Clinical trial results:
Efficacy and safety of turoctocog alfa for prophylaxis and treatment of bleeding episodes in previously treated Chinese patients with haemophilia A

Summary

EudraCT number	2013-004791-35
Trial protocol	Outside EU/EEA
Global end of trial date	12 December 2018

Results information

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

Trial information

Trial identification

Sponsor protocol code	NN7008-4028

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02938585
WHO universal trial number (UTN)	U1111-1150-0765

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2018
Global end of trial reached?	Yes
Global end of trial date	12 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical efficacy of turoctocog alfa in the treatment of bleeding episodes in Chinese patients with severe haemophilia A (FVIII≤1%).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice, including archiving of essential documents.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	12 December 2016
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	China: 68
Worldwide total number of subjects	68
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	42
Adolescents (12-17 years)	11
Adults (18-64 years)	15
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 10 sites in mainland China.

Pre-assignment

Screening details:

Study design: This was an open-label and non-randomised trial. Participants with severe haemophilia A were administered a prophylaxis (preventive) or on-demand regimen of turoctocog alfa (trial product) at the investigator's discretion.

Period 1

Period 1 title	Main phase: 6 months
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 to <6 years)

Arm description:

Participants were to receive turoctocog alfa for a minimum of 6 months as either prophylaxis or on-demand treatment at the investigator's discretion.

Arm type	Experimental
Investigational medicinal product name	Turoctocog alfa
Investigational medicinal product code	
Other name	NovoEight®
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The recommended prophylaxis starting dose was 30 IU/kg. Prophylaxis doses ranged from 25−50 IU/kg with every-second-day treatment, or 25−60 IU/kg with 3-times-weekly treatment. Bleeds were treated with one or more turoctocog alfa intravenous (i.v.) bolus injections. The individual dose levels were decided by the investigator based on recommendations from the World Federation of Hemophilia (WFH). Participants who underwent surgery were treated with turoctocog alfa according to WFH recommendations and the following guidance: Minor surgery; to maintain coagulation factor VIII (FVIII) activity levels at 30−60 IU/dL. Major surgery; to maintain FVIII activity levels at 80−100 IU/dL pre- and postoperatively.

Arm title	Older children (6 to <12 years)

Arm description:

Participants were to receive turoctocog alfa for a minimum of 6 months as either prophylaxis or on-demand treatment at the investigator's discretion.

Arm type	Experimental
Investigational medicinal product name	Turoctocog alfa
Investigational medicinal product code	
Other name	NovoEight®
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The recommended prophylaxis starting dose was 30 IU/kg. Prophylaxis doses ranged from 25−50 IU/kg with every-second-day treatment, or 25−60 IU/kg with 3-times-weekly treatment. Bleeds were treated with one or more turoctocog alfa i.v. bolus injections. The individual dose levels were decided by the

investigator based on recommendations from the WFH. Participants who underwent surgery were treated with turoctocog alfa according to WFH recommendations and the following guidance: Minor surgery; to maintain FVIII activity levels at 30−60 IU/dL. Major surgery; to maintain FVIII activity levels at 80−100 IU/dL pre- and postoperatively.

Arm title	Adolescents (12 to <18 years)

Arm description:

Participants were to receive turoctocog alfa for a minimum of 6 months as either prophylaxis or on-demand treatment at the investigator's discretion.

Arm type	Experimental
Investigational medicinal product name	Turoctocog alfa
Investigational medicinal product code	
Other name	NovoEight®
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The recommended prophylaxis starting dose was 25 IU/kg. Prophylaxis doses ranged from 20−40 IU/kg with every-second-day treatment, or 20−50 IU/kg with 3-times-weekly treatment. Bleeds were treated with one or more turoctocog alfa i.v. bolus injections. The individual dose levels were decided by the investigator based on recommendations from the WFH. Participants who underwent surgery were treated with turoctocog alfa according to WFH recommendations and the following guidance: Minor surgery; to maintain FVIII activity levels at 30−60 IU/dL. Major surgery; to maintain FVIII activity levels at 80−100 IU/dL pre- and postoperatively.

Arm title	Adults (>=18 years)

Arm description:

Participants were to receive turoctocog alfa for a minimum of 6 months as either prophylaxis or on-demand treatment at the investigator's discretion.

Arm type	Experimental
Investigational medicinal product name	Turoctocog alfa
Investigational medicinal product code	
Other name	NovoEight®
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The recommended prophylaxis starting dose was 25 IU/kg. Prophylaxis doses ranged from 20−40 IU/kg with every-second-day treatment, or 20−50 IU/kg with 3-times-weekly treatment. Bleeds were treated with one or more turoctocog alfa i.v. bolus injections. The individual dose levels were decided by the investigator based on recommendations from the WFH. Participants who underwent surgery were treated with turoctocog alfa according to WFH recommendations and the following guidance: Minor surgery; to maintain FVIII activity levels at 30−60 IU/dL. Major surgery; to maintain FVIII activity levels at 80−100 IU/dL pre- and postoperatively.

Number of subjects in period 1	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)
Started	9	33	11
Completed	9	32	11
Not completed	0	1	0
Consent withdrawn by subject	-	-	-
Withdrawal by parent or guardian	-	1	-

Number of subjects in period 1	Adults (>=18 years)

Started	15
Completed	14
Not completed	1
Consent withdrawn by subject	1
Withdrawal by parent or guardian	-

Period 2

Period 2 title	Extension phase: Up to approx. 18 months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not Applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Small children (0 to <6 years)

Arm description:

Participants who completed 6 months of treatment (prophylaxis or on-demand) in the main phase, were to continue the same treatment for up to approximately 18 months. Participants were allowed to switch between treatments 'in the extension phase'.

Arm type	Experimental
Investigational medicinal product name	Turoctocog alfa
Investigational medicinal product code	
Other name	NovoEight®
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The recommended prophylaxis starting dose was 30 IU/kg. Prophylaxis doses ranged from 25−50 IU/kg with every-second-day treatment, or 25−60 IU/kg with 3-times-weekly treatment. Bleeds were treated with one or more turoctocog alfa i.v. bolus injections. The individual dose levels were decided by the investigator based on recommendations from the WFH. Participants who underwent surgery were treated with turoctocog alfa according to WFH recommendations and the following guidance: Minor surgery; to maintain FVIII activity levels at 30−60 IU/dL. Major surgery; to maintain FVIII activity levels at 80−100 IU/dL pre- and postoperatively.

Arm title	Older children (6 to <12 years)

Arm description:

Participants who completed 6 months of treatment (prophylaxis or on-demand) in the main phase, were to continue the same treatment for up to approximately 18 months. Participants were allowed to switch between treatments 'in the extension phase'.

Arm type	Experimental
Investigational medicinal product name	Turoctocog alfa
Investigational medicinal product code	
Other name	NovoEight®
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The recommended prophylaxis starting dose was 30 IU/kg. Prophylaxis doses ranged from 25−50 IU/kg with every-second-day treatment, or 25−60 IU/kg with 3-times-weekly treatment. Bleeds were treated with one or more turoctocog alfa i.v. bolus injections. The individual dose levels were decided by the

investigator based on recommendations from the WFH. Participants who underwent surgery were treated with turoctocog alfa according to WFH recommendations and the following guidance: Minor surgery; to maintain FVIII activity levels at 30−60 IU/dL. Major surgery; to maintain FVIII activity levels at 80−100 IU/dL pre- and postoperatively.

Arm title	Adolescents (12 to <18 years)

Arm description:

Participants who completed 6 months of treatment (prophylaxis or on-demand) in the main phase, were to continue the same treatment for up to approximately 18 months. Participants were allowed to switch between treatments 'in the extension phase'.

Arm type	Experimental
Investigational medicinal product name	Turoctocog alfa
Investigational medicinal product code	
Other name	NovoEight®
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The recommended prophylaxis starting dose was 25 IU/kg. Prophylaxis doses ranged from 20−40 IU/kg with every-second-day treatment, or 20−50 IU/kg with 3-times-weekly treatment. Bleeds were treated with one or more turoctocog alfa i.v. bolus injections. The individual dose levels were decided by the investigator based on recommendations from the WFH. Participants who underwent surgery were treated with turoctocog alfa according to WFH recommendations and the following guidance: Minor surgery; to maintain FVIII activity levels at 30−60 IU/dL. Major surgery; to maintain FVIII activity levels at 80−100 IU/dL pre- and postoperatively.

Arm title	Adults (>=18 years)

Arm description:

Participants who completed 6 months of treatment (prophylaxis or on-demand) in the main phase, were to continue the same treatment for up to approximately 18 months. Participants were allowed to switch between treatments 'in the extension phase'.

Arm type	Experimental
Investigational medicinal product name	Turoctocog alfa
Investigational medicinal product code	
Other name	NovoEight®
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The recommended prophylaxis starting dose was 25 IU/kg. Prophylaxis doses ranged from 20−40 IU/kg with every-second-day treatment, or 20−50 IU/kg with 3-times-weekly treatment. Bleeds were treated with one or more turoctocog alfa i.v. bolus injections. The individual dose levels were decided by the investigator based on recommendations from the WFH. Participants who underwent surgery were treated with turoctocog alfa according to WFH recommendations and the following guidance: Minor surgery; to maintain FVIII activity levels at 30−60 IU/dL. Major surgery; to maintain FVIII activity levels at 80−100 IU/dL pre- and postoperatively.

Number of subjects in period 2[1]	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)
Started	9	32	11
Completed	9	32	11
Not completed	0	0	0
Consent withdrawn by subject	-	-	-

Number of subjects in period 2[1]	Adults (>=18 years)
Started	12
Completed	10
Not completed	2
Consent withdrawn by subject	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 2 participants completed the main period, but withdrew their consent before entering the extension period.

Baseline characteristics

Reporting groups	
Reporting group title	Small children (0 to <6 years)
Reporting group description:	
Participants were to receive turoctocog alfa for a minimum of 6 months as either prophylaxis or on-demand treatment at the investigator's discretion.	
Reporting group title	Older children (6 to <12 years)
Reporting group description:	
Participants were to receive turoctocog alfa for a minimum of 6 months as either prophylaxis or on-demand treatment at the investigator's discretion.	
Reporting group title	Adolescents (12 to <18 years)
Reporting group description:	
Participants were to receive turoctocog alfa for a minimum of 6 months as either prophylaxis or on-demand treatment at the investigator's discretion.	
Reporting group title	Adults (>=18 years)
Reporting group description:	
Participants were to receive turoctocog alfa for a minimum of 6 months as either prophylaxis or on-demand treatment at the investigator's discretion.	

Reporting group values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)
Number of subjects	9	33	11
Age categorical Units: Subjects			
Children (2-11 years)	9	33	0
Adolescents (12-17 years)	0	0	11
Adults (18-64 years)	0	0	0
Age Continuous Units: Years			
arithmetic mean	4.00	8.70	14.55
standard deviation	± 1.12	± 1.91	± 1.92
Sex: Female, Male Units: Subjects			
Female	0	0	0
Male	9	33	11

Reporting group values	Adults (>=18 years)	Total	
Number of subjects	15	68	
Age categorical Units: Subjects			
Children (2-11 years)	0	42	
Adolescents (12-17 years)	0	11	
Adults (18-64 years)	15	15	
Age Continuous Units: Years			
arithmetic mean	31.00		
standard deviation	± 11.20	-	

Sex: Female, Male Units: Subjects			
Female	0	0	
Male	15	68	

End points

End points reporting groups

Reporting group title	Small children (0 to <6 years)
Reporting group description:	
Participants were to receive turoctocog alfa for a minimum of 6 months as either prophylaxis or on-demand treatment at the investigator's discretion.	
Reporting group title	Older children (6 to <12 years)
Reporting group description:	
Participants were to receive turoctocog alfa for a minimum of 6 months as either prophylaxis or on-demand treatment at the investigator's discretion.	
Reporting group title	Adolescents (12 to <18 years)
Reporting group description:	
Participants were to receive turoctocog alfa for a minimum of 6 months as either prophylaxis or on-demand treatment at the investigator's discretion.	
Reporting group title	Adults (>=18 years)
Reporting group description:	
Participants were to receive turoctocog alfa for a minimum of 6 months as either prophylaxis or on-demand treatment at the investigator's discretion.	
Reporting group title	Small children (0 to <6 years)
Reporting group description:	
Participants who completed 6 months of treatment (prophylaxis or on-demand) in the main phase, were to continue the same treatment for up to approximately 18 months. Participants were allowed to switch between treatments 'in the extension phase'.	
Reporting group title	Older children (6 to <12 years)
Reporting group description:	
Participants who completed 6 months of treatment (prophylaxis or on-demand) in the main phase, were to continue the same treatment for up to approximately 18 months. Participants were allowed to switch between treatments 'in the extension phase'.	
Reporting group title	Adolescents (12 to <18 years)
Reporting group description:	
Participants who completed 6 months of treatment (prophylaxis or on-demand) in the main phase, were to continue the same treatment for up to approximately 18 months. Participants were allowed to switch between treatments 'in the extension phase'.	
Reporting group title	Adults (>=18 years)
Reporting group description:	
Participants who completed 6 months of treatment (prophylaxis or on-demand) in the main phase, were to continue the same treatment for up to approximately 18 months. Participants were allowed to switch between treatments 'in the extension phase'.	
Subject analysis set title	Small children (0 to <6 years)
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) included all dosed participants with data after dosing.	
Subject analysis set title	Older children (6 to <12 years)
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS included all dosed participants with data after dosing.	
Subject analysis set title	Adolescents (12 to <18 years)
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS included all dosed participants with data after dosing.	
Subject analysis set title	Adults (>=18 years)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS included all dosed participants with data after dosing.

Primary: Haemostatic effect of turoctocog alfa when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none): 6 months

End point title	Haemostatic effect of turoctocog alfa when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none): 6 months[1]

End point description:

The haemostatic effect of turoctocog alfa when used for treatment of bleeding episodes in both prophylaxis and on-demand regimen was evaluated during the main phase of 6 months. The effect was assessed on a four-point scale for haemostatic response, excellent, good, moderate and none. Results are based on the full analysis set, which included all dosed participants with data after dosing. "Number of subjects analysed" should be read as "number of bleeding episodes treated with turoctocog alfa, both in prophylaxis and on-demand regimen".

End point type	Primary

End point timeframe:

During the main phase (6 months duration per patient)

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: The evaluation of the primary endpoint was based mainly upon descriptive statistics. Hence, no statistical analysis was performed.

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	48[2]	245[3]	28[4]	290[5]
Units: Bleeding episodes				
Excellent	35	156	20	190
Good	12	73	8	87
Moderate	1	15	0	13
None	0	0	0	0
Missing	0	1	0	0

Notes:

[2] - Out of 9 participants in the FAS, 6 had 48 bleeding episodes

[3] - Out of 33 participants in the FAS, 20 had 245 bleeding episodes

[4] - Out of 11 participants in the FAS, 6 had 28 bleeding episodes

[5] - Out of 15 participants in the FAS, 15 had 290 bleeding episodes

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The haemostatic effect of turoctocog alfa when used for treatment of bleeding episodes in both prophylaxis and on-demand regimen was evaluated during the trial period of 24 months (main + extended phase). The effect was assessed on a four-point scale for haemostatic response, excellent, good, moderate and none. Results are based on the FAS. "Number of subjects analysed" should be read as "number of bleeding episodes treated with turoctocog alfa, both in prophylaxis and on-demand

regimen”.

End point type	Secondary

End point timeframe:

During the trial period of 24 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65[6]	405[7]	53[8]	402[9]
Units: Bleeding episodes				
Excellent	45	275	42	272
Good	18	103	11	116
Moderate	2	26	0	14
None	0	0	0	0
Missing	0	1	0	0

Notes:

[6] - Out of 9 participants in the FAS, 7 had 65 bleeding episodes

[7] - Out of 33 participants in the FAS, 24 had 405 bleeding episodes

[8] - Out of 11 participants in the FAS, 8 had 53 bleeding episodes

[9] - Out of 15 participants in the FAS, 15 had 402 bleeding episodes

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rate of inhibitory antibodies against FVIII (≥0.6 Bethesda unit (BU)): 6 months

End point title	Incidence rate of inhibitory antibodies against FVIII (≥0.6 Bethesda unit (BU)): 6 months

End point description:

Incidence rate of inhibitory antibodies against FVIII (≥0.6 BU, presented as percentage of participants) in both prophylaxis and on-demand regimen was evaluated during the main phase of 6 months. Results are based on the FAS. “Number of subjects analysed” = number of participants, both on prophylaxis and on-demand regimen.

End point type	Secondary

End point timeframe:

During the main phase of 6 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	33	11	15
Units: Percentage of participants	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rate of inhibitory antibodies against FVIII (≥0.6 Bethesda unit (BU)): 24 months

End point title	Incidence rate of inhibitory antibodies against FVIII (≥0.6 Bethesda unit (BU)): 24 months

End point description:

Incidence rate of inhibitory antibodies against FVIII (≥0.6 BU, presented as percentage of participants) in both prophylaxis and on-demand regimen was evaluated during the trial period of 24 months (main + extended phase). Results are based on the FAS. "Number of subjects analysed" = number of participants, both on prophylaxis and on-demand regimen.

End point type	Secondary

End point timeframe:

During the trial period of 24 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	33	11	15
Units: Percentage of participants	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of bleeds (total bleeds assessed as annual bleeding rate) per patient: 6 months

End point title	Number of bleeds (total bleeds assessed as annual bleeding rate) per patient: 6 months

End point description:

Number of bleeds (total bleeds assessed as annual bleeding rate [ABR]) per participant in the prophylaxis regimen was evaluated during the main phase of 6 months. The annual bleeding rate was analysed by a negative binomial model. Presented result are 'negative binomial estimate of ABR' and corresponding 95% confidence interval (CI). Results are based on the FAS. "Number of subjects analysed" = number of participants in the prophylaxis regimen.

End point type	Secondary

End point timeframe:

During the main phase of 6 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	26	10	7
Units: Bleeding episodes/year/participant				
number (confidence interval 95%)	4.36 (1.71 to 11.14)	4.11 (2.15 to 7.87)	2.34 (0.81 to 6.72)	10.67 (5.53 to 20.57)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of bleeds (total bleeds assessed as annual bleeding rate) per patient: 24 months

End point title	Number of bleeds (total bleeds assessed as annual bleeding rate) per patient: 24 months

End point description:

Number of bleeds (total bleeds assessed as ABR) per participant in the prophylaxis regimen was evaluated during the trial period of 24 months (main + extended phase). The annual bleeding rate was analysed by a negative binomial model. Presented result are 'negative binomial estimate of ABR' and corresponding 95% CI. Results are based on the FAS. "Number of subjects analysed" = number of participants in the prophylaxis regimen.

End point type	Secondary

End point timeframe:

During the trial period of 24 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	31	11	12
Units: Bleeding episodes/year/participant				
number (confidence interval 95%)	2.28 (1.02 to 5.10)	2.63 (1.53 to 4.51)	1.97 (0.83 to 4.67)	4.97 (1.96 to 12.60)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of turoctocog alfa for bleeding treatment: Average dose to treat a bleed (6 months)

End point title	Consumption of turoctocog alfa for bleeding treatment: Average dose to treat a bleed (6 months)

End point description:

Average dose of turoctocog alfa consumed to treat a bleed in both prophylaxis and on-demand regimen was evaluated during the main phase of 6 months. Results are based on the FAS. "Number of subjects

analysed" should be read as the number of turoctocog alfa doses taken by the participants to treat the bleeding episodes, both in prophylaxis and on-demand regimen.

End point type	Secondary

End point timeframe:

During the main phase of 6 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	69	361	60	400
Units: IU/kg BW				
arithmetic mean (standard deviation)	42.96 (± 5.35)	36.69 (± 14.04)	46.79 (± 5.31)	20.29 (± 6.48)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of turoctocog alfa for bleeding treatment: Average dose to treat a bleed (24 months)

End point title	Consumption of turoctocog alfa for bleeding treatment: Average dose to treat a bleed (24 months)

End point description:

Average dose of turoctocog alfa consumed to treat a bleed in both prophylaxis and on-demand regimen was evaluated during the trial period of 24 months (main + extended phase). Results are based on the FAS. "Number of subjects analysed" should be read as the number of turoctocog alfa doses taken by the participants to treat the bleeding episodes, both in prophylaxis and on-demand regimen.

End point type	Secondary

End point timeframe:

During the trial period of 24 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	94	624	95	565
Units: IU/kg BW				
arithmetic mean (standard deviation)	43.99 (± 6.95)	36.00 (± 12.32)	43.58 (± 6.93)	21.07 (± 7.49)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of turoctocog alfa for bleeding treatment: Number of injections per bleed (6 months)

End point title	Consumption of turoctocog alfa for bleeding treatment: Number of injections per bleed (6 months)

End point description:

Consumption of turoctocog alfa (number of injections per bleed) for bleeding treatment in both prophylaxis and on-demand regimen was evaluated during the main phase of 6 months. Results are based on the FAS. "Number of subjects analysed" should be read as "number of bleeding episodes treated with turoctocog alfa, both in prophylaxis and on-demand regimen".

End point type	Secondary

End point timeframe:

During the main phase of 6 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	48	245	28	290
Units: Number of injections				
arithmetic mean (standard deviation)	1.31 (± 0.59)	1.22 (± 0.61)	1.07 (± 0.26)	1.29 (± 0.89)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of turoctocog alfa for bleeding treatment: Number of injections per bleed (24 months)

End point title	Consumption of turoctocog alfa for bleeding treatment: Number of injections per bleed (24 months)

End point description:

Consumption of turoctocog alfa (number of injections per bleed) for bleeding treatment in both prophylaxis and on-demand regimen was evaluated during the trial period of 24 months (main + extended phase). Results are based on the FAS. "Number of subjects analysed" should be read as "number of bleeding episodes treated with turoctocog alfa, both in prophylaxis and on-demand regimen".

End point type	Secondary

End point timeframe:

During the trial period of 24 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65	405	53	402
Units: Number of injections				
arithmetic mean (standard deviation)	1.34 (± 0.62)	1.30 (± 0.88)	1.09 (± 0.30)	1.33 (± 1.21)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of turoctocog alfa for bleeding treatment: IU/kg per bleed (6 months)

End point title	Consumption of turoctocog alfa for bleeding treatment: IU/kg per bleed (6 months)

End point description:

Consumption of turoctocog alfa (IU/kg BW per bleed) for bleeding treatment in both prophylaxis and on-demand regimen was evaluated during the main phase of 6 months. Results are based on the FAS. "Number of subjects analysed" should be read as "number of bleeding episodes treated with turoctocog alfa, both in prophylaxis and on-demand regimen".

End point type	Secondary

End point timeframe:

During the main phase of 6 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	48	245	28	290
Units: IU/kg BW				
arithmetic mean (standard deviation)	56.60 (± 25.32)	42.37 (± 26.54)	48.82 (± 15.05)	26.20 (± 17.55)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of turoctocog alfa for bleeding treatment: IU/kg per bleed (24 months)

End point title	Consumption of turoctocog alfa for bleeding treatment: IU/kg per bleed (24 months)

End point description:

Consumption of turoctocog alfa (IU/kg BW per bleed) for bleeding treatment in both prophylaxis and on-demand regimen was evaluated during the trial period of 24 months (main + extended phase). Results are based on the FAS. "Number of subjects analysed" should be read as "number of bleeding episodes treated with turoctocog alfa, both in prophylaxis and on-demand regimen".

End point type	Secondary

End point timeframe:

During the trial period of 24 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65	405	53	402
Units: IU/kg BW				
arithmetic mean (standard deviation)	59.01 (± 28.61)	44.75 (± 34.15)	45.07 (± 15.33)	27.44 (± 22.52)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of turoctocog alfa during prophylaxis treatment per participant: Average prophylaxis dose (6 months)

End point title	Consumption of turoctocog alfa during prophylaxis treatment per participant: Average prophylaxis dose (6 months)

End point description:

Average preventive dose of turoctocog alfa consumed per participant in the prophylaxis regimen was evaluated during the main phase of 6 months. Results are based on the FAS. "Number of subjects analysed" should be read as the "number of preventive turoctocog alfa doses taken by the participants in the prophylaxis regimen".

End point type	Secondary

End point timeframe:

During the main phase of 6 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	530	1689	661	484
Units: IU/kg BW				
arithmetic mean (standard deviation)	47.05 (± 9.21)	39.46 (± 7.12)	35.40 (± 7.41)	37.28 (± 5.22)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of turoctocog alfa during prophylaxis treatment per participant: Average prophylaxis dose (24 months)

End point title	Consumption of turoctocog alfa during prophylaxis treatment per participant: Average prophylaxis dose (24 months)

End point description:

Average preventive dose of turoctocog alfa consumed per participant in the prophylaxis regimen was evaluated during the trial period of 24 months (main + extended phase). Results are based on the FAS. "Number of subjects analysed" should be read as the "number of preventive turoctocog alfa doses taken by the participants in the prophylaxis regimen".

End point type	Secondary

End point timeframe:

During the trial period of 24 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2314	6729	2794	1999
Units: IU/kg BW				
arithmetic mean (standard deviation)	47.97 (± 8.00)	40.33 (± 7.05)	36.20 (± 7.15)	38.13 (± 7.51)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of turoctocog alfa during prophylaxis treatment per participant: IU/kg per month (6 months)

End point title	Consumption of turoctocog alfa during prophylaxis treatment per participant: IU/kg per month (6 months)

End point description:

Preventive dose of turoctocog alfa (IU/kg body weight (BW) per month) per participant in the prophylaxis regimen was evaluated during the main phase of 6 months. Results are based on the FAS. "Number of subjects analysed" = number of participants in the prophylaxis regimen.

End point type	Secondary

End point timeframe:

During the main phase of 6 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	26	10	7
Units: IU/kg BW/month/participant				
arithmetic mean (standard deviation)	600.3 (± 112.6)	522.5 (± 87.59)	454.5 (± 92.79)	500.7 (± 84.39)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of turoctocog alfa during prophylaxis treatment per participant: IU/kg per month (24 months)

End point title	Consumption of turoctocog alfa during prophylaxis treatment per participant: IU/kg per month (24 months)

End point description:

Preventive dose of turoctocog alfa (IU/kg BW per month) per participant in the prophylaxis regimen was evaluated during the trial period of 24 months (main + extended phase). Results are based on the FAS. "Number of subjects analysed" = number of participants in the prophylaxis regimen.

End point type	Secondary

End point timeframe:

During the trial period of 24 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	31	11	12
Units: IU/kg BW/month/participant				
arithmetic mean (standard deviation)	606.3 (± 118.5)	533.0 (± 82.90)	467.6 (± 91.40)	490.8 (± 115.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of turoctocog alfa during prophylaxis treatment per participant: IU/kg per year (6 months)

End point title	Consumption of turoctocog alfa during prophylaxis treatment per participant: IU/kg per year (6 months)

End point description:

Preventive dose of turoctocog alfa (IU/kg body weight per year) per participant in the prophylaxis regimen was evaluated during the main phase of 6 months. Results are based on the FAS. "Number of subjects analysed" = number of participants in the prophylaxis regimen.

End point type	Secondary

End point timeframe:

During the main phase of 6 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	26	10	7
Units: IU/kg BW/year/participant				
arithmetic mean (standard deviation)	7204 (± 1351)	6270 (± 1051)	5454 (± 1113)	6009 (± 1013)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of turoctocog alfa during prophylaxis treatment per participant: IU/kg per year (24 months)

End point title	Consumption of turoctocog alfa during prophylaxis treatment per participant: IU/kg per year (24 months)

End point description:

Preventive dose of turoctocog alfa (IU/kg body weight per year) per participant in the prophylaxis regimen was evaluated during the trial period of 24 months (main + extended phase). Results are based on the FAS. "Number of subjects analysed" = number of participants in the prophylaxis regimen.

End point type	Secondary

End point timeframe:

During the trial period of 24 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	31	11	12
Units: IU/kg BW/year/participant				
arithmetic mean (standard deviation)	7276 (± 1422)	6396 (± 994.7)	5611 (± 1097)	5890 (± 1388)

Statistical analyses

No statistical analyses for this end point

Secondary: Total consumption of turoctocog alfa per participant: IU/kg per month (6 months)

End point title	Total consumption of turoctocog alfa per participant: IU/kg per month (6 months)

End point description:

Total consumption of turoctocog alfa (IU/kg body weight per month) per participant in both prophylaxis and on-demand regimen was evaluated during the main phase of 6 months. Results are based on the FAS. "Number of subjects analysed" = number of participants both on prophylaxis and on-demand regimen.

End point type	Secondary

End point timeframe:

During the main phase of 6 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	33	11	15
Units: IU/kg BW/month/participant				
arithmetic mean (standard deviation)	603.5 (± 141.2)	496.0 (± 146.7)	479.6 (± 103.9)	377.2 (± 218.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Total consumption of turoctocog alfa per participant: IU/kg per month (24 months)

End point title	Total consumption of turoctocog alfa per participant: IU/kg per month (24 months)

End point description:

Total consumption of turoctocog alfa (IU/kg body weight per month) per participant in both prophylaxis and on-demand regimen was evaluated during the trial period of 24 months (main + extended phase). Results are based on the FAS. "Number of subjects analysed" = number of participants both on prophylaxis and on-demand regimen.

End point type	Secondary

End point timeframe:

During the trial period of 24 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	33	11	15
Units: IU/kg BW/month/participant				
arithmetic mean (standard deviation)	615.3 (± 123.8)	516.7 (± 121.1)	477.0 (± 94.37)	429.1 (± 192.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Total consumption of turoctocog alfa per participant: IU/kg per year (6 months)

End point title	Total consumption of turoctocog alfa per participant: IU/kg per year (6 months)

End point description:

Total consumption of turoctocog alfa (IU/kg body weight per year) per participant in both prophylaxis and on-demand regimen was evaluated during the main phase of 6 months. Results are based on the FAS. "Number of subjects analysed" = number of participants both on prophylaxis and on-demand regimen.

End point type	Secondary

End point timeframe:

During the main phase of 6 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	33	11	15
Units: IU/kg BW/year/participant				
arithmetic mean (standard deviation)	7242 (± 1695)	5951 (± 1760)	5756 (± 1247)	4527 (± 2627)

Statistical analyses

No statistical analyses for this end point

Secondary: Total consumption of turoctocog alfa per participant: IU/kg per year (24 months)

End point title	Total consumption of turoctocog alfa per participant: IU/kg per year (24 months)

End point description:

Total consumption of turoctocog alfa (IU/kg body weight per year) per participant in both prophylaxis and on-demand regimen was evaluated during the trial period of 24 months (main + extended phase). Results are based on the FAS. "Number of subjects analysed" = number of participants both on prophylaxis and on-demand regimen.

End point type	Secondary

End point timeframe:

During the trial period of 24 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	33	11	15
Units: IU/kg BW/year/participant				
arithmetic mean (standard deviation)	7384 (± 1486)	6201 (± 1453)	5724 (± 1132)	5149 (± 2312)

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of adverse events (AEs): 6 months

End point title	Frequency of adverse events (AEs): 6 months

End point description:

Frequency of adverse events (AEs) are presented as rate of events, which was calculated as the number of AEs per patient years. All presented AEs are treatment emergent (TEAEs), which were defined as the events reported after trial product administration until the end of the post-treatment follow-up period. AEs were recorded during the main phase of 6 months. Results are based on the safety analysis set, which included participants, who received at least one dose of the trial product. "Number of subjects analysed" = all participants in the safety analysis set.

End point type	Secondary

End point timeframe:

During the main phase of 6 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	33	11	15
Units: Rate of events				
number (not applicable)	4.908	2.093	2.325	1.922

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of adverse events (AEs): 24 months

End point title	Frequency of adverse events (AEs): 24 months

End point description:

Frequency of AEs are presented as rate of events, which was calculated as the number of AEs per patient years. All presented AEs are TEAEs. AEs were recorded during the trial period of 24 months (main + extended phase). Results are based on the safety analysis set, which included participants, who received at least one dose of the trial product. "Number of subjects analysed" = all participants in the safety analysis set.

End point type	Secondary

End point timeframe:

During the trial period of 24 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	33	11	15
Units: Rate of events				
number (not applicable)	2.941	1.210	1.074	1.123

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of serious adverse events (SAEs): 6 months

End point title	Frequency of serious adverse events (SAEs): 6 months

End point description:

Frequency of SAEs are presented as rate of events, which was calculated as the number of SAEs per patient years. All the SAEs were treatment emergent and recorded during the main phase of 6 months. Results are based on the safety analysis set. "Number of subjects analysed" = all participants in the safety analysis set.

End point type	Secondary

End point timeframe:

During the main phase of 6 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	33	11	15
Units: Rate of events				
number (not applicable)	0	0	0.634	0

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of serious adverse events (SAEs): 24 months

End point title	Frequency of serious adverse events (SAEs): 24 months

End point description:

Frequency of SAEs are presented as rate of events, which was calculated as the number of SAEs per patient years. All the SAEs were treatment emergent and recorded during the trial period of 24 months (main + extended phase). Results are based on the safety analysis set. "Number of subjects analysed" = all participants in the safety analysis set.

End point type	Secondary

End point timeframe:

During the trial period of 24 months

End point values	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)	Adults (>=18 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	33	11	15
Units: Rate of events				
number (not applicable)	0.065	0	0.161	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All presented AEs are treatment emergent (TEAEs), which were defined as the events reported after trial product administration (day 1) until the end of the post-treatment follow-up period (i.e. month 24 + 14 days).

Adverse event reporting additional description:

All the AE values are based on the safety analysis set.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

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

Reporting group description:

Participants were to receive turoctocog alfa for 6 months in the main phase and up to approximately 18 months in the extension phase of this study.

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

Reporting group description:

Participants were to receive turoctocog alfa for 6 months in the main phase and up to approximately 18 months in the extension phase of this study.

Reporting group title	Adolescents (12 to <18 years)

Reporting group description:

Participants were to receive turoctocog alfa for 6 months in the main phase and up to approximately 18 months in the extension phase of this study.

Reporting group title	Adults (>=18 years)

Reporting group description:

Participants were to receive turoctocog alfa for 6 months in the main phase and up to approximately 18 months in the extension phase of this study.

Serious adverse events	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	2 / 11 (18.18%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	0 / 11 (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
Lung infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung infection			

subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Small children (0 to <6 years)	Older children (6 to <12 years)	Adolescents (12 to <18 years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 9 (88.89%)	18 / 33 (54.55%)	7 / 11 (63.64%)
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Puncture site reaction			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	4 / 9 (44.44%)	2 / 33 (6.06%)	0 / 11 (0.00%)
occurrences (all)	7	2	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 9 (11.11%)	1 / 33 (3.03%)	1 / 11 (9.09%)
occurrences (all)	2	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 9 (0.00%)	2 / 33 (6.06%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Rhinorrhoea			

subjects affected / exposed	0 / 9 (0.00%)	3 / 33 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Investigations			
Antiphospholipid antibodies positive			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Platelet count increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Neuralgia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Xerophthalmia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 9 (0.00%)	1 / 33 (3.03%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Dental caries			

subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	1 / 9 (11.11%)	2 / 33 (6.06%)	1 / 11 (9.09%)
occurrences (all)	1	2	1
Gastritis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 33 (3.03%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Loose tooth			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Tooth development disorder			
subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorder			
subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 9 (11.11%)	1 / 33 (3.03%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Urticaria papular			

subjects affected / exposed	1 / 9 (11.11%)	1 / 33 (3.03%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Urticaria			
subjects affected / exposed	0 / 9 (0.00%)	2 / 33 (6.06%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Urethral disorder			
subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Fungal skin infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 33 (3.03%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal fungal infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 9 (11.11%)	6 / 33 (18.18%)	2 / 11 (18.18%)
occurrences (all)	1	7	2
Oral herpes			
subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Otitis externa			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			

subjects affected / exposed	1 / 9 (11.11%)	1 / 33 (3.03%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Pneumonia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	2 / 33 (6.06%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Tonsillitis			
subjects affected / exposed	1 / 9 (11.11%)	2 / 33 (6.06%)	0 / 11 (0.00%)
occurrences (all)	2	6	0
Upper respiratory tract infection			
subjects affected / exposed	7 / 9 (77.78%)	7 / 33 (21.21%)	2 / 11 (18.18%)
occurrences (all)	12	9	3
Viral rash			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Laryngitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Mumps			
subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 9 (0.00%)	2 / 33 (6.06%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Tinea manuum			
subjects affected / exposed	1 / 9 (11.11%)	0 / 33 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			

Malnutrition			
subjects affected / exposed	0 / 9 (0.00%)	1 / 33 (3.03%)	1 / 11 (9.09%)
occurrences (all)	0	1	1

Non-serious adverse events	Adults (>=18 years)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 15 (66.67%)		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Puncture site reaction			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Investigations			

Antiphospholipid antibodies positive subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Platelet count increased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Injury, poisoning and procedural complications Wound subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
Nervous system disorders Neuralgia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Eye disorders Xerophthalmia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Constipation subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Dental caries subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Diarrhoea			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Loose tooth			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tooth development disorder			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorder			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Urticaria papular			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Urticaria			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Renal and urinary disorders Urethral disorder subjects affected / exposed occurrences (all)	 0 / 15 (0.00%) 0		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	 0 / 15 (0.00%) 0		
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all) Fungal skin infection subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Gastrointestinal fungal infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all) Otitis externa subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Pneumonia	 0 / 15 (0.00%) 0 1 / 15 (6.67%) 1 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 1 / 15 (6.67%) 1 0 / 15 (0.00%) 0 1 / 15 (6.67%) 1 0 / 15 (0.00%) 0		

subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Tonsillitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Viral rash			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Gastrointestinal infection			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Laryngitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Mumps			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Tinea manuum			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2016	Update to the trial timelines as the trial was on hold for about 1.5 years. Furthermore, changes in Novo Nordisk standard operating procedures and haemophilia standards during the hold were added to the protocol, such as clinical data interchange standards and request from the Chinese Food and Drug Administration regarding more frequent human immunodeficiency virus and hepatitis testing.
30 September 2016	1) Clarification of the clinical trial insurance coverage in case of inhibitor development during the trial. Previously, it was described in general terms and was changed in order to describe inhibitor development and taking into consideration the Chinese law. 2) The switch between on demand and prophylaxis treatment regimen was also clarified. 3) Addition of height measurements for paediatric patients during the trial. 4) Added that the remaining samples for FVIII were shipped out of China in order to perform chromogenic testing in a centralized lab. 5) Section related to 'adverse events and technical complaints' and 'case report forms' have been updated to reflect current mandatory text and clarifying use of electronic case report form (eCRF)/ paper CRF in safety reporting. 6) Minor grammatical changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported