Clinical trial results:
A Multinational, Open-Label, Non-Controlled Trial on Safety, Efficacy and Pharmacokinetics of NNC 0129-0000-1003 in Previously Treated Paediatric Patients with Severe Haemophilia A

Summary

EudraCT number	2012-001711-23
Trial protocol	DE PT GB IT GR LT
Global end of trial date	28 September 2018

Results information

Result version number	v1 (current)
This version publication date	12 April 2019
First version publication date	12 April 2019

Trial information

Trial identification

Sponsor protocol code	NN7088-3885

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01731600
WHO universal trial number (UTN)	U1111-1129-6009
Other trial identifiers	Japanese trial registration: 132214

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 September 2014
Global end of trial reached?	Yes
Global end of trial date	28 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate immunogenicity of NNC 0129-0000-1003 (hereafter referred to as N8-GP)

Protection of trial subjects:

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

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	20 February 2013
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	Canada: 2
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	Lithuania: 5
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	Ukraine: 6
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	68
EEA total number of subjects	23

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)	6
Children (2-11 years)	62
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 36 sites in 15 countries as follows: Canada (1), France (2), Germany (1), Greece (2 sites screened/1 site randomised subjects), Israel (1), Italy (1), Japan (2), Lithuania (1), Malaysia (1), Portugal (1), Switzerland (3), Turkey (3), Ukraine (2), United Kingdom (3), and United States (12).

Pre-assignment

Screening details:

Not applicable

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Younger children (0 - 5 years)

Arm description:

Subjects (0 - 5 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days). After completion of main phase, subjects could continue until the end of the extension phase, which was defined as last patient last visit (LPLV). All subjects continued twice weekly or every third day prophylaxis regimen in extension phase as prescribed for main phase. However, after 12 months' treatment with N8-GP (main phase+extension phase) the investigator was permitted to prescribe extra coverage before physical activities.

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:

Prophylaxis: N8-GP was administered as a single intravenous (iv) bolus injection 60 IU/kg twice weekly. There were two vials which were used (500 U/vial 53µg/vial, 2000 U/vial 211 µg/vial). An increase in dose frequency from twice weekly to every third day was permitted at investigator’s discretion (based on bleeding pattern). Extra doses of N8-GP were administered, if the subject experienced a treatment-requiring bleeding episode or in case of minor surgery. Treatment of bleeding episodes: Treatment-requiring bleeding episodes were treated with doses of N8-GP ranging from 20−75 IU/kg, according to the severity and location of the bleeding episode. Bleeding episodes due to abdominal, head trauma, surgery were treated with extra dose of N8-GP similar to that used for severe bleeding episodes.

Arm title	Older children (6 - 11 years)

Arm description:

Subjects (6 - 11 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days). After completion of main phase, subjects could continue until the end of the extension phase, which was defined as LPLV. All subjects continued twice weekly or every third day prophylaxis regimen in extension phase as prescribed for main phase. However, after 12 months' treatment with N8-GP (main phase+extension phase) the investigator was permitted to prescribe extra coverage before physical activities.

Arm type	Experimental

Investigational medicinal product name	N8-GP rFVIII
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Dosage and administration details:

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Number of subjects in period 1	Younger children (0 - 5 years)	Older children (6 - 11 years)
Started	34	34
Completed	28	34
Not completed	6	0
Adverse event, non-fatal	2	-
Withdrawal criteria	1	-
Other reasons	3	-

Baseline characteristics

Reporting groups

Reporting group title	Younger children (0 - 5 years)

Reporting group description:

Subjects (0 - 5 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days). After completion of main phase, subjects could continue until the end of the extension phase, which was defined as last patient last visit (LPLV). All subjects continued twice weekly or every third day prophylaxis regimen in extension phase as prescribed for main phase. However, after 12 months' treatment with N8-GP (main phase+extension phase) the investigator was permitted to prescribe extra coverage before physical activities.

Reporting group title	Older children (6 - 11 years)

Reporting group description:

Subjects (6 - 11 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days). After completion of main phase, subjects could continue until the end of the extension phase, which was defined as LPLV. All subjects continued twice weekly or every third day prophylaxis regimen in extension phase as prescribed for main phase. However, after 12 months' treatment with N8-GP (main phase+extension phase) the investigator was permitted to prescribe extra coverage before physical activities.

Reporting group values	Younger children (0 - 5 years)	Older children (6 - 11 years)	Total
Number of subjects	34	34	68
Age Categorical			
Units: Subjects			
Infants and toddlers (28 days-23 months)	6	0	6
Children (2-11 years)	28	34	62
Age Continuous			
Units: years			
arithmetic mean	3.0	8.9	
standard deviation	± 1.3	± 1.7	-
Gender Categorical			
Units: Subjects			
Female	0	0	0
Male	34	34	68

Subject analysis sets

Subject analysis set title	Younger children (0 - 5 years) [Main trial]
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (0 - 5 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days).

Subject analysis set title	Older children (6 - 11 years) [Main trial]
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (6 - 11 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days).

Subject analysis set title	Younger children (0 - 5 years) [Full trial]

Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (0 - 5 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days). After completion of main phase, subjects could continue until the end of the extension phase, which was defined as LPLV. All subjects continued twice weekly or every third day prophylaxis regimen in extension phase as prescribed for main phase. However, after 12 months treatment with N8-GP (main phase+extension phase) the investigator was permitted to prescribe extra coverage before physical activities.

Subject analysis set title	Older children (6 - 11 years) [Full trial]
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (6 - 11 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days). After completion of main phase, subjects could continue until the end of the extension phase, which was defined as LPLV. All subjects continued twice weekly or every third day prophylaxis regimen in extension phase as prescribed for main phase. However, after 12 months treatment with N8-GP (main phase+extension phase) the investigator was permitted to prescribe extra coverage before physical activities.

Reporting group values	Younger children (0 - 5 years) [Main trial]	Older children (6 - 11 years) [Main trial]	Younger children (0 - 5 years) [Full trial]
Number of subjects	34	34	34
Age Categorical Units: Subjects			
Infants and toddlers (28 days-23 months) Children (2-11 years)			
Age Continuous Units: years arithmetic mean standard deviation	±	±	±
Gender Categorical Units: Subjects			
Female Male	0 34	0 34	0 34

Reporting group values	Older children (6 - 11 years) [Full trial]		
Number of subjects	34		
Age Categorical Units: Subjects			
Infants and toddlers (28 days-23 months) Children (2-11 years)			
Age Continuous Units: years arithmetic mean standard deviation	±		
Gender Categorical Units: Subjects			
Female Male	0 34		

End points

End points reporting groups

Reporting group title	Younger children (0 - 5 years)

Reporting group description:

Subjects (0 - 5 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days). After completion of main phase, subjects could continue until the end of the extension phase, which was defined as last patient last visit (LPLV). All subjects continued twice weekly or every third day prophylaxis regimen in extension phase as prescribed for main phase. However, after 12 months' treatment with N8-GP (main phase+extension phase) the investigator was permitted to prescribe extra coverage before physical activities.

Reporting group title	Older children (6 - 11 years)

Reporting group description:

Subjects (6 - 11 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days). After completion of main phase, subjects could continue until the end of the extension phase, which was defined as LPLV. All subjects continued twice weekly or every third day prophylaxis regimen in extension phase as prescribed for main phase. However, after 12 months' treatment with N8-GP (main phase+extension phase) the investigator was permitted to prescribe extra coverage before physical activities.

Subject analysis set title	Younger children (0 - 5 years) [Main trial]
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (0 - 5 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days).

Subject analysis set title	Older children (6 - 11 years) [Main trial]
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (6 - 11 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days).

Subject analysis set title	Younger children (0 - 5 years) [Full trial]
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (0 - 5 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days). After completion of main phase, subjects could continue until the end of the extension phase, which was defined as LPLV. All subjects continued twice weekly or every third day prophylaxis regimen in extension phase as prescribed for main phase. However, after 12 months treatment with N8-GP (main phase+extension phase) the investigator was permitted to prescribe extra coverage before physical activities.

Subject analysis set title	Older children (6 - 11 years) [Full trial]
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (6 - 11 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days). After completion of main phase, subjects could continue until the end of the extension phase, which was defined as LPLV. All subjects continued twice weekly or every third day prophylaxis regimen in extension phase as prescribed for main phase. However, after 12 months treatment with N8-GP (main phase+extension phase) the investigator was permitted to prescribe extra coverage before physical activities.

Primary: Incidence of inhibitory antibodies against coagulation factor VIII (FVIII) ≥0.6 Bethesda units

End point title	Incidence of inhibitory antibodies against coagulation factor VIII (FVIII) ≥0.6 Bethesda units

End point description:

The incidence of inhibitory antibodies was calculated as number of patients with inhibitors during the main phase of the trial divided by number of patients in the main phase of the trial. Results were based on safety analysis set (SAS). The SAS consists of all patients exposed to at least one dose of turoctocog alfa pegol.

End point type	Primary

End point timeframe:

During the main phase of the trial (from 0-26 weeks of treatment)

End point values	Younger children (0 - 5 years) [Main trial]	Older children (6 - 11 years) [Main trial]		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	34		
Units: Proportion of subjects	0	0		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

A one-sided, upper 97.5% confidence limit was provided based on an exact calculation in the binomial distribution.

Comparison groups	Older children (6 - 11 years) [Main trial] v Younger children (0 - 5 years) [Main trial]
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Incidence rate
Point estimate	0
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	0.067

Secondary: Frequency of adverse events including serious adverse events reported during the trial period

End point title	Frequency of adverse events including serious adverse events reported during the trial period

End point description:

The frequency of adverse events including serious adverse events reported during the main and extension phase of the trial. Results were based on SAS.

End point type	Secondary

End point timeframe:

Main phase: (from 0-26 weeks of treatment) and full trial: (0 weeks to last patient’s completion of the trial)

End point values	Younger children (0 - 5 years) [Main trial]	Older children (6 - 11 years) [Main trial]	Younger children (0 - 5 years) [Full trial]	Older children (6 - 11 years) [Full trial]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	34	34	34	34
Units: Events per patient years of exposure				
number (not applicable)	4.87	4.74	3.09	2.45

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Haemostatic effect of turoctocog alfa pegol for treatment of bleeding episodes was assessed by 4-point response scale: none, moderate, good or excellent. Evaluation during trial was done by patient and/or parent(s)/caregiver 8 hours after first injection as follows: Excellent: Abrupt pain relief and/or clear improvement in objective signs of bleeding within approximately 8 hours after a single injection; Good: Definite pain relief and/or improvement in signs of bleeding within approximately 8 hours 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 full analysis set (FAS). All trial patients allocated to treatment, for which at least one of the pharmacokinetic or efficacy endpoints was assessed, were included in the FAS.

End point type	Secondary

End point timeframe:

Main phase: (from 0-26 weeks of treatment) and full trial: (0 weeks to last patient’s completion of the trial)

End point values	Younger children (0 - 5 years) [Main trial]	Older children (6 - 11 years) [Main trial]	Younger children (0 - 5 years) [Full trial]	Older children (6 - 11 years) [Full trial]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30[1]	40[2]	108[3]	222[4]
Units: Bleeding episodes				
Excellent	11	12	47	96
Good	13	19	48	74
Moderate	4	7	9	44

None	1	0	2	2
Missing	1	2	2	6

Notes:

[1] - "Number of subjects analyzed" = number of bleeds in subjects

[2] - "Number of subjects analyzed" = number of bleeds in subjects

[3] - "Number of subjects analyzed" = number of bleeds in subjects

[4] - "Number of subjects analyzed" = number of bleeds in subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Number of bleeding episodes during prophylactic treatment with N8-GP (annualised bleeding rate)

End point title	Number of bleeding episodes during prophylactic treatment with N8-GP (annualised bleeding rate)

End point description:

The number of bleeding episodes per year reported during the prophylactic treatment with N8-GP. Results were based on FAS.

End point type	Secondary

End point timeframe:

Main phase: (from 0-26 weeks of treatment) and full trial: (0 weeks to last patient's completion of the trial)

End point values	Younger children (0 - 5 years) [Main trial]	Older children (6 - 11 years) [Main trial]	Younger children (0 - 5 years) [Full trial]	Older children (6 - 11 years) [Full trial]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	34	34	34	34
Units: bleeds/patient/year				
median (inter-quartile range (Q1-Q3))	1.94 (0.00 to 2.08)	1.97 (0.00 to 3.91)	0.61 (0.20 to 1.19)	0.93 (0.20 to 2.11)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of N8-GP per bleeding episode (number of injections)

End point title	Consumption of N8-GP per bleeding episode (number of injections)

End point description:

The mean number of injections of turoctocog alfa pegol used for treatment of a bleed from start to stop of a bleed. Results were based on FAS.

End point type	Secondary

End point timeframe:

Main phase: (from 0-26 weeks of treatment) and full trial: (0 weeks to last patient's completion of the trial)

End point values	Younger children (0 - 5 years) [Main trial]	Older children (6 - 11 years) [Main trial]	Younger children (0 - 5 years) [Full trial]	Older children (6 - 11 years) [Full trial]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30[5]	40[6]	108[7]	222[8]
Units: Number of injections				
arithmetic mean (standard deviation)	1.9 (± 1.5)	1.6 (± 0.9)	1.6 (± 1.3)	1.5 (± 1.1)

Notes:

[5] - "Number of subjects analyzed"=number of bleeds

[6] - "Number of subjects analyzed"=number of bleeds

[7] - "Number of subjects analyzed"=number of bleeds

[8] - "Number of subjects analyzed"=number of bleeds

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of N8-GP per bleeding episode (U/kg)

End point title	Consumption of N8-GP per bleeding episode (U/kg)

End point description:

The mean consumption of turoctocog alfa pegol used for treatment of a bleed from start to stop of a bleed. Results were based on FAS.

End point type	Secondary

End point timeframe:

Main phase: (from 0-26 weeks of treatment) and full trial: (0 weeks to last patient’s completion of the trial)

End point values	Younger children (0 - 5 years) [Main trial]	Older children (6 - 11 years) [Main trial]	Younger children (0 - 5 years) [Full trial]	Older children (6 - 11 years) [Full trial]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	40	108	222
Units: IU/kg/bleed				
arithmetic mean (standard deviation)	123 (± 104.9)	99.0 (± 54.4)	102.8 (± 81.0)	91.0 (± 58.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of N8-GP during prophylaxis (number of injections)

End point title	Consumption of N8-GP during prophylaxis (number of injections)

End point description:

The mean number of injections of turoctocog alfa pegol used for treatment of a bleed from start to stop of a bleed during prophylaxis. Results were based on FAS.

End point type	Secondary

End point timeframe:

Main phase: (from 0-26 weeks of treatment) and full trial: (0 weeks to last patient's completion of the trial)

End point values	Younger children (0 - 5 years) [Main trial]	Older children (6 - 11 years) [Main trial]	Younger children (0 - 5 years) [Full trial]	Older children (6 - 11 years) [Full trial]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1592[9]	1799[10]	14442[11]	17243[12]
Units: Number of injections				
arithmetic mean (standard deviation)	65.3 (± 6.5)	62.3 (± 7.4)	65.4 (± 7.5)	64.1 (± 5.3)

Notes:

[9] - "Number of subjects analyzed"=Number of injections"

[10] - "Number of subjects analyzed"=Number of injections"

[11] - "Number of subjects analyzed"=Number of injections"

[12] - "Number of subjects analyzed"=Number of injections"

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of N8-GP during prophylaxis (U/kg per month)

End point title	Consumption of N8-GP during prophylaxis (U/kg per month)

End point description:

The mean consumption of turoctocog alfa pegol used for treatment of a bleed from start to stop of a bleed during prophylaxis (per month per subject). Results were based on FAS. Consumption used for treatment includes all doses given (prophylaxis, treatment of bleed, minor surgery and pharmacokinetics [PK])

End point type	Secondary

End point timeframe:

Main phase: (from 0-26 weeks of treatment) and full trial: (0 weeks to last patient's completion of the trial)

End point values	Younger children (0 - 5 years) [Main trial]	Older children (6 - 11 years) [Main trial]	Younger children (0 - 5 years) [Full trial]	Older children (6 - 11 years) [Full trial]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	34	34	34	34
Units: U/kg/month				
arithmetic mean (standard deviation)	572.5 (± 97.4)	555.8 (± 44.6)	564.9 (± 86.6)	563.4 (± 15.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of N8-GP during prophylaxis (U/kg per year)

End point title	Consumption of N8-GP during prophylaxis (U/kg per year)

End point description:

The mean consumption of turoctocog alfa pegol used for treatment of a bleed from start to stop of a bleed during prophylaxis (per year per subject). Results were based on FAS. Consumption used for treatment includes all doses given (prophylaxis, treatment of bleed, minor surgery and pharmacokinetics)

End point type	Secondary

End point timeframe:

Main phase: (from 0-26 weeks of treatment) and full trial: (0 weeks to last patient’s completion of the trial).

End point values	Younger children (0 - 5 years) [Main trial]	Older children (6 - 11 years) [Main trial]	Younger children (0 - 5 years) [Full trial]	Older children (6 - 11 years) [Full trial]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	34	34	34	34
Units: U/kg/year				
arithmetic mean (standard deviation)	6870.3 (± 1169)	6669.6 (± 535.8)	6778.6 (± 1039)	6760.4 (± 181.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental recovery (defined as the peak level recorded 60 min after end of injection) evaluated for previous FVIII product

End point title	Incremental recovery (defined as the peak level recorded 60 min after end of injection) evaluated for previous FVIII product

End point description:

The incremental recovery was defined as the increase in plasma FVIII activity per IU/kg of factor administered recorded 60 minutes after end of injection. It was calculated as (Factor VIII procoagulant [FVIII:C] activity measured in plasma 60 min after dosing - FVIII:C activity measured in plasma immediately before dosing) / (dose injected at time 0 min), where the dose was expressed as U FVIII product per kg body weight. A chromogenic assay with normal human plasma (NHP) as calibrator was used. Results were based on FAS.

End point type	Secondary

End point timeframe:

2-6 weeks prior to initial dosing with N8-GP and up to 30 hours after administration of previous FVIII product

End point values	Younger children (0 - 5 years) [Main trial]	Older children (6 - 11 years) [Main trial]		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13[13]	12[14]		
Units: (IU/mL)/(U/kg)				
least squares mean (confidence interval 95%)	0.017 (0.014 to 0.021)	0.022 (0.018 to 0.027)		

Notes:

[13] - "Number of subjects analysed"=subjects with available data

[14] - "Number of subjects analysed"=subjects with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental recovery (defined as the peak level recorded 60 min after end of injection) evaluated for N8-GP

End point title	Incremental recovery (defined as the peak level recorded 60 min after end of injection) evaluated for N8-GP

End point description:

The incremental recovery was defined as the peak level recorded 60 min after end of injection and dose-normalised. It was calculated as (FVIII:C activity measured in plasma 60 min after dosing - FVIII:C activity measured in plasma immediately before dosing) / (dose injected at time 0 min), where the dose was expressed as U FVIII product per kg body weight. A chromogenic assay with product specific calibrator (PSS) as calibrator was used. Results were based on FAS.

End point type	Secondary

End point timeframe:

From 1 hour prior to and up to 96 hours after initial administration of N8-GP.

End point values	Younger children (0 - 5 years) [Full trial]	Older children (6 - 11 years) [Full trial]		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13[15]	12[16]		
Units: (IU/mL)/(U/kg)				
least squares mean (confidence interval 95%)	0.018 (0.015 to 0.022)	0.020 (0.016 to 0.024)		

Notes:

[15] - "Number of subjects analyzed"=subjects with available data

[16] - "Number of subjects analyzed"=subjects with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve evaluated for previous FVIII product

End point title	Area under the curve evaluated for previous FVIII product

End point description:

Area under the curve (AUC) versus time from zero to infinity. This is calculated as AUC = AUClast + (C(t) / λz), where C(t) is the last measurable concentration. A chromogenic assay with NHP as calibrator was used. Results were based on FAS.

End point type	Secondary

End point timeframe:

2-6 weeks prior to initial dosing with N8-GP and up to 30 hours after administration of previous FVIII product

End point values	Younger children (0 - 5 years) [Full trial]	Older children (6 - 11 years) [Full trial]		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14[17]	11[18]		
Units: IU×h/mL				
least squares mean (confidence interval 95%)	11.628 (9.170 to 14.744)	12.203 (9.336 to 15.951)		

Notes:

[17] - "Number of subjects analyzed"=subjects with available data

[18] - "Number of subjects analyzed"=subjects with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve evaluated for N8-GP

End point title	Area under the curve evaluated for N8-GP

End point description:

Area under the curve versus time from zero to infinity. This is calculated as AUC = AUClast + (C(t) / λz), where C(t) is the last measurable concentration. A chromogenic assay with PSS as calibrator was used. Results were based on FAS.

End point type	Secondary

End point timeframe:

From 1 hour prior to and up to 96 hours after initial administration of N8-GP

End point values	Younger children (0 - 5 years) [Full trial]	Older children (6 - 11 years) [Full trial]		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13[19]	11[20]		
Units: IU*h/mL				
least squares mean (confidence interval 95%)	21.489 (16.785 to 27.511)	25.026 (19.145 to 32.713)		

Notes:

[19] - "Number of subjects analyzed"=subjects with available data

[20] - "Number of subjects analyzed"=subjects with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal half-life evaluated for previous FVIII product

End point title	Terminal half-life evaluated for previous FVIII product

End point description:

t½ = ln(2) / λz, where λz is the terminal elimination rate. The terminal elimination rate was planned estimated using linear regression on the terminal part of the time versus log(concentration) curve. A population-based method simultaneously estimating individual t½ values for all patients was applied, including patients with few values above the lower limit of quantification (LLOQ). This was estimated using time points from 1h to 30h. A chromogenic assay with PSS as calibrator was used. Results were based on FAS.

End point type	Secondary

End point timeframe:

2-6 weeks prior to initial dosing with N8-GP and up to 30 hours after administration of previous FVIII product

End point values	Younger children (0 - 5 years) [Full trial]	Older children (6 - 11 years) [Full trial]		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14[21]	12[22]		
Units: hours				
geometric mean (geometric coefficient of variation)	7.2 (± 20.1)	7.5 (± 19.1)		

Notes:

[21] - "Number of subjects analyzed"=subjects with available data

[22] - "Number of subjects analyzed"=subjects with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal half-life evaluated for N8-GP

End point title	Terminal half-life evaluated for N8-GP

End point description:

t½ = ln(2) / λz, where λz is the terminal elimination rate. The terminal elimination rate was planned estimated using linear regression on the terminal part of the time versus log(concentration) curve. A population-based method simultaneously estimating individual t½ values for all patients was applied, including patients with few values above the LLOQ. This was estimated using time points from 6h to 96h. A chromogenic assay with PSS as calibrator was used. Results were based on FAS.

End point type	Secondary

End point timeframe:

From 1 hour prior to and up to 96 hours after initial administration of N8-GP

End point values	Younger children (0 - 5 years) [Full trial]	Older children (6 - 11 years) [Full trial]		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13[23]	12[24]		
Units: hours				
geometric mean (geometric coefficient	13.6 (± 20.4)	14.1 (± 25.0)		

of variation)

Notes:

[23] - "Number of subjects analyzed"=subjects with available data

[24] - "Number of subjects analyzed"=subjects with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance evaluated for previous FVIII product

End point title	Clearance evaluated for previous FVIII product

End point description:

Total plasma clearance of drug after intravenous administration measured as actual dose/AUC. A chromogenic assay with NHP as calibrator was used. Results were based on FAS.

End point type	Secondary

End point timeframe:

2-6 weeks prior to initial dosing with N8-GP and up to 30 hours after administration of previous FVIII product

End point values	Younger children (0 - 5 years) [Full trial]	Older children (6 - 11 years) [Full trial]		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14[25]	11[26]		
Units: mL/h/kg				
least squares mean (confidence interval 95%)	4.322 (3.404 to 5.486)	3.867 (2.955 to 5.061)		

Notes:

[25] - "Number of subjects analyzed"=subjects with available data

[26] - "Number of subjects analyzed"=subjects with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance evaluated for N8-GP

End point title	Clearance evaluated for N8-GP

End point description:

Total plasma clearance of drug after intravenous administration measured as actual dose/AUC. A chromogenic assay with PSS as calibrator was used. Results were based on FAS.

End point type	Secondary

End point timeframe:

From 1 hour prior to and up to 96 hours after initial administration of N8-GP.

End point values	Younger children (0 - 5 years) [Full trial]	Older children (6 - 11 years) [Full trial]		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	11		
Units: mL/h/kg				
least squares mean (confidence interval 95%)	2.601 (2.030 to 3.333)	2.386 (1.823 to 3.123)		

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 (visit 2) of main phase to end of extension phase (>=4 days after last dose of N8-GP).

Adverse event reporting additional description:

The safety analysis set consists of all patients exposed to at least one dose of N8-GP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Younger children (0-5 years)

Reporting group description:

Subjects (0 - 5 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days). After completion of main phase, subjects could continue until the end of the extension phase, which was defined as LPLV. All subjects continued twice weekly or every third day prophylaxis regimen in extension phase as prescribed for main phase. However, after 12 months treatment with N8-GP (main phase+extension phase) the investigator was permitted to prescribe extra coverage before physical activities.

Reporting group title	Older children (6-11 years)

Reporting group description:

Subjects (6 - 11 years) previously treated with FVIII received N8-GP (prophylaxis or treatment of bleeding episodes). The trial consisted of main and extension phase. Duration of main phase for each subject was approximately 26 weeks (50 exposure days). After completion of main phase, subjects could continue until the end of the extension phase, which was defined as LPLV. All subjects continued twice weekly or every third day prophylaxis regimen in extension phase as prescribed for main phase. However, after 12 months treatment with N8-GP (main phase+extension phase) the investigator was permitted to prescribe extra coverage before physical activities.

Serious adverse events	Younger children (0-5 years)	Older children (6-11 years)	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 34 (32.35%)	5 / 34 (14.71%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			

subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Acquired phimosis			

subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis syndrome			

subjects affected / exposed	1 / 34 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Younger children (0-5 years)	Older children (6-11 years)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 34 (97.06%)	33 / 34 (97.06%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 34 (20.59%)	6 / 34 (17.65%)	
occurrences (all)	16	9	
Hyperthermia			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
Peripheral swelling			
subjects affected / exposed	0 / 34 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	3	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 34 (5.88%)	2 / 34 (5.88%)	
occurrences (all)	2	2	

Food allergy			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	
occurrences (all)	2	4	
Reproductive system and breast disorders			
Penile adhesion			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 34 (41.18%)	6 / 34 (17.65%)	
occurrences (all)	26	6	
Oropharyngeal pain			
subjects affected / exposed	2 / 34 (5.88%)	8 / 34 (23.53%)	
occurrences (all)	2	10	
Rhinorrhoea			
subjects affected / exposed	4 / 34 (11.76%)	3 / 34 (8.82%)	
occurrences (all)	4	4	
Asthma			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	
occurrences (all)	4	1	
Epistaxis			
subjects affected / exposed	4 / 34 (11.76%)	1 / 34 (2.94%)	
occurrences (all)	28	3	
Nasal congestion			
subjects affected / exposed	2 / 34 (5.88%)	2 / 34 (5.88%)	
occurrences (all)	3	2	
Rhinitis allergic			
subjects affected / exposed	3 / 34 (8.82%)	1 / 34 (2.94%)	
occurrences (all)	3	1	
Psychiatric disorders			
Attention deficit/hyperactivity disorder			
subjects affected / exposed	3 / 34 (8.82%)	1 / 34 (2.94%)	
occurrences (all)	3	1	
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	4 / 34 (11.76%)	4 / 34 (11.76%)	
occurrences (all)	4	4	
Joint injury			
subjects affected / exposed	2 / 34 (5.88%)	3 / 34 (8.82%)	
occurrences (all)	2	4	
Ligament sprain			
subjects affected / exposed	0 / 34 (0.00%)	5 / 34 (14.71%)	
occurrences (all)	0	6	
Limb injury			
subjects affected / exposed	5 / 34 (14.71%)	4 / 34 (11.76%)	
occurrences (all)	5	12	
Skin abrasion			
subjects affected / exposed	2 / 34 (5.88%)	3 / 34 (8.82%)	
occurrences (all)	2	4	
Arthropod bite			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
Arthropod sting			
subjects affected / exposed	1 / 34 (2.94%)	3 / 34 (8.82%)	
occurrences (all)	3	3	
Face injury			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	
occurrences (all)	1	3	
Fall			
subjects affected / exposed	5 / 34 (14.71%)	3 / 34 (8.82%)	
occurrences (all)	8	4	
Head injury			
subjects affected / exposed	3 / 34 (8.82%)	4 / 34 (11.76%)	
occurrences (all)	4	5	
Laceration			
subjects affected / exposed	2 / 34 (5.88%)	4 / 34 (11.76%)	
occurrences (all)	2	4	
Nervous system disorders			
Headache			

subjects affected / exposed	5 / 34 (14.71%)	9 / 34 (26.47%)	
occurrences (all)	6	16	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Ear pain			
subjects affected / exposed	4 / 34 (11.76%)	1 / 34 (2.94%)	
occurrences (all)	5	2	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 34 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 34 (14.71%)	2 / 34 (5.88%)	
occurrences (all)	7	2	
Diarrhoea			
subjects affected / exposed	5 / 34 (14.71%)	4 / 34 (11.76%)	
occurrences (all)	7	5	
Nausea			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	9 / 34 (26.47%)	3 / 34 (8.82%)	
occurrences (all)	10	7	
Chapped lips			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	2 / 34 (5.88%)	3 / 34 (8.82%)	
occurrences (all)	2	5	
Dental caries			

subjects affected / exposed	3 / 34 (8.82%)	1 / 34 (2.94%)	
occurrences (all)	5	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 34 (0.00%)	4 / 34 (11.76%)	
occurrences (all)	0	5	
Dermatitis contact			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Eczema			
subjects affected / exposed	2 / 34 (5.88%)	5 / 34 (14.71%)	
occurrences (all)	2	5	
Rash			
subjects affected / exposed	7 / 34 (20.59%)	0 / 34 (0.00%)	
occurrences (all)	11	0	
Dermatitis			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	3	
Erythema			
subjects affected / exposed	3 / 34 (8.82%)	1 / 34 (2.94%)	
occurrences (all)	5	1	
Rash pruritic			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Skin lesion			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Urticaria			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 34 (8.82%)	4 / 34 (11.76%)	
occurrences (all)	4	5	
Pain in extremity			

subjects affected / exposed	5 / 34 (14.71%)	6 / 34 (17.65%)	
occurrences (all)	11	8	
Tendonitis			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Joint swelling			
subjects affected / exposed	3 / 34 (8.82%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	2 / 34 (5.88%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
Gastroenteritis			
subjects affected / exposed	7 / 34 (20.59%)	9 / 34 (26.47%)	
occurrences (all)	10	13	
Influenza			
subjects affected / exposed	5 / 34 (14.71%)	6 / 34 (17.65%)	
occurrences (all)	9	10	
Nasopharyngitis			
subjects affected / exposed	11 / 34 (32.35%)	10 / 34 (29.41%)	
occurrences (all)	21	16	
Pharyngitis			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	
occurrences (all)	2	2	
Rhinitis			
subjects affected / exposed	8 / 34 (23.53%)	4 / 34 (11.76%)	
occurrences (all)	8	7	
Sinusitis			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Tonsillitis			
subjects affected / exposed	2 / 34 (5.88%)	2 / 34 (5.88%)	
occurrences (all)	2	5	
Upper respiratory tract infection			
subjects affected / exposed	10 / 34 (29.41%)	13 / 34 (38.24%)	
occurrences (all)	20	31	

Acute sinusitis			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Bronchitis			
subjects affected / exposed	3 / 34 (8.82%)	3 / 34 (8.82%)	
occurrences (all)	5	3	
Ear infection			
subjects affected / exposed	5 / 34 (14.71%)	3 / 34 (8.82%)	
occurrences (all)	5	5	
Gastroenteritis viral			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Molluscum contagiosum			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
Otitis media			
subjects affected / exposed	4 / 34 (11.76%)	5 / 34 (14.71%)	
occurrences (all)	4	5	
Pharyngitis streptococcal			
subjects affected / exposed	2 / 34 (5.88%)	1 / 34 (2.94%)	
occurrences (all)	2	2	
Pharyngotonsillitis			
subjects affected / exposed	0 / 34 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Pneumonia			
subjects affected / exposed	1 / 34 (2.94%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Varicella			
subjects affected / exposed	6 / 34 (17.65%)	1 / 34 (2.94%)	
occurrences (all)	6	1	
Viral infection			
subjects affected / exposed	4 / 34 (11.76%)	3 / 34 (8.82%)	
occurrences (all)	5	3	
Viral pharyngitis			
subjects affected / exposed	2 / 34 (5.88%)	0 / 34 (0.00%)	
occurrences (all)	2	0	

Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 34 (11.76%) 5	3 / 34 (8.82%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2012	1) Changes introduced to the dose table in order to extend weight predictions. 2) Port restrictions text in connection with blood samplings removed. Included together with detailed instructions for laboratory sampling in other trial documents (e.g., in the laboratory manual). 3) Inconsistencies and typing errors corrected.
11 March 2014	1) Withdrawal criteria amended to allow patients with a low titre inhibitor (≤ 5 BU), that does not result in clinically ineffective treatment with N8-GP, to continue in the trial. 2) Reference unit for inhibitors has been aligned to BU. 3) Lupus anticoagulant added to flowchart main and extension phase. 4) Patients allowed continuing in the extension phase as soon as minimum 25 patients for each cohort had completed the main phase. 5) List of participating countries updated. 6) FVIII results to investigators changed to one-stage clotting assay to align across N8-GP project. 7) Inclusion of an assay to analyse for antibodies towards polyethylene glycol (PEG). 8) Clarification that FVIII activity should be analysed in case of severe allergic reaction. 9) Labelling allowed by third party vendors. 10) Section added: suspected transmission of infectious agents to the serious adverse event (SAE) definition. 11) Extension of monitoring window during extension phase to reflect the visit scheduled. 12) Multiple bleeding from the same event or time point counted as one bleeding episode. 13) Minor updates to the interim analysis
14 April 2014	1) Patients with low titre inhibitors who continue on N8-GP treatment are followed systematically and should attend an unscheduled visit monthly. 2) Novo Nordisk safety committee consulted by the investigator to determine the best management of individual patients with low titre inhibitors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported