Clinical trial results:
An Open-Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc; BIIB029) in the Prevention and Treatment of Bleeding in Previously Untreated Patients With Severe Hemophilia B

Summary

EudraCT number	2013-003629-27
Trial protocol	IE GB DE SE BE ES IT DK NL PL FR
Global end of trial date	20 August 2019

Results information

Result version number	v1 (current)
This version publication date	01 March 2020
First version publication date	01 March 2020

Trial information

Trial identification

Sponsor protocol code	998HB303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02234310
WHO universal trial number (UTN)	-
Other trial identifiers	PUPs B-LONG: EFC16227

Notes:

Sponsors

Sponsor organisation name	Bioverativ, a Sanofi company
Sponsor organisation address	225 Second Avenue, Waltham, Massachusetts (MA), United States, 02451
Public contact	Trial Transparency Team, Bioverativ, a Sanofi company, clinicaltrials@bioverativ.com
Scientific contact	Trial Transparency Team, Bioverativ, a Sanofi company, clinicaltrials@bioverativ.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000914-PIP01-10
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	04 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of recombinant coagulation Factor IX Fc fusion protein (rFIXFc) in previously untreated patients (PUPs) with severe hemophilia B.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	United States: 11
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	33
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)	0
Infants and toddlers (28 days-23 months)	31
Children (2-11 years)	2
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 study was conducted at 28 active centres in 11 countries between 13-Nov-2014 to 23-Jul-2018.

Pre-assignment

Screening details:

A total of 38 subjects were screened for eligibility. A total of 33 subjects were enrolled, 22 subjects began study participation on episodic treatment regimen and 11 subjects began study participation on the prophylactic treatment regimen. Of 22 subjects on the episodic treatment, 17 subjects switched to prophylactic treatment during the study.

Period 1

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

Arms

Arm title	Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc)

Arm description:

Subjects received rFIXFc intravenous (IV) injection as follows: Prophylactic treatment regimen: started with rFIXFc 50 International Units per kilogram (IU/kg) weekly until subject reached at least 50 exposure days (ED=24-hour period in which >=1 injection/dose of rFIXFc was given) to rFIXFc, withdrawal from study or end of study. Adjustments to dose and dosing interval was based on incremental recovery, subsequent Factor IX levels, physical activity, bleeding pattern, in accordance with local standards of care for prophylactic regimen (PR). Treatment with episodic (on demand) regimen can be initiated before PR at investigators discretion. Episodic (On demand; optional): rFIXFc at individual doses based on subject's clinical condition, type and severity of bleeding event until PR.

Arm type	Experimental
Investigational medicinal product name	Recombinant coagulation factor IX-Fc fusion protein
Investigational medicinal product code	rFIXFc
Other name	BIIB029, Alprolix
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received rFIXFc as an IV injection

Number of subjects in period 1	Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc)
Started	33
Episodic Treatment Regimen	22 [1]
Prophylactic Treatment Regimen	28
Completed	27
Not completed	6
Consent withdrawn by subject	2
Physician decision	1
Adverse event	1

Eligibility Criteria not fulfilled	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects were treated in more than one regimen and counted in all categories wherever applicable. 17 subjects among the 22 who started in episodic regimen, switched to the prophylactic treatment regimen.

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description:

Subjects received rFIXFc IV injection as follows: Prophylactic treatment regimen: started with rFIXFc 50 IU/kg weekly until subject reached at least 50 exposure days (ED=24-hour period in which >=1 injection/dose of rFIXFc was given) to rFIXFc, withdrawal from study or end of study. Adjustments to dose and dosing interval was based on incremental recovery, subsequent Factor IX levels, physical activity, bleeding pattern, in accordance with local standards of care for PR. Treatment with episodic (on demand) regimen can be initiated before PR at investigators discretion. Episodic (On demand; optional): rFIXFc at individual doses based on subject's clinical condition, type and severity of bleeding event until PR.

Reporting group values	Overall study	Total	
Number of subjects	33	33	
Age categorical Units: Subjects			
Age continuous Units: years			
median	0.60		
full range (min-max)	0.08 to 2.00	-	
Gender categorical Units: Subjects			
Male	33	33	
Female	0	0	
Race Units: Subjects			
White	22	22	
Black or African-American	1	1	
Asian	1	1	
American Indian or Alaska Native	0	0	
Native Hawaiian or other Pacific Islander	0	0	
Unknown or Not reported	5	5	
Other	4	4	

End points

End points reporting groups

Reporting group title	Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc)

Reporting group description:

Subjects received rFIXFc intravenous (IV) injection as follows: Prophylactic treatment regimen: started with rFIXFc 50 International Units per kilogram (IU/kg) weekly until subject reached at least 50 exposure days (ED=24-hour period in which >=1 injection/dose of rFIXFc was given) to rFIXFc, withdrawal from study or end of study. Adjustments to dose and dosing interval was based on incremental recovery, subsequent Factor IX levels, physical activity, bleeding pattern, in accordance with local standards of care for prophylactic regimen (PR). Treatment with episodic (on demand) regimen can be initiated before PR at investigators discretion. Episodic (On demand; optional): rFIXFc at individual doses based on subject's clinical condition, type and severity of bleeding event until PR.

Primary: Percentage of Subjects With Confirmed Inhibitor Development as Measured by the Nijmegen-Modified Bethesda Assay

End point title	Percentage of Subjects With Confirmed Inhibitor Development as Measured by the Nijmegen-Modified Bethesda Assay[1]

End point description:

Development of an inhibitor was defined as an inhibitor test result of greater than or equal to (>=) 0.60 Bethesda units per millilitre (BU/mL) that was confirmed by a second test result of >=0.60 BU/mL from a separate sample, drawn 2 to 4 weeks after the date when the original sample was drawn, with both tests performed by the central laboratory using Nijmegen-modified Bethesda assay. Analysis performed on Safety Analysis set which included all subjects who had received at least 1 dose of study treatment.

End point type	Primary

End point timeframe:

Up to 3 years

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: Analysis was descriptive in nature, no inferential was provided.

End point values	Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage of subjects				
number (confidence interval 95%)	3.03 (0.08 to 15.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Number of Bleeding Episodes (Spontaneous and Traumatic) per Subject (Annualized Bleeding Rate [ABR])

End point title	Annualized Number of Bleeding Episodes (Spontaneous and Traumatic) per Subject (Annualized Bleeding Rate [ABR])

End point description:

ABR was annualized number of bleeding episodes during efficacy period (EP) per subject normalized to a 1-year interval of time. Bleeding episodes were classified as: spontaneous- if parent/caregiver/subject records bleeding event when there is no known contributing factor such as definite trauma or antecedent strenuous activity; and traumatic- when there is known reason for bleed. ABR=(Number of bleeding episodes during EP/total number of days during EP)*365.25. EP reflects the sum of all intervals of time during which subjects were treated with rFIXFc per treatment regimens excluding surgical/rehabilitation periods and large injection intervals (greater than [>]28 days). Subjects were included in summary of more than 1 treatment regimen if their regimen changed during study. Analysis performed on Full Analysis Set (FAS) which included all enrolled subjects with at least 1 dose of study treatment. Here, 'n' signifies number of FAS subjects who were analysed in each treatment regimen.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: episodes per subject per year				
median (full range (min-max))				
Episodic regimen (n= 22)	0.21 (0.0 to 6.8)			
Prophylaxis regimen (n= 28)	1.24 (0.0 to 5.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Number of Spontaneous Joint Bleeding Episodes

End point title	Annualized Number of Spontaneous Joint Bleeding Episodes

End point description:

Bleeding episodes were classified as spontaneous if parent/caregiver/subject records a bleeding event when there is no known contributing factor such as a definite trauma or antecedent "strenuous" activity. Annualized spontaneous joint bleeding episodes=(Total number of spontaneous joint bleeding episodes during efficacy period (EP) divided by total number of days during EP)*365.25. EP reflects the sum of all intervals of time during which subjects were treated with rFIXFc per treatment regimen excluding major and minor surgical/rehabilitation periods and large injection intervals (>28 days). Subjects were included in summary of more than 1 treatment regimen if their regimen changed during study. Analysis performed on FAS. Here, 'n' signifies number of FAS subjects who were analysed in each treatment regimen.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: episodes per subject per year				
median (full range (min-max))				
Episodic regimen (n= 22) Prophylaxis regimen (n= 28)	0.00 (0.0 to 5.6) 0.00 (0.0 to 2.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of rFIXFc Injections with Excellent or Good, Moderate or None Treatment Response Assessed Using a 4-Point Scale

End point title	Number of rFIXFc Injections with Excellent or Good, Moderate or None Treatment Response Assessed Using a 4-Point Scale

End point description:

Using e-diary, each subject’s parent/caregiver rated treatment response to any bleeding episode (BE) at approximately (approx.) 8 to 12 hours from time of injection and prior to additional doses of rFIXFc given for same BE using 4-point scale:- 1=Excellent: abrupt pain relief and/or improvement in signs of bleeding within approx. 8 hours after initial injection; 2=Good: definite pain relief and/or improvement in signs of bleeding within approx. 8 hours after injection, but possibly requiring more than 1 injection after 24–48 hours for complete resolution; 3=Moderate: Probable/slight beneficial effect within 8 hours after initial injection and requires more than 1 injection and 4=None: No improvement or condition worsens within approx. 8 hours after initial injection. Subjects were included in summary of more than 1 treatment regimen if their regimen changed during study. Analysis was based on all injections. Here, ‘n' signifies number of injections reported for each treatment regimen.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: responses to injections				
Episodic regimen: Excellent or Good (n=80) Episodic regimen: Moderate (n= 80)	22 0			

Episodic regimen: None (n= 80)	0			
Episodic regimen: Response not provided (n= 80)	58			
Prophylaxis regimen: Excellent or Good (n= 74)	50			
Prophylaxis regimen: Moderate (n= 74)	6			
Prophylaxis regimen: None (n= 74)	1			
Prophylaxis regimen: Response not provided (n=74)	17			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Exposure Days (EDs)

End point title	Total Number of Exposure Days (EDs)

End point description:

An ED was defined as a 24-hour period in which a subject received one or more doses of rFIXFc injections, with the time of the first injection of rFIXFc defined as the start of the ED. Subjects who did not have a particular injection type are counted as having zero injections for that type. Analysis performed on safety analysis set.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: days				
median (full range (min-max))	76.0 (1 to 137)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Annualized rFIXFc Consumption per Subject for the Prevention and Treatment of Bleeding Episodes

End point title	Total Annualized rFIXFc Consumption per Subject for the Prevention and Treatment of Bleeding Episodes

End point description:

Total annualized rFIXFc consumption (in IU/kg) was calculated for each subject as: Annualized consumption = (Total IU/kg of rFIXFc during efficacy period (EP) divided by total number of days during EP)*365.25. EP reflects the sum of all intervals of time during which subjects were treated with rFIXFc

according to the treatment regimens of the study excluding surgical/rehabilitation periods and large injection intervals (> 28 days). Subjects were included in summary of more than 1 treatment regimen if their regimen changed during study. Analysis performed on FAS. Here, 'n' signifies number of FAS subjects who were analysed in each treatment regimen.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: IU per kilogram per subject per year				
median (full range (min-max))				
Episodic regimen (n= 22)	203.2 (0 to 5719)			
Prophylaxis regimen (n= 28)	3175.0 (2544 to 13164)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Injections of rFIXFc Required to Resolve a Bleeding Episode

End point title	Number of Injections of rFIXFc Required to Resolve a Bleeding Episode

End point description:

Number of injections of rFIXFc required to resolve a bleeding episode during efficacy period (EP) were reported. EP reflects the sum of all intervals of time during which subjects were treated with rFIXFc according to the treatment regimens of the study excluding surgical/rehabilitation periods and large injection intervals (>28 days). All injections given from the initial sign of a bleed, until the last date/time within the bleed window were counted. Subjects were included in summary of more than 1 treatment regimen if their regimen changed during study. Analysis performed on FAS. Here, 'n' signifies number of FAS subjects who were analysed in each treatment regimen.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc)			
Subject group type	Reporting group			
Number of subjects analysed	33[2]			
Units: injections				
median (full range (min-max))				
Episodic regimen (n= 22)	1.0 (1 to 31)			
Prophylaxis regimen (n= 28)	1.0 (1 to 4)			

Notes:

[2] - Number of bleeding episodes= 27 (Episodic regimen) and 58 (Prophylaxis regimen).

Statistical analyses

No statistical analyses for this end point

Secondary: Average dose per Injection of rFIXFc Required to Resolve a Bleeding Episode

End point title	Average dose per Injection of rFIXFc Required to Resolve a Bleeding Episode

End point description:

The average dose of rFIXFc per injection per bleeding episode was calculated as the average of all doses (IU/kg) administered to treat the bleeding episode during efficacy period (EP). EP begins with the first treatment regimen dose of rFIXFc and ends with the last dose (regardless of the reason for dosing). Surgery/rehabilitation periods are not included in the EP. Subjects were included in summary of more than 1 treatment regimen if their regimen changed during study. Analysis performed on FAS. Here, 'n' signifies number of FAS subjects who were analysed in each treatment regimen.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc)			
Subject group type	Reporting group			
Number of subjects analysed	33[3]			
Units: IU/kg				
median (full range (min-max))				
Episodic regimen (n= 22)	88.50 (41.7 to 178.6)			
Prophylaxis regimen (n= 28)	71.92 (23.3 to 181.8)			

Notes:

[3] - Total number of bleeding episodes= 27 (Episodic regimen) and 58 (Prophylaxis regimen).

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in rFIXFc Incremental Recovery (IR)

End point title	Change From Baseline in rFIXFc Incremental Recovery (IR)

End point description:

Blood samples were taken at trough and Cmax for assessment of incremental recovery, measured by the one-stage clotting assay. IR (International Units per decilitre [IU/dL] per IU/kg) = (Cmax for FIX activity – Pre-dose FIX activity) (IU/dL)/ Actual dose (IU/kg), where Cmax (maximum concentration) is 30 minute FIX activity post-dose and FIX activity less than (<)0.5 IU/dL was set to 0 IU/dL for calculation of IR. Analysis performed on FAS. Here 'n' signifies number of FAS subjects with available data for each visit.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, and 144

End point values	Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc)			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: IU/dL per IU/kg				
median (inter-quartile range (Q1-Q3))				
Change at Week 12 (n= 14)	0.0 (-0.08 to 0.12)			
Change at Week 24 (n= 15)	0.0 (-0.17 to 0.15)			
Change at Week 36 (n= 18)	-0.0 (-0.18 to 0.11)			
Change at Week 48 (n= 20)	-0.0 (-0.13 to 0.03)			
Change at Week 60 (n= 17)	-0.1 (-0.1 to 0.03)			
Change at Week 72 (n= 12)	-0.1 (-0.20 to 0.07)			
Change at Week 84 (n= 10)	-0.1 (-0.23 to -0.04)			
Change at Week 96 (n= 7)	-0.1 (-0.14 to 0.03)			
Change at Week 108 (n= 4)	-0.1 (-0.36 to -0.01)			
Change at Week 120 (n= 1)	-0.1 (-0.1 to -0.1)			
Change at Week 132 (n= 1)	-0.1 (-0.1 to -0.1)			
Change at Week 144 (n= 1)	0.0 (0.0 to 0.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to end of the study (up to 3 years) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AE are treatment-emergent AE i.e. AE that was present prior to receiving first injection of rFIXFc and subsequently worsened in severity, or was not present prior to receiving first injection but subsequently appeared before last visit/follow-up call, whichever came later. Analysis performed on safety analysis set.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc)

Reporting group description:

Subjects received rFIXFc IV injection as follows: Prophylactic treatment regimen: started with rFIXFc 50 IU/kg weekly until subject reached at least 50 exposure days (ED=24-hour period in which >=1 injection/dose of rFIXFc was given) to rFIXFc, withdrawal from study or end of study. Adjustments to dose and dosing interval was based on incremental recovery, subsequent Factor IX levels, physical activity, bleeding pattern, in accordance with local standards of care for PR. Treatment with episodic (on demand) regimen can be initiated before PR at investigators discretion. Episodic (On demand; optional): rFIXFc at individual doses based on subject's clinical condition, type and severity of bleeding event until PR.

Serious adverse events	Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc)		
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 33 (69.70%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Accidental exposure to product			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Craniocerebral injury			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Face injury			

subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	5 / 33 (15.15%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	3 / 33 (9.09%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Skull fracture				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Phimosis				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Haematoma				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Poor venous access				
subjects affected / exposed	3 / 33 (9.09%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			

Surgical and medical procedures			
Central venous catheterisation			
subjects affected / exposed	9 / 33 (27.27%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Coma			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile convulsion			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord haematoma			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tongue biting			
subjects affected / exposed	1 / 33 (3.03%)		
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	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Factor ix inhibition			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune thrombocytopenic purpura			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Vessel puncture site haematoma			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tongue haemorrhage			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prepuce redundant			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Compartment syndrome			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemarthrosis			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Croup infectious			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion site pustule			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral rash			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 33 (81.82%)		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
White blood cell count increased			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	13		
Head injury			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	7		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	14 / 33 (42.42%)		
occurrences (all)	33		
Ear and labyrinth disorders			
Middle ear effusion			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	9		
Teething			
subjects affected / exposed	6 / 33 (18.18%)		
occurrences (all)	15		
Vomiting			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	8		
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Cough			
subjects affected / exposed	6 / 33 (18.18%)		
occurrences (all)	11		
Nasal congestion			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Rhinorrhoea			
subjects affected / exposed	6 / 33 (18.18%)		
occurrences (all)	18		
Skin and subcutaneous tissue disorders			
Dermatitis diaper			

subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	5		
Dry skin			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Eczema			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Erythema			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Psychiatric disorders			
Irritability			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	4		
Conjunctivitis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Croup infectious			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Hand-foot-and-mouth disease			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Influenza			

subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	11 / 33 (33.33%)		
occurrences (all)	22		
Otitis media			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	8		
Pharyngitis			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	5		
Rhinitis			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	12		
Varicella			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Viral infection			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	6		
Viral rash			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2017	The primary reasons for this amendment were as follows: allowed subjects to begin treatment with rFIXFc study drug (including episodic treatment) after confirmation of eligibility, without requiring them to complete the baseline IR visit prior to starting treatment with study drug; removed exclusion criterion 3, which excluded subjects with hypersensitivity reaction associated with any intravenous immunoglobulin administration; added an optional collection of concomitant medication received by breastfeeding mothers of subjects; this data collection requires additional consent. An exception was included for infants who were receiving breast milk from sources other than their own mother (e.g., a breast milk bank); clarified how and when to calculate doses using actual potency versus nominal strength, and how and where to report dosing information (electronic case report form [eCRF] versus electronic patient diary [EPD]), as well as timing requirements for reporting dosing data in the EPD; explicitly described and justified the collection of race and ethnicity data.
06 August 2018	The primary reason for this amendment was to update the end of study (EOS) definition to align with the revised EU pediatric PIP by changing the enrollment target from 60 subjects enrolled to achieve at least 40 subjects with no less than 50 EDs, to 30 subjects enrolled to achieve at least 20 subjects reaching at least 50 EDs. This change resulted in redefining of the study treatment period from at least 100 EDs to at least 50 EDs, and removal of planned interim analysis. Additional clarification regarding use of bypassing agents to ensure subject safety was also added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported