Clinical trial results:
Safety and efficacy of turoctocog alfa pegol (N8-GP) in previously untreated patients with haemophilia A

Summary

EudraCT number	2013-004025-88
Trial protocol	DE AT ES PT GR BG RO IT FR
Global end of trial date	07 June 2023

Results information

Result version number	v1
This version publication date	22 December 2023
First version publication date	22 December 2023

Trial information

Trial identification

Sponsor protocol code	NN7088-3908

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02137850
WHO universal trial number (UTN)	U1111-1148-1897
Other trial identifiers	Japanese trial registration: JapicCTI-142577

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 November 2021
Global end of trial reached?	Yes
Global end of trial date	07 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate immunogenicity of N8-GP (turoctocog alfa pegol) in previously untreated patients (PUPs) with severe haemophilia A

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice, including archiving of essential documents, and Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) 312.12.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	26 June 2014
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	Australia: 5
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Malaysia: 11
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Thailand: 12
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	81
EEA total number of subjects	20

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	12
Infants and toddlers (28 days-23 months)	61
Children (2-11 years)	8
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:

The trial was conducted in 14 countries as follows: Australia (2), Austria (2), Bulgaria (1), Canada (1), Germany (1), Greece (2), Israel (1), Italy (1), Japan (3), Malaysia (3), Spain (2), Taiwan (1), Thailand (3), United States (8).

Pre-assignment

Screening details:

44 subjects were switched from pre-prophylaxis to other two groups during main phase (42 subjects were switched to prophylaxis group and 2 subjects were switched to immune tolerance induction (ITI) group). Out of 2 subjects in immune tolerance induction (ITI) group, 1 subject was again switched from the ITI group to the prophylaxis group.

Period 1

Period 1 title	Main Phase
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Pre-prophylaxis

Arm description:

At the beginning of the main phase of the trial, slow start prophylaxis and on-demand treatment of bleeding episodes with trial product (N8-GP) were allowed at the discretion of the investigator and Subject’s parent(s)/ legally acceptable representative (LAR). The N8-GP dose for pre-prophylaxis treatment (except for bleeding episodes) was 60 International unit per kilogram (IU/kg) body weight (within the range of 50-75 IU/kg) to be administered as a single bolus dose intravenously (i.v.) with more than one week between doses (at the discretion of the investigator).

Arm type	Experimental
Investigational medicinal product name	turoctocog alfa pegol (N8-GP)
Investigational medicinal product code	
Other name	Esperoct
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The N8-GP dose for pre-prophylaxis treatment (except for bleeding episodes) was 60 International unit per kilogram (IU/kg) body weight (within the range of 50-75 IU/kg) to be administered as a single bolus dose intravenously (i.v.) with more than one week between doses (at the discretion of the investigator).

Arm title	Prophylaxis

Arm description:

For prophylaxis treatment, regular N8-GP administration was initiated no later than at the subject’s age of 24 months, or after 20 EDs on pre-prophylaxis, whatever came first. During the main phase of the trial, subjects received prophylaxis with i.v. injections of N8-GP preferably twice weekly, with doses separated by at least 3, and no more than 4, calendar days. Furthermore, it was permissible to start prophylaxis in the main phase with an every 3rd day or once-weekly dosing regimen. The N8-GP dose for prophylaxis treatment was 60 IU/kg (within the range of 50-75 IU/kg) to be administered as a single bolus dose i.v. on each administration day.

Arm type	Experimental
Investigational medicinal product name	turoctocog alfa pegol (N8-GP)
Investigational medicinal product code	
Other name	Esperoct
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The N8-GP dose for prophylaxis treatment was 60 IU/kg (within the range of 50-75 IU/kg) to be administered as a single bolus dose i.v. on each administration day.

Arm title	Immune tolerance induction (ITI)

Arm description:

Subjects who developed FVIII inhibitors in the trial were offered ITI treatment with N8-GP. If a newly diagnosed inhibitor subject still responded well to treatment with N8-GP, initiation of ITI could be postponed with up to 6 months, or ITI could be cancelled if the inhibitors had resolved during the 6 months. N8-GP treatment could continue in case of low titre FVIII inhibitor (lesser than or equal (≤) 5 Bethesda Units). In case of high titre FVIII inhibitor (greater than (>) 5 Bethesda Units), the investigator had to decide how to proceed with treatment. ITI with N8-GP had to be initiated within 6 months of the confirmatory inhibitor test. The N8-GP dose for ITI treatment was according to local standard. Maximum of 75 IU/kg as single dose, maximum of 200 IU/kg over 24 hours.

Arm type	Experimental
Investigational medicinal product name	turoctocog alfa pegol (N8-GP)
Investigational medicinal product code	
Other name	Esperoct
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The N8-GP dose for ITI treatment was according to local standard. Maximum of 75 IU/kg as single dose, maximum of 200 IU/kg over 24 hours.

Number of subjects in period 1	Pre-prophylaxis	Prophylaxis	Immune tolerance induction (ITI)
Started	55	69	8
Completed	44	59	6
Not completed	11	10	2
Consent withdrawn by subject	2	-	-
Adverse event, non-fatal	3	4	-
Unspecified	3	1	-
Lost to follow-up	-	1	-
Withdrawal by parent/guardian	1	2	1
Protocol deviation	1	1	-
Lack of efficacy	1	1	1

Period 2

Period 2 title	Extension phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Prophylaxis

Arm description:

For prophylaxis treatment, regular N8-GP administration was initiated no later than at the subject's age of 24 months, or after 20 EDs on pre-prophylaxis, whatever came first. In the extension phase, subjects were to continue the prophylaxis dosing regimen as prescribed at the end of the main phase. Based on the subjects individual bleeding patterns, modification of N8-GP dose and/or frequency was permitted at the investigator's discretion.

Arm type	Experimental
Investigational medicinal product name	turoctocog alfa pegol (N8-GP)
Investigational medicinal product code	
Other name	Esperoct
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The N8-GP dose for prophylaxis treatment was 60 IU/kg (within the range of 50-75 IU/kg) to be administered as a single bolus dose i.v. on each administration day.

Number of subjects in period 2	Prophylaxis
Started	55
Completed	48
Not completed	7
Adverse event, non-fatal	1
Other	4
Withdrawal by parent/guardian	1
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Main Phase

Reporting group description:

In the main phase of the trial, Subjects received treatment with N8-GP until they reached a minimum of 50 exposure days (EDs) each. An ED was defined as any day during which the subject exposed to N8-GP, including doses given for treatment of bleeding episodes, prophylaxis, surgery, and for the purpose of PK assessment. When at least 50 Subjects had reached a minimum of 50 EDs each in the main phase, the analysis and evaluation for the main trial report was performed.

Reporting group values	Main Phase	Total	
Number of subjects	81	81	
Age Categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	12	12	
Infants and toddlers (28 days-23 months)	61	61	
Children (2-11 years)	8	8	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	10.2		
standard deviation	± 11.0	-	
Gender Categorical			
Units: Subjects			
Female	0	0	
Male	81	81	

End points

End points reporting groups

Reporting group title	Pre-prophylaxis

Reporting group description:

At the beginning of the main phase of the trial, slow start prophylaxis and on-demand treatment of bleeding episodes with trial product (N8-GP) were allowed at the discretion of the investigator and Subject's parent(s)/ legally acceptable representative (LAR). The N8-GP dose for pre-prophylaxis treatment (except for bleeding episodes) was 60 International unit per kilogram (IU/kg) body weight (within the range of 50-75 IU/kg) to be administered as a single bolus dose intravenously (i.v.) with more than one week between doses (at the discretion of the investigator).

Reporting group title	Prophylaxis

Reporting group description:

For prophylaxis treatment, regular N8-GP administration was initiated no later than at the subject's age of 24 months, or after 20 EDs on pre-prophylaxis, whatever came first. During the main phase of the trial, subjects received prophylaxis with i.v. injections of N8-GP preferably twice weekly, with doses separated by at least 3, and no more than 4, calendar days. Furthermore, it was permissible to start prophylaxis in the main phase with an every 3rd day or once-weekly dosing regimen. The N8-GP dose for prophylaxis treatment was 60 IU/kg (within the range of 50-75 IU/kg) to be administered as a single bolus dose i.v. on each administration day.

Reporting group title	Immune tolerance induction (ITI)

Reporting group description:

Subjects who developed FVIII inhibitors in the trial were offered ITI treatment with N8-GP. If a newly diagnosed inhibitor subject still responded well to treatment with N8-GP, initiation of ITI could be postponed with up to 6 months, or ITI could be cancelled if the inhibitors had resolved during the 6 months. N8-GP treatment could continue in case of low titre FVIII inhibitor (lesser than or equal (≤) 5 Bethesda Units). In case of high titre FVIII inhibitor (greater than (>) 5 Bethesda Units), the investigator had to decide how to proceed with treatment. ITI with N8-GP had to be initiated within 6 months of the confirmatory inhibitor test. The N8-GP dose for ITI treatment was according to local standard. Maximum of 75 IU/kg as single dose, maximum of 200 IU/kg over 24 hours.

Reporting group title	Prophylaxis

Reporting group description:

For prophylaxis treatment, regular N8-GP administration was initiated no later than at the subject's age of 24 months, or after 20 EDs on pre-prophylaxis, whatever came first. In the extension phase, subjects were to continue the prophylaxis dosing regimen as prescribed at the end of the main phase. Based on the subjects individual bleeding patterns, modification of N8-GP dose and/or frequency was permitted at the investigator's discretion.

Subject analysis set title	Main + extension phase: pre-prophylaxis
Subject analysis set type	Full analysis

Subject analysis set description:

At the beginning of the main phase of the trial, slow start prophylaxis and on-demand treatment of bleeding episodes with trial product (N8-GP) were allowed at the discretion of the investigator and Subject's parent(s)/ legally acceptable representative (LAR).

Subject analysis set title	Main + extension phase: prophylaxis
Subject analysis set type	Full analysis

Subject analysis set description:

For prophylaxis treatment, regular N8-GP administration was initiated no later than at the subject's age of 24 months, or after 20 EDs on pre-prophylaxis, whatever came first. During the main phase of the trial, subjects received prophylaxis with i.v. injections of N8-GP preferably twice weekly, with doses separated by at least 3, and no more than 4, calendar days. Furthermore, it was permissible to start prophylaxis in the main phase with an every 3rd day or once-weekly dosing regimen. In the extension phase, subjects were to continue the prophylaxis dosing regimen as prescribed at the end of the main phase. Based on the subjects individual bleeding patterns, modification of N8-GP dose and/or frequency was permitted at the investigator's discretion.

Subject analysis set title	Main + extension phase: immune tolerance induction (ITI)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who developed FVIII inhibitors in the trial were offered ITI treatment with N8-GP. If a newly diagnosed inhibitor subject still responded well to treatment with N8-GP, initiation of ITI could be postponed with up to 6 months, or ITI could be cancelled if the inhibitors had resolved during the 6

months. N8-GP treatment could continue in case of low titre FVIII inhibitor (lesser than or equal (≤) 5 Bethesda Units). In case of high titre FVIII inhibitor (greater than (>) 5 Bethesda Units), the investigator had to decide how to proceed with treatment. ITI with N8-GP had to be initiated within 6 months of the confirmatory inhibitor test.

Primary: Incidence of inhibitory antibodies against coagulation factor VIII (FVIII)

End point title	Incidence of inhibitory antibodies against coagulation factor VIII (FVIII)

End point description:

The incidence of inhibitory antibodies was reported during the main and extension phase of the trial. Results were based on safety analysis set (SAS). The SAS consist of all subjects exposed to N8-GP. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Primary

End point timeframe:

When the first 50 PUPs have reached at least 50 exposure days and at end of trial. End of trial will be up to 4 years after the first patient has reached 100 exposure days

End point values	Main + extension phase: pre-prophylaxis	Main + extension phase: prophylaxis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	68		
Units: Subjects	11	10		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

A one-sided, upper 97.5% confidence limit was provided based on an exact calculation in the binomial distribution.

Comparison groups	Main + extension phase: pre-prophylaxis v Main + extension phase: prophylaxis
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Incidence rate
Point estimate	0.3
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	0.421

Notes:

[1] - Total number of subjects included in statistical analysis is 80. The number given here is auto-calculated by the system.

Secondary: Frequency of adverse events including serious adverse events and medical events of special interest

End point title	Frequency of adverse events including serious adverse events and medical events of special interest

End point description:

The frequency of adverse events including serious adverse events and medical events of special interest reported during the main and extension phase of the trial. An adverse event (AE) is any untoward medical occurrence in a patient administered a product, and which does not necessarily have a causal relationship with this treatment. Serious adverse event (SAE) is an experience that at any dose results in any of the following: Death, a life-threatening experience, in-patient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability or incapacity, congenital anomaly or birth defect and important medical events that may not result in death, be life threatening or require hospitalisation. Medical event of special interest (MESI) is an event which, in the evaluation of safety, has a special focus. Results were based on SAS. The SAS consists of all subjects exposed to N8-GP.

End point type	Secondary

End point timeframe:

When the first 50 PUPs have reached at least 50 exposure days and at end of trial. End of trial will be up to 4 years after the first patient has reached 100 exposure days

End point values	Main + extension phase: pre-prophylaxis	Main + extension phase: prophylaxis	Main + extension phase: immune tolerance induction (ITI)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	55	69	8	
Units: Events				
number (not applicable)				
Adverse events	116	644	30	
Serious adverse events	24	56	3	
Medical events of special interest	17	47	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of breakthrough bleeding episodes during prophylaxis with turoctocog alfa pegol (N8-GP) (annualised bleeding rate)

End point title	Number of breakthrough bleeding episodes during prophylaxis with turoctocog alfa pegol (N8-GP) (annualised bleeding rate)

End point description:

The number of bleeding episodes per year reported during the prophylactic treatment with N8-GP. Results were based on full analysis set (FAS). The FAS consists of all subjects exposed to N8-GP. The endpoint is applicable for only reported group.

End point type	Secondary

End point timeframe:

When the first 50 PUPs have reached at least 50 exposure days and at end of trial. End of trial will be up to 4 years after the first patient has reached 100 exposure days

End point values	Main + extension phase: prophylaxis			
Subject group type	Subject analysis set			
Number of subjects analysed	69			
Units: bleeds/patient/year				
median (inter-quartile range (Q1-Q3))	1.35 (0.60 to 3.50)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of confirmed high titre inhibitors (defined as inhibitor titre above 5 Bethesda Units (BU)

End point title	Incidence of confirmed high titre inhibitors (defined as inhibitor titre above 5 Bethesda Units (BU)

End point description:

The incidence of confirmed high titre inhibitors (defined as inhibitor titre above 5 Bethesda Units (BU) was reported during the main and extension phase of the trial. Results were based on safety analysis set (SAS). The SAS consist of all subjects exposed to N8-GP. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

When the first 50 PUPs have reached at least 50 exposure days and at end of trial. End of trial will be up to 4 years after the first patient has reached 100 exposure days

End point values	Main + extension phase: pre-prophylaxis	Main + extension phase: prophylaxis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	68		
Units: Subjects	3	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic effect of N8-GP in treatment of bleeding episodes, assessed by a predefined 4-point haemostatic response scale (“excellent”, “good”, “moderate” and “none”)

End point title	Haemostatic effect of N8-GP in treatment of bleeding episodes, assessed by a predefined 4-point haemostatic response scale (“excellent”, “good”, “moderate” and “none”)

End point description:

Haemostatic effect of turoctocog alfa pegol for treatment of bleeding episodes was assessed by 4-point response scale: none, moderate, good or excellent. Excellent: Abrupt pain relief and/or clear

improvement in objective signs of bleeding within approximately 8 hours after a single injection; Good: Definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after a single injection, but possibly requiring more than one injection for complete resolution; Moderate: Probable or slight beneficial effect within approximately 8 hours after the first injection, but usually requiring more than one injection; None: No improvement, or worsening of symptoms. Results were based on full analysis set (FAS). The FAS consists of all subjects exposed to N8-GP. Number of subjects analyzed = number of bleeds in subjects.

End point type	Secondary

End point timeframe:

When the first 50 PUPs have reached at least 50 exposure days and at end of trial. End of trial will be up to 4 years after the first patient has reached 100 exposure days

End point values	Main + extension phase: pre-prophylaxis	Main + extension phase: prophylaxis	Main + extension phase: immune tolerance induction (ITI)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	48	59	4	
Units: Bleeding episodes				
number (not applicable)				
Excellent	69	227	2	
Good	62	92	3	
Moderate	18	18	3	
None	3	6	0	
Missing	8	2	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first exposure to N8-GP of main phase to end of extension phase

Adverse event reporting additional description:

All the presented adverse events (AEs) are treatment emergent adverse events (TEAEs). AEs occurring in a patient before being exposed to N8-GP. Safety analysis set included all patients exposed to N8-GP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Pre-prophylaxis

Reporting group description:

At the beginning of the main phase of the trial, slow start prophylaxis and on-demand treatment of bleeding episodes with trial product (N8-GP) were allowed at the discretion of the investigator and Subject's parent(s)/ legally acceptable representative (LAR). The N8-GP dose for pre-prophylaxis treatment was 60 IU/kg body weight (within the range of 50-75 IU/kg) to be administered as a single bolus dose intravenously (i.v.) with more than one week between doses (at the discretion of the investigator).

Reporting group title	Immune tolerance induction (ITI)

Reporting group description:

Patients who developed FVIII inhibitors in the trial were offered ITI treatment with N8-GP. If a newly diagnosed inhibitor patient still responded well to treatment with N8-GP, initiation of ITI could be postponed with up to 6 months, or ITI could be cancelled if the inhibitors had resolved during the 6 months. N8-GP treatment could continue in case of low titre FVIII inhibitor (lesser than or equal (≤) 5 Bethesda Units). In case of high titre FVIII inhibitor (greater than (>) 5 Bethesda Units), the investigator had to decide how to proceed with treatment. ITI with N8-GP had to be initiated within 6 months of the confirmatory inhibitor test.

Reporting group title	Prophylaxis

Reporting group description:

For prophylaxis treatment, regular N8-GP administration was initiated no later than at the subject's age of 24 months, or after 20 EDs on pre-prophylaxis, whatever came first. The N8-GP dose for prophylaxis treatment was 60 IU/kg (within the range of 50-75 IU/kg) to be administered as a single bolus dose intravenously (i.v.) on each administration day.

Serious adverse events	Pre-prophylaxis	Immune tolerance induction (ITI)	Prophylaxis
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 55 (32.73%)	1 / 8 (12.50%)	34 / 69 (49.28%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 55 (1.82%)	0 / 8 (0.00%)	0 / 69 (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
Surgical and medical procedures			

Arteriovenous fistula operation			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth extraction			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urogenital fistula repair			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral repair			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Therapy non-responder			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaccination site haemorrhage			
subjects affected / exposed	1 / 55 (1.82%)	0 / 8 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			

subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device issue			
subjects affected / exposed	0 / 55 (0.00%)	1 / 8 (12.50%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Anti factor VIII antibody positive			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart rate increased			
subjects affected / exposed	1 / 55 (1.82%)	0 / 8 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 55 (1.82%)	0 / 8 (0.00%)	0 / 69 (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
Head injury			

subjects affected / exposed	2 / 55 (3.64%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue injury			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural fistula			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haematoma			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth injury			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth fracture			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound haemorrhage			

subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 55 (1.82%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile convulsion			
subjects affected / exposed	1 / 55 (1.82%)	0 / 8 (0.00%)	0 / 69 (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
Spinal epidural haematoma			
subjects affected / exposed	1 / 55 (1.82%)	0 / 8 (0.00%)	0 / 69 (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
Seizure			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Factor VIII inhibition			
subjects affected / exposed	10 / 55 (18.18%)	0 / 8 (0.00%)	12 / 69 (17.39%)
occurrences causally related to treatment / all	10 / 10	0 / 0	12 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Mouth haemorrhage			
subjects affected / exposed	1 / 55 (1.82%)	0 / 8 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash erythematous			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 8 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 55 (0.00%)	1 / 8 (12.50%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterobacter infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 8 (0.00%)	0 / 69 (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
Gastroenteritis			

subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngotonsillitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia haemophilus			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
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 syncytial virus infection			

subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
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 syncytial virus bronchiolitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 8 (0.00%)	0 / 69 (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
Vascular device infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster virus infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Pre-prophylaxis	Immune tolerance induction (ITI)	Prophylaxis
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 55 (50.91%)	7 / 8 (87.50%)	51 / 69 (73.91%)
Investigations			
Anti factor VIII antibody positive			
subjects affected / exposed	3 / 55 (5.45%)	0 / 8 (0.00%)	1 / 69 (1.45%)
occurrences (all)	3	0	1
Injury, poisoning and procedural			

complications			
Anaesthetic complication			
subjects affected / exposed	0 / 55 (0.00%)	1 / 8 (12.50%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	3 / 55 (5.45%)	1 / 8 (12.50%)	5 / 69 (7.25%)
occurrences (all)	5	2	72
Cardiac disorders			
Cyanosis			
subjects affected / exposed	4 / 55 (7.27%)	0 / 8 (0.00%)	0 / 69 (0.00%)
occurrences (all)	4	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 55 (3.64%)	1 / 8 (12.50%)	0 / 69 (0.00%)
occurrences (all)	3	2	0
Factor VIII inhibition			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	4 / 69 (5.80%)
occurrences (all)	0	0	6
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 55 (9.09%)	2 / 8 (25.00%)	26 / 69 (37.68%)
occurrences (all)	6	2	75
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 55 (1.82%)	1 / 8 (12.50%)	6 / 69 (8.70%)
occurrences (all)	1	1	9
Vomiting			
subjects affected / exposed	1 / 55 (1.82%)	1 / 8 (12.50%)	5 / 69 (7.25%)
occurrences (all)	1	1	10
Tooth loss			
subjects affected / exposed	0 / 55 (0.00%)	1 / 8 (12.50%)	1 / 69 (1.45%)
occurrences (all)	0	3	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 55 (5.45%)	0 / 8 (0.00%)	9 / 69 (13.04%)
occurrences (all)	3	0	13
Tonsillar hypertrophy			

subjects affected / exposed	0 / 55 (0.00%)	1 / 8 (12.50%)	1 / 69 (1.45%)
occurrences (all)	0	1	1
Rhinorrhoea			
subjects affected / exposed	0 / 55 (0.00%)	1 / 8 (12.50%)	7 / 69 (10.14%)
occurrences (all)	0	1	13
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	1 / 55 (1.82%)	1 / 8 (12.50%)	1 / 69 (1.45%)
occurrences (all)	1	1	2
Infections and infestations			
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 55 (0.00%)	1 / 8 (12.50%)	3 / 69 (4.35%)
occurrences (all)	0	1	3
Gastroenteritis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 8 (0.00%)	9 / 69 (13.04%)
occurrences (all)	1	0	10
Ear infection			
subjects affected / exposed	3 / 55 (5.45%)	0 / 8 (0.00%)	9 / 69 (13.04%)
occurrences (all)	7	0	13
Conjunctivitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	5 / 69 (7.25%)
occurrences (all)	0	0	6
Cellulitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 8 (12.50%)	1 / 69 (1.45%)
occurrences (all)	0	1	1
Bronchitis			
subjects affected / exposed	1 / 55 (1.82%)	1 / 8 (12.50%)	6 / 69 (8.70%)
occurrences (all)	1	1	6
Influenza			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	6 / 69 (8.70%)
occurrences (all)	0	0	7
Varicella			
subjects affected / exposed	1 / 55 (1.82%)	1 / 8 (12.50%)	2 / 69 (2.90%)
occurrences (all)	1	1	2
Upper respiratory tract infection			

subjects affected / exposed	7 / 55 (12.73%)	2 / 8 (25.00%)	16 / 69 (23.19%)
occurrences (all)	8	3	35
Tonsillitis			
subjects affected / exposed	2 / 55 (3.64%)	0 / 8 (0.00%)	6 / 69 (8.70%)
occurrences (all)	2	0	8
Rhinitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	5 / 69 (7.25%)
occurrences (all)	0	0	10
Pharyngotonsillitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 8 (0.00%)	4 / 69 (5.80%)
occurrences (all)	0	0	4
Pharyngitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 8 (0.00%)	5 / 69 (7.25%)
occurrences (all)	1	0	8
Otitis media			
subjects affected / exposed	2 / 55 (3.64%)	1 / 8 (12.50%)	4 / 69 (5.80%)
occurrences (all)	2	1	6
Nasopharyngitis			
subjects affected / exposed	6 / 55 (10.91%)	1 / 8 (12.50%)	22 / 69 (31.88%)
occurrences (all)	7	4	80
Viral infection			
subjects affected / exposed	1 / 55 (1.82%)	0 / 8 (0.00%)	5 / 69 (7.25%)
occurrences (all)	1	0	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2015	Detailed information on major surgery and ITI, extended trial timelines.
01 November 2016	This protocol amendment included a new secondary endpoint to assess the ITI treatment outcome and included monitoring of antibody development against Host Cell Protein (HCP).
13 June 2019	This protocol amendment specified interim analysis when approximately 45 subjects had reached 50 EDs each, and additional administrative changes.
15 June 2020	This protocol amendment specified the closure of recruitment to the trial, and that more than 50 but less than 100 subjects would complete the trial. LPLV date 13 November 2021 was kept. Due to the observations of non-inhibitor subjects with low IR, anti-PEG IgG and additional IgM antibody analyses were added to the assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported