Clinical trial results:
Safety and Efficacy of Turoctocog Alfa in Prevention and On-demand Treatment of Bleeding Episodes in Subjects with Haemophilia A

Sub-trial:
Efficacy and Safety of Turoctocog Alfa in Prevention and Treatment of Bleeding During Surgical Procedures in Subjects with Haemophilia A

Summary

EudraCT number	2008-005945-46
Trial protocol	DE ES IT GB PL LT LV
Global end of trial date	30 June 2016

Results information

Result version number	v1 (current)
This version publication date	07 January 2017
First version publication date	07 January 2017

Trial information

Trial identification

Sponsor protocol code	NN7008-3568

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00984126
WHO universal trial number (UTN)	U1111-1111-9377
Other trial identifiers	Japanese trial registration: JapicCTI-101357

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-000428-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2016
Global end of trial reached?	Yes
Global end of trial date	30 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety of turoctocog alfa for prevention (only applicable for subjects in the preventive regimen) and treatment of bleeds.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996).

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	27 October 2009
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	Brazil: 26
Country: Number of subjects enrolled	Croatia: 14
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Latvia: 8
Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 5
Country: Number of subjects enrolled	Malaysia: 12
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Serbia: 24
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Taiwan: 5

Country: Number of subjects enrolled	Turkey: 16
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 31
Worldwide total number of subjects	213
EEA total number of subjects	60

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)	1
Children (2-11 years)	52
Adolescents (12-17 years)	24
Adults (18-64 years)	136
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The subjects were enrolled at 52 sites in 19 countries:Brazil (4 sites), Croatia (2), Germany (3), Israel (1), Italy (2), Japan (5), Latvia (1), Lithuania (1), Macedonia (1), Malaysia (1), Poland (2), Russian Federation (2), Serbia (5), Spain (2), Switzerland (1), Taiwan (1), Turkey (5), the United Kingdom (1) and the United States (12).

Pre-assignment

Screening details:

Subjects completing 1 of the trials NN7008-3543 (2008-003960-20),NN7008-3545 (2009-016383-36),NN7008-3600,NN7008-3893 (2010-023921-39) and NN7008-4015 (2012-001444-21) could continue treatment with turoctocog alfa in the extension trial (NN7008-3568). Both new subjects and those from the main trial (NN7008-3568) could enter the on-demand sub-trial.

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	Small children (0 - <6 years)

Arm description:

Subjects (0-<6 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during the trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen. Preventive: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg once every third day or twice weekly. On-Demand: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in the relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in the relevant country. The maximum treatment duration (27 Oct 2009 - 30 Jun 2016)

Arm type	Experimental
Investigational medicinal product name	Turoctocog alfa
Investigational medicinal product code	
Other name	Recombinant Factor VIII
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Turoctocog alfa was administered as a slow iv bolus injection at a rate of approximately 2 mL/min for all preventive doses and bleed treatments. Preventive regimen: Subjects received turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day, 20−60 IU/kg three times weekly or 40−60 IU/kg BW once every third day or twice weekly. On-Demand regimen: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for the treatment of bleeds as they occurred and occasionally as preventive treatment.

Arm title	Older children (6 - <12 years)

Arm description:

Subjects (6-<12 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen. Preventive: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg BW once every third day or twice weekly. On-Demand: Dose level

aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. The maximum treatment duration (27 Oct 2009 - 30 Jun 2016)

Arm type	Experimental
Investigational medicinal product name	Turoctocog alfa
Investigational medicinal product code	
Other name	Recombinant Factor VIII
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Turoctocog alfa was administered as a slow iv bolus injection at a rate of approximately 2 mL/min for all preventive doses and bleed treatments. Preventive regimen: Subjects received turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day, 20−60 IU/kg three times weekly or 40−60 IU/kg BW once every third day or twice weekly. On-Demand regimen: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for the treatment of bleeds as they occurred and occasionally as preventive treatment.

Arm title	Adolescents (12 - <18 years)

Arm description:

Subjects (12-<18 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen.Preventive regimen: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg once every third day or twice weekly.On-Demand: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. The maximum treatment duration (27 Oct 2009 - 30 Jun 2016)

Arm type	Experimental
Investigational medicinal product name	Turoctocog alfa
Investigational medicinal product code	
Other name	Recombinant Factor VIII
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Turoctocog alfa was administered as a slow iv bolus injection at a rate of approximately 2 mL/min for all preventive doses and bleed treatments. Preventive regimen: Subjects received turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day, 20−60 IU/kg three times weekly or 40−60 IU/kg BW once every third day or twice weekly. On-Demand regimen: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for the treatment of bleeds as they occurred and occasionally as preventive treatment.

Arm title	Adults (≥18 years)

Arm description:

Subjects (≥18 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen. Preventive regimen: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg once every third day or twice weekly. On-Demand: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. The maximum treatment duration (27 Oct 2009 - 30 Jun 2016)

Arm type	Experimental

Investigational medicinal product name	Turoctocog alfa
Investigational medicinal product code	
Other name	Recombinant Factor VIII
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Turoctocog alfa was administered as a slow iv bolus injection at a rate of approximately 2 mL/min for all preventive doses and bleed treatments. Preventive regimen: Subjects received turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day, 20−60 IU/kg three times weekly or 40−60 IU/kg BW once every third day or twice weekly. On-Demand regimen: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for the treatment of bleeds as they occurred and occasionally as preventive treatment.

Number of subjects in period 1	Small children (0 - <6 years)	Older children (6 - <12 years)	Adolescents (12 - <18 years)
Started	27	28	23
Completed	20	20	16
Not completed	7	8	7
Adverse event, non-fatal	-	-	-
Withdrawal criteria	-	1	3
Choose to join Pathfinder trial™ + other	7	7	3
Protocol deviation	-	-	1

Number of subjects in period 1	Adults (≥18 years)
Started	135
Completed	76
Not completed	59
Adverse event, non-fatal	2
Withdrawal criteria	9
Choose to join Pathfinder trial™ + other	46
Protocol deviation	2

Baseline characteristics

Reporting groups

Reporting group title	Small children (0 - <6 years)

Reporting group description:

Subjects (0-<6 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during the trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen. Preventive: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg once every third day or twice weekly. On-Demand: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in the relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in the relevant country. The maximum treatment duration (27 Oct 2009 - 30 Jun 2016)

Reporting group title	Older children (6 - <12 years)

Reporting group description:

Subjects (6-<12 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen. Preventive: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg BW once every third day or twice weekly. On-Demand: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. The maximum treatment duration (27 Oct 2009 - 30 Jun 2016)

Reporting group title	Adolescents (12 - <18 years)

Reporting group description:

Subjects (12-<18 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen.Preventive regimen: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg once every third day or twice weekly.On-Demand: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. The maximum treatment duration (27 Oct 2009 - 30 Jun 2016)

Reporting group title	Adults (≥18 years)

Reporting group description:

Subjects (≥18 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen. Preventive regimen: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg once every third day or twice weekly. On-Demand: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. The maximum treatment duration (27 Oct 2009 - 30 Jun 2016)

Reporting group values	Small children (0 - <6 years)	Older children (6 - <12 years)	Adolescents (12 - <18 years)
Number of subjects	27	28	23
Age Categorical Units: Subjects			
Small children (0 - <6 years)	27	0	0
Older children (6 - <12 Years)	0	28	0

Adolescents (12 - <18 Years)	0	0	23
Adults (≥18 Years)	0	0	0

Age Continuous			
Units: years			
arithmetic mean	4.6	9	14.9
standard deviation	± 1.4	± 1.8	± 1.7
Gender Categorical			
Units: Subjects			
Female	0	0	0
Male	27	28	23

Reporting group values	Adults (≥18 years)	Total	
Number of subjects	135	213	
Age Categorical			
Units: Subjects			
Small children (0 - <6 years)	0	27	
Older children (6 - <12 Years)	0	28	
Adolescents (12 - <18 Years)	0	23	
Adults (≥18 Years)	135	135	
Age Continuous			
Units: years			
arithmetic mean	32		
standard deviation	± 11.5	-	
Gender Categorical			
Units: Subjects			
Female	0	0	
Male	135	213	

Subject analysis sets

Subject analysis set title	Small children (0 - <6 years)-Preventive regimen [Main trial]
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (0-<6 years) in main trial received turoctocog alfa (Preventive regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. However during on-demand sub-trial, it was not possible for new subjects to switch to another regimen, subjects who did not comply with on-demand treatment regimen were to be withdrawn. Subjects coming from main trial were allowed to switch back to main trial before completion of 6 months on-demand treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or trial site was terminated by Novo Nordisk or relevant authority for any reason in relevant country. Maximum treatment duration (27 Oct 2009–30 Jun 2016). Preventive regimen: Turoctocog alfa as slow iv bolus injection 20−50 IU/kg once every second day, 20−60 IU/kg 3 times weekly or 40−60 IU/kg once every third day or twice weekly

Subject analysis set title	Older children (6 - <12 years)-Preventive regimen [Main trial]
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (6-<12 years) in main trial received turoctocog alfa (Preventive regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. However during on-demand sub-trial, it was not possible for new subjects to switch to another regimen, subjects who did not comply with on-demand treatment regimen were to be withdrawn. Subjects coming from main trial were allowed to switch back to main trial before completion of 6 months on-demand treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. Maximum treatment duration (27 Oct 2009 – 30 Jun 2016). Preventive regimen: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second

day, 20−60 IU/kg three times weekly or 40−60 IU/kg once every third day or twice weekly.

Subject analysis set title	Adolescents (12 - <18 years) - Preventive regimen [Main trial]
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (12-<18 years) in main trial received turoctocog alfa (Preventive regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. However during on-demand sub-trial, it was not possible for new subjects to switch to another regimen, subjects who did not comply with on-demand treatment regimen were to be withdrawn. Subjects coming from main trial were allowed to switch back to main trial before completion of 6 months on-demand treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. Maximum treatment duration (27 Oct 2009 – 30 Jun 2016). Preventive regimen: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day, 20−60 IU/kg three times weekly or 40−60 IU/kg once every third day or twice weekly.

Subject analysis set title	Adults (>= 18 years) - Preventive regimen [Main trial]
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (>=18 years) in main trial received turoctocog alfa (Preventive regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. However during on-demand sub-trial, it was not possible for new subjects to switch to another regimen, subjects who did not comply with on-demand treatment regimen were to be withdrawn. Subjects coming from main trial were allowed to switch back to main trial before completion of 6 months on-demand treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. Maximum treatment duration (27 Oct 2009 – 30 Jun 2016). Preventive regimen: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day, 20−60 IU/kg three times weekly or 40−60 IU/kg once every third day or twice weekly.

Subject analysis set title	Adolescents (12-<18 years)-(On-Demand regimen [Main trial])
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (12-<18 Years) in main trial received turoctocog alfa (on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. However during on-demand sub-trial, it was not possible for new subjects to switch to another regimen, subjects who did not comply with on-demand treatment regimen were to be withdrawn. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. Maximum treatment duration (27 Oct 2009–30 Jun 2016). On-Demand regimen: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment.

Subject analysis set title	Adults (>=18 years)-(On-Demand regimen [Main trial])
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (≥18 Years) in main trial received turoctocog alfa (on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. However during on-demand sub-trial, it was not possible for new subjects to switch to another regimen, subjects who did not comply with on-demand treatment regimen were to be withdrawn. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. Maximum treatment duration (27 Oct 2009 – 30 Jun 2016). On-Demand regimen: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment.

Subject analysis set title	Adults (>=18 years)-(On-Demand regimen [Sub-trial])
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (≥18 Years) in sub-trial received turoctocog alfa (on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. However during on-demand sub-trial, it was not possible for new subjects to switch to another regimen, subjects who did not comply with on-demand treatment regimen were to be withdrawn. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority

for any reason in relevant country. Maximum treatment duration (27 Oct 2009 – 30 Jun 2016). On-Demand regimen: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment.

Subject analysis set title	Surgery sub-trial
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who had possibility to undergo major and minor surgery were included in the surgery sub-trial. Either bolus and continuous infusion with turoctocog alfa were chosen during surgery. However, continuous infusion was selected only if subjects were scheduled for major elective surgery and if the centre had experience with the use of continuous infusion. All subjects received a preoperative loading dose of turoctocog alfa immediately prior to the surgical procedure. The dose was chosen according to the standard practice at the centre. Switching regimens from continuous infusion to bolus administration was possible at the investigator's discretion during the surgery period.

Reporting group values	Small children (0 - <6 years)- Preventive regimen [Main trial]	Older children (6 - <12 years)- Preventive regimen [Main trial]	Adolescents (12 - <18 years) - Preventive regimen [Main trial]
Number of subjects	27	28	23
Age Categorical Units: Subjects			
Small children (0 - <6 years) Older children (6 - <12 Years) Adolescents (12 - <18 Years) Adults (≥18 Years)			
Age Continuous Units: years arithmetic mean standard deviation	±	±	±
Gender Categorical Units: Subjects			
Female	0	0	0
Male	27	28	23

Reporting group values	Adults (>= 18 years) - Preventive regimen [Main trial]	Adolescents (12-<18 years)-(On-Demand regimen [Main trial])	Adults (>=18 years)-(On-Demand regimen [Main trial])
Number of subjects	129	1	8
Age Categorical Units: Subjects			
Small children (0 - <6 years) Older children (6 - <12 Years) Adolescents (12 - <18 Years) Adults (≥18 Years)			
Age Continuous Units: years arithmetic mean standard deviation	±	±	±
Gender Categorical Units: Subjects			
Female	0	0	0
Male	129	1	8

Reporting group values	Adults (>=18 years)-(On-Demand regimen [Sub-trial])	Surgery sub-trial	

Number of subjects	14	17	
Age Categorical Units: Subjects			
Small children (0 - <6 years) Older children (6 - <12 Years) Adolescents (12 - <18 Years) Adults (≥18 Years)			
Age Continuous Units: years arithmetic mean standard deviation	±	±	
Gender Categorical Units: Subjects			
Female Male	0 14		

End points reporting groups

Reporting group title	Small children (0 - <6 years)

Reporting group description:

Subjects (0-<6 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during the trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen. Preventive: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg once every third day or twice weekly. On-Demand: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in the relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in the relevant country. The maximum treatment duration (27 Oct 2009 - 30 Jun 2016)

Reporting group title	Older children (6 - <12 years)

Reporting group description:

Subjects (6-<12 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen. Preventive: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg BW once every third day or twice weekly. On-Demand: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. The maximum treatment duration (27 Oct 2009 - 30 Jun 2016)

Reporting group title	Adolescents (12 - <18 years)

Reporting group description:

Subjects (12-<18 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen.Preventive regimen: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg once every third day or twice weekly.On-Demand: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. The maximum treatment duration (27 Oct 2009 - 30 Jun 2016)

Reporting group title	Adults (≥18 years)

Reporting group description:

Subjects (≥18 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen. Preventive regimen: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg once every third day or twice weekly. On-Demand: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. The maximum treatment duration (27 Oct 2009 - 30 Jun 2016)

Subject analysis set title	Small children (0 - <6 years)-Preventive regimen [Main trial]
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (0-<6 years) in main trial received turoctocog alfa (Preventive regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. However during on-demand sub-trial, it was not possible for new subjects to switch to another regimen, subjects who did not comply with on-demand treatment regimen were to be withdrawn. Subjects coming from main trial were allowed to switch back to main trial before completion of 6 months on-demand treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or trial site was terminated by Novo Nordisk or relevant authority for any reason in relevant country. Maximum treatment duration (27 Oct 2009–30 Jun 2016).

Preventive regimen: Turoctocog alfa as slow iv bolus injection 20−50 IU/kg once every second day, 20−60 IU/kg 3 times weekly or 40−60 IU/kg once every third day or twice weekly

Subject analysis set title	Older children (6 - <12 years)-Preventive regimen [Main trial]
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (6-<12 years) in main trial received turoctocog alfa (Preventive regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. However during on-demand sub-trial, it was not possible for new subjects to switch to another regimen, subjects who did not comply with on-demand treatment regimen were to be withdrawn. Subjects coming from main trial were allowed to switch back to main trial before completion of 6 months on-demand treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. Maximum treatment duration (27 Oct 2009 – 30 Jun 2016). Preventive regimen: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day, 20−60 IU/kg three times weekly or 40−60 IU/kg once every third day or twice weekly.

Subject analysis set title	Adolescents (12 - <18 years) - Preventive regimen [Main trial]
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (12-<18 years) in main trial received turoctocog alfa (Preventive regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. However during on-demand sub-trial, it was not possible for new subjects to switch to another regimen, subjects who did not comply with on-demand treatment regimen were to be withdrawn. Subjects coming from main trial were allowed to switch back to main trial before completion of 6 months on-demand treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. Maximum treatment duration (27 Oct 2009 – 30 Jun 2016). Preventive regimen: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day, 20−60 IU/kg three times weekly or 40−60 IU/kg once every third day or twice weekly.

Subject analysis set title	Adults (>= 18 years) - Preventive regimen [Main trial]
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (>=18 years) in main trial received turoctocog alfa (Preventive regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. However during on-demand sub-trial, it was not possible for new subjects to switch to another regimen, subjects who did not comply with on-demand treatment regimen were to be withdrawn. Subjects coming from main trial were allowed to switch back to main trial before completion of 6 months on-demand treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. Maximum treatment duration (27 Oct 2009 – 30 Jun 2016). Preventive regimen: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day, 20−60 IU/kg three times weekly or 40−60 IU/kg once every third day or twice weekly.

Subject analysis set title	Adolescents (12-<18 years)-(On-Demand regimen [Main trial])
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (12-<18 Years) in main trial received turoctocog alfa (on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. However during on-demand sub-trial, it was not possible for new subjects to switch to another regimen, subjects who did not comply with on-demand treatment regimen were to be withdrawn. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. Maximum treatment duration (27 Oct 2009–30 Jun 2016). On-Demand regimen: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment.

Subject analysis set title	Adults (>=18 years)-(On-Demand regimen [Main trial])
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (≥18 Years) in main trial received turoctocog alfa (on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. However during on-demand sub-trial, it was not possible for new subjects to switch to another regimen, subjects who did not comply with on-demand treatment regimen were to be withdrawn. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant

country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. Maximum treatment duration (27 Oct 2009 – 30 Jun 2016). On-Demand regimen: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment.

Subject analysis set title	Adults (>=18 years)-(On-Demand regimen [Sub-trial])
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects (≥18 Years) in sub-trial received turoctocog alfa (on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. However during on-demand sub-trial, it was not possible for new subjects to switch to another regimen, subjects who did not comply with on-demand treatment regimen were to be withdrawn. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. Maximum treatment duration (27 Oct 2009 – 30 Jun 2016). On-Demand regimen: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment.

Subject analysis set title	Surgery sub-trial
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who had possibility to undergo major and minor surgery were included in the surgery sub-trial. Either bolus and continuous infusion with turoctocog alfa were chosen during surgery. However, continuous infusion was selected only if subjects were scheduled for major elective surgery and if the centre had experience with the use of continuous infusion. All subjects received a preoperative loading dose of turoctocog alfa immediately prior to the surgical procedure. The dose was chosen according to the standard practice at the centre. Switching regimens from continuous infusion to bolus administration was possible at the investigator's discretion during the surgery period.

Primary: Frequency of development of FVIII inhibitors (≥0.6 BU/mL)

End point title	Frequency of development of FVIII inhibitors (≥0.6 BU/mL)

End point description:

The frequency of inhibitors was calculated as number of patients with inhibitors during the trial divided by number of patients in the trial. This endpoint was measured during the trial.

End point type	Primary

End point timeframe:

After 90 months

End point values	Small children (0 - <6 years)	Older children (6 - <12 years)	Adolescents (12 - <18 years)	Adults (≥18 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	28	23	135
Units: Proportion of subjects	0	0	0	0

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

A one-sided 95% upper confidence limit was based on an exact calculation for a binomial distribution.

Comparison groups	Small children (0 - <6 years) v Older children (6 - <12 years) v Adolescents (12 - <18 years) v Adults (≥18 years)

Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Incidence rate
Point estimate	0
Confidence interval	
level	95 %
sides	1-sided
upper limit	1.4

Primary: Frequency of AE, SAE and MESI reported

End point title	Frequency of AE, SAE and MESI reported[1]

End point description:

In the protocol amendment 1, objectives and endpoints were updated to reflect changes in the pivotal trial (NN7008-3543) and to be consistent with the paediatric trial (NN7008-3545) and the Japanese trial (NN7008-3600). The primary endpoint "Frequency of AEs, SAE and MESI reported" was changed to secondary safety endpoint "Frequency of Adverse Events and Serious Adverse Events". This endpoint was planned to be measured during the trial.

End point type	Primary

End point timeframe:

After 90 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint which was previously cited as primary endpoint was changed to secondary endpoint as a result of amendment 1. As a result, this endpoint was analysed as secondary endpoint (except for MESIs) using descriptive statistics.

End point values	Small children (0 - <6 years)	Older children (6 - <12 years)	Adolescents (12 - <18 years)	Adults (≥18 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[2]	0[3]	0[4]	0[5]
Units: Number of events				

Notes:

[2] - The endpoint was not analysed (reason described in outcome description)

[3] - The endpoint was not analysed (reason described in outcome description)

[4] - The endpoint was not analysed (reason described in outcome description)

[5] - The endpoint was not analysed (reason described in outcome description)

Statistical analyses

No statistical analyses for this end point

Primary: Haemostatic response to turoctocog alfa (none, moderate, good or excellent) (surgery sub-trial)

End point title	Haemostatic response to turoctocog alfa (none, moderate, good or excellent) (surgery sub-trial)[6]

End point description:

Haemostatic response to turoctocog alfa (none, moderate, good or excellent) during and after surgery using a four-point response scale: none, moderate, good or excellent. The evaluation during surgery was done by the surgeon as follows: Excellent: blood loss less than expected; Good: blood loss as expected; Fair/Moderate: blood loss more than expected; None: uncontrolled bleeding. Haemostatic response after surgery was evaluated by investigator as follows: Excellent: good or better than

expected in this type of patient and procedure; Good: minimal negative impact on quality of haemostasis; Fair/Moderate: less than optimal for the type of procedure, maintained without change of treatment regimen; None: bleeding due to inadequate therapeutic response with adequate dosing, change of regimen required. This endpoint is measured during the surgery sub-trial from the day of surgery until the end of post-surgical period.

End point type	Primary

End point timeframe:

From the day of surgery until the end of post-surgical period.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was measured using a four-point response scale: none, moderate, good or excellent. There was no statistical analysis performed.

End point values	Surgery sub-trial			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Number of surgeries				
During major surgery (Excellent)	10			
During major surgery (Good)	8			
During major surgery (Moderate)	0			
During major surgery (None)	0			
During minor surgery (Excellent)	3			
During minor surgery (Good)	0			
During minor surgery (Moderate)	0			
During minor surgery (None)	0			
After major surgery (Excellent)	10			
After major surgery (Good)	8			
After major surgery (Moderate)	0			
After major surgery (none)	0			
After minor surgery (Excellent)	3			
After minor surgery (Good)	0			
After minor surgery (Moderate)	0			
After minor surgery (None)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of adverse events and serious adverse events

End point title	Frequency of adverse events and serious adverse events

End point description:

The number of adverse events and serious adverse events reported during the main trial and the on-demand sub-trial (during 90 months).

End point type	Secondary

End point timeframe:

After 90 months

End point values	Small children (0 - <6 years)	Older children (6 - <12 years)	Adolescents (12 - <18 years)	Adults (≥18 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	28	23	135
Units: Number of events				
Adverse events	180	204	240	636
Serious adverse events	6	8	6	27

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised bleeding rate reported during the prevention period (only applicable for subjects in the preventive regimen)

End point title	Annualised bleeding rate reported during the prevention period (only applicable for subjects in the preventive regimen)

End point description:

The number of bleeding episodes per year reported during the prevention period (during 90 months).

End point type	Secondary

End point timeframe:

After 90 months

End point values	Small children (0 - <6 years)- Preventive regimen [Main trial]	Older children (6 - <12 years)- Preventive regimen [Main	Adolescents (12 - <18 years) - Preventive regimen [Main trial]	Adults (>= 18 years) - Preventive regimen [Main trial]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	28	23	129
Units: Bleeding episodes/year				
median (full range (min-max))	1.08 (0 to 12.12)	1.57 (0 to 10.8)	1.57 (0 to 6.01)	1.37 (0 to 17.82)

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic response to turoctocog alfa (none, moderate, good or excellent) in treatment of bleeds

End point title	Haemostatic response to turoctocog alfa (none, moderate, good or excellent) in treatment of bleeds

End point description:

Haemostatic response to turoctocog alfa (none, moderate, good or excellent) in treatment of bleeds using a four-point response scale: none, moderate, good or excellent. The evaluation was done by patient, caregiver and/or investigator based on experience as follows: 1. Excellent: Abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a

single infusion 2. Good: Definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an infusion, but possibly requiring more than 1 infusion for complete resolution. 3. Moderate: Probable or slight beneficial effect within approximately 8 hours after the first infusion; usually requiring more than 1 infusion. 4. None: No improvement, or worsening of symptoms. This endpoint is measured during the preventive and on-demand sub-trial (during 90 months).

End point type	Secondary
End point timeframe:	
After 90 months	

End point values	Small children (0 - <6 years)-Preventive regimen [Main trial]	Older children (6 - <12 years)-Preventive regimen [Main	Adolescents (12 - <18 years) - Preventive regimen [Main trial]	Adults (>= 18 years) - Preventive regimen [Main trial]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	24	22	103
Units: Number of bleeds				
Excellent	124	189	72	565
Good	62	103	103	382
Moderate	17	37	19	91
None	1	1	0	7
Not known	0	0	0	1
Missing	0	1	2	5

End point values	Adolescents (12-<18 years)-(On-Demand regimen [Main	Adults (>=18 years)-(On-Demand regimen [Main trial])	Adults (>=18 years)-(On-Demand regimen [Sub-trial])	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	7	14	
Units: Number of bleeds				
Excellent	1	150	94	
Good	6	22	105	
Moderate	0	2	11	
None	0	0	0	
Not known	0	0	0	
Missing	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: The number of infusions of turoctocog alfa required per bleeding episode

End point title	The number of infusions of turoctocog alfa required per bleeding episode

End point description:

Number of infusions of turoctocog alfa that are required to stop the bleed, per bleeding episode (during 90 months).

End point type	Secondary

End point timeframe:

After 90 months

End point values	Small children (0 - <6 years)-Preventive regimen [Main trial]	Older children (6 - <12 years)-Preventive regimen [Main	Adolescents (12 - <18 years) -Preventive regimen [Main trial]	Adults (>= 18 years) -Preventive regimen [Main trial]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	24	22	103
Units: Number of infusions				
arithmetic mean (standard deviation)	1.8 (± 2.1)	1.7 (± 1.6)	1.8 (± 2.1)	1.6 (± 3)

End point values	Adolescents (12-<18 years)-(On-Demand regimen [Main	Adults (>=18 years)-(On-Demand regimen [Main trial])	Adults (>=18 years)-(On-Demand regimen [Sub-trial])	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	7	14	
Units: Number of infusions				
arithmetic mean (standard deviation)	1.3 (± 0.5)	1.1 (± 0.4)	1.4 (± 0.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to control of bleeding after the first dose of turoctocog alfa used for treatment of bleeds

End point title	Time to control of bleeding after the first dose of turoctocog alfa used for treatment of bleeds

End point description:

Time to stop of bleed from first dose of turoctocog alfa used for treatment of bleeds. This endpoint was measured during 90 months.

End point type	Secondary

End point timeframe:

After 90 months

End point values	Small children (0 - <6 years)-Preventive regimen [Main trial]	Older children (6 - <12 years)-Preventive regimen [Main	Adolescents (12 - <18 years) - Preventive regimen [Main trial]	Adults (>= 18 years) - Preventive regimen [Main trial]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	24	22	103
Units: Hours				
arithmetic mean (standard deviation)	12.63 (± 23.52)	19.32 (± 44.91)	19.57 (± 31.26)	16.61 (± 39.45)

End point values	Adolescents (12-<18 years)-(On-Demand regimen [Main	Adults (>=18 years)-(On-Demand regimen [Main trial])	Adults (>=18 years)-(On-Demand regimen [Sub-trial])	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	7	14	
Units: Hours				
arithmetic mean (standard deviation)	10.96 (± 7.52)	8.01 (± 8.2)	17.95 (± 17.64)	

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the actual consumption of turoctocog alfa (IU/kg BW/bleeding episode)

End point title	Assessment of the actual consumption of turoctocog alfa (IU/kg BW/bleeding episode)

End point description:

The mean consumption of turoctocog alfa used for treatment of a bleed from start to stop of a bleed. This endpoint was measured during 90 months.

End point type	Secondary

End point timeframe:

After 90 months

End point values	Small children (0 - <6 years)-Preventive regimen [Main trial]	Older children (6 - <12 years)-Preventive regimen [Main	Adolescents (12 - <18 years) - Preventive regimen [Main trial]	Adults (>= 18 years) - Preventive regimen [Main trial]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	24	22	103
Units: IU/kg BW/bleeding episode				
arithmetic mean (standard deviation)	75.9 (± 86.4)	70.5 (± 72.4)	56.6 (± 56.2)	57.9 (± 157.3)

End point values	Adolescents (12-<18 years)-(On-Demand regimen [Main	Adults (>=18 years)-(On-Demand regimen [Main trial])	Adults (>=18 years)-(On-Demand regimen [Sub-trial])	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	7	14	
Units: IU/kg BW/bleeding episode				
arithmetic mean (standard deviation)	37.6 (± 21.7)	43 (± 11.1)	44.9 (± 30.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the actual consumption of turoctocog alfa for prevention (only applicable for subjects in the preventive regimen)

End point title	Assessment of the actual consumption of turoctocog alfa for prevention (only applicable for subjects in the preventive regimen)

End point description:

The mean consumption of turoctocog alfa used for treatment of a bleed from start to stop of a bleed during the preventive regimen (per month per subject). This endpoint was measured during 90 months.

End point type	Secondary

End point timeframe:

After 90 months

End point values	Small children (0 - <6 years)-Preventive regimen [Main trial]	Older children (6 - <12 years)-Preventive regimen [Main	Adolescents (12 - <18 years) - Preventive regimen [Main trial]	Adults (>= 18 years) - Preventive regimen [Main trial]
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	28	23	128
Units: IU/kg BW/month				
arithmetic mean (standard deviation)	547.3 (± 106.9)	501 (± 113.9)	378.1 (± 113.3)	390.2 (± 112)

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of adverse events and serious adverse events

End point title	Frequency of adverse events and serious adverse events

End point description:

The number of adverse events and serious adverse events reported during the surgery sub-trial.

End point type	Secondary

End point timeframe:

After 90 months

End point values	Surgery sub-trial			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Number of events				
Adverse events	18			
Serious adverse events	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening (visit 1) starting after first exposure to Turoctocog alfa and until post treatment follow-up period

Adverse event reporting additional description:

The safety analysis set consists of all patients exposed to turoctocog alfa

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Small children (0 - <6 Years)

Reporting group description:

Subjects (0-<6 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen. Preventive: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg once every third day or twice weekly. On-Demand: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. The maximum treatment duration (27 Oct 2009 - 30 Jun 2016)

Reporting group title	Older children (6 - <12 Years)

Reporting group description:

Subjects (6-<12 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen. Preventive: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg BW once every third day or twice weekly. On-Demand: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. The maximum treatment duration (27 Oct 2009 - 30 Jun 2016)

Reporting group title	Adolescents (12 - <18 Years)

Reporting group description:

Subjects (12-<18 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen. Preventive regimen: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg once every third day or twice weekly. On-Demand: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country. The maximum treatment duration (27 Oct 2009 - 30 Jun 2016)

Reporting group title	Adults (≥18 Years)

Reporting group description:

Subjects (≥18 years) received turoctocog alfa (preventive or on-demand regimen). Subjects switched between regimens during trial (main and on-demand sub-trial) upon investigators' discretion. Subjects coming from main trial were allowed to switch back before completion of 6 months on-demand regimen. Preventive regimen: Turoctocog alfa as a slow iv bolus injection 20−50 IU/kg once every second day,20−60 IU/kg 3 times weekly or 40−60 IU/kg once every third day or twice weekly. On-Demand: Dose level aimed at a post injection level of at least 0.50 IU/mL of turoctocog alfa for treatment of bleeds as they occurred and occasionally as preventive treatment. All subjects were offered participation until either turoctocog alfa was commercially available in relevant country or until the trial, part of trial or a trial site was terminated by Novo Nordisk or a relevant authority for any reason in relevant country.

Serious adverse events	Small children (0 - <6 Years)	Older children (6 - <12 Years)	Adolescents (12 - <18 Years)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 27 (18.52%)	9 / 28 (32.14%)	6 / 23 (26.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic cancer metastatic			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	0 / 23 (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
Social circumstances			
Physical assault			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	0 / 23 (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
Laryngeal stenosis			

subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar I disorder			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	0 / 23 (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
Schizophrenia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device loosening			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 27 (0.00%)	2 / 28 (7.14%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Muscle strain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	0 / 23 (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 haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin injury			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic fracture			
subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Haemorrhage intracranial			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic neuritis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radial nerve palsy			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Pterygium			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal haemorrhage			
subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	0 / 23 (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
Pancreatitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Peritoneal haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	0 / 23 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal aneurysm			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Haemophilic arthropathy			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	0 / 23 (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
Osteoarthritis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendinous contracture			

subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	0 / 23 (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
Device related infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	0 / 23 (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
Gastroenteritis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	0 / 23 (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
Hepatitis C			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Adults (≥18 Years)		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 135 (15.56%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic cancer metastatic			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Physical assault			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Laryngeal stenosis			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Bipolar I disorder			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Schizophrenia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device loosening			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Forearm fracture			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hand fracture			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury			

subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscle strain				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin injury				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haemorrhage				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Traumatic fracture				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				

subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Optic neuritis			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radial nerve palsy			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Pterygium			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal haemorrhage			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pancreatitis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritoneal haemorrhage			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal aneurysm			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Haemophilic arthropathy			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscle haemorrhage			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			

subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tendinous contracture				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis C				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	2 / 135 (1.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Small children (0 - <6 Years)	Older children (6 - <12 Years)	Adolescents (12 - <18 Years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 27 (85.19%)	25 / 28 (89.29%)	20 / 23 (86.96%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 27 (3.70%)	5 / 28 (17.86%)	4 / 23 (17.39%)
occurrences (all)	1	8	5
Fall			
subjects affected / exposed	3 / 27 (11.11%)	4 / 28 (14.29%)	5 / 23 (21.74%)
occurrences (all)	6	19	8
Head injury			
subjects affected / exposed	2 / 27 (7.41%)	1 / 28 (3.57%)	0 / 23 (0.00%)
occurrences (all)	2	1	0
Joint injury			
subjects affected / exposed	0 / 27 (0.00%)	2 / 28 (7.14%)	2 / 23 (8.70%)
occurrences (all)	0	2	3
Laceration			
subjects affected / exposed	2 / 27 (7.41%)	0 / 28 (0.00%)	2 / 23 (8.70%)
occurrences (all)	3	0	2
Ligament sprain			
subjects affected / exposed	0 / 27 (0.00%)	5 / 28 (17.86%)	1 / 23 (4.35%)
occurrences (all)	0	19	1
Limb injury			

subjects affected / exposed	1 / 27 (3.70%)	2 / 28 (7.14%)	4 / 23 (17.39%)
occurrences (all)	3	3	4
Muscle strain			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Skin abrasion			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Traumatic haematoma			
subjects affected / exposed	2 / 27 (7.41%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Wound			
subjects affected / exposed	2 / 27 (7.41%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 27 (7.41%)	3 / 28 (10.71%)	6 / 23 (26.09%)
occurrences (all)	4	8	29
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 27 (7.41%)	1 / 28 (3.57%)	1 / 23 (4.35%)
occurrences (all)	2	2	1
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 27 (7.41%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences (all)	3	0	0
Pyrexia			
subjects affected / exposed	4 / 27 (14.81%)	2 / 28 (7.14%)	5 / 23 (21.74%)
occurrences (all)	5	6	6
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 27 (7.41%)	1 / 28 (3.57%)	1 / 23 (4.35%)
occurrences (all)	3	1	1
Abdominal pain upper			
subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	2

Dental caries			
subjects affected / exposed	5 / 27 (18.52%)	1 / 28 (3.57%)	0 / 23 (0.00%)
occurrences (all)	5	1	0
Diarrhoea			
subjects affected / exposed	5 / 27 (18.52%)	1 / 28 (3.57%)	2 / 23 (8.70%)
occurrences (all)	5	1	2
Dyspepsia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Gastritis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 28 (7.14%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Tooth development disorder			
subjects affected / exposed	2 / 27 (7.41%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences (all)	3	0	0
Tooth loss			
subjects affected / exposed	0 / 27 (0.00%)	3 / 28 (10.71%)	0 / 23 (0.00%)
occurrences (all)	0	3	0
Toothache			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	3 / 23 (13.04%)
occurrences (all)	0	1	3
Vomiting			
subjects affected / exposed	5 / 27 (18.52%)	2 / 28 (7.14%)	2 / 23 (8.70%)
occurrences (all)	5	2	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 27 (25.93%)	1 / 28 (3.57%)	4 / 23 (17.39%)
occurrences (all)	11	1	5
Nasal congestion			
subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	3
Oropharyngeal pain			

subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	3 / 23 (13.04%)
occurrences (all)	0	0	3
Respiratory disorder			
subjects affected / exposed	1 / 27 (3.70%)	2 / 28 (7.14%)	0 / 23 (0.00%)
occurrences (all)	5	4	0
Rhinitis allergic			
subjects affected / exposed	5 / 27 (18.52%)	1 / 28 (3.57%)	2 / 23 (8.70%)
occurrences (all)	5	1	2
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	3 / 27 (11.11%)	1 / 28 (3.57%)	1 / 23 (4.35%)
occurrences (all)	4	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	4 / 23 (17.39%)
occurrences (all)	0	2	7
Arthropathy			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Back pain			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Haemophilic arthropathy			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Myalgia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Pain in extremity			
subjects affected / exposed	2 / 27 (7.41%)	0 / 28 (0.00%)	1 / 23 (4.35%)
occurrences (all)	3	0	1
Synovitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	3
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 27 (3.70%)	2 / 28 (7.14%)	2 / 23 (8.70%)
occurrences (all)	3	2	2
Conjunctivitis			
subjects affected / exposed	0 / 27 (0.00%)	4 / 28 (14.29%)	0 / 23 (0.00%)
occurrences (all)	0	4	0
Gastroenteritis			
subjects affected / exposed	3 / 27 (11.11%)	2 / 28 (7.14%)	1 / 23 (4.35%)
occurrences (all)	3	2	1
Gastroenteritis viral			
subjects affected / exposed	3 / 27 (11.11%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences (all)	5	0	0
Influenza			
subjects affected / exposed	0 / 27 (0.00%)	2 / 28 (7.14%)	9 / 23 (39.13%)
occurrences (all)	0	5	13
Nasopharyngitis			
subjects affected / exposed	1 / 27 (3.70%)	2 / 28 (7.14%)	5 / 23 (21.74%)
occurrences (all)	1	4	18
Pharyngitis			
subjects affected / exposed	1 / 27 (3.70%)	7 / 28 (25.00%)	3 / 23 (13.04%)
occurrences (all)	2	24	9
Pharyngitis streptococcal			
subjects affected / exposed	0 / 27 (0.00%)	2 / 28 (7.14%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Respiratory tract infection viral			
subjects affected / exposed	2 / 27 (7.41%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Rhinitis			
subjects affected / exposed	2 / 27 (7.41%)	1 / 28 (3.57%)	2 / 23 (8.70%)
occurrences (all)	2	1	3
Sinusitis			
subjects affected / exposed	5 / 27 (18.52%)	1 / 28 (3.57%)	4 / 23 (17.39%)
occurrences (all)	6	1	7
Tonsillitis			
subjects affected / exposed	4 / 27 (14.81%)	2 / 28 (7.14%)	2 / 23 (8.70%)
occurrences (all)	8	2	6

Upper respiratory tract infection			
subjects affected / exposed	5 / 27 (18.52%)	5 / 28 (17.86%)	2 / 23 (8.70%)
occurrences (all)	9	16	2
Varicella			
subjects affected / exposed	3 / 27 (11.11%)	3 / 28 (10.71%)	0 / 23 (0.00%)
occurrences (all)	3	3	0

Non-serious adverse events	Adults (≥18 Years)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	94 / 135 (69.63%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	13		
Fall			
subjects affected / exposed	7 / 135 (5.19%)		
occurrences (all)	8		
Head injury			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Joint injury			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Laceration			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Ligament sprain			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	5		
Limb injury			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	4		
Muscle strain			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Skin abrasion			

subjects affected / exposed occurrences (all) Traumatic haematoma subjects affected / exposed occurrences (all) Wound subjects affected / exposed occurrences (all)	0 / 135 (0.00%) 0 1 / 135 (0.74%) 1 1 / 135 (0.74%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	17 / 135 (12.59%) 46		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	4 / 135 (2.96%) 5		
General disorders and administration site conditions Chills subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1 5 / 135 (3.70%) 6		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Dental caries subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	4 / 135 (2.96%) 4 2 / 135 (1.48%) 2 3 / 135 (2.22%) 4 4 / 135 (2.96%) 4		

Dyspepsia			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Gastritis			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Tooth development disorder			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Tooth loss			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	11 / 135 (8.15%)		
occurrences (all)	12		
Vomiting			
subjects affected / exposed	6 / 135 (4.44%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 135 (6.67%)		
occurrences (all)	11		
Nasal congestion			
subjects affected / exposed	5 / 135 (3.70%)		
occurrences (all)	5		
Oropharyngeal pain			
subjects affected / exposed	14 / 135 (10.37%)		
occurrences (all)	16		
Respiratory disorder			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Rhinitis allergic			

subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 135 (14.07%)		
occurrences (all)	29		
Arthropathy			
subjects affected / exposed	6 / 135 (4.44%)		
occurrences (all)	8		
Back pain			
subjects affected / exposed	12 / 135 (8.89%)		
occurrences (all)	13		
Haemophilic arthropathy			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	4		
Synovitis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Conjunctivitis			
subjects affected / exposed	6 / 135 (4.44%)		
occurrences (all)	6		
Gastroenteritis			

subjects affected / exposed	5 / 135 (3.70%)		
occurrences (all)	5		
Gastroenteritis viral			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	9 / 135 (6.67%)		
occurrences (all)	9		
Nasopharyngitis			
subjects affected / exposed	23 / 135 (17.04%)		
occurrences (all)	41		
Pharyngitis			
subjects affected / exposed	9 / 135 (6.67%)		
occurrences (all)	15		
Pharyngitis streptococcal			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Respiratory tract infection viral			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Tonsillitis			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	7		
Upper respiratory tract infection			
subjects affected / exposed	16 / 135 (11.85%)		
occurrences (all)	26		
Varicella			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2010	1. One of the main reasons for amending the protocol was that the pivotal trial (NN7008-3543) was substantially amended based on responses from health authorities. Furthermore, the paediatric trial protocol (NN7008-3545) had been finalised. To make a smooth transfer of patients from the above mentioned trials into the present trial, the trial protocol was amended. 2. The sub-trial was originally intended for patients undergoing elective surgery with continuous infusion. This was changed to allow surgery with both bolus and continuous infusion. Furthermore, emergency surgery was also allowed with this amendment. 3. Objectives and endpoints were updated to reflect changes in the pivotal trial (NN7008-3543) and to be consistent with the paediatric trial (NN7008-3545) and the Japanese trial (NN7008-3600). 4. The dose intervals for preventive treatments were changed based on higher dose levels for paediatric patients. 5. The maximum daily dose that was allowed was increased from 150 IU/kg to 200 IU/kg. 6. Sections 5 and 8 of the protocol were updated for readability and understanding. Especially the surgery sections were updated. 7. The section describing inhibitor formation and handling of inhibitors was updated for readability and understanding. 8. Concomitant medication not allowed in the trial was clarified. 9. Definition of hospitalisation was changed in accordance with Food and Drug Administration's (FDA) definition. 10. Medical events of special interest were thoroughly described in the safety section. 11. A stopping rule was added to the safety section.
02 September 2011	1. Change of the diary data entry from data management at Novo Nordisk to diary data entry at site performed by the investigator or delegated trial staff. 2. Clarification of the continuous infusion surgery procedure. 3. Update of the total number of patients, sites and countries. 4. Change in exclusion criteria to include withdrawn patients from previous trial if allowed in previous protocol. 5. Removal of lupus anticoagulant test from the assessment visits 6. Specification of when HIV test and hepatitis test were to be performed. 7. Change to the master patient information/informed consent form (ICF) to include PK-trial NN7008-3893, update of the number of patients, sites and countries, and specification of when HIV test and hepatitis test were to be performed. 8. Change to the master patient information/informed consent form to remove the possibility of having trial product shipped to the patients home by courier.
02 September 2011	To correct a typing error in the master subject information/informed consent form which changed the meaning of a sentence to the opposite.

19 July 2012	1. This amendment opened the possibility of transferring subjects into the pathfinder™ trials (these are trials with glycopegylated turoctocog alfa [N8-GP]) and the possibility of transferring subjects into and back from the NN7008-4015 trial. 2. PRO questionnaires HAEMO-A-QOL for adult patients at every second assessment visit. 3. Extension of the study from year 2013 until 2016. 4. Change of the MESI definition. 5. For severe bleeds patients were given the option of phoning or visiting the site. 6. An extra preventive treatment outside of scheduled preventive dose was allowed. 7. Whole blood transfusions were allowed during the surgery sub-trial.
05 February 2014	1. UTN number was added. 2. On-demand sub-trial added to collect data on efficacy in treatment of bleeds occurring in an on-demand treatment setting for 6 months. 3. Removal of withdrawal criteria # 15. 4. Statistical section and end-points updated to align with the analysis being done in other turoctocog alfa trials and to reflect analysis for the on-demand sub-trial 5. Interim analyses added to support submission and questions from authorities and to report results from the on-demand sub-trial. 6. Continuation into NN7008-3553 removed. 7. Safety section updated. 8. Severity of bleed clarified/updated. 9. Lab value at visit 1 for patients coming from NN7008-4015: patients coming from NN7008-4015 had the lab data transferred from NN7008-4015 to NN7008-3568 visit 1, however the lab sample panel was not completely the same, and the differences were highlighted with this amendment 10. Monitoring visits when last patient had had his last visit at site: as long time could occur between last patient at site until closure of site, it has been added that monitoring visit frequency does not have to be at least 12 weeks when the last patients has had his last visit at site. 11. Minor corrections and consistency updates. 12. Attachment I updated with new information. 13. Patient information/informed consent form were adapted accordingly.
27 March 2015	1. Two (2) new treatment regimens were added – once every third day and twice weekly regimens. 2. PK sub-trial in patients with high BMI (BMI ≥30 kg/m2) was added. 3. The statistical section was updated to include the latest Statistical Analysis Plan version 3.0 from 9-Feb-2012. 4. Signatory investigator was updated. 5. Patient Information/Informed Consent Form was adapted accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27291066

http://www.ncbi.nlm.nih.gov/pubmed/26058730

http://www.ncbi.nlm.nih.gov/pubmed/27291066