Clinical trial results:
A Multi-centre, Single-blind Trial Evaluating Safety and Efficacy, including Pharmacokinetics, of NNC-0156-0000-0009 when used for Treatment and Prophylaxis of Bleeding Episodes in Patients with Haemophilia B

Summary

EudraCT number	2010-023069-24
Trial protocol	FR NL DE GB IT
Global end of trial date	02 April 2013

Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	30 July 2015

Trial information

Trial identification

Sponsor protocol code	NN7999-3747

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01333111
WHO universal trial number (UTN)	U1111-1119-6415

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Global Clinical Registry (GCR, 1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Global Clinical Registry (GCR, 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-000731-PIP01-09
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	18 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 April 2013
Global end of trial reached?	Yes
Global end of trial date	02 April 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the immunogenicity of NNC-0156-0000-0009 (nonacog beta pegol)

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Seoul, October 2008), the 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	29 April 2011
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	Japan: 8
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 4
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	Turkey: 4
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	74
EEA total number of subjects	20

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	18
Adults (18-64 years)	55
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 39 sites in 13 countries, as follows: France: 1 site; Germany: 3 sites; Italy: 2 sites; Japan: 5 sites; Macedonia: 2 sites; Malaysia: 1 site; Netherlands: 1 site; Russia: 2 sites; South Africa: 1 site; Thailand: 2 sites; Turkey: 3 sites; United Kingdom: 4 sites; United States: 12 sites.

Pre-assignment

Screening details:

Not applicable

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Prophylaxis 10 IU/kg

Arm description:

The patients were randomised to either prophylaxis 10 IU/kg or 40 IU/kg arm. Patients enrolled in this arm received 10 IU/kg nonacog beta pegol dose once weekly (every 7th day ± 24 hours). Mild and moderate bleeding episodes were treated with 40 IU/kg. Severe bleeding episodes were treated with 80 IU/kg.

Arm type	Experimental
Investigational medicinal product name	Nonacog beta pegol
Investigational medicinal product code	
Other name	NNC-0156-0000-0009, N9-GP
Pharmaceutical forms	Powder and solvent for solution for injection/skin-prick test
Routes of administration	Intravenous use

Dosage and administration details:

Administration of the appropriate volume of nonacog beta pegol was given as an i.v. bolus injection. The maximum injection rate was 4 mL/min.

Arm title	Prophylaxis 40 IU/kg

Arm description:

The patients were randomised to either prophylaxis 10 IU/kg or 40 IU/kg arm. Patients enrolled in this arm received 40 IU/kg nonacog beta pegol dose once weekly (every 7th day ± 24 hours). Mild and moderate bleeding episodes were treated with 40 IU/kg. Severe bleeding episodes were treated with 80 IU/kg.

Arm type	Experimental
Investigational medicinal product name	Nonacog beta pegol
Investigational medicinal product code	
Other name	NNC-0156-0000-0009, N9-GP
Pharmaceutical forms	Powder and solvent for solution for injection/skin-prick test
Routes of administration	Intravenous use

Dosage and administration details:

Administration of the appropriate volume of nonacog beta pegol was given as an i.v. bolus injection. The maximum injection rate was 4 mL/min.

Arm title	On-demand

Arm description:

Mild and moderate bleeding episodes were treated with 40 IU/kg. Severe bleeding episodes were

treated with 80 IU/kg.

Arm type	Experimental
Investigational medicinal product name	Nonacog beta pegol
Investigational medicinal product code	
Other name	NNC-0156-0000-0009, N9-GP
Pharmaceutical forms	Powder and solvent for solution for injection/skin-prick test
Routes of administration	Intravenous use

Dosage and administration details:

Administration of the appropriate volume of nonacog beta pegol was given as an i.v. bolus injection. The maximum injection rate was 4 mL/min.

Number of subjects in period 1	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	On-demand
Started	30	29	15
Completed	28	26	13
Not completed	2	3	2
Withdrawal criteria	-	1	-
Patient undergoing major surgery	-	2	-
Unclassified	1	-	1
Protocol deviation	1	-	-
Lack of efficacy	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Prophylaxis 10 IU/kg
Reporting group description:	
The patients were randomised to either prophylaxis 10 IU/kg or 40 IU/kg arm. Patients enrolled in this arm received 10 IU/kg nonacog beta pegol dose once weekly (every 7th day ± 24 hours). Mild and moderate bleeding episodes were treated with 40 IU/kg. Severe bleeding episodes were treated with 80 IU/kg.	
Reporting group title	Prophylaxis 40 IU/kg
Reporting group description:	
The patients were randomised to either prophylaxis 10 IU/kg or 40 IU/kg arm. Patients enrolled in this arm received 40 IU/kg nonacog beta pegol dose once weekly (every 7th day ± 24 hours). Mild and moderate bleeding episodes were treated with 40 IU/kg. Severe bleeding episodes were treated with 80 IU/kg.	
Reporting group title	On-demand
Reporting group description:	
Mild and moderate bleeding episodes were treated with 40 IU/kg. Severe bleeding episodes were treated with 80 IU/kg.	

Reporting group values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	On-demand
Number of subjects	30	29	15
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	7	9	2
Adults (18-64 years)	23	19	13
From 65-84 years	0	1	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	32.4	30	32.4
standard deviation	± 13.9	± 15.8	± 12
Gender categorical Units: Subjects			
Female	0	0	0
Male	30	29	15

Reporting group values	Total		
Number of subjects	74		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		

Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	18		
Adults (18-64 years)	55		
From 65-84 years	1		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	0		
Male	74		

End points

End points reporting groups

Reporting group title	Prophylaxis 10 IU/kg

Reporting group description:

The patients were randomised to either prophylaxis 10 IU/kg or 40 IU/kg arm. Patients enrolled in this arm received 10 IU/kg nonacog beta pegol dose once weekly (every 7th day ± 24 hours). Mild and moderate bleeding episodes were treated with 40 IU/kg. Severe bleeding episodes were treated with 80 IU/kg.

Reporting group title	Prophylaxis 40 IU/kg

Reporting group description:

The patients were randomised to either prophylaxis 10 IU/kg or 40 IU/kg arm. Patients enrolled in this arm received 40 IU/kg nonacog beta pegol dose once weekly (every 7th day ± 24 hours). Mild and moderate bleeding episodes were treated with 40 IU/kg. Severe bleeding episodes were treated with 80 IU/kg.

Reporting group title	On-demand

Reporting group description:

Mild and moderate bleeding episodes were treated with 40 IU/kg. Severe bleeding episodes were treated with 80 IU/kg.

Primary: Incidence of inhibitory antibodies against FIX defined as titre ≥0.6 BU

End point title	Incidence of inhibitory antibodies against FIX defined as titre ≥0.6 BU[1]

End point description:

End point type	Primary

End point timeframe:

For the subjects treated with prophylaxis, inhibitory antibodies were assessed for 52 weeks + 4 weeks. For the subjects treated on-demand, inhibitory antibodies were assessed for 28 weeks + 4 weeks.

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: Rate of inhibitory antibodies estimates were based on exact calculations for a binomial distribution. Adequate safety in the total population with regard to inhibitory antibodies was concluded if the observed rate was <= 2% and the upper 1-sided 97.5% confidence limit was <= 10.7%.
Result: No inhibitory antibodies were detected and the 1-sided 97.5% upper confidence limit for the inhibitor incidence rate of 0 was 6%, thus the primary test succeeded as the upper confidence limit was below 10.7%.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	On-demand	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30[2]	28[3]	9[4]	
Units: Patients with inhibitory antibodies	0	0	0	

Notes:

[2] - Any patient with a minimum 10 exposure days plus any patient with inhibitory antibodies is included.
[3] - Any patient with a minimum 10 exposure days plus any patient with inhibitory antibodies is included.
[4] - Any patient with a minimum 10 exposure days plus any patient with inhibitory antibodies is included.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For the subjects treated with prophylaxis, adverse events were assessed for 52 weeks + 4 weeks. For the subjects treated on-demand, adverse events were assessed for 28 weeks + 4 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Prophylaxis 10 IU/kg

Reporting group description:

The patients were randomised to either prophylaxis 10 IU/kg or 40 IU/kg arm. Patients enrolled in this arm received 10 IU/kg nonacog beta pegol dose once weekly (every 7th day ± 24 hours). Mild and moderate bleeding episodes were treated with 40 IU/kg. Severe bleeding episodes were treated with 80 IU/kg.

Reporting group title	Prophylaxis 40 IU/kg

Reporting group description:

The patients were randomised to either prophylaxis 10 IU/kg or 40 IU/kg arm. Patients enrolled in this arm received 40 IU/kg nonacog beta pegol dose once weekly (every 7th day ± 24 hours). Mild and moderate bleeding episodes were treated with 40 IU/kg. Severe bleeding episodes were treated with 80 IU/kg.

Reporting group title	On-demand

Reporting group description:

Mild and moderate bleeding episodes were treated with 40 IU/kg. Severe bleeding episodes were treated with 80 IU/kg.

Serious adverse events	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	On-demand
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 30 (3.33%)	3 / 29 (10.34%)	0 / 15 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	0 / 15 (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			
Abdominal pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	0 / 15 (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

Retroperitoneal haematoma			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	0 / 15 (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 and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	0 / 15 (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

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

Non-serious adverse events	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	On-demand
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 30 (70.00%)	19 / 29 (65.52%)	11 / 15 (73.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 30 (10.00%)	2 / 29 (6.90%)	1 / 15 (6.67%)
occurrences (all)	3	2	1
Pyrexia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 29 (6.90%)	1 / 15 (6.67%)
occurrences (all)	2	4	1
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	0 / 15 (0.00%)
occurrences (all)	0	3	0
Epistaxis			

subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	0 / 15 (0.00%)
occurrences (all)	0	6	0
Oropharyngeal pain			
subjects affected / exposed	0 / 30 (0.00%)	3 / 29 (10.34%)	1 / 15 (6.67%)
occurrences (all)	0	3	1
Rhinorrhoea			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Psychiatric disorders			
Attention deficit/hyperactivity disorder			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Investigations			
C-reactive protein increased			
subjects affected / exposed	4 / 30 (13.33%)	0 / 29 (0.00%)	0 / 15 (0.00%)
occurrences (all)	4	0	0
Prothrombin level increased			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 30 (6.67%)	2 / 29 (6.90%)	1 / 15 (6.67%)
occurrences (all)	2	2	1
Fall			
subjects affected / exposed	1 / 30 (3.33%)	3 / 29 (10.34%)	0 / 15 (0.00%)
occurrences (all)	1	4	0
Laceration			
subjects affected / exposed	1 / 30 (3.33%)	1 / 29 (3.45%)	1 / 15 (6.67%)
occurrences (all)	2	1	1
Overdose			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Thermal burn			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 30 (6.67%)	3 / 29 (10.34%)	2 / 15 (13.33%)
occurrences (all)	2	7	3
Speech disorder developmental			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 29 (6.90%)	0 / 15 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 30 (3.33%)	1 / 29 (3.45%)	1 / 15 (6.67%)
occurrences (all)	1	2	1
Mouth ulceration			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 29 (3.45%)	1 / 15 (6.67%)
occurrences (all)	2	2	2
Back pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 29 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Groin pain			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Myalgia			

subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 30 (0.00%)	3 / 29 (10.34%)	0 / 15 (0.00%)
occurrences (all)	0	3	0
Pain in extremity			
subjects affected / exposed	1 / 30 (3.33%)	3 / 29 (10.34%)	1 / 15 (6.67%)
occurrences (all)	1	3	1
Tendonitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Synovitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Infections and infestations			
Influenza			
subjects affected / exposed	4 / 30 (13.33%)	3 / 29 (10.34%)	1 / 15 (6.67%)
occurrences (all)	4	5	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	7 / 30 (23.33%)	3 / 29 (10.34%)	0 / 15 (0.00%)
occurrences (all)	9	4	0
Paronychia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pharyngotonsillitis			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 30 (10.00%)	3 / 29 (10.34%)	2 / 15 (13.33%)
occurrences (all)	4	4	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 December 2011	Reduced number of physical examinations. Blood samples and tests that were to be taken in case a patient developed a severe allergic reaction related to nonacog beta pegol. All post-dose vital signs assessments were deleted from the flow charts in order to align with the visit descriptions in the protocol. It was specified that unused vials of trial product dispensed to the patient for treatment of bleeding episodes did not need to be returned to the site at each visit. The patient information and consent form were updated based on the changes to the protocol.
11 May 2012	Information on stop time of bleeding episode, on number of months on on-demand treatment and on screening of antibodies was updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable

Notes: