The TEAEs were defined as the events reported after trial product administration (day 1) until the last patient last visit or end of the post-treatment follow-up period (i.e. 1 month). Results are based on the safety analysis set (SAS) which included all enrolled subjects as they were previously been exposed to trial product.

End point type	Primary

End point timeframe:

Week 0 to week 104

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: Since the primary endpoint is number of adverse events reported in the trial, the statistical analysis has not been done.

End point values	N8-GP, Once weekly	N8-GP, Twice weekly (subjects transferred from other arm)	N8-GP,Three times weekly (subjects transferred from other arm)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	135	7	
Units: Events	58	444	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of FVIII inhibitors ≥0.6 BU

End point title	Incidence of FVIII inhibitors ≥0.6 BU

End point description:

The Incidence of inhibitors against coagulation factor eight (FVIII) is defined as titre ≥0.6 Bethesda unit (BU). The inhibitor antibodies were measured using a heat modified Nijmegen FVIII Bethesda assay. The number of subjects who developed inhibitors against FVIII are reported. Results are based on Full analysis set (FAS), which included all subjects exposed to at least one dose of trial product in the current trial.

End point type	Secondary

End point timeframe:

After 104 weeks

End point values	N8-GP, Once weekly	N8-GP, Twice weekly (subjects transferred from other arm)	N8-GP,Three times weekly (subjects transferred from other arm)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	135	7	
Units: Subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of bleeding episodes on prophylaxis

End point title	Number of bleeding episodes on prophylaxis

End point description:

Number of bleeding episodes per subject in the prophylaxis regimen was evaluated during 104 weeks. Results are based on FAS, which included all subjects exposed to at least one dose of trial product in the current trial.

End point type	Secondary

End point timeframe:

After 104 weeks

End point values	N8-GP, Once weekly	N8-GP, Twice weekly (subjects transferred from other arm)	N8-GP,Three times weekly (subjects transferred from other arm)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	135	7	
Units: Episodes	123	190	14	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of spontaneous bleeding episodes on prophylaxis

End point title	Number of spontaneous bleeding episodes on prophylaxis

End point description:

Spontaneous bleeding referred as bleeding episodes that occurred without apparent cause. The number of spontaneous bleeding episodes was evaluated during 104 weeks. Results are based on FAS, which included all subjects exposed to at least one dose of trial product in the current trial.

End point type	Secondary

End point timeframe:

After 104 weeks

End point values	N8-GP, Once weekly	N8-GP, Twice weekly (subjects transferred from other arm)	N8-GP,Three times weekly (subjects transferred from other arm)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	135	7	
Units: Episodes	98	73	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic effect of N8-GP when used for treatment of bleeding episodes assessed as: Excellent, Good, Moderate, or None

End point title	Haemostatic effect of N8-GP when used for treatment of bleeding episodes assessed as: Excellent, Good, Moderate, or None

End point description:

The haemostatic effect after treatment of a bleed with turoctocog alfa pegol was assessed using a 4-point scale: 'excellent', 'good', 'moderate' or 'none'. The evaluation was done as follows: 1. Excellent: Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single injection. 2. Good: Definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an injection, but possibly requiring more than one injection for complete resolution. 3. Moderate: Probable or slight beneficial effect within approximately 8 hours after the first injection; usually requiring more than one injection 4. None: No improvement or worsening of symptoms. Results are based on FAS, which included all subjects exposed to at least one dose of trial product in the current trial.

End point type	Secondary

End point timeframe:

After 104 weeks

End point values	N8-GP, Once weekly	N8-GP, Twice weekly (subjects transferred from other arm)	N8-GP,Three times weekly (subjects transferred from other arm)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	135	7	
Units: Score on a scale				
Excellent	114	94	8	
Good	8	80	6	
Moderate	0	4	0	
None	0	0	0	
Missing	0	8	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of turoctocog alfa pegol injections required per bleeding episode

End point title	Number of turoctocog alfa pegol injections required per bleeding episode

End point description:

The number of N8-GP injections required per bleeding episode was evaluated from week 0 to week 104. All bleeds including surgery bleeds are included. Results are based on FAS, which included all subjects exposed to at least one dose of trial product in the current trial.

End point type	Secondary

End point timeframe:
After 104 weeks

End point values	N8-GP, Once weekly	N8-GP, Twice weekly (subjects transferred from other arm)	N8-GP,Three times weekly (subjects transferred from other arm)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	135	7	
Units: Injections per bleed				
1 injection	110	136	12	
2 injections	10	39	2	
3 injections	2	5	0	
4 injections	0	2	0	
5 injections	0	3	0	
6 injections	1	2	0	
8 injections	0	1	0	
9 injections	0	1	0	
10 injections	0	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 to week 104 (treatment period) + 1 month (follow-up period).

Adverse event reporting additional description:

All adverse events are treatment emergent (TEAEs). The TEAEs were defined as the events reported after trial product administration (day 1) until the last patient last visit or end of the post-treatment follow-up period (i.e. 1 month). SAS included all enrolled subjects as they were previously been exposed to trial product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	N8-GP, Once weekly

Reporting group description:

Subjects received once weekly (dosing every 7 day) prophylaxis doses of N8-GP, 75 IU/kg intravenous injections for 104 weeks. Subjects treated with N8-GP once weekly or were on the on demand regimen in the previous trial NN7088-3859 (pathfinder2) were included in this arm. At the investigator's discretion an intensification of the dosing regimen to twice weekly was allowed if the subject experienced more than 2 bleeds within an 8 week period or experienced a severe bleed requiring hospitalization. Otherwise any treatment regimen was preferably be kept for a minimum of 6 months.

Reporting group title	N8-GP, Twice weekly

Reporting group description:

Subjects received twice weekly (dosing every 3 and 4 days) prophylaxis doses of N8-GP intravenous injections for 104 weeks: N8-GP, 50 IU/kg for subjects aged ≥ 12 years and N8-GP, 60 IU/kg for subjects aged < 12 years. Subjects treated with N8-GP in the previous trials NN7088-3859 (pathfinder2) and NN7088-3885 (pathfinder5) were included in this arm. At the investigator's discretion, an intensification of the dosing regimen to thrice weekly was allowed if the subject experienced spontaneous bleeding episodes. Subjects in this arm were permitted to switch to three times weekly at any time if clinically justified. Otherwise any treatment regimen was preferably be kept for a minimum of 6 months. During the trial, 2 subjects switched from once weekly to twice weekly regimen for treatment intensification. Thus, though 133 subjects have started the trial with twice weekly regimen, AE data is presented for 135 subjects in this arm (i.e. 133+2 = 135).

Reporting group title	N8-GP, Three times weekly

Reporting group description:

Subjects received three times weekly (dosing every 2, 2 and 3 days) prophylaxis doses of N8-GP, 50 IU/kg as intravenous injections for a duration of 104 weeks. Subjects treated with N8-GP in the previous trials NN7088-3859 (pathfinder2) and NN7088-3885 (pathfinder5) were included in this arm. Subjects in this arm were permitted to switch to twice weekly at any time if clinically justified. Otherwise any treatment regimen was preferably be kept for a minimum of 6 months. During the trial, 5 subjects switched from twice weekly to three times weekly regimen for treatment intensification. Thus, though 2 subjects have started the trial with three times regimen, AE data is presented for 7 subjects in this arm (i.e. 2+5 = 7).

Reporting group title	Total

Reporting group description:

Total number of subjects from 3 arms

Serious adverse events	N8-GP, Once weekly	N8-GP, Twice weekly	N8-GP, Three times weekly
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 25 (16.00%)	15 / 135 (11.11%)	0 / 7 (0.00%)
number of deaths (all causes)	0	1	0

number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 135 (0.74%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Melanocytic naevus			
subjects affected / exposed	0 / 25 (0.00%)	1 / 135 (0.74%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 25 (0.00%)	1 / 135 (0.74%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 25 (0.00%)	1 / 135 (0.74%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)	0 / 135 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 25 (4.00%)	0 / 135 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 25 (0.00%)	1 / 135 (0.74%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haemorrhage			

subjects affected / exposed	0 / 25 (0.00%)	1 / 135 (0.74%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound secretion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 135 (0.74%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Mole excision			
subjects affected / exposed	0 / 25 (0.00%)	1 / 135 (0.74%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cervical radiculopathy			
subjects affected / exposed	1 / 25 (4.00%)	0 / 135 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 25 (0.00%)	1 / 135 (0.74%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 25 (0.00%)	3 / 135 (2.22%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 135 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression suicidal			

subjects affected / exposed	0 / 25 (0.00%)	1 / 135 (0.74%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	1 / 25 (4.00%)	0 / 135 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 25 (4.00%)	0 / 135 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 135 (0.74%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	0 / 25 (0.00%)	1 / 135 (0.74%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 25 (4.00%)	0 / 135 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 160 (11.88%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			

subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Melanocytic naevus				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of the tongue				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Humerus fracture				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Procedural haemorrhage				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin laceration				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Traumatic haemorrhage				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound secretion				

subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Mole excision			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cervical radiculopathy			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	3 / 160 (1.88%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression suicidal			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthropathy			

subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subcutaneous abscess			
subjects affected / exposed	1 / 160 (0.63%)		
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	N8-GP, Once weekly	N8-GP, Twice weekly	N8-GP, Three times weekly
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 25 (36.00%)	46 / 135 (34.07%)	4 / 7 (57.14%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 25 (0.00%)	3 / 135 (2.22%)	1 / 7 (14.29%)
occurrences (all)	0	3	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 25 (0.00%)	10 / 135 (7.41%)	0 / 7 (0.00%)
occurrences (all)	0	11	0

Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	3 / 25 (12.00%)	0 / 135 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Psychiatric disorders			
Attention deficit hyperactivity disorder			
subjects affected / exposed	0 / 25 (0.00%)	0 / 135 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	0 / 25 (0.00%)	1 / 135 (0.74%)	2 / 7 (28.57%)
occurrences (all)	0	1	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 25 (8.00%)	11 / 135 (8.15%)	1 / 7 (14.29%)
occurrences (all)	2	12	1
Limb discomfort			
subjects affected / exposed	0 / 25 (0.00%)	0 / 135 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 25 (0.00%)	9 / 135 (6.67%)	0 / 7 (0.00%)
occurrences (all)	0	9	0
Nasopharyngitis			
subjects affected / exposed	3 / 25 (12.00%)	21 / 135 (15.56%)	0 / 7 (0.00%)
occurrences (all)	3	23	0
Upper respiratory tract infection			
subjects affected / exposed	4 / 25 (16.00%)	11 / 135 (8.15%)	1 / 7 (14.29%)
occurrences (all)	13	18	2
Metabolism and nutrition disorders			
Vitamin B12 deficiency			
subjects affected / exposed	2 / 25 (8.00%)	0 / 135 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 160 (35.00%)		

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 160 (1.88%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 160 (6.25%)		
occurrences (all)	11		
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	3 / 160 (1.88%)		
occurrences (all)	3		
Psychiatric disorders			
Attention deficit hyperactivity disorder			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	3 / 160 (1.88%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 160 (8.75%)		
occurrences (all)	15		
Limb discomfort			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences (all)	1		
Infections and infestations			
Influenza			
subjects affected / exposed	9 / 160 (5.63%)		
occurrences (all)	9		
Nasopharyngitis			
subjects affected / exposed	24 / 160 (15.00%)		
occurrences (all)	26		
Upper respiratory tract infection			
subjects affected / exposed	16 / 160 (10.00%)		
occurrences (all)	33		

Metabolism and nutrition disorders Vitamin B12 deficiency subjects affected / exposed occurrences (all)	 2 / 160 (1.25%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2019	- Visits 2, 4, 6 and 8 (weeks 13, 39, 65 and 91) could be conducted as phone visits for patients receiving trial drug at home as part of the Direct to Patient (DTP) programme. - The choice of vial strength for each patient was based on the body weight at the last scheduled visit conducted in trial NN7088-3859 or 3885 prior to the initial shipment of trial product in current trial NN7088-4410. This was to ensure availability of trial product at the start of trial. - Added that patients may be discontinued from the trial when commercial N8-GP becomes available in their respective country. Trial discontinuation will allow for patients to undertake commercial treatment instead of participating in a clinical trial. - Sentence in the haematology section deleted to clarify that only FVIII activity must be taken 30 min post dose, not haematology. - "Web-portal for document exchange" section added to appendix 3 – Trial governance considerations. - A few minor administrative changes performed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported