Clinical trial results:
An Open-Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031) in the Prevention and Treatment of Bleeding in Previously Untreated Patients With Severe Hemophilia A

Summary

EudraCT number	2013-005512-10
Trial protocol	GB IE IT ES SE DE PL FR DK NL
Global end of trial date	23 September 2019

Results information

Result version number	v1 (current)
This version publication date	03 April 2020
First version publication date	03 April 2020

Trial information

Trial identification

Sponsor protocol code	997HA306

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02234323
WHO universal trial number (UTN)	-
Other trial identifiers	PUPs A: EFC16225

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-001114-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	18 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 September 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 VIII Fc Fusion Protein (rFVIIIFc) in previously untreated patients (PUPs) with severe hemophilia A.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric patients. 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	12 January 2015
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	Poland: 8
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Ireland: 6
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	108
EEA total number of subjects	54

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	6
Infants and toddlers (28 days-23 months)	93
Children (2-11 years)	9
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 44 active centers in 13 countries between 12-Jan-2015 to 23-Sep-2019.

Pre-assignment

Screening details:

110 subjects screened, 108 enrolled, 103 received drug.

Period 1

Period 1 title	All Enrolled
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Not Applicable
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Not Applicable
Started	108
Completed	103
Not completed	5
Not Treated: Exceeded lab value limit	1
Not Treated: Consent withdrawn by subject	2
Not Treated: Completed study in database (DB)	2

Period 2

Period 2 title	All Treated
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Recombinant Coagulation Factor VIII Fc Fusion Protein

Arm description:

Subjects were to receive rFVIIIFc as follows -PR (Prophylaxis regimen): rFVIIIFc 25-80 international units per kilogram (IU/kg), weekly until subject reached >= 50 exposure days (ED: 24-hour period in which >=1 injection/dose of rFVIIIFc was given), or study withdrawal/end of study. Adjustments to dose/dosing interval was done as needed by investigator; Treatment with an optional ER (Episodic regimen) can be initiated before PR at investigators discretion; ITI: rFVIIIFc 200 IU/kg, daily for subjects who, after exposure to rFVIIIFc, had positive high titre inhibitor (>=5.00 Bethesda Units per milliliter [BU/mL]) or positive low titre inhibitor (>=0.60 and <5.00 BU/mL) and had poorly controlled bleeding despite increased rFVIIIFc doses, or required bypassing agent to treat bleeding.

Arm type	Experimental
Investigational medicinal product name	rFVIIIFc
Investigational medicinal product code	
Other name	BIIB031
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received rFVIIIFc as an intravenous (IV) injection for one or more of three treatment regimens: episodic, prophylactic and ITI.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline data was reported for safety analysis set which was less than all enrolled set. Period 2 shows the disposition of safety analysis set.

Number of subjects in period 2[2]	Recombinant Coagulation Factor VIII Fc Fusion Protein
Started	103
Episodic Treatment Regimen	81 [3]
Prophylactic Treatment Regimen	89
Immune Tolerance Induction (ITI)	15 [4]
Completed	85
Not completed	18
Physician decision	5
Death	1
Unspecified	7
Exceeded lab value limit	2
Lack of efficacy	3

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline data was reported for safety analysis set which was less than all enrolled set. Period 2 shows the disposition of safety analysis set.
[3] - 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 could be treated in more than one regimen and were counted in all categories wherever applicable.
[4] - 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 could be treated in more than one regimen and were counted in all categories wherever applicable.

Baseline characteristics

Reporting groups	
Reporting group title	All Treated
Reporting group description:	
The Safety Analysis Set was defined as all subjects who received at least 1 dose of rFVIIIFc.	

Reporting group values	All Treated	Total	
Number of subjects	103	103	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
median	0.58		
full range (min-max)	0.02 to 4.00	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	103	103	
Race			
Units: Subjects			
White	79	79	
Black or African-American	2	2	
Asian	5	5	
American Indian or Alaska Native	0	0	
Native Hawaiian or other Pacific Islander	2	2	
Not reported due to confidentiality regulations	4	4	
Other	11	11	

End points

End points reporting groups

Reporting group title	Not Applicable
Reporting group description: -	
Reporting group title	Recombinant Coagulation Factor VIII Fc Fusion Protein

Reporting group description:

Subjects were to receive rFVIIIFc as follows -PR (Prophylaxis regimen): rFVIIIFc 25-80 international units per kilogram (IU/kg), weekly until subject reached >= 50 exposure days (ED: 24-hour period in which >=1 injection/dose of rFVIIIFc was given), or study withdrawal/end of study. Adjustments to dose/dosing interval was done as needed by investigator; Treatment with an optional ER (Episodic regimen) can be initiated before PR at investigators discretion; ITI: rFVIIIFc 200 IU/kg, daily for subjects who, after exposure to rFVIIIFc, had positive high titre inhibitor (>=5.00 Bethesda Units per milliliter [BU/mL]) or positive low titre inhibitor (>=0.60 and <5.00 BU/mL) and had poorly controlled bleeding despite increased rFVIIIFc doses, or required bypassing agent to treat bleeding.

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:

A positive inhibitor result occurs when a subject has a value >=0.6 Bethesda Units (BU)/mL by central laboratory testing using Nijmegen-modified Bethesda assay, that is confirmed on re-testing of a separate sample collected >=2 weeks after the initial sample. Exposure day (ED) is a 24-hour period in which subject received >=1 dose of rFVIIIFc injections. Positive inhibitor incidence rate=Number of subjects with an inhibitor/Number of subjects reaching >=10 EDs and had >=1 inhibitor test performed at or beyond this milestone or who have an inhibitor. Any subject who develops an inhibitor following the initial rFVIIIFc administration will be included in the numerator and denominator. Analysis performed on subjects in safety analysis set (all subjects who received >=1 dose of study treatment) meeting above criteria.

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 analysis was provided.

End point values	Recombinant Coagulation Factor VIII Fc Fusion Protein			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: percentage of subjects				
number (confidence interval 95%)	31.11 (21.77 to 41.74)			

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 is annualized number of bleeding episodes during efficacy period (EP) per subject annualized 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 as traumatic when there is known reason for bleed. ABR=(Number of bleeding episodes during EP/total number of days during EP)*365.25. EP is sum of all intervals of time during which subjects were treated with rFVIIIFc per treatment regimens of study 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) subjects within the EP. FAS included all enrolled subjects with >=1 dose of study treatment. n= number of FAS subjects analysed in each treatment regimen.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	Recombinant Coagulation Factor VIII Fc Fusion Protein			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: episodes per subject per year				
median (full range (min-max))				
Episodic Treatment (n= 81)	2.24 (0.0 to 39.8)			
Prophylaxis Treatment (n= 89)	1.49 (0.0 to 18.7)			
ITI Treatment (n= 15)	0.00 (0.0 to 6.6)			

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 EP divided by total number of days during EP)*365.25. EP reflects sum of all intervals of time during which subjects were treated with rFVIIIFc per treatment regimen excluding major and minor surgical/rehabilitation periods and large injection intervals (> 28 days). Bleeding episodes were summarized by treatment regimen. Subjects were included in summary of more than 1 treatment regimen if their regimen changed during study. Analysis performed on FAS subjects within the EP. 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 VIII Fc Fusion Protein			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))				
Episodic Treatment (n= 81)	0.00 (0.0 to 0.0)			
Prophylaxis Treatment (n= 89)	0.00 (0.0 to 0.0)			
ITI Treatment (n= 15)	0.00 (0.0 to 0.0)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of rFVIIIFc 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.) 8-12 hours(hr) from time of injection and prior to additional doses of rFVIIIFc given for same BE, using 4-point scale: 1=Excellent: abrupt pain relief and/or improvement in signs of bleeding within approx. 8hr after initial injection; 2=Good: definite pain relief and/or improvement in signs of bleeding within approx. 8hr after injection, but possibly requiring more than 1 injection after 24–48 hr for complete resolution; 3=Moderate: Probable/slight beneficial effect within 8 hr after initial injection and requires more than 1 injection and 4=None: No improvement or condition worsens within approx. 8 hr after initial injection. Subjects included in more than 1 treatment regimen if their regimen changed during study. Analysis performed on FAS subjects within the EP and based on all injections. n= 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 VIII Fc Fusion Protein			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: responses to injections				
number (not applicable)				
Episodic Regimen: Excellent or Good (n=238)	102			
Episodic Regimen: Moderate (n=238)	16			

Episodic Regimen: None (n=238)	2			
Episodic Regimen: Response not provided (n=238)	118			
Prophylaxis regimen: Excellent or Good (n=293)	163			
Prophylaxis regimen: Moderate (n=293)	27			
Prophylaxis regimen: None (n=293)	14			
Prophylaxis regimen: Response not provided (n=293)	89			
ITI regimen: Excellent or Good (n=48)	20			
ITI regimen: Moderate (n=48)	14			
ITI regimen: None (n=48)	3			
ITI regimen: Response not provided (n=48)	11			

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 rFVIIIFc injections, with the time of the first injection of rFVIIIFc 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 VIII Fc Fusion Protein			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: days				
median (full range (min-max))	100.0 (0 to 649)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Total annualized rFVIIIFc consumption (in IU/kg) was calculated for each subject as: Annualized consumption = (Total IU/kg of rFVIIIFc during EP divided by total number of days during EP)*365.25. EP reflects the sum of all intervals of time during which subjects are treated with rFVIIIFc 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 subjects within the EP. 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 VIII Fc Fusion Protein			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: IU per kilogram per subject per year				
median (full range (min-max))				
Episodic Treatment (n= 81)	197.6 (0 to 3177)			
Prophylaxis Treatment (n= 89)	5384.4 (0 to 40126)			
ITI Treatment (n= 15)	67310.0 (33323 to 78871)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Number of Injections of rFVIIIFc required to resolve a bleeding episode during EP were reported. EP reflects the sum of all intervals of time during which subjects were treated with rFVIIIFc 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 subjects within the EP. 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 VIII Fc Fusion Protein			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: injections				
median (full range (min-max))				
Episodic Treatment (n= 81)	1.0 (1 to 13)			
Prophylaxis Treatment (n= 89)	1.0 (1 to 7)			
ITI Treatment (n= 15)	1.0 (1 to 22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average Dose per Injection of rFVIIIFc Required to Resolve a Bleeding Episode

End point title	Average Dose per Injection of rFVIIIFc Required to Resolve a Bleeding Episode

End point description:

The average dose of rFVIIIFc 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 rFVIIIFc 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 subjects within the EP. 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 VIII Fc Fusion Protein			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: IU/kg				
median (full range (min-max))				
Episodic Treatment (n= 81)	45.45 (19.2 to 106.0)			
Prophylaxis Treatment (n= 89)	48.08 (17.9 to 144.0)			
ITI Treatment (n= 15)	189.44 (76.9 to 250.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in rFVIIIFc Incremental Recovery

End point title	Change From Baseline in rFVIIIFc Incremental Recovery

End point description:

Blood samples were taken at trough (predose) and Cmax for assessment of incremental recovery, measured by the one-stage clotting assay. IR (International Units per deciliter [IU/dL] per IU/kg) = (Cmax for FVIII activity – Pre-dose FVIII activity) (IU/dL)/ Actual dose (IU/kg), where Cmax (maximum concentration) is 30-minute FVIII activity post-dose and FVIII activity less than (<)0.5 IU/dL was set to 0 IU/dL for calculation of IR. Analysis performed on FAS subjects within the EP. 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 and 120

End point values	Recombinant Coagulation Factor VIII Fc Fusion Protein			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: IU/dL per IU/kg				
median (inter-quartile range (Q1-Q3))				
Change at Week 12 (n= 35)	-0.5 (-1.26 to -0.26)			
Change at Week 24 (n= 34)	-0.7 (-1.50 to 0.05)			
Change at Week 36 (n= 39)	-0.4 (-1.06 to 0.27)			
Change at Week 48 (n= 37)	-0.5 (-1.09 to -0.05)			
Change at Week 60 (n= 25)	-0.4 (-1.06 to 0.04)			
Change at Week 72 (n= 21)	-0.8 (-1.10 to -0.24)			
Change at Week 84 (n= 15)	-0.6 (-1.55 to 0.01)			
Change at Week 96 (n= 7)	-0.6 (-1.21 to -0.34)			
Change at Week 108 (n= 2)	-1.5 (-2.68 to -0.31)			
Change at Week 120 (n= 1)	-0.6 (-0.6 to -0.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Response to Immune Tolerance Induction (ITI)

End point title	Number of Subjects with Response to Immune Tolerance Induction (ITI)

End point description:

Complete Success was defined as meeting all of the following criteria: Negative inhibitor titres in 2 consecutive determinations at least 4 weeks apart; IR >=66% of baseline in 2 consecutive determinations at least 4 weeks apart; Half life >=6 hours. Partial Success was defined as meeting the first criteria for Complete Success and one of the other 2 after 33 months of ITI. Analysis performed on ITI analysis set which was defined as all subjects who consented to and initiated the ITI sub-study.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	Recombinant Coagulation Factor VIII Fc Fusion Protein			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: subjects				
Complete Success	5			
Partial Success	2			
Early Withdrawal	3			
ITI Ongoing at end of Study	5			

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 rFVIIIFc 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 VIII Fc Fusion Protein

Reporting group description:

Subjects were to receive rFVIIIFc as follows -PR (Prophylaxis regimen): rFVIIIFc 25-80 international units per kilogram (IU/kg), weekly until subject reached >= 50 exposure days (ED: 24-hour period in which >=1 injection/dose of rFVIIIFc was given), or study withdrawal/end of study. Adjustments to dose/dosing interval was done as needed by investigator; Treatment with an optional ER (Episodic regimen) can be initiated before PR at investigators discretion; ITI: rFVIIIFc 200 IU/kg, daily for subjects who, after exposure to rFVIIIFc, had positive high titre inhibitor (>=5.00 Bethesda Units per milliliter [BU/mL]) or positive low titre inhibitor (>=0.60 and <5.00 BU/mL) and had poorly controlled bleeding despite increased rFVIIIFc doses, or required bypassing agent to treat bleeding.

Serious adverse events	Recombinant Coagulation Factor VIII Fc Fusion Protein		
Total subjects affected by serious adverse events			
subjects affected / exposed	60 / 103 (58.25%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	3 / 103 (2.91%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Poor venous access			

subjects affected / exposed	3 / 103 (2.91%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Subgaleal haematoma			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Arteriovenous fistula operation			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Central venous catheter removal			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Central venous catheterisation			
subjects affected / exposed	26 / 103 (25.24%)		
occurrences causally related to treatment / all	0 / 30		
deaths causally related to treatment / all	0 / 0		
Ventriculo-peritoneal shunt			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Device related thrombosis			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	4 / 103 (3.88%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device issue			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Craniocerebral injury			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Facial bones fracture			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			

subjects affected / exposed	11 / 103 (10.68%)		
occurrences causally related to treatment / all	0 / 19		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	8 / 103 (7.77%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 0		
Palate injury			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin laceration			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic haematoma			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular access site haematoma			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Febrile convulsion				
subjects affected / exposed	2 / 103 (1.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	2 / 103 (1.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Intraventricular haemorrhage				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Factor viii inhibition				
subjects affected / exposed	28 / 103 (27.18%)			
occurrences causally related to treatment / all	28 / 29			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spontaneous haematoma				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Tongue haemorrhage				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Haemarthrosis				

subjects affected / exposed	2 / 103 (1.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haematoma muscle				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Soft tissue haemorrhage				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bacterial sepsis				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis norovirus				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematoma infection				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis aseptic				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Parainfluenzae virus infection				
subjects affected / exposed	2 / 103 (1.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	2 / 103 (1.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Rotavirus infection			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Staphylococcal skin infection			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular device infection			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 103 (1.94%)		
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	Recombinant Coagulation Factor VIII Fc Fusion Protein		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 103 (82.52%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	9 / 103 (8.74%)		
occurrences (all)	16		
Fall			
subjects affected / exposed	52 / 103 (50.49%)		
occurrences (all)	146		
Head injury			
subjects affected / exposed	28 / 103 (27.18%)		
occurrences (all)	63		
Limb injury			
subjects affected / exposed	8 / 103 (7.77%)		
occurrences (all)	9		
Lip injury			
subjects affected / exposed	6 / 103 (5.83%)		
occurrences (all)	6		
Mouth injury			
subjects affected / exposed	9 / 103 (8.74%)		
occurrences (all)	10		
Skin abrasion			
subjects affected / exposed	7 / 103 (6.80%)		
occurrences (all)	19		
Skin laceration			
subjects affected / exposed	9 / 103 (8.74%)		
occurrences (all)	13		
Vaccination complication			
subjects affected / exposed	6 / 103 (5.83%)		
occurrences (all)	6		
Blood and lymphatic system disorders			

Iron deficiency anaemia subjects affected / exposed occurrences (all)	10 / 103 (9.71%) 10		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	31 / 103 (30.10%) 47		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Teething subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 9 / 103 (8.74%) 9 18 / 103 (17.48%) 23 12 / 103 (11.65%) 23 19 / 103 (18.45%) 20		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	 13 / 103 (12.62%) 20 9 / 103 (8.74%) 9		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 6 / 103 (5.83%) 9 10 / 103 (9.71%) 12		
Infections and infestations			

Conjunctivitis				
subjects affected / exposed	8 / 103 (7.77%)			
occurrences (all)	8			
Ear infection				
subjects affected / exposed	19 / 103 (18.45%)			
occurrences (all)	28			
Gastroenteritis				
subjects affected / exposed	7 / 103 (6.80%)			
occurrences (all)	7			
Hand-foot-and-mouth disease				
subjects affected / exposed	6 / 103 (5.83%)			
occurrences (all)	6			
Influenza				
subjects affected / exposed	10 / 103 (9.71%)			
occurrences (all)	14			
Nasopharyngitis				
subjects affected / exposed	31 / 103 (30.10%)			
occurrences (all)	54			
Otitis media				
subjects affected / exposed	10 / 103 (9.71%)			
occurrences (all)	11			
Rhinitis				
subjects affected / exposed	7 / 103 (6.80%)			
occurrences (all)	11			
Upper respiratory tract infection				
subjects affected / exposed	28 / 103 (27.18%)			
occurrences (all)	41			
Varicella				
subjects affected / exposed	6 / 103 (5.83%)			
occurrences (all)	6			
Viral infection				
subjects affected / exposed	17 / 103 (16.50%)			
occurrences (all)	32			
Viral upper respiratory tract infection				
subjects affected / exposed	11 / 103 (10.68%)			
occurrences (all)	27			

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2015	The primary reason for this amendment was to change the cut-off age for the study from <18 years old to <6 years old to align with other studies focusing on previously untreated pediatric subjects.
22 July 2016	The primary reason for this amendment was to add provisions requested by regulatory authorities including revision of definitions of ITI therapy outcomes; addition of a tapering regimen and a monitoring period after ITI; replacement of the exclusion criterion related to hypersensitivity to IV immunoglobulin (IVIG) administration, with an exclusion criterion related to hypersensitivity to FVIIIFc administration; addition of data collection for concomitant medications administered to breastfeeding mothers of subjects; justification of collection of race and ethnicity data.
22 September 2016	The primary reason for this amendment was to correct outdated information regarding the enrollment criteria that was inadvertently left in the protocol. These changes included: the collection of AEs was removed from the screening period and subjects awaiting ITI were asked to follow the Prophylaxis Regimen rather than the Episodic Regimen.
24 February 2017	The primary reason for this amendment was to incorporate a change in responsibility and obligations of the study sponsor (according to Directive 2001/20/EC as well as International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline on Good Clinical Practice (GCP) E6[RI]). Bioverativ Therapeutics Inc took over the responsibility and obligations of the study sponsor from Biogen Idec Research Limited (UK) or Biogen MA Inc (US) or Biogen Australia Pty Ltd (Australia).
12 February 2018	The primary reason for this amendment was to redefine the EOS criteria for the study in light of the new draft version of the updated EMA guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported