Clinical trial results:
A multi-national trial evaluating safety and efficacy, including pharmacokinetics, of NNC 0129-0000-1003 when administered for treatment and prophylaxis of bleeding in patients with haemophilia A

Summary

EudraCT number	2011-001142-15
Trial protocol	NL DE SE NO DK ES GB HU IT BG
Global end of trial date	10 December 2018

Results information

Result version number	v1 (current)
This version publication date	22 June 2019
First version publication date	22 June 2019

Trial information

Trial identification

Sponsor protocol code	NN7088-3859

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01480180
WHO universal trial number (UTN)	U1111-1119-7416
Other trial identifiers	Japanese trial registration: JapicCTI-121749

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsværd, 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	10 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2018
Global end of trial reached?	Yes
Global end of trial date	10 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The two co-primary objectives for this trial were:
To evaluate the immunogenicity of NNC 0129-0000-1003 (hereafter referred to as N8-GP) in previously treated subjects with haemophilia A;
To evaluate the clinical efficacy of N8-GP in bleeding prophylaxis (number of bleeds during prophylaxis)

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Seoul, October 2008) and ICH Good Clinical Practice (Geneva, May 1996) and 21 CFR 312.120.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	30 January 2012
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: 4
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Japan: 15
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 1

Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Turkey: 10
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	United States: 46
Worldwide total number of subjects	186
EEA total number of subjects	77

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)	25
Adults (18-64 years)	158
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 77 sites in 22 countries as follows: Australia:3; Brazil:1; Croatia:1; Denmark:2; France:3; Germany:5; Hungary:2; Israel:1; Italy:2; Japan:8; Malaysia:2; Netherlands:2; Norway:1; Russian Federation:1; Korea, Republic of:1; Spain:2; Sweden:1; Switzerland:3; Taiwan:2; Turkey:3; United Kingdom:6; United States:25.

Pre-assignment

Screening details:

The trial had a main phase and an extension phase (part 1 and 2). Subjects completing the NN7088-3776 study were eligible to participate in this study. If the subjects needed a surgery during the present trial, they could switch into the NN7088-3860 surgery trial and on completion/withdrawal from it, they could return to the NN7088-3859 study.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Arm title	Overall Period

Arm description:

There were two arms in this period - Prophylaxis arm and the On-demand arm. Subjects in the prophylaxis arm received N8-GP for approximately 7 to 19 months. Subjects in the on-demand arm received treatment with N8-GP in case of a bleeding episode.

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

Dosage and administration details:

There were two arms in the main phase – 1) Prophylaxis - Subjects received one single bolus dose of 50 IU/kg body weight (BW) of N8-GP every 4th day (96 hours interval). During treatment a shortening of the dosing interval for prophylaxis to twice weekly might be undertaken at the investigator’s discretion, if deemed necessary for the individual subject. Extra doses of N8-GP were administered, if the subject experienced a treatment-requiring bleeding episode or in case of minor surgery. 2) On-demand – Subjects received treatment with N8-GP if they experienced a treatment-requiring bleed. All bleeds were to be treated with doses between 20-75 IU/kg BW according to the severity and location of the bleeding episode. In both the arms, N8-GP was administered as a slow bolus i.v. injection over approximately 2 minutes (from start to completion of injection).

Number of subjects in period 1	Overall Period
Started	186
Completed	165
Not completed	21
Withdrawal criteria	13
Non-compliance	3
Unclassified	4
Lack of efficacy	1

Period 2

Period 2 title	Extension phase, part-1
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Overall period

Arm description:

There were three arms in the extension phase part-1: 1) N8-GP 50 IU/kg prophylaxis Q4D (once in 4 days) 2) N8-GP 75 IU/kg prophylaxis Q7D (once in 7 days) and 3) N8-GP 20-75 IU/kg on-demand. Subjects who were on N8-GP Q4D prophylaxis treatment in the main phase and had 0-2 bleeding episodes in last 6 months were randomised to receive N8-GP Q4D or Q7D in this period. Subjects with 3 or more bleeding episodes within the last 6 months of the main phase and subjects with low bleeding rates who were unwilling to be randomised continued with N8-GP Q4D. Subjects who received N8-GP on-demand treatment throughout the main phase continued with the on-demand regimen in the extension phase.

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

Dosage and administration details:

There were three arms in the extension phase, part-1: 1) N8-GP 50 IU/kg prophylaxis Q4D- single bolus dose; 2) N8-GP 75 IU/kg prophylaxis Q7D – single bolus dose and 3) N8-GP 20-75 IU/kg on-demand. In the first 2 arms, extra doses of N8-GP were given if the subject had a treatment requiring bleeding episode or in case of a minor surgery. Based on bleeding pattern, the investigator could change the dosing frequency from Q7D to Q4D but changing from Q4D to Q7D was not permitted. Subjects on Q7D having 2 or more bleeding episodes or 1 episode requiring hospitalisation were shifted back to Q4D regimen. The trial product in all arms was to be administered as a slow bolus i.v. injection over approximately 2 minutes (from start to completion of injection).

Number of subjects in period 2[1]	Overall period
Started	150
Completed	139
Not completed	11
Adverse event, non-fatal	5
Withdrawal criteria	5
Unclassified	1

Notes:

[1] - 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: Out of the patients that completed the main phase, 15 patients chose not to continue in the extension part of the study.

Period 3

Period 3 title	Extension phase, part-2
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Overall Period

Arm description:

There were three arms in the extension phase, part-2: 1) N8-GP 50 IU/kg prophylaxis Q4D- single bolus dose; 2) N8-GP 75 IU/kg prophylaxis Q7D – single bolus dose and 3) N8-GP 20-75 IU/kg on-demand. In the first 2 arms, subjects could continue on the same prophylaxis dose as received in extension phase (part-1) but could change between Q4D and Q7D dosing. Subjects received treatment for up to approximately 1.5 years or until N8-GP became commercially available in the subject's country. In the third arm, subjects who received N8-GP on-demand treatment throughout the main phase continued with the on-demand regimen in the extension phase part-2.

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

Dosage and administration details:

There were three arms in the extension phase, part-2: 1) N8-GP 50 IU/kg prophylaxis Q4D- single bolus dose; 2) N8-GP 75 IU/kg prophylaxis Q7D – single bolus dose and 3) N8-GP 20-75 IU/kg on-demand. In the first 2 arms, extra doses of N8-GP were given if the subject had a treatment requiring bleeding episode or in case of a minor surgery. During this period, it was possible to change the prophylaxis treatment of subjects to Q4D or Q7D. Subjects with 0-2 bleeds in last 6 months could move to Q7D. Subjects on Q7D having 2 or more bleeding episodes were shifted back to Q4D regimen. The trial product in all arms was to be administered as a slow bolus i.v. injection over approximately 2 minutes (from start to completion of injection).

Number of subjects in period 3	Overall Period
Started	139
Completed	113
Not completed	26
Withdrawal criteria	17
Unclassified	5
Lack of efficacy	4

Baseline characteristics

Reporting groups	
Reporting group title	Overall Period

Reporting group description:

There were two arms in this period - Prophylaxis arm and the On-demand arm. Subjects in the prophylaxis arm received N8-GP for approximately 7 to 19 months. Subjects in the on-demand arm received treatment with N8-GP in case of a bleeding episode.

Reporting group values	Overall Period	Total	
Number of subjects	186	186	
Age Categorical Units: Subjects			
Adolescents (12-17 years)	25	25	
Adults (18-64 years)	158	158	
Elderly (65-84 years)	3	3	
Age Continuous Units: years			
arithmetic mean	31.1		
standard deviation	± 12.6	-	
Gender Categorical Units: Subjects			
Female	0	0	
Male	186	186	

End points

End points reporting groups

Reporting group title	Overall Period

Reporting group description:

There were two arms in this period - Prophylaxis arm and the On-demand arm. Subjects in the prophylaxis arm received N8-GP for approximately 7 to 19 months. Subjects in the on-demand arm received treatment with N8-GP in case of a bleeding episode.

Reporting group title	Overall period

Reporting group description:

There were three arms in the extension phase part-1: 1) N8-GP 50 IU/kg prophylaxis Q4D (once in 4 days) 2) N8-GP 75 IU/kg prophylaxis Q7D (once in 7 days) and 3) N8-GP 20-75 IU/kg on-demand. Subjects who were on N8-GP Q4D prophylaxis treatment in the main phase and had 0-2 bleeding episodes in last 6 months were randomised to receive N8-GP Q4D or Q7D in this period. Subjects with 3 or more bleeding episodes within the last 6 months of the main phase and subjects with low bleeding rates who were unwilling to be randomised continued with N8-GP Q4D. Subjects who received N8-GP on-demand treatment throughout the main phase continued with the on-demand regimen in the extension phase.

Reporting group title	Overall Period

Reporting group description:

There were three arms in the extension phase, part-2: 1) N8-GP 50 IU/kg prophylaxis Q4D- single bolus dose; 2) N8-GP 75 IU/kg prophylaxis Q7D – single bolus dose and 3) N8-GP 20-75 IU/kg on-demand. In the first 2 arms, subjects could continue on the same prophylaxis dose as received in extension phase (part-1) but could change between Q4D and Q7D dosing. Subjects received treatment for up to approximately 1.5 years or until N8-GP became commercially available in the subject’s country. In the third arm, subjects who received N8-GP on-demand treatment throughout the main phase continued with the on-demand regimen in the extension phase part-2.

Subject analysis set title	N8-GP 50 IU/kg Prophylaxis Q4D
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in this arm received one single bolus dose of 50 U/kg BW of N8-GP administered intravenously (IV) every 4th day (96 hours) or twice weekly (investigator's discretion). The dose was adjusted to ensure a trough level of >1% FVIII:C activity in this arm.

Subject analysis set title	N8-GP 75 IU/kg Prophylaxis Q7D
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in this arm received one single bolus dose of 75 IU/kg BW of N8-GP administered intravenously (IV) every 7th day. Based on the bleeding pattern, the investigator could change the dosing frequency from Q7D to Q4D, but not vice versa.

Subject analysis set title	N8-GP 20-75 IU/kg on-demand
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in this arm received treatment with N8-GP in case of a bleeding episode. All bleeds were to be treated with doses between 20-75 U/kg BW according to the severity and location of the bleeding episode. The dosage (N8-GP units) was calculated by multiplying the subject’s weight in kilograms by the desired factor level multiplied by 0.5.

Subject analysis set title	N8-GP prophylaxis
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in this arm includes subjects both from the 50 IU/kg Q4D and the 75 IU/kg Q7d prophylaxis arms

Subject analysis set title	Prophylaxis
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in this arm received one single bolus dose of 50 U/kg BW of N8-GP administered intravenously (IV) every 4th day (96 hours) or twice weekly (investigator's discretion). The dose was adjusted to ensure a trough level of >1% FVIII:C activity in this arm.

Subject analysis set title	On-demand

Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in this arm received treatment with N8-GP in case of a bleeding episode. All bleeds were to be treated with doses between 20-75 U/kg BW according to the severity and location of the bleeding episode. The dosage (N8-GP units) was calculated by multiplying the subject's weight in kilograms by the desired factor level multiplied by 0.5.

Primary: The Incidence rate of FVIII-inhibitors ≥0.6 BU: After approximately 24 months

End point title	The Incidence rate of FVIII-inhibitors ≥0.6 BU: After approximately 24 months[1]

End point description:

All subjects with neutralizing antibodies were included in the numerator and any subject with a minimum 50 exposure days plus any subject with inhibitory inhibitors was included in the denominator. A positive inhibitor test was defined as ≥0.6 bethesda unit (BU). Results are based on the safety analysis set. The safety analysis set consisted of all subjects exposed to N8-GP in this trial. Estimates are based on exact calculations for a binomial distribution. End point 'time frame' should be read as 'After approximately 19 months'. Number of subjects analysed (n) = Number of subjects with available data for respective arm.

End point type	Primary

End point timeframe:

After approximately 24 months

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: Evaluation of 'incidence rate of FVIII inhibitors ≥0.6 BU' was based on descriptive statistics. Hence statistical analysis is not applicable for this endpoint.

End point values	N8-GP 50 IU/kg Prophylaxis Q4D	N8-GP 20-75 IU/kg on-demand		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	175	12		
Units: Rate of inhibitory antibodies				
number (not applicable)	0.006	0		

Statistical analyses

No statistical analyses for this end point

Primary: Annualised bleeding rate in the prophylaxis arm: After approximately 24 months

End point title	Annualised bleeding rate in the prophylaxis arm: After approximately 24 months[2]

End point description:

Annualised bleeding rate (ABR) is the number of bleeding episodes per year reported during the prophylactic treatment with N8-GP. Results were based on the full analysis set (FAS) which included all subjects exposed to N8-GP in this trial. End point 'time frame' should be read as 'After approximately 19 months'. Number of subjects analysed (n) = Number of subjects with available data for respective arm.

End point type	Primary

End point timeframe:

After approximately 24 months

Notes:

[2] - 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: Statistical analysis data for the co-primary endpoint – Annualised bleeding rate is based on one arm only, and can therefore not be provided in the present EudraCT results set-up.

End point values	Prophylaxis			
Subject group type	Subject analysis set			
Number of subjects analysed	175			
Units: Bleeds/subject/year				
median (inter-quartile range (Q1-Q3))	1.33 (0 to 4.61)			

Statistical analyses

No statistical analyses for this end point

Primary: The Incidence rate of FVIII-inhibitors ≥0.6 BU: After approximately 36 months

End point title	The Incidence rate of FVIII-inhibitors ≥0.6 BU: After approximately 36 months[3]

End point description:

All subjects with neutralizing antibodies were included in the numerator and any subject with a minimum 50 exposure days plus any subject with inhibitory inhibitors was included in the denominator. A positive inhibitor test was defined as ≥0.6 bethesda unit (BU). Results are based on the safety analysis set. The safety analysis set consisted of all subjects exposed to N8-GP in this trial. Estimates are based on exact calculations for a binomial distribution. End point time frame should be read as 'After approximately 25 months' (including 19 months from the Main phase and 6 months from the Extension phase, part 1). Number of subjects analysed (n) = Number of subjects with available data for respective arm.

End point type	Primary

End point timeframe:

After approximately 36 months

Notes:

[3] - 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: Evaluation of 'incidence rate of FVIII inhibitors ≥0.6 BU' was based on descriptive statistics. Hence statistical analysis is not applicable for this endpoint.

End point values	N8-GP 50 IU/kg Prophylaxis Q4D	N8-GP 75 IU/kg Prophylaxis Q7D	N8-GP 20-75 IU/kg on-demand	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	175	38	12	
Units: Rate of inhibitory antibodies				
number (not applicable)	0.006	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Annualised bleeding rate in the prophylaxis arm: After approximately 36 months

End point title	Annualised bleeding rate in the prophylaxis arm: After approximately 36 months[4]

End point description:

ABR is the number of bleeding episodes per year reported during the prophylactic treatment with N8-GP. Results were based on the FAS which included all subjects exposed to N8-GP in this trial. End point time frame should be read as 'After approximately 25 months' (including 19 months from the Main phase and 6 months from the Extension phase, part 1). Number of subjects analysed (n) = Number of subjects with available data for respective arm.

End point type	Primary

End point timeframe:

After approximately 36 months

Notes:

[4] - 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: Statistical analysis data for the co-primary endpoint – Annualised bleeding rate is based on one arm only, and can therefore not be provided in the present EudraCT results set-up.

End point values	N8-GP 50 IU/kg Prophylaxis Q4D	N8-GP 75 IU/kg Prophylaxis Q7D		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	175	38		
Units: Bleeds/subject/year				
median (inter-quartile range (Q1-Q3))	1.36 (0.00 to 4.00)	0 (0.00 to 2.36)		

Statistical analyses

No statistical analyses for this end point

Primary: Incidence rate of FVIII-inhibitors ≥0.6 BU: At the end of treatment (EOT) visit

End point title	Incidence rate of FVIII-inhibitors ≥0.6 BU: At the end of treatment (EOT) visit[5]

End point description:

All subjects with neutralizing antibodies were included in the numerator and any subject with a minimum 50 exposure days plus any subject with inhibitory inhibitors was included in the denominator. A positive inhibitor test was defined as ≥0.6 bethesda unit (BU). Results are based on the safety analysis set. The safety analysis set consisted of all subjects exposed to N8-GP in this trial. Estimates are based on exact calculations for a binomial distribution. Number of subjects analysed (n) = Number of subjects with available data for respective arm.

End point type	Primary

End point timeframe:

At the end of treatment visit

Notes:

[5] - 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: Evaluation of 'incidence rate of FVIII inhibitors ≥0.6 BU' was based on descriptive statistics. Hence statistical analysis is not applicable for this endpoint.

End point values	N8-GP 20-75 IU/kg on-demand	N8-GP prophylaxis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	177		
Units: Rate of inhibitory antibodies				
number (not applicable)	0	0.006		

Statistical analyses

No statistical analyses for this end point

Primary: Annualised bleeding rate in the prophylaxis arm: At the end of treatment (EOT) visit

End point title	Annualised bleeding rate in the prophylaxis arm: At the end of treatment (EOT) visit[6]

End point description:

Annualised bleeding rate (ABR) is the number of bleeding episodes per year reported during the prophylactic treatment with N8-GP. Results were based on the FAS which included all subjects exposed to N8-GP in this trial. Number of subjects analysed (n) = Number of subjects with available data for respective arm.

End point type	Primary

End point timeframe:

At the end of treatment period

Notes:

[6] - 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: Statistical analysis data for the co-primary endpoint – Annualised bleeding rate is based on one arm only, and can therefore not be provided in the present EudraCT results set-up.

End point values	N8-GP 50 IU/kg Prophylaxis Q4D	N8-GP 75 IU/kg Prophylaxis Q7D		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	177	61		
Units: Bleeds/subject/year				
median (inter-quartile range (Q1-Q3))	0.99 (0.00 to 2.68)	1.95 (0.43 to 6.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic effect of N8-GP when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) - After approximately 24 months

End point title	Haemostatic effect of N8-GP when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) - After approximately 24 months

End point description:

Haemostatic effect of N8-GP for treatment of bleeding episodes was assessed by 4-point response scale: none, moderate, good or excellent. Evaluation during trial was done by subject and/or parent(s)/caregiver within approximately 8 hours after a single injection as follows: Excellent: Abrupt pain relief and/or clear improvement in objective signs of bleeding within approximately 8 hrs after a single injection; Good: Definite pain relief and/or improvement in signs of bleeding within approximately 8 hrs after a single injection, but possibly requiring more than one injection for complete resolution; Moderate: Probable or slight beneficial effect within approximately 8 hours after the first injection, but usually requiring more than one injection; None: No improvement, or worsening of symptoms. Results were based on the FAS. 'Number of subjects analysed' should be read as 'Number of bleeds analysed'.

End point type	Secondary

End point timeframe:

After approximately 24 months

End point values	N8-GP 50 IU/kg Prophylaxis Q4D	N8-GP 20-75 IU/kg on-demand		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	436[7]	532[8]		
Units: Bleeding episodes				
Excellent	192	320		
Good	174	170		
Moderate	62	41		
None	4	1		
Missing	4	0		

Notes:

[7] - Out of 175 exposed subjects, 105 had 436 bleeds.

[8] - All 12 exposed subjects had a total of 532 bleeds.

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic effect of N8-GP when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) - After approximately 36 months

End point title	Haemostatic effect of N8-GP when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) - After approximately 36 months

End point description:

Haemostatic effect of N8-GP for treatment of bleeding episodes was assessed by 4-point response scale: none, moderate, good or excellent. Evaluation during trial was done by subject and/or parent(s)/caregiver within approximately 8 hours after a single injection as follows: Excellent: Abrupt pain relief and/or clear improvement in objective signs of bleeding within approximately 8 hrs after a single injection; Good: Definite pain relief and/or improvement in signs of bleeding within approximately 8 hrs after a single injection, but possibly requiring more than one injection for complete resolution; Moderate: Probable or slight beneficial effect within approximately 8 hours after the first injection, but usually requiring more than one injection; None: No improvement, or worsening of symptoms. Results were based on the FAS. 'Number of subjects analysed' should be read as 'Number of bleeds analysed'.

End point type	Secondary

End point timeframe:

After approximately 36 months

End point values	N8-GP 50 IU/kg Prophylaxis Q4D	N8-GP 75 IU/kg Prophylaxis Q7D	N8-GP 20-75 IU/kg on-demand	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	716[9]	25[10]	695[11]	
Units: Bleeding episodes				
Excellent	330	9	406	
Good	270	11	233	
Moderate	98	3	55	
None	4	0	1	
Missing	14	2	0	

Notes:

[9] - Out of 175 exposed subjects, 116 subjects had 716 bleeds

[10] - Out of 38 exposed subjects16 subjects had 25 bleeds

[11] - Out of 12 exposed subjects 12 subjects had 695 bleeds

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic effect of N8-GP when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) - At end of treatment (EOT) visit

End point title	Haemostatic effect of N8-GP when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) - At end of treatment (EOT) visit

End point description:

Haemostatic effect of N8-GP for treatment of bleeding episodes was assessed by 4-point response scale: none, moderate, good or excellent. Evaluation during trial was done by subject and/or parent(s)/caregiver within approximately 8 hours after a single injection as follows: Excellent: Abrupt pain relief and/or clear improvement in objective signs of bleeding within approximately 8 hrs after a single injection; Good: Definite pain relief and/or improvement in signs of bleeding within approximately 8 hrs after a single injection, but possibly requiring more than one injection for complete resolution; Moderate: Probable or slight beneficial effect within approximately 8 hours after the first injection, but usually requiring more than one injection; None: No improvement, or worsening of symptoms. Results were based on the FAS. 'Number of subjects analysed' should be read as 'Number of bleeds analysed'.

End point type	Secondary

End point timeframe:

At the end of treatment visit

End point values	N8-GP 50 IU/kg Prophylaxis Q4D	N8-GP 75 IU/kg Prophylaxis Q7D	N8-GP 20-75 IU/kg on-demand	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1312[12]	176[13]	1270[14]	
Units: Bleeding episodes				
Excellent	600	75	859	

Good	532	65	339	
Moderate	153	29	71	
None	6	2	1	
Missing	21	5	0	

Notes:

[12] - Out of 177 exposed subjects 126 subjects had 1312 bleeds

[13] - Out of 61 exposed subjects, 53 subjects had 176 bleeds

[14] - Out of 12 exposed subjects, all 12 subjects had a toal of 1270 bleeds

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first exposure to N8-GP (week 0) to follow up visit after end of treatment in extension phase part 2. (Main phase:19 months; Extension phase:approximately 2 years or until N8-GP becomes commercially available in the subject's country).

Adverse event reporting additional description:

The results are based on the safety analysis set. 'Number of deaths causally related to treatment' is the data considered to present under 'total number of deaths resulting from adverse events (AE)'. All the presented AEs were treatment-emergent. A treatment-emergent AE was defined as an event with onset after first N8-GP administration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	N8-GP 50 IU/kg Q4D prophylaxis

Reporting group description:

The trial consisted of a Main phase and extension phase (part 1 and part 2). In the main phase, subjects received N8-GP 50 IU/kg Q4D as prophylaxis treatment for a period of 19 months. In the extension phase, subjects received N8-GP 50 IU/kg Q4D as prophylaxis treatment for an overall period of up to two years or until N8-GP becomes commercially available in the subject's country.

Reporting group title	N8-GP 20-75 U/kg on-demand

Reporting group description:

The trial consisted of a Main phase and extension phase (part 1 and part 2). In the main phsae, subjects received N8-GP 20-75 IU/kg on-demand treatment for a period of 19 months. In the extension phase, subjects received N8-GP 20-75 IU/kg on-demand treatment for an overall period of two years or until N8-GP becomes commercially available in the subject's country.

Reporting group title	N8-GP 75 IU/kg Q7D prophylaxis

Reporting group description:

The trial consisted of a Main phase and extension phase (part 1 and part 2). In the main phase, subjects received N8-GP 75 IU/kg Q7D as prophylaxis treatment for a period of 19 months. In the extension phase, subjects received N8-GP 50 IU/kg Q7D as prophylaxis treatment for an overall period of up to two years or until N8-GP becomes commercially available in the subject's country.

Serious adverse events	N8-GP 50 IU/kg Q4D prophylaxis	N8-GP 20-75 U/kg on-demand	N8-GP 75 IU/kg Q7D prophylaxis
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 177 (13.56%)	3 / 12 (25.00%)	7 / 61 (11.48%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Neuroma			

subjects affected / exposed	0 / 177 (0.00%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 177 (0.00%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Complication associated with device			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Product issues			
Device dislocation			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 177 (0.00%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest injury			

subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (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
Clavicle fracture			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (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
Extradural haematoma			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (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
Face injury			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Fall			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (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
Femoral neck fracture			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Forearm fracture			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Injury			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Pelvic fracture			

subjects affected / exposed	0 / 177 (0.00%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Sternal fracture			
subjects affected / exposed	0 / 177 (0.00%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 177 (0.00%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Hypertrophic cardiomyopathy			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Cardiac disorders			

Aortic valve stenosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Cerebral microhaemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Seizure			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Syncope			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Blood and lymphatic system disorders			
Factor VIII inhibition			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (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
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Duodenal ulcer			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric varices			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Gastric varices haemorrhage			
subjects affected / exposed	0 / 177 (0.00%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric haemorrhage			
subjects affected / exposed	0 / 177 (0.00%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 177 (0.00%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Renal and urinary disorders			

Calculus urinary			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (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
IgA nephropathy			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 177 (0.00%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (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			
Pathological fracture			
subjects affected / exposed	0 / 177 (0.00%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Bacterial sepsis			
subjects affected / exposed	0 / 177 (0.00%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Catheter site infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Cellulitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Diverticulitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Enteritis infectious			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Infective spondylitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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 discitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Osteomyelitis			

subjects affected / exposed	0 / 177 (0.00%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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 graft infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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
Viral infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 12 (0.00%)	0 / 61 (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

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

Non-serious adverse events	N8-GP 50 IU/kg Q4D prophylaxis	N8-GP 20-75 U/kg on-demand	N8-GP 75 IU/kg Q7D prophylaxis
Total subjects affected by non-serious adverse events			
subjects affected / exposed	144 / 177 (81.36%)	10 / 12 (83.33%)	50 / 61 (81.97%)
Vascular disorders			
Essential hypertension			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	17 / 177 (9.60%)	0 / 12 (0.00%)	4 / 61 (6.56%)
occurrences (all)	18	0	5
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 177 (1.13%)	1 / 12 (8.33%)	2 / 61 (3.28%)
occurrences (all)	2	1	2
Fatigue			

subjects affected / exposed	4 / 177 (2.26%)	1 / 12 (8.33%)	1 / 61 (1.64%)
occurrences (all)	4	1	2
Pyrexia			
subjects affected / exposed	9 / 177 (5.08%)	2 / 12 (16.67%)	5 / 61 (8.20%)
occurrences (all)	10	2	7
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	11 / 177 (6.21%)	0 / 12 (0.00%)	2 / 61 (3.28%)
occurrences (all)	14	0	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 177 (9.04%)	1 / 12 (8.33%)	4 / 61 (6.56%)
occurrences (all)	20	2	5
Haemothorax			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Nasal obstruction			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	16 / 177 (9.04%)	1 / 12 (8.33%)	4 / 61 (6.56%)
occurrences (all)	20	1	5
Pneumothorax			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	9 / 177 (5.08%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences (all)	12	0	1
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	1 / 61 (1.64%)
occurrences (all)	0	1	1
Depression			
subjects affected / exposed	9 / 177 (5.08%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences (all)	9	0	1
Mental status changes			

subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	12 / 177 (6.78%)	3 / 12 (25.00%)	3 / 61 (4.92%)
occurrences (all)	17	6	3
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 177 (5.65%)	3 / 12 (25.00%)	3 / 61 (4.92%)
occurrences (all)	11	5	5
Blood bilirubin increased			
subjects affected / exposed	1 / 177 (0.56%)	2 / 12 (16.67%)	0 / 61 (0.00%)
occurrences (all)	1	2	0
Blood pressure increased			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
C-reactive protein increased			
subjects affected / exposed	5 / 177 (2.82%)	0 / 12 (0.00%)	4 / 61 (6.56%)
occurrences (all)	7	0	4
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 177 (3.39%)	3 / 12 (25.00%)	1 / 61 (1.64%)
occurrences (all)	10	5	1
Liver function test abnormal			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Sputum abnormal			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	11 / 177 (6.21%)	2 / 12 (16.67%)	3 / 61 (4.92%)
occurrences (all)	15	10	3
Fall			
subjects affected / exposed	10 / 177 (5.65%)	0 / 12 (0.00%)	2 / 61 (3.28%)
occurrences (all)	10	0	2
Foot fracture			

subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Joint injury			
subjects affected / exposed	5 / 177 (2.82%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	5	1	0
Limb injury			
subjects affected / exposed	6 / 177 (3.39%)	0 / 12 (0.00%)	5 / 61 (8.20%)
occurrences (all)	7	0	6
Scratch			
subjects affected / exposed	1 / 177 (0.56%)	1 / 12 (8.33%)	1 / 61 (1.64%)
occurrences (all)	1	1	1
Skin laceration			
subjects affected / exposed	10 / 177 (5.65%)	0 / 12 (0.00%)	5 / 61 (8.20%)
occurrences (all)	12	0	5
Spinal fracture			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	1 / 177 (0.56%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	1	1	0
Dizziness			
subjects affected / exposed	6 / 177 (3.39%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	7	1	0
Headache			
subjects affected / exposed	35 / 177 (19.77%)	3 / 12 (25.00%)	13 / 61 (21.31%)
occurrences (all)	79	4	25
Seizure			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			

Lymphadenopathy			
subjects affected / exposed	2 / 177 (1.13%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	2	1	0
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 177 (2.26%)	1 / 12 (8.33%)	1 / 61 (1.64%)
occurrences (all)	5	1	1
Abdominal pain upper			
subjects affected / exposed	9 / 177 (5.08%)	0 / 12 (0.00%)	3 / 61 (4.92%)
occurrences (all)	12	0	3
Dental caries			
subjects affected / exposed	6 / 177 (3.39%)	1 / 12 (8.33%)	2 / 61 (3.28%)
occurrences (all)	11	1	2
Diarrhoea			
subjects affected / exposed	17 / 177 (9.60%)	2 / 12 (16.67%)	5 / 61 (8.20%)
occurrences (all)	22	2	6
Dyspepsia			
subjects affected / exposed	4 / 177 (2.26%)	1 / 12 (8.33%)	1 / 61 (1.64%)
occurrences (all)	4	1	1
Flatulence			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	2	0
Haemorrhoids			
subjects affected / exposed	1 / 177 (0.56%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	1	1	0
Irritable bowel syndrome			
subjects affected / exposed	1 / 177 (0.56%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	1	2	0
Nausea			
subjects affected / exposed	14 / 177 (7.91%)	1 / 12 (8.33%)	3 / 61 (4.92%)
occurrences (all)	20	1	3
Toothache			

subjects affected / exposed	10 / 177 (5.65%)	1 / 12 (8.33%)	3 / 61 (4.92%)
occurrences (all)	11	1	5
Vomiting			
subjects affected / exposed	9 / 177 (5.08%)	1 / 12 (8.33%)	4 / 61 (6.56%)
occurrences (all)	11	1	4
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	3 / 177 (1.69%)	0 / 12 (0.00%)	4 / 61 (6.56%)
occurrences (all)	4	0	4
Blister			
subjects affected / exposed	1 / 177 (0.56%)	1 / 12 (8.33%)	1 / 61 (1.64%)
occurrences (all)	3	1	1
Dry skin			
subjects affected / exposed	2 / 177 (1.13%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	2	1	0
Eczema			
subjects affected / exposed	5 / 177 (2.82%)	1 / 12 (8.33%)	2 / 61 (3.28%)
occurrences (all)	8	2	2
Eczema asteatotic			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	2 / 177 (1.13%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	2	1	0
Rash			
subjects affected / exposed	9 / 177 (5.08%)	0 / 12 (0.00%)	2 / 61 (3.28%)
occurrences (all)	10	0	2
Urticaria			
subjects affected / exposed	2 / 177 (1.13%)	1 / 12 (8.33%)	2 / 61 (3.28%)
occurrences (all)	2	1	2
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	1 / 61 (1.64%)
occurrences (all)	0	1	1
Urinary incontinence			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	27 / 177 (15.25%)	3 / 12 (25.00%)	15 / 61 (24.59%)
occurrences (all)	43	4	21
Back pain			
subjects affected / exposed	8 / 177 (4.52%)	3 / 12 (25.00%)	6 / 61 (9.84%)
occurrences (all)	11	3	6
Musculoskeletal chest pain			
subjects affected / exposed	3 / 177 (1.69%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	3	1	0
Musculoskeletal pain			
subjects affected / exposed	14 / 177 (7.91%)	1 / 12 (8.33%)	4 / 61 (6.56%)
occurrences (all)	14	1	4
Osteoarthritis			
subjects affected / exposed	3 / 177 (1.69%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	3	1	0
Pain in extremity			
subjects affected / exposed	12 / 177 (6.78%)	0 / 12 (0.00%)	1 / 61 (1.64%)
occurrences (all)	14	0	1
Rheumatic disorder			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	2	0
Synovitis			
subjects affected / exposed	3 / 177 (1.69%)	0 / 12 (0.00%)	5 / 61 (8.20%)
occurrences (all)	5	0	5
Tendonitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	6 / 61 (9.84%)
occurrences (all)	0	1	6
Tenosynovitis			

subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 177 (5.08%)	1 / 12 (8.33%)	1 / 61 (1.64%)
occurrences (all)	9	1	1
Citrobacter infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	5 / 177 (2.82%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	5	1	0
Folliculitis			
subjects affected / exposed	2 / 177 (1.13%)	1 / 12 (8.33%)	0 / 61 (0.00%)
occurrences (all)	2	2	0
Gastroenteritis			
subjects affected / exposed	6 / 177 (3.39%)	1 / 12 (8.33%)	1 / 61 (1.64%)
occurrences (all)	9	1	1
Influenza			
subjects affected / exposed	16 / 177 (9.04%)	2 / 12 (16.67%)	6 / 61 (9.84%)
occurrences (all)	22	2	7
Nasopharyngitis			
subjects affected / exposed	48 / 177 (27.12%)	5 / 12 (41.67%)	12 / 61 (19.67%)
occurrences (all)	78	12	16
Periodontitis			
subjects affected / exposed	1 / 177 (0.56%)	2 / 12 (16.67%)	1 / 61 (1.64%)
occurrences (all)	1	2	1
Tinea infection			
subjects affected / exposed	1 / 177 (0.56%)	1 / 12 (8.33%)	1 / 61 (1.64%)
occurrences (all)	1	1	1
Tonsillitis			
subjects affected / exposed	10 / 177 (5.65%)	1 / 12 (8.33%)	4 / 61 (6.56%)
occurrences (all)	11	2	5
Upper respiratory tract infection			
subjects affected / exposed	37 / 177 (20.90%)	0 / 12 (0.00%)	9 / 61 (14.75%)
occurrences (all)	59	0	14

Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1	1 / 12 (8.33%) 2	1 / 61 (1.64%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2011	This global substantial amendment was issued primarily as a response to a voluntary harmonised procedure (VHP) assessment, which involve the clinical trial application (CTA) submission of the NN7088-3859 and NN7088-3860 protocol in 8 European countries: VHP recommend a more detailed guidance on the treatment of bleeds. Therefore section 5.3.2 had been updated accordingly. VHP recommended a more clear guidance for the required observation period for adverse reactions in connection to administration of the two first doses of N8-GP. This had been added in the relevant sections. Anti-coagulants and heparin had been added in section 6.5 as prohibited medication to the protocols withdrawal criteria to make this more consistent.
13 April 2012	This global substantial protocol amendment was issued primarily as a response to a Special Protocol Assessment request sent to the US FDA in connection with submission of the NN7088-3859 protocol in the United States: 1) Annualised bleeding rate in prophylaxis arm. The calculation of annualised bleeding rate for withdrawals has been changed. Imputation will also be performed for withdrawals within the first month. An annualised bleeding rate of 24 will be used for imputation for all subjects withdrawing in the first month, including those with zero bleeds. 2) Sample size calculations have been changed. For the inhibitor test a true inhibitor rate of 0.5% instead of 1% is now assumed. This is based on the experience with clinical trials with turoctocog alfa. For the prophylaxis test, the impact on the power of the change in imputation rule for early withdrawals without bleeding episodes is accounted for. 3) An interim analysis has been added in order to evaluate the over-dispersion (only) once approximately 90 subjects have entered into the prophylaxis arm. If the estimated overdispersion is greater than 6 then the planned sample size will be adjusted up to include 160 prophylaxis subjects instead of 120 subjects. The planned sample size will not be increased without issuing a further amendment.
21 December 2012	This global substantial protocol amendment was issued in order to allow for an increase in sample size following the described interim analysis, should it be determined to be necessary.
05 April 2013	This global substantial amendment was issued in order to extend the maximum treatment period with 3 months, from 24 to 27 months, due to an extension of the recruitment period. Therefore additional visits 12a to visit 12j have been added. Subjects for the surgery trial, NN7088-3860, are recruited via this trial where they must have had at least 5 EDs before entering the surgery trial. This amendment will allow the continued recruitment of major surgery subjects after the recruitment of this trial has been completed. This is in order to ensure recruitment into the surgery trial and fulfilment of regulatory requirements regarding collection of major surgery data. The extension trial will not await these subjects to complete 50 EDs before it is initiated.
04 July 2013	This global amendment was issued to include the following: In version 6.0 of the NN7088-3859 protocol subjects could be transferred to the extension trial NN7088-3861 where they could continue treatment with N8-GP until it was commercially available. Instead of setting up a separate trial, the extension trial will be included in the current trial as an extension phase.

17 September 2013	This global amendment was issued primarily as a response to a VHP assessment, which involved a central EU CTA submission of the NN7088-3859 protocol version 7.0 in 8 European countries. Main changes were a description of rules for when a subject should be switched from Q7D to Q4D treatment regimen and deletion of every 5 and 6 day dosing regimens from the protocol.
17 September 2013	The VHP requested that subjects in the Q7D treatment arm receive the same visit schedule as subjects in the Q4D treatment arm of the main study phase i.e. monthly visits at the start of treatment, followed by visits every second month. In addition, it was agreed with the VHP to also implement this visit schedule for subjects randomised to Q4D in the extension phase part 1. This is to avoid any bias in the randomised arms. Part 1 of the extension is 6 months in duration, therefore monthly visits for the first 4 months have been introduced, followed by a visit 2 months later. The VHP stipulated that this visit schedule should apply for every switch to Q7D independent of the part of the extension phase. Therefore, this requirement has also been implemented for Q7D subjects in part 2 of the extension. In part 2, those switching to Q7D, will have visits every month for the first 4 months and subsequently every two months while on Q7D.
23 January 2014	The withdrawal criteria section 6.5 of the protocol was amended to allow subjects with a low titre inhibitor [≤5 Bethesda units (BU)], that does not result in clinically ineffective treatment with N8-GP, to continue in the trial. Text regarding adverse events was updated.
19 November 2015	This global amendment was issued to allow subjects to transfer to a separate pharmacokinetics (PK) trial NN7088-4033 and back again; to monitor antibody development against host cell protein; addition of interim analyses before submission; prolonged storage of leftover blood samples to enable further characterisation as new biomarkers related to the disease or related diseases and/or safety, efficacy or mechanism of action may evolve.
21 June 2016	The purpose of this amendment was to clarify when the subjects could complete the trial (to continue in another N8-GP trial, NN7088-4410).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported