Clinical trial results:
Safety and Efficacy of NNC-0156-0000-0009 after Long-Term Exposure in Patients with Haemophilia B

Summary

EudraCT number	2010-023072-17
Trial protocol	FR GB NL DE IT ES AT GR
Global end of trial date	31 March 2014

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	NN7999-3775

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01395810
WHO universal trial number (UTN)	U1111-1121-5408

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)	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	30 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2014
Global end of trial reached?	Yes
Global end of trial date	31 March 2014
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	16 April 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	Netherlands: 3
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 4
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	Turkey: 4
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	71
EEA total number of subjects	21

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)	15
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 41 sites in 15 countries as follows: France: 1 site; Germany: 3 sites; Italy: 2 sites; Japan: 4 sites; Macedonia: 2 sites; Malaysia: 1 site; Netherlands: 1 site; Romania: 1 site, Russia: 1 site; South Africa: 1 site; Taiwan: 1 site, Thailand: 2 sites; Turkey: 3 sites; United Kingdom: 5 sites; United States: 13 sites.

Pre-assignment

Screening details:

Not applicable

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Prophylaxis 10 IU/kg

Arm description:

Subjects were given 10 IU/kg weekly nonacog beta pegol. Subjects were free to switch between treatment arms if agreed between the investigator and the subject.

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
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:

Subjects were dosed with 40 IU/kg weekly. Subjects were free to switch between treatment arms if agreed between the investigator and the subject.

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
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 80 IU/kg

Arm description:

Subjects were dosed with 80 IU/kg every second week. Subjects were free to switch between treatment arms if agreed between the investigator and the subject.

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
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:

The recommended dose for treatment of a mild or moderate bleeding episode, for example a joint bleed, was a single dose of 40 IU/kg nonacog beta pegol. If there was no observed effect of 40 IU/kg, the investigator was to be contacted prior to administration of the second dose of 40 IU/kg. The recommended dose for treatment of severe bleeds was 80 IU/kg nonacog beta pegol. Subjects were free to switch between treatment arms if agreed between the investigator and the subject.

Arm type	Active comparator
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
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	Prophylaxis 80 IU/kg
Started	21	52	2
Completed	19	48	2
Not completed	2	4	0
Adverse event, non-fatal	-	1	-
Withdrawal criteria	-	2	-
Unclassified	2	-	-
Lack of efficacy	-	1	-

Number of subjects in period 1	On-demand
Started	5
Completed	5
Not completed	0
Adverse event, non-fatal	-
Withdrawal criteria	-
Unclassified	-
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description:

The trial included four different treatment (nonacog beta pegol) arms: three prophylaxis treatment arms with 10 IU/kg or 40 IU/kg weekly, or 80 IU/kg every second week, and one on-demand treatment with single dose of 40 IU/kg.

Reporting group values	Overall study	Total	
Number of subjects	71	71	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	15	15	
Adults (18-64 years)	55	55	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	32		
standard deviation	± 14.2	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	71	71	

End points

End points reporting groups

Reporting group title	Prophylaxis 10 IU/kg

Reporting group description:

Subjects were given 10 IU/kg weekly nonacog beta pegol. Subjects were free to switch between treatment arms if agreed between the investigator and the subject.

Reporting group title	Prophylaxis 40 IU/kg

Reporting group description:

Subjects were dosed with 40 IU/kg weekly. Subjects were free to switch between treatment arms if agreed between the investigator and the subject.

Reporting group title	Prophylaxis 80 IU/kg

Reporting group description:

Subjects were dosed with 80 IU/kg every second week. Subjects were free to switch between treatment arms if agreed between the investigator and the subject.

Reporting group title	On-demand

Reporting group description:

The recommended dose for treatment of a mild or moderate bleeding episode, for example a joint bleed, was a single dose of 40 IU/kg nonacog beta pegol. If there was no observed effect of 40 IU/kg, the investigator was to be contacted prior to administration of the second dose of 40 IU/kg. The recommended dose for treatment of severe bleeds was 80 IU/kg nonacog beta pegol. Subjects were free to switch between treatment arms if agreed between the investigator and the subject.

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:

The primary endpoint was incidence of inhibitors against coagulation factor nine (FIX) defined as titre ≥0.6 Bethesda unit (BU).

End point type	Primary

End point timeframe:

This efficacy endpoint was evaluated based on all available information until the end of trial (EOT) visit.

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: No statistical analysis was planned for the primary endpoint.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	52	2	5[2]
Units: patients with inhibitory antibodies	0	0	0	0

Notes:

[2] - Patients who switched arms are represented in multiple columns.

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic effect of nonacog beta pegol when used for treatment of bleeding episodes.

End point title	Haemostatic effect of nonacog beta pegol when used for treatment of bleeding episodes.

End point description:

The haemostatic effect was evaluated by a four-point scale where an "excellent" or "good" outcome translated into a successful treatment, and a "moderate" / "poor" outcome was considered a treatment failure.

End point type	Secondary

End point timeframe:

Available information until the end of trial (EOT) visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	52	2	5
Units: Number				
Number of bleeding episodes	35	98	1	73
Excellent	16	37	0	5
Good	18	54	1	63
Moderate	1	4	0	4
Poor	0	1	0	1
Missing	0	2	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of bleeding episodes during routine prophylaxis.

End point title	Number of bleeding episodes during routine prophylaxis.

End point description:

End point type	Secondary

End point timeframe:

All available information until the end of trial (EOT) visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	52	2	5
Units: Number				
Number of patients with bleeds	14	31	1	5
Number of bleeding episodes	35	98	1	73

Statistical analyses

No statistical analyses for this end point

Secondary: FIX trough levels

End point title	FIX trough levels[3]

End point description:

During the trial, the mean pre-dose coagulation factor nine (FIX) levels were measured with a one-stage clotting assay.

End point type	Secondary

End point timeframe:

All available information until the EOT visit.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analysed only for the prophylaxis arms (i.e., 10 IU/kg, 40 IU/kg and 80 IU/kg). No trough measurements were collected for patients on 80 IU/kg every second week prophylaxis.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	52		
Units: U/mL				
arithmetic mean (confidence interval 95%)	0.098 (0.08 to 0.119)	0.213 (0.189 to 0.241)		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events (AEs).

End point title	Adverse Events (AEs).

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	52	2	5
Units: Number				
Number of subjects with adverse events	15	32	0	5
Number of adverse events	46	91	0	18

Statistical analyses

No statistical analyses for this end point

Secondary: Serious Adverse Events (SAEs)

End point title	Serious Adverse Events (SAEs)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	52	2	5
Units: Number				
Number of subjects with serious adverse events	1	5	0	0
Number of serious adverse events	1	5	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Platelets (Visit 1- Baseline)

End point title	Laboratory parameter - haematology: Platelets (Visit 1-Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	47	0[4]	5
Units: x10^9/L				
arithmetic mean (standard deviation)	224.7 (± 55.9)	240.5 (± 84.2)	()	240 (± 54.1)

Notes:

[4] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Platelets (End of Trial)

End point title	Laboratory parameter - haematology: Platelets (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	44	2	4
Units: x10^9/L				
arithmetic mean (standard deviation)	230.7 (± 75)	235.3 (± 63.3)	247.3 (± 26.4)	256 (± 78.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Haemoglobin (Visit 1- Baseline)

End point title	Laboratory parameter - haematology: Haemoglobin (Visit 1-Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[5]	5
Units: mmol/L				
arithmetic mean (standard deviation)	9.45 (± 0.61)	8.98 (± 1.06)	()	9.22 (± 0.66)

Notes:

[5] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Haemoglobin (End of Trial)

End point title	Laboratory parameter - haematology: Haemoglobin (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	44	2	4
Units: mmol/L				
arithmetic mean (standard deviation)	9.58 (± 0.6)	9.22 (± 0.73)	10 (± 1.7)	9.65 (± 0.84)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Red blood cell count (Visit 1- Baseline)

End point title	Laboratory parameter - haematology: Red blood cell count (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[6]	5
Units: 10^12/L				
arithmetic mean (standard deviation)	5.18 (± 0.41)	4.96 (± 0.64)	()	4.9 (± 0.5)

Notes:

[6] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Red blood cell count (End of Trial)

End point title	Laboratory parameter - haematology: Red blood cell count (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	44	2	4
Units: 10^12/L				
arithmetic mean (standard deviation)	5.2 (± 0.33)	5.1 (± 0.52)	5.57 (± 0.41)	5.09 (± 0.26)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Mean corpuscular volume (Visit 1- Baseline)

End point title	Laboratory parameter - haematology: Mean corpuscular volume (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[7]	5
Units: fL				
arithmetic mean (standard deviation)	87 (± 4.7)	87.5 (± 7.3)	()	89.7 (± 11.3)

Notes:

[7] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Mean corpuscular volume (End of Trial)

End point title	Laboratory parameter - haematology: Mean corpuscular volume (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	44	2	4
Units: fL				
arithmetic mean (standard deviation)	86.8 (± 4.9)	87.6 (± 6.6)	84.9 (± 5.8)	89.2 (± 6.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Haematocrit (Visit 1- Baseline)

End point title	Laboratory parameter - haematology: Haematocrit (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[8]	5
Units: Percentage (%)				
arithmetic mean (standard deviation)	44.8 (± 2.7)	43.2 (± 4.6)	()	43.6 (± 3)

Notes:

[8] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Haematocrit (End of Trial)

End point title	Laboratory parameter - haematology: Haematocrit (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	44	2	4
Units: Percentage (%)				
arithmetic mean (standard deviation)	45 (± 1.7)	44.4 (± 3.2)	47.4 (± 6.7)	45.3 (± 3.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Mean corpuscular haemoglobin (Visit 1- Baseline)

End point title	Laboratory parameter - haematology: Mean corpuscular haemoglobin (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[9]	5
Units: fmol				
arithmetic mean (standard deviation)	1.83 (± 0.11)	1.82 (± 0.18)	()	1.89 (± 0.26)

Notes:

[9] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Mean corpuscular haemoglobin (End of Trial)

End point title	Laboratory parameter - haematology: Mean corpuscular haemoglobin (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	44	2	4
Units: fmol				
arithmetic mean (standard deviation)	1.85 (± 0.13)	1.82 (± 0.16)	1.79 (± 0.17)	1.9 (± 0.17)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: White blood cell count (Visit 1- Baseline)

End point title	Laboratory parameter - haematology: White blood cell count (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[10]	5
Units: 10^9/L				
arithmetic mean (standard deviation)	6.64 (± 1.75)	6.33 (± 1.54)	()	6.02 (± 0.86)

Notes:

[10] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: White blood cell count (End of Trial)

End point title	Laboratory parameter - haematology: White blood cell count (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	44	2	4
Units: 10^9/L				
arithmetic mean (standard deviation)	6.73 (± 1.67)	6.6 (± 1.74)	6.25 (± 0.63)	6.44 (± 1.59)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Lymphocytes (Visit 1- Baseline)

End point title	Laboratory parameter - haematology: Lymphocytes (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[11]	5
Units: Percentage (%)				
arithmetic mean (standard deviation)	29.8 (± 8)	33.2 (± 7.4)	()	30.1 (± 7.1)

Notes:

[11] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Lymphocytes (End of Trial)

End point title	Laboratory parameter - haematology: Lymphocytes (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	43	2	4
Units: Percentage (%)				
arithmetic mean (standard deviation)	33.3 (± 9.5)	30.7 (± 7.3)	34 (± 5)	31.1 (± 4.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Monocytes (Visit 1- Baseline)

End point title	Laboratory parameter - haematology: Monocytes (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[12]	5
Units: Percentage (%)				
arithmetic mean (standard deviation)	6.88 (± 2.66)	8.2 (± 3.02)	()	6.9 (± 1.88)

Notes:

[12] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Monocytes (End of Trial)

End point title	Laboratory parameter - haematology: Monocytes (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	43	2	4
Units: Percentage (%)				
arithmetic mean (standard deviation)	7.14 (± 1.92)	8.33 (± 2.61)	6.79 (± 3.95)	7.18 (± 1.89)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Neutrophils (Visit 1- Baseline)

End point title	Laboratory parameter - haematology: Neutrophils (Visit 1-Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[13]	5
Units: Percentage (%)				
arithmetic mean (standard deviation)	60.9 (± 10.6)	55.1 (± 7.4)	()	60.3 (± 7.2)

Notes:

[13] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Neutrophils (End of Trial)

End point title	Laboratory parameter - haematology: Neutrophils (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	43	2	4
Units: Percentage (%)				
arithmetic mean (standard deviation)	56.5 (± 11)	57.7 (± 8.9)	56.7 (± 8.1)	59.1 (± 6.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Eosinophils (Visit 1- Baseline)

End point title	Laboratory parameter - haematology: Eosinophils (Visit 1-Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[14]	5
Units: Percentage (%)				
arithmetic mean (standard deviation)	2.26 (± 2.16)	2.91 (± 1.71)	()	2.02 (± 0.71)

Notes:

[14] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Eosinophils (End of Trial)

End point title	Laboratory parameter - haematology: Eosinophils (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	43	2	4
Units: Percentage (%)				
arithmetic mean (standard deviation)	2.46 (± 1.62)	2.78 (± 1.99)	1.21 (± 0.44)	1.8 (± 1.18)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Basophils (Visit 1- Baseline)

End point title	Laboratory parameter - haematology: Basophils (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[15]	5
Units: Percentage (%)				
arithmetic mean (standard deviation)	0.54 (± 0.57)	0.56 (± 0.37)	()	0.44 (± 0.52)

Notes:

[15] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - haematology: Basophils (End of Trial)

End point title	Laboratory parameter - haematology: Basophils (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	43	2	4
Units: Percentage (%)				
arithmetic mean (standard deviation)	0.58 (± 0.48)	0.47 (± 0.39)	0.46 (± 0.06)	0.4 (± 0.49)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Sodium (Visit 1- Baseline)

End point title	Laboratory parameter - biochemistry: Sodium (Visit 1-Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	45	0[16]	5
Units: mmol/L				
arithmetic mean (standard deviation)	141.8 (± 2.3)	141.7 (± 2.6)	()	142.6 (± 3.4)

Notes:

[16] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Sodium (End of Trial)

End point title	Laboratory parameter - biochemistry: Sodium (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	45	2	4
Units: mmol/L				
arithmetic mean (standard deviation)	141.9 (± 2)	141.8 (± 2.9)	142.5 (± 2.1)	143.5 (± 2.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Potassium (Visit 1- Baseline)

End point title	Laboratory parameter - biochemistry: Potassium (Visit 1-Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	45	0[17]	5
Units: mmol/L				
arithmetic mean (standard deviation)	4.2 (± 0.39)	4.25 (± 0.31)	()	4.06 (± 0.36)

Notes:

[17] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Potassium (End of Trial)

End point title	Laboratory parameter - biochemistry: Potassium (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	44	2	4
Units: mmol/L				
arithmetic mean (standard deviation)	4.25 (± 0.35)	4.29 (± 0.26)	4.25 (± 0.21)	4.08 (± 0.43)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Creatinine (Visit 1- Baseline)

End point title	Laboratory parameter - biochemistry: Creatinine (Visit 1-Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	45	0[18]	5
Units: µmol/L				
arithmetic mean (standard deviation)	73.2 (± 8.8)	74.2 (± 17)	()	74 (± 6.5)

Notes:

[18] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Creatinine (End of Trial)

End point title	Laboratory parameter - biochemistry: Creatinine (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	45	2	4
Units: µmol/L				
arithmetic mean (standard deviation)	76.8 (± 13.7)	80.6 (± 19.6)	68.5 (± 16.3)	71.5 (± 13.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Albumin (Visit 1- Baseline)

End point title	Laboratory parameter - biochemistry: Albumin (Visit 1-Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	45	0[19]	5
Units: g/L				
arithmetic mean (standard deviation)	47.8 (± 2.8)	46.2 (± 4.7)	()	47.4 (± 1.8)

Notes:

[19] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Albumin (End of Trial)

End point title	Laboratory parameter - biochemistry: Albumin (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	45	2	4
Units: g/L				
arithmetic mean (standard deviation)	45.6 (± 2.8)	46.5 (± 2.9)	48 (± 0)	47.3 (± 3)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Total bilirubin (Visit 1- Baseline)

End point title	Laboratory parameter - biochemistry: Total bilirubin (Visit 1-Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	45	0[20]	5
Units: µmol/L				
arithmetic mean (standard deviation)	9.8 (± 5.9)	10.8 (± 11.3)	()	11.2 (± 1.8)

Notes:

[20] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Total bilirubin (End of Trial)

End point title	Laboratory parameter - biochemistry: Total bilirubin (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	45	2	4
Units: µmol/L				
arithmetic mean (standard deviation)	9.8 (± 6.2)	9.5 (± 5.5)	8 (± 1.4)	8.3 (± 1.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Aspartate aminotransferase (ASAT) (Visit 1- Baseline)

End point title	Laboratory parameter - biochemistry: Aspartate aminotransferase (ASAT) (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	45	0[21]	5
Units: IU/L				
arithmetic mean (standard deviation)	24.4 (± 7.8)	32.3 (± 27.8)	()	25.8 (± 9.1)

Notes:

[21] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Aspartate aminotransferase (ASAT) (End of Trial)

End point title	Laboratory parameter - biochemistry: Aspartate aminotransferase (ASAT) (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	44	2	4
Units: IU/L				
arithmetic mean (standard deviation)	25.5 (± 12.3)	30.6 (± 30.8)	17.5 (± 0.7)	24.8 (± 6.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Alanine aminotransferase (ALAT) (Visit 1- Baseline)

End point title	Laboratory parameter - biochemistry: Alanine aminotransferase (ALAT) (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	45	0[22]	5
Units: IU/L				
arithmetic mean (standard deviation)	25.3 (± 15.1)	36.8 (± 45.7)	()	25.6 (± 14.7)

Notes:

[22] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Alanine aminotransferase (ALAT) (End of Trial)

End point title	Laboratory parameter - biochemistry: Alanine aminotransferase (ALAT) (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	45	2	4
Units: IU/L				
arithmetic mean (standard deviation)	27.3 (± 19)	31.9 (± 33.1)	14.5 (± 4.9)	32.8 (± 11.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Gamma glutamyltransferase (GGT) (Visit 1- Baseline)

End point title	Laboratory parameter - biochemistry: Gamma glutamyltransferase (GGT) (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	45	0[23]	5
Units: IU/L				
arithmetic mean (standard deviation)	28.9 (± 19.1)	46.2 (± 58.3)	()	39.8 (± 44.2)

Notes:

[23] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Gamma glutamyltransferase (GGT) (End of Trial)

End point title	Laboratory parameter - biochemistry: Gamma glutamyltransferase (GGT) (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	45	2	4
Units: IU/L				
arithmetic mean (standard deviation)	44.1 (± 48.2)	38 (± 51.6)	26 (± 21.2)	33 (± 16)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Alkaline phosphatase (Visit 1- Baseline)

End point title	Laboratory parameter - biochemistry: Alkaline phosphatase (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	45	0[24]	5
Units: IU/L				
arithmetic mean (standard deviation)	82.2 (± 30.8)	101 (± 55)	()	79.2 (± 16)

Notes:

[24] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: Alkaline phosphatase (End of Trial)

End point title	Laboratory parameter - biochemistry: Alkaline phosphatase (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	44	2	4
Units: IU/L				
arithmetic mean (standard deviation)	77.3 (± 25.1)	89.6 (± 33.2)	106 (± 52.3)	75.3 (± 17.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: C-reactive protein (Visit 1-Baseline)

End point title	Laboratory parameter - biochemistry: C-reactive protein (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	45	0[25]	5
Units: mg/L				
arithmetic mean (standard deviation)	3.14 (± 5.22)	5.52 (± 19.01)	()	2.7 (± 2.77)

Notes:

[25] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory parameter - biochemistry: C-reactive protein (End of Trial)

End point title	Laboratory parameter - biochemistry: C-reactive protein (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	45	2	4
Units: mg/L				
arithmetic mean (standard deviation)	2.75 (± 4.76)	2.47 (± 3.4)	2.75 (± 3.18)	2.5 (± 1.29)

Statistical analyses

No statistical analyses for this end point

Secondary: Physical examination - deterioration of pre-existing condition or new finding (Visit 2)

End point title	Physical examination - deterioration of pre-existing condition or new finding (Visit 2)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	14	0[26]	1
Units: Number				
New Finding: Yes	0	1		1
New Finding: No	0	9		0
Not applicable	2	1		0
Not done	1	3		0

Notes:

[26] - For this endpoint (at Visit 2), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Physical examination - deterioration of pre-existing condition or new finding (End of Trial)

End point title	Physical examination - deterioration of pre-existing condition or new finding (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	46	2	4
Units: Number				
New Finding: Yes	0	2	0	1
New Finding: No	16	44	2	3

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs: Systolic blood pressure (Visit 1- Baseline)

End point title	Vital signs: Systolic blood pressure (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[27]	5
Units: mmHg				
arithmetic mean (standard deviation)	125.8 (± 8.4)	118.3 (± 9.4)	()	124 (± 23)

Notes:

[27] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs: Systolic blood pressure (End of Trial)

End point title	Vital signs: Systolic blood pressure (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	46	2	4
Units: mmHg				
arithmetic mean (standard deviation)	129.3 (± 13)	123.5 (± 8.8)	105 (± 7.1)	130 (± 23)

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs: Diastolic blood pressure (Visit 1- Baseline)

End point title	Vital signs: Diastolic blood pressure (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[28]	5
Units: mmHg				
arithmetic mean (standard deviation)	77.8 (± 10)	74.1 (± 9.8)	()	75.4 (± 14)

Notes:

[28] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs: Diastolic blood pressure (End of Trial)

End point title	Vital signs: Diastolic blood pressure (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	46	2	4
Units: mmHg				
arithmetic mean (standard deviation)	78.1 (± 12)	74.5 (± 11)	70 (± 14)	84.8 (± 12)

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs: Pulse (Visit 1- Baseline)

End point title	Vital signs: Pulse (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[29]	5
Units: beats/min				
arithmetic mean (standard deviation)	76.2 (± 10)	73.1 (± 10)	()	67.2 (± 11)

Notes:

[29] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs: Pulse (End of Trial)

End point title	Vital signs: Pulse (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	46	2	4
Units: beats/min				
arithmetic mean (standard deviation)	75 (± 11)	77.2 (± 13)	71 (± 1.4)	70.8 (± 7)

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs: Respiratory rate (Visit 1- Baseline)

End point title	Vital signs: Respiratory rate (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[30]	5
Units: breaths/min				
arithmetic mean (standard deviation)	16.7 (± 3.2)	17 (± 2.4)	()	19.2 (± 1.8)

Notes:

[30] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs: Respiratory rate (End of Trial)

End point title	Vital signs: Respiratory rate (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	46	2	4
Units: breaths/min				
arithmetic mean (standard deviation)	17 (± 2.3)	16.8 (± 2.4)	19 (± 4.2)	18 (± 2.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs: Body temperature (Visit 1- Baseline)

End point title	Vital signs: Body temperature (Visit 1- Baseline)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	48	0[31]	5
Units: Celsius (C)				
arithmetic mean (standard deviation)	36.6 (± 0.4)	36.5 (± 0.4)	()	36.6 (± 0.5)

Notes:

[31] - For this endpoint (at Visit 1), no subjects were analysed in prophylaxis 80 IU/kg treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs: Body temperature (End of Trial)

End point title	Vital signs: Body temperature (End of Trial)

End point description:

End point type	Secondary

End point timeframe:

All available information until the last visit.

End point values	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg	On-demand
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	46	2	4
Units: Celsius (C)				
arithmetic mean (standard deviation)	36.6 (± 0.4)	36.5 (± 0.4)	36.1 (± 0.1)	36.7 (± 0.5)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
AEs from baseline visit (visit 1) and until one week after last treatment with nonacog beta pegol (±2 days)	
Adverse event reporting additional description:	
The safety analysis set consists of all patients exposed to nonacog beta pegol.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Prophylaxis 10 IU/kg
Reporting group description:	
Patients were given 10 IU/kg weekly nonacog beta pegol.	
Reporting group title	Prophylaxis 40 IU/kg
Reporting group description:	
Patients were dosed with 40 IU/kg weekly nonacog beta pegol.	
Reporting group title	Prophylaxis 80 IU/kg
Reporting group description:	
Patients were dosed with 80 IU/kg every second week.	
Reporting group title	On-demand
Reporting group description:	
The recommended dose for treatment of a mild or moderate bleeding episode, for example a joint bleed, was a single dose of 40 IU/kg nonacog beta pegol. If there was no observed effect of 40 IU/kg, the investigator was to be contacted prior to administration of the second dose of 40 IU/kg. The recommended dose for treatment of severe bleeds was 80 IU/kg nonacog beta pegol.	

Serious adverse events	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)	5 / 52 (9.62%)	0 / 2 (0.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 21 (0.00%)	1 / 52 (1.92%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			

subjects affected / exposed	0 / 21 (0.00%)	1 / 52 (1.92%)	0 / 2 (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
Road traffic accident			
subjects affected / exposed	0 / 21 (0.00%)	1 / 52 (1.92%)	0 / 2 (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
General disorders and administration site conditions			
Local swelling			
subjects affected / exposed	0 / 21 (0.00%)	1 / 52 (1.92%)	0 / 2 (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			
Faecaloma			
subjects affected / exposed	1 / 21 (4.76%)	0 / 52 (0.00%)	0 / 2 (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			
Gastroenteritis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 52 (1.92%)	0 / 2 (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
Post procedural infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 52 (1.92%)	0 / 2 (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

Serious adverse events	On-demand		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Local swelling			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Faecaloma			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural infection			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Prophylaxis 10 IU/kg	Prophylaxis 40 IU/kg	Prophylaxis 80 IU/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 21 (38.10%)	8 / 52 (15.38%)	0 / 2 (0.00%)
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 21 (0.00%)	3 / 52 (5.77%)	0 / 2 (0.00%)
occurrences (all)	0	5	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 21 (0.00%)	0 / 52 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 21 (9.52%)	1 / 52 (1.92%)	0 / 2 (0.00%)
occurrences (all)	2	2	0
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 21 (4.76%)	1 / 52 (1.92%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 52 (1.92%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Chest discomfort			
subjects affected / exposed	0 / 21 (0.00%)	0 / 52 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Swelling			
subjects affected / exposed	0 / 21 (0.00%)	0 / 52 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Asthenopia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 52 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	2 / 21 (9.52%)	0 / 52 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 21 (9.52%)	1 / 52 (1.92%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 21 (0.00%)	0 / 52 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Libido decreased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 52 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Joint range of motion decreased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 52 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 21 (0.00%)	0 / 52 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 21 (14.29%)	4 / 52 (7.69%)	0 / 2 (0.00%)
occurrences (all)	5	5	0
Influenza			
subjects affected / exposed	4 / 21 (19.05%)	0 / 52 (0.00%)	0 / 2 (0.00%)
occurrences (all)	6	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 52 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 52 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 52 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	On-demand		

Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 5 (100.00%)		
Injury, poisoning and procedural complications Ligament sprain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
General disorders and administration site conditions Influenza like illness subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Chest discomfort subjects affected / exposed occurrences (all) Swelling subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 3 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Eye disorders Asthenopia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Gastrointestinal disorders Dental caries subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Psychiatric disorders			
Libido decreased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Joint range of motion decreased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	3		
Bronchitis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 December 2011	Linguistic revision to one of the stopping rules. Protocol updated on a few operational issues and inconsistencies.
11 May 2012	Changes in the visual appearance of the trial product. Information on stop time of bleeding episode. Information on number of months on on-demand treatment.
05 April 2013	Austria, Greece, Latvia, Lithuania and Romania were added to the trial.
05 April 2013	Implementation of a fourth treatment option (80 IU/kg every second week).
23 July 2013	The protocol was updated due to temporary trial product treatment arm restrictions.
27 September 2013	The protocol was updated due to shortening of trial and temporary restrictions had been permanent.

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: