



Clinical trial results:

Safety and Efficacy of turoctocog alfa in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A Summary

EudraCT number	2011-001033-16
Trial protocol	GB AT ES GR DK HU LT PL PT
Global end of trial date	05 December 2018

Results information

Result version number	v1 (current)
This version publication date	20 June 2019
First version publication date	20 June 2019

Trial information

Trial identification

Sponsor protocol code	NN7008-3809
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01493778
WHO universal trial number (UTN)	U1111-1119-6116

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-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	02 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 August 2017
Global end of trial reached?	Yes
Global end of trial date	05 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate safety of turoctocog alfa in paediatric previously untreated patients (PUP) with haemophilia A.

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	17 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Algeria: 4
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	China: 7
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Lithuania: 1
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	60
EEA total number of subjects	13

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	2
Infants and toddlers (28 days-23 months)	55
Children (2-11 years)	3
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 40 sites in 15 countries: Algeria (1 site), Austria (2 sites), China (6 sites), Denmark (1 site), Greece (2 sites), Hong Kong (1 site), Hungary (1 site), Japan (2 sites), Lithuania (1 site), Poland (2 sites), Russian Federation (2 sites), Serbia (1 site), Spain (3 sites), Turkey (3 sites), United States (12 sites).

Pre-assignment

Screening details:

60 subjects were enrolled in the trial and received at least one dose of turoctocog alfa. The trial consisted of two phases: the main phase and an extension phase. 26 subjects developed inhibitors during the course of the trial and followed an alternative treatment regimen (inhibitor cohort).

Period 1

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

Blinding implementation details:

Not applicable

Arms

Arm title	Turoctocog alfa : Overall study
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Arm description:

Subjects received turoctocog alfa for the prevention of bleeding. The investigator decided the dose of turoctocog alfa based on the child's clinical profile. The trial consists of two phases. The main phase was completed when either the patient received treatment with turoctocog alfa for at least 50 exposure days (ED) or developed FVIII inhibitors. After completing the main phase, the patient could transition to the extension phase, if the main phase was completed without inhibitors, or start an alternative visit schedule, if FVIII inhibitors were detected. Subjects developing inhibitors anytime during the trial were considered as a separate 'inhibitor' cohort and evaluated accordingly. Upon successful eradication of the inhibitors these patients enter the extension phase (if the inhibitor developed during the main phase) or re-enter it (if it had developed after they had started the extension phase). The total duration of the trial was around 7 years.

Arm type	Experimental
Investigational medicinal product name	turoctocog alfa 2000 IU/vial
Investigational medicinal product code	
Other name	NovoEight®/Novoeight®
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received turoctocog alfa doses of 15–60 IU/kg body weight (BW) administered as an intravenous (i.v) injection for the prevention of bleeding. The investigator decided the dose based on the child's clinical profile. Preventive treatment: A bolus dose of turoctocog alfa was administered intravenously at each administration day, preferably in the morning. A starting dose of 15 –50 IU/kg BW once weekly was recommended with gradual increases to 20–50 IU/kg BW every second day or 20–60 IU/kg BW two or three times weekly. Treatment of bleeds: Investigators determined the doses based on recommendations from the World Federation of Haemophilia (WFH) guidelines. Treatment of surgery: According to standard of practice at the participating site. The post injection level of FVIII for major surgery was to be at least 0.50 IU/mL. Treatment of subjects with inhibitors: Treatment with turoctocog alfa for up to 24 months.

Number of subjects in period 1	Turoctocog alfa : Overall study
Started	60
Completed	52
Not completed	8
Consent withdrawn by subject	1
Adverse event, non-fatal	2
2 unclassified and 3 withdrawal criteria	5

Baseline characteristics

Reporting groups

Reporting group title	Turoctocog alfa : Overall study
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Reporting group description:

Subjects received turoctocog alfa for the prevention of bleeding. The investigator decided the dose of turoctocog alfa based on the child's clinical profile. The trial consists of two phases. The main phase was completed when either the patient received treatment with turoctocog alfa for at least 50 exposure days (ED) or developed FVIII inhibitors. After completing the main phase, the patient could transition to the extension phase, if the main phase was completed without inhibitors, or start an alternative visit schedule, if FVIII inhibitors were detected. Subjects developing inhibitors anytime during the trial were considered as a separate 'inhibitor' cohort and evaluated accordingly. Upon successful eradication of the inhibitors these patients enter the extension phase (if the inhibitor developed during the main phase) or re-enter it (if it had developed after they had started the extension phase). The total duration of the trial was around 7 years.

Reporting group values	Turoctocog alfa : Overall study	Total	
Number of subjects	60	60	
Age categorical			
Units: Subjects			
Newborns (0-27 days)	2	2	
Infants and toddlers (28 days-23 months)	55	55	
Children (2-11 years)	3	3	
Age Continuous			
Units: months			
arithmetic mean	10.2		
standard deviation	± 7.88	-	
Sex: Female, Male			
Units: Subjects			
Female	0	0	
Male	60	60	

End points

End points reporting groups

Reporting group title	Turoctocog alfa : Overall study
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Reporting group description:

Subjects received turoctocog alfa for the prevention of bleeding. The investigator decided the dose of turoctocog alfa based on the child's clinical profile. The trial consists of two phases. The main phase was completed when either the patient received treatment with turoctocog alfa for at least 50 exposure days (ED) or developed FVIII inhibitors. After completing the main phase, the patient could transition to the extension phase, if the main phase was completed without inhibitors, or start an alternative visit schedule, if FVIII inhibitors were detected. Subjects developing inhibitors anytime during the trial were considered as a separate 'inhibitor' cohort and evaluated accordingly. Upon successful eradication of the inhibitors these patients enter the extension phase (if the inhibitor developed during the main phase) or re-enter it (if it had developed after they had started the extension phase). The total duration of the trial was around 7 years.

Subject analysis set title	Turoctocog alfa: Main Phase (On-demand)
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Subject analysis set type	Full analysis
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Subject analysis set description:

Children ≤ 2 years received on-demand treatment while waiting to start on a preventive regimen. This treatment period included Visit 2 to first preventive dose. Subjects received turoctocog alfa doses of 15-60 IU/kg body weight (BW) administered as an intravenous injection for the prevention of bleeding. The investigator decided what dose of turoctocog alfa to give based on the child's clinical profile.

Subject analysis set title	Turoctocog alfa: Main Phase (Preventive treatment)
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects received prophylactic factor VIII replacement therapy (preventive treatment) until Visit 5 or until development of inhibitor, whichever came first. Subjects received turoctocog alfa doses of 15-60 IU/kg body weight (BW) administered as an intravenous injection for the prevention of bleeding. The investigator decided what dose of turoctocog alfa to give based on the child's clinical profile.

Subject analysis set title	Turoctocog alfa: Main Phase (On-demand+Preventive treatment)
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects who completed the main phase of the trial. These included children ≤ 2 years who received on-demand treatment while waiting to start on a preventive regimen and subjects on prophylactic factor VIII replacement therapy until Visit 5 or until development of inhibitor, whichever came first.

Subject analysis set title	Turoctocog alfa: Extension phase (Preventive treatment)
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects received prophylactic treatment administered from completion of the main phase or completion of the inhibitor cohort until the end-of-trial visit in the extension phase. Subjects received turoctocog alfa doses of 15-60 IU/kg body weight (BW) administered as an intravenous injection for the prevention of bleeding. The investigator decided what dose of turoctocog alfa to give based on the child's clinical profile.

Subject analysis set title	Turoctocog alfa: Inhibitor cohort
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects who developed an inhibitor during the course of the trial and followed an alternative treatment regimen. They were offered continued treatment with turoctocog alfa for up to 24 months.

Primary: Incidence rate of FVIII inhibitors (≥ 0.6 BU)

End point title	Incidence rate of FVIII inhibitors (≥ 0.6 BU) ^[1]
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End point description:

The incidence rate of FVIII inhibitors is defined as inhibitor titres ≥ 0.6 bethesda unit (BU) for main phase of the trial. The result is presented as percentage of subjects who developed FVIII inhibitor during the main phase out of subjects who have completed the main phase (N=58). The time frame for the main phase of the trial was from Visit 2 (21 days after screening) to Visit 5 (50-55 exposure day). Analysis population: The full analysis set included all subjects who completed the main phase.

End point type	Primary			
End point timeframe:				
Evaluated for the main phase of the trial.				
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: As there is no comparator arm, the primary endpoint was analysed based on exact calculation of a binomial distribution.				
End point values	Turoctocog alfa: Main Phase (On-demand+Preventive treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	58			
Units: Percentage of participants				
number (confidence interval 95%)	43.1 (30.2 to 56.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic effect of turoctocog alfa on treatment of bleeds assessed on a predefined four point scale: Excellent, Good, Moderate and None: Main phase

End point title	Haemostatic effect of turoctocog alfa on treatment of bleeds assessed on a predefined four point scale: Excellent, Good, Moderate and None: Main phase
End point description: The haemostatic effect of turoctocog alfa was summarised by frequency tables and assessed on a predefined four point scale: excellent, good, moderate and none. The analysis was based on the total number of bleeds and their response to treatment. Results are presented for the main phase of the trial (from Visit 2 (21 days after screening) to Visit 5 (50-55 exposure day)). Analysis population: The full analysis set included all dosed subjects with data after dosing.	
End point type	Secondary
End point timeframe: Main phase of the trial	

End point values	Turoctocog alfa: Main Phase (On-demand)	Turoctocog alfa: Main Phase (Preventive treatment)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36 ^[2]	38 ^[3]		
Units: Bleeds				
Excellent	53	83		
Good	36	29		
Moderate	5	12		
None	0	1		

Missing	4	8		
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Notes:

[2] - Out of 51 subjects, 36 had 98 bleeds.

[3] - Out of 58 subjects, 38 had 133 bleeds.

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic effect of turoctocog alfa on treatment of bleeds assessed on a predefined four point scale: Excellent, Good, Moderate and None: Extension phase

End point title	Haemostatic effect of turoctocog alfa on treatment of bleeds assessed on a predefined four point scale: Excellent, Good, Moderate and None: Extension phase
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End point description:

The haemostatic effect of turoctocog alfa was summarised by frequency tables containing count of all bleeds and assessed on a predefined four point scale: excellent, good, moderate and none. The analysis was based on the total number of bleeds and their response to treatment. The results are presented for the extension phase of the trial (from completion of the main phase or completion of the inhibitor cohort until the end-of-trial visit). Analysis population: The full analysis set included all dosed subjects treated for prevention in the extension phase.

End point type	Secondary
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End point timeframe:

Extension phase of the trial

End point values	Turoctocog alfa: Extension phase (Preventive treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	40 ^[4]			
Units: Bleeds				
Excellent	161			
Good	73			
Moderate	31			
None	1			
Missing	3			

Notes:

[4] - Out of 49 subjects, 40 had 269 bleeds

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic effect of turoctocog alfa on treatment of bleeds assessed on a predefined four point scale: excellent, good, moderate and none: Combined main and extension phases

End point title	Haemostatic effect of turoctocog alfa on treatment of bleeds assessed on a predefined four point scale: excellent, good,
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End point description:

The haemostatic effect of turoctocog alfa was summarised by frequency tables containing count of all bleeds and assessed on a predefined four point scale: Excellent, Good, Moderate and None. The analysis was based on the total number of bleeds and their response to treatment. The results are presented for the combined main and extension phases for preventive treatment of the trial (from visit 2 to until end of trial). The results of inhibitor cohort are also presented. Analysis population: The full analysis set included all dosed subjects treated for prevention in the main and extension phase.

End point type	Secondary
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End point timeframe:

Combined main and extension phases

End point values	Turoctocog alfa : Overall study	Turoctocog alfa: Inhibitor cohort		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	59 ^[5]	19 ^[6]		
Units: Bleeds				
Excellent	244	9		
Good	102	19		
Moderate	43	10		
None	2	4		
Missing	11	137		

Notes:

[5] - Out of 60 subjects, 59 had 402 bleeds.

[6] - Out of 26 subjects, 19 had 179 bleeds.

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised bleeding rate: Main phase

End point title	Annualised bleeding rate: Main phase
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End point description:

Mean annualised bleeding rate defined as number of bleeds in total per patient per year following treatment were estimated by a Poisson model allowing for over-dispersion. The Poisson estimate is presented with a 95% confidence interval (CI). Results are presented for the main phase of the trial (from Visit 2 (21 days after screening) to Visit 5 (50-55 exposure day)). Analysis population: The full analysis set included all dosed subjects with data after dosing.

End point type	Secondary
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End point timeframe:

Main phase of the trial

End point values	Turoctocog alfa: Main Phase (On-demand)	Turoctocog alfa: Main Phase (Preventive treatment)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51 ^[7]	57 ^[8]		

Units: bleeds/patient/year				
least squares mean (confidence interval 95%)	4.27 (3.09 to 5.89)	5.63 (4.27 to 7.43)		

Notes:

[7] - 98 bleeds of 51 subjects were analysed

[8] - 133 bleeds of 57 subjects were analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised bleeding rate: Extension phase

End point title	Annualised bleeding rate: Extension phase
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End point description:

Mean annualised bleeding rate defined as number of bleeds in total per patient per year following treatment were estimated by a Poisson model allowing for over-dispersion. The Poisson estimate is presented with a 95% confidence interval (CI). The results are presented for the extension phase of the trial (from completion of the main phase or completion of the inhibitor cohort until the end-of-trial visit). Analysis population: The full analysis set included all dosed subjects with data after dosing.

End point type	Secondary
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End point timeframe:

Extension phase of the trial

End point values	Turoctocog alfa: Extension phase (Preventive treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	49 ^[9]			
Units: bleeds/patient/year				
least squares mean (confidence interval 95%)	3.81 (2.84 to 5.11)			

Notes:

[9] - 269 bleeds of 49 subjects was analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised bleeding rate: Combined main and extension phases

End point title	Annualised bleeding rate: Combined main and extension phases
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End point description:

Mean annualised bleeding rate defined as number of bleeds in total per patient per year following treatment were estimated by a Poisson model allowing for over-dispersion. The Poisson estimate is presented with a 95% confidence interval (CI). The results are presented for the combined main and extension phases of the trial (from visit 2 to until end of trial). The results of inhibitor cohort are also presented. Analysis population: The full analysis set included all dosed subjects except one subject, with data after dosing. One subject with only one exposure day during main and total period was excluded from the analysis.

End point type	Secondary
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End point timeframe:

Combined main and extension phases

End point values	Turoctocog alfa : Overall study	Turoctocog alfa: Inhibitor cohort		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	58 ^[10]	26 ^[11]		
Units: bleeds/patient/year				
least squares mean (confidence interval 95%)	4.26 (3.34 to 5.44)	6.09 (3.77 to 9.84)		

Notes:

[10] - 402 bleeds of 58 patients was analysed

[11] - 179 bleeds of 26 subjects was analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rate of FVIII inhibitors (≥ 0.6 BU): Extension phase

End point title	Incidence rate of FVIII inhibitors (≥ 0.6 BU): Extension phase
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End point description:

The incidence rate of FVIII inhibitors is defined as inhibitor titres ≥ 0.6 bethesda unit (BU) for extension phase of the trial. The result is presented as percentage of subjects who developed FVIII inhibitor during the extension phase out of subjects who were exposed in the extension phase without inhibitor in the main phase. Analysis population: The full analysis set included all subjects who were exposed in the extension phase without inhibitor in the main phase.

End point type	Secondary
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End point timeframe:

Extension phase of the trial

End point values	Turoctocog alfa: Extension phase (Preventive treatment)			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Percentage of participants				
number (confidence interval 95%)	3.0 (0.1 to 15.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rate of FVIII inhibitors (≥ 0.6 BU): Combined main and

extension phases

End point title	Incidence rate of FVIII inhibitors (≥ 0.6 BU): Combined main and extension phases
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End point description:

The incidence rate of FVIII inhibitors is defined as inhibitor titres ≥ 0.6 bethesda unit (BU) for the combined main and extension phase of the trial. The result is presented as percentage of subjects who developed FVIII inhibitor during the combined main and extension phase out of subjects who completed the main phase. Analysis population: The full analysis set included all subjects who completed the main phase.

End point type	Secondary
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End point timeframe:

Combined main and extension phases

End point values	Turoctocog alfa : Overall study			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: percentage				
number (confidence interval 95%)	44.8 (31.7 to 58.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events from the first trial related activity after the patient had signed the informed consent (visit 1) until the end-of-trial visit.

Adverse event reporting additional description:

Analysis population: Safety analysis set, which included all dosed subjects with data after dosing. All reported adverse events in this trial were treatment emergent adverse events (TEAEs).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21
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Reporting groups

Reporting group title	Turoctocog alfa
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Reporting group description:

Subjects received turoctocog alfa for the prevention of bleeding. The investigator decided the dose of turoctocog alfa based on the child's clinical profile. The trial consists of two phases. The main phase was completed when either the patient received treatment with turoctocog alfa for at least 50 exposure days (ED) or developed FVIII inhibitors. After completing the main phase, the patient could transition to the extension phase, if the main phase was completed without inhibitors, or start an alternative visit schedule, if FVIII inhibitors were detected. Subjects developing inhibitors anytime during the trial were considered as a separate 'inhibitor' cohort and evaluated accordingly. Upon successful eradication of the inhibitors these patients enter the extension phase (if the inhibitor developed during the main phase) or re-enter it (if it had developed after they had started the extension phase). The total duration of the trial was around 7 years.

Serious adverse events	Turoctocog alfa		
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 60 (60.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Poor venous access			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Phlebitis deep			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Central venous catheter removal			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Central venous catheterisation			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Circumcision			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hospitalisation			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Catheter site haematoma			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Catheter site oedema			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Status asthmaticus			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device dislocation			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device damage			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Head injury			

subjects affected / exposed	3 / 60 (5.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Traumatic haemorrhage			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Cryptorchism			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydrocele			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial haematoma			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Factor VIII inhibition			
subjects affected / exposed	25 / 60 (41.67%)		
occurrences causally related to treatment / all	27 / 27		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mouth haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Joint effusion			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter site infection			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			

subjects affected / exposed	2 / 60 (3.33%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal infection				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nasopharyngitis				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis media acute				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed	2 / 60 (3.33%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Streptococcal bacteraemia				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Systemic bacterial infection				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				

subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injection site infection			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular device infection			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Turoctocog alfa		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 60 (91.67%)		
Investigations			
Body temperature increased			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	4		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	5		
Contusion			

subjects affected / exposed occurrences (all)	6 / 60 (10.00%) 9		
Head injury subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 9		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	6 / 60 (10.00%) 8		
Factor VIII inhibition subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 4		
Iron deficiency anaemia subjects affected / exposed occurrences (all)	8 / 60 (13.33%) 12		
General disorders and administration site conditions Catheter site inflammation subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3		
Pyrexia subjects affected / exposed occurrences (all)	32 / 60 (53.33%) 85		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3		
Diarrhoea subjects affected / exposed occurrences (all)	12 / 60 (20.00%) 25		
Teething subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3		
Vomiting subjects affected / exposed occurrences (all)	11 / 60 (18.33%) 19		
Reproductive system and breast disorders			

Balanoposthitis subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	15 / 60 (25.00%) 26 4 / 60 (6.67%) 6 7 / 60 (11.67%) 10		
Skin and subcutaneous tissue disorders Dermatitis diaper subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Rash papular subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3 5 / 60 (8.33%) 6 5 / 60 (8.33%) 11 3 / 60 (5.00%) 3		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Ear infection subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all)	7 / 60 (11.67%) 7 6 / 60 (10.00%) 10 8 / 60 (13.33%) 8		

Hand-foot-and-mouth disease subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 5		
Influenza subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 5		
Nasopharyngitis subjects affected / exposed occurrences (all)	16 / 60 (26.67%) 36		
Otitis media subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 4		
Otitis media acute subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 7		
Pharyngitis subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 4		
Pneumonia subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 5		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	15 / 60 (25.00%) 64		
Viral infection subjects affected / exposed occurrences (all)	7 / 60 (11.67%) 9		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 11		
Catheter site infection subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 7		
Conjunctivitis subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3		

Gastroenteritis viral subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 4		
Tonsillitis subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 6		
Varicella subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3		
Metabolism and nutrition disorders Iron deficiency subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2012	<p>Amendment 1: In Section 1, 3, 5, and 6 the number of patients and number of ED were reduced.</p> <p>In Section 12.5.2 and 18.4, number of pre-planned safety interim analysis was reduced from two to one.</p> <p>In Section 6.2, an inclusion criteria "Immunocompetent, defined as either cells >200 cells/μl", was added.</p> <p>In Section 6.4, one withdrawal criteria, "For inhibitor patients – inhibitor treatment failure with N8 treatment", was removed.</p> <p>In Section 12.1.2, All hypersensitivity reactions reported as MESIs were to be followed up with a hypersensitivity questionnaire was added under Adverse events of special interest.</p> <p>Several minor inconsistencies /ambiguities, and apparent mistakes were corrected in the protocol.</p>
13 October 2012	<p>Amendment 5: In Section 1, 2, the concept of two different phases of the trial, a main phase and an extension phase was introduced.</p> <p>In Section 4.2, secondary endpoints were updated, "The secondary endpoints will be evaluated for the main phase of trial, for the extension phase of trial, and for the combined main and extension phases."</p> <p>In Section 5.1, trial duration extended from approximately 50 months to 5 years.</p> <p>In Section 5.3.4, treatment schedule for patients who develop inhibitors was changed, "If needed and decided by the Investigator, the initiation of the inhibitor treatment with turoctocog alfa can be delayed for up to 6 months from the time of diagnosis of inhibitor.</p> <p>If the inhibitor disappears (BU <0.6/mL) during the ITI treatment, the patient should resume preventive treatment as recommended in this protocol, following the visit schedule in the extension phase. For patients still with positive inhibitors after 12 months ITI treatment, continued trial participation will be evaluated based on the level of inhibitors."</p> <p>In Section 6.1, the planned number of patients to be screened (i.e. documented informed consent) was decreased from 75 to 65.</p> <p>In Section 6.4, one withdrawal criteria, "Haemostasis not achievable with turoctocog alfa: The bleed could not be controlled after 48 hours using recommended doses of turoctocog alfa", was removed.</p> <p>In Section 8.1, visit details were updated including Extension phase visit, EoT visit</p> <p>In Section, 8.2.9, pulse and blood pressure were removed from the list of vital signs assessment.</p> <p>In Section 18.2.4, supportive secondary efficacy and safety endpoints were updated according to the concept of main phase and extension phase.</p>

19 January 2013	<p>Amendment 6: In Section 2 and 5.1, Visit 1 and Visit 2 combined to be performed at the same occasion. This was done to minimize the bleeding risks in untreated patients.</p> <p>In Section 6.2, "Immunocompetent, defined as either HIV negative or if HIV positive, CD4+ cells >200 cells/μL" was removed from inclusion criteria since the immune competency was expected to be present in the vast majority of PUP. This criteria was removed so as to avoid having unnecessary criteria.</p> <p>In Section 6.2, inclusion criteria #2 was updated. Patients had to be diagnosed as opposed to be presenting with congenital severe haemophilia A (FVIII \leq1%).</p> <p>In Section 6.3, Platelet count <50,000 platelets/μL was removed from exclusion criteria. The exclusion criteria "patients with FVIII inhibitor (>0.6 BU) should be excluded from the trial" was removed. Exclusion criterion was updated to "Any history of FVIII inhibitor".</p> <p>In Section 12.1.2, Inhibitor formation against FVIII was updated to be always considered as MESI. Analysis of haematology to be performed at central lab. However, if an investigator obtains any indication of inhibitor formation by clinical signs or local laboratory results, it should be reported as MESIs.</p>
03 February 2014	<p>Amendment 7: In Section 5.1 and 7, the trial duration (from 5 to 7 years) and end-of-trial date were revised.</p> <p>In Section 5.3, the duration and conditions for the treatment of patients with inhibitors were redefined. In Section 6.1, planned number of patients to complete the main phase of the trial was updated.</p> <p>In Section 6.4, below withdrawal criteria were updated to ensure the safety of patients, who do not benefit from inhibitor treatment with turoctocog alfa. *</p> <p>"Inhibitor treatment has not been started within 6 months from the date of confirmation of positive FVIII inhibitor (BU \geq 0.6/mL) * FVIII inhibitor titre decline from peak level is less than 20% after 12 months of inhibitor treatment * FVIII inhibitor is positive (BU \geq 0.6/mL) after 24 months of inhibitor treatment. *After completed inhibitor treatment (maximum 24 months), preventive treatment as described in the protocol is not resumed/started."</p> <p>In Section 7, trial schedule was updated including details about LPLV, Planned completion of main and updated clinical trial report protocol exceptions.</p> <p>In Section 8.2.2.2, non-neutralising antibodies were defined.</p> <p>In Section 8.3.1, definition of bleeds, severe bleed, and re-bleed were defined.</p> <p>In Section 12.1, definitions of serious adverse events were re-defined, final outcome of an AE and MESI were updated.</p> <p>The possibility to further investigate immunogenicity of turoctocog alfa e.g. binding antibody assessment and HLA genotyping was introduced.</p>
04 September 2014	<p>Amendment 9: In Section 7, recruitment period was prolonged to ensure possibility of recruiting Chinese patients as the clinical trial application (CTA) in China was delayed</p> <p>In Section 12.5.2, timing of interim analysis changed to ensure timely interim analysis independent of number of inhibitor patients</p> <p>Number of planned sites increased to fulfil the number of planned recruited patients.</p> <p>Exclusion criteria "Preventive treatment not initiated at age of 24 months" was added</p> <p>In Section 8.2.6, a withdrawal criteria about Lupus Anticoagulant test – (preventive treatment not initiated at age 24 months), long-term retention of blood samples, a new preventive treatment (2x weekly), monitoring visits every 12 weeks – was added. This was done to align with other PUP trials in haemophilia and to ensure better evaluation of inhibitor patients</p> <p>Twice weekly dosing option was introduced. This was done since the gap from once weekly to 3 times weekly infusion of preventive treatment was too big. Sites requested twice weekly frequency to avoid overdosing of patients.</p> <p>Definition of 'disease-related' bleeding was changed from being AE to not AE. This was done to align with other guardian protocols and Global Safeties current definition of disease related bleedings</p> <p>In Section, 5.3.2, Guide for dosing in bleeding episodes was added on request of sites.</p> <p>In Section 25, methods of retention of blood samples were defined.</p>
18 January 2016	<p>Amendment 10: In Section 7, planned duration of recruitment was increased from 39 to 45 months. Planned dates for last patient first visit (LPPV) and LPLV were also updated.</p> <p>Minor inconsistencies, ambiguities and typographical errors were corrected.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported