



Clinical trial results:

An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant, Human Coagulation Factor IX Fusion Protein (rFIXFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia B

Summary

EudraCT number	2011-003075-11
Trial protocol	GB DE BE SE PL IT IE NL
Global end of trial date	31 October 2017

Results information

Result version number	v1 (current)
This version publication date	13 May 2018
First version publication date	13 May 2018

Trial information

Trial identification

Sponsor protocol code	9HB01EXT
-----------------------	----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01425723
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bioverativ Therapeutics Inc.
Sponsor organisation address	225 Second Avenue, Waltham, Massachusetts (MA), United States, 02451
Public contact	Not available, Bioverativ Therapeutics Inc., clinicaltrials@bioverativ.com
Scientific contact	Not available, Bioverativ Therapeutics Inc., clinicaltrials@bioverativ.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2017
Global end of trial reached?	Yes
Global end of trial date	31 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the long-term safety of rFIXFc in subjects with hemophilia B.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Safety evaluations included monitoring of adverse events (AEs) and serious adverse events (SAEs), physical examination, medical history (from previous study and updated), height, weight and Concomitant therapy and procedure recording and Laboratory Safety Assessments (hematology, blood chemistry and Nijmegen modified Bethesda assay).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 December 2011
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: 8
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	China: 6
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Hong Kong: 7
Country: Number of subjects enrolled	India: 7
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	South Africa: 10
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 19

Country: Number of subjects enrolled	United States: 33
Worldwide total number of subjects	120
EEA total number of subjects	34

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	26
Adolescents (12-17 years)	9
Adults (18-64 years)	85
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects provided their written informed consent to participate in this study after the Investigator has verified that they are eligible per protocol defined criteria. For subjects, unable to provide written informed consent, parents or legal guardian(s) obtained the informed consent form.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	rFIXFc [Subjects from 9HB02PED]

Arm description:

Weekly prophylaxis (P): Subjects received 20 IU/kg to 100 IU/kg rFIXFc once weekly during weekly prophylaxis. Dose was based on the subject's clinical profile observed in the parent rFIXFc study and the individual pharmacokinetic profile, trough, and/or peak (recovery) values. Individualized P: 100 IU/kg rFIXFc every 8 to 16 days, or twice a month in individualized prophylaxis. Personalized P: included addition of prevention doses prior to strenuous activity; targeting a FIX trough level of greater than (>) 5%, if warranted by the bleeding history and/or activity level or dosing twice a week (25 IU/kg, twice weekly, versus 50 IU/kg, once weekly) for subjects who may have better control with such a regimen. Subjects who reached the age of 12 during the study could also choose to switch to the episodic treatment group, with dosing based on subject's clinical condition and type and severity of bleeding event; no subjects had entered the episodic treatment group as of the end of study.

Arm type	Experimental
Investigational medicinal product name	rFIXFc
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received rFIXFc as weekly, individualized, personalized or episodic (on-demand) prophylaxis. Subjects could switch between treatment regimen upon enrollment into the study and at any time during the study, a subject may be included in summary analyses for more than one treatment group.

Arm title	rFIXFc [Subjects from 998HB102]
------------------	---------------------------------

Arm description:

Weekly prophylaxis: Subjects received 20 IU/kg to 100 IU/kg rFIXFc once weekly during weekly prophylaxis. Dose was based on the subject's clinical profile observed in the parent rFIXFc study and the individual pharmacokinetic profile, trough, and/or peak (recovery) values. Individual prophylaxis: Subjects received 100 IU/kg rFIXFc every 8 to 16 days, or twice a month in individualized prophylaxis. Personalized Prophylaxis: Personalized prophylaxis included addition of prevention doses prior to strenuous activity; targeting a FIX trough level of greater than (>) 5 percent (%), if warranted by the bleeding history and/or activity level or dosing twice a week (25 IU/kg, twice weekly, versus 50 IU/kg, once weekly) for subjects who may have better control with such a regimen. Episodic (On Demand): The individual dose of rFIXFc to treat bleeding episodes was based on subject's clinical condition, type and severity of the bleeding event.

Arm type	Experimental
----------	--------------

Investigational medicinal product name	rFIXFc
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received rFIXFc as weekly, individualized, personalized or episodic (on demand) prophylaxis. Subjects could switch between treatment regimen upon enrollment into the study and at any time during the study, a subject may be included in summary analyses for more than one treatment group.

Number of subjects in period 1	rFIXFc [Subjects from 9HB02PED]	rFIXFc [Subjects from 998HB102]
Started	27	93
Completed	23	75
Not completed	4	18
Physician decision	2	-
Consent withdrawn by subject	1	4
Other	1	10
Lost to follow-up	-	3
Lack of efficacy	-	1

Baseline characteristics

Reporting groups

Reporting group title	rFIXFc [Subjects from 9HB02PED]
-----------------------	---------------------------------

Reporting group description:

Weekly prophylaxis (P): Subjects received 20 IU/kg to 100 IU/kg rFIXFc once weekly during weekly prophylaxis. Dose was based on the subject's clinical profile observed in the parent rFIXFc study and the individual pharmacokinetic profile, trough, and/or peak (recovery) values. Individualized P: 100 IU/kg rFIXFc every 8 to 16 days, or twice a month in individualized prophylaxis. Personalized P: included addition of prevention doses prior to strenuous activity; targeting a FIX trough level of greater than (>) 5%, if warranted by the bleeding history and/or activity level or dosing twice a week (25 IU/kg, twice weekly, versus 50 IU/kg, once weekly) for subjects who may have better control with such a regimen. Subjects who reached the age of 12 during the study could also choose to switch to the episodic treatment group, with dosing based on subject's clinical condition and type and severity of bleeding event; no subjects had entered the episodic treatment group as of the end of study.

Reporting group title	rFIXFc [Subjects from 998HB102]
-----------------------	---------------------------------

Reporting group description:

Weekly prophylaxis: Subjects received 20 IU/kg to 100 IU/kg rFIXFc once weekly during weekly prophylaxis. Dose was based on the subject's clinical profile observed in the parent rFIXFc study and the individual pharmacokinetic profile, trough, and/or peak (recovery) values. Individual prophylaxis: Subjects received 100 IU/kg rFIXFc every 8 to 16 days, or twice a month in individualized prophylaxis. Personalized Prophylaxis: Personalized prophylaxis included addition of prevention doses prior to strenuous activity; targeting a FIX trough level of greater than (>) 5 percent (%), if warranted by the bleeding history and/or activity level or dosing twice a week (25 IU/kg, twice weekly, versus 50 IU/kg, once weekly) for subjects who may have better control with such a regimen. Episodic (On Demand): The individual dose of rFIXFc to treat bleeding episodes was based on subject's clinical condition, type and severity of the bleeding event.

Reporting group values	rFIXFc [Subjects from 9HB02PED]	rFIXFc [Subjects from 998HB102]	Total
Number of subjects	27	93	120
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	26	0	26
Adolescents (12-17 years)	1	8	9
Adults (18-64 years)	0	85	85
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	6.7	32.7	-
standard deviation	± 3.22	± 14.09	
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	27	93	120

End points

End points reporting groups

Reporting group title	rFIXFc [Subjects from 9HB02PED]
Reporting group description:	
Weekly prophylaxis (P): Subjects received 20 IU/kg to 100 IU/kg rFIXFc once weekly during weekly prophylaxis. Dose was based on the subject's clinical profile observed in the parent rFIXFc study and the individual pharmacokinetic profile, trough, and/or peak (recovery) values. Individualized P: 100 IU/kg rFIXFc every 8 to 16 days, or twice a month in individualized prophylaxis. Personalized P: included addition of prevention doses prior to strenuous activity; targeting a FIX trough level of greater than (>) 5%, if warranted by the bleeding history and/or activity level or dosing twice a week (25 IU/kg, twice weekly, versus 50 IU/kg, once weekly) for subjects who may have better control with such a regimen. Subjects who reached the age of 12 during the study could also choose to switch to the episodic treatment group, with dosing based on subject's clinical condition and type and severity of bleeding event; no subjects had entered the episodic treatment group as of the end of study.	
Reporting group title	rFIXFc [Subjects from 998HB102]
Reporting group description:	
Weekly prophylaxis: Subjects received 20 IU/kg to 100 IU/kg rFIXFc once weekly during weekly prophylaxis. Dose was based on the subject's clinical profile observed in the parent rFIXFc study and the individual pharmacokinetic profile, trough, and/or peak (recovery) values. Individual prophylaxis: Subjects received 100 IU/kg rFIXFc every 8 to 16 days, or twice a month in individualized prophylaxis. Personalized Prophylaxis: Personalized prophylaxis included addition of prevention doses prior to strenuous activity; targeting a FIX trough level of greater than (>) 5 percent (%), if warranted by the bleeding history and/or activity level or dosing twice a week (25 IU/kg, twice weekly, versus 50 IU/kg, once weekly) for subjects who may have better control with such a regimen. Episodic (On Demand): The individual dose of rFIXFc to treat bleeding episodes was based on subject's clinical condition, type and severity of the bleeding event.	
Subject analysis set title	rFIXFc [9HB02PED (<6 years old age cohort)]
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects enrolled from the study 9HB02PED with <6 years old age.	
Subject analysis set title	rFIXFc [9HB02PED (6 - <12 years old age cohort)]
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects enrolled from the study 9HB02PED with 6 - <12 years old age.	
Subject analysis set title	rFIXFc [Subjects from 998HB102]
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects enrolled from the study 998HB102.	

Primary: Number of Subjects with any Positive Inhibitor Development

End point title	Number of Subjects with any Positive Inhibitor Development ^[1]
End point description:	
An inhibitor test result ≥ 0.6 Bethesda units (BU)/mL, confirmed on 2 separate samples drawn 2 to 4 weeks apart, was considered positive. Both tests were to be performed by the central laboratory using the Nijmegen-modified Bethesda Assay. Safety Analysis Set included subjects who received at least 1 dose of rFIXFc in study 9HB01EXT.	
End point type	Primary
End point timeframe:	
Approximately 5 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	rFIXFc [Subjects from 9HB02PED]	rFIXFc [Subjects from 998HB102]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	93		
Units: subjects with any positive inhibitor	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rate (ABR)

End point title	Annualized Bleeding Rate (ABR)
-----------------	--------------------------------

End point description:

ABR is annualized number of bleeding episodes (spontaneous or traumatic) per subject. Bleeding episodes should be classified as spontaneous if a subject records a bleeding event when there is no known contributing factor such as definite trauma or antecedent strenuous activity. Bleeding episodes should be classified as traumatic if a subject records a bleeding event when there is a known or believed reason for the bleed. FAS=all subjects who received at least 1 dose of rFIXFc. "n"= number of subject analyzed in specified treatment regimen. "99999" indicates that data was not analyzed for the arm in specified category. Annualized bleeding episodes=(Number of bleeding episodes during efficacy period/number of days during efficacy period)*365.25. Efficacy period reflects the sum of all intervals of time during which subjects were treated with rFIXFc according to the treatment regimens of the study excluding major and minor surgical/rehabilitation periods and large injection intervals.

End point type	Secondary
----------------	-----------

End point timeframe:

Approximately 5 years

End point values	rFIXFc [9HB02PED (<6 years old age cohort)]	rFIXFc [9HB02PED (6 - <12 years old age cohort)]	rFIXFc [Subjects from 998HB102]	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	14	93	
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))				
Weekly Prophylaxis (n= 13, 10, 51)	1.04 (0.00 to 2.28)	1.14 (0.54 to 2.34)	2.26 (0.40 to 5.16)	
Individualized Prophylaxis (n= 0, 5, 31)	99999 (99999 to 99999)	3.69 (3.54 to 5.21)	1.85 (0.76 to 4.00)	
Personalized Prophylaxis (n= 1, 1, 16)	0.54 (0.54 to 0.54)	3.13 (3.13 to 3.13)	2.91 (1.14 to 5.36)	
Episodic (n= 0, 0, 15)	99999 (99999 to 99999)	99999 (99999 to 99999)	11.64 (5.12 to 18.54)	

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Spontaneous Joint Bleeding Episodes

End point title	Annualized Spontaneous Joint Bleeding Episodes
-----------------	--

End point description:

Bleeding episodes should be classified as spontaneous if a subject records a bleeding event when there is no known contributing factor such as definite trauma or antecedent strenuous activity. In addition of type of bleeding episode (e.g., spontaneous, traumatic), the location of the bleed (joint, internal, skin/mucosa, or muscle) were also collected. FAS included all subjects who received at least 1 dose of rFIXFc. Annualized spontaneous joint bleeding episodes = (Number of spontaneous joint bleeding episodes during the efficacy period/number of days during efficacy period)*365.25. Here, "n" indicates number of subject analyzed in specified treatment regimen. "99999" indicates that the data was not analyzed for the arm in the specified category.

End point type	Secondary
----------------	-----------

End point timeframe:

Approximately 5 years

End point values	rFIXFc [9HB02PED (<6 years old age cohort)]	rFIXFc [9HB02PED (6 - <12 years old age cohort)]	rFIXFc [Subjects from 998HB102]	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	14	93	
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))				
Weekly Prophylaxis (n= 13, 10, 51)	0.00 (0.00 to 1.06)	0.00 (0.00 to 1.40)	0.38 (0.00 to 2.25)	
Individualized Prophylaxis (n= 0, 5, 31)	99999 (99999 to 99999)	0.00 (0.00 to 0.29)	0.38 (0.00 to 1.43)	
Personalized Prophylaxis (n= 1, 1, 16)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.30 (0.00 to 1.37)	
Episodic (n= 0, 0, 15)	99999 (99999 to 99999)	99999 (99999 to 99999)	2.15 (0.58 to 11.68)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Days of Exposure per Subject

End point title	Total Number of Days of Exposure per Subject
-----------------	--

End point description:

An exposure day is a 24-hour period in which one or more rFIXFc injections are given. The total number of days of exposure to rFIXFc were summarized. Safety Analysis Set included subjects who received at least 1 dose of rFIXFc in study 9HB01EXT. Here, "n" indicates number of subject analyzed in specified treatment regimen. "99999" indicates that the data was not analyzed for the arm in the specified category.

End point type	Secondary
----------------	-----------

End point timeframe:

Approximately 5 years

End point values	rFIXFc [9HB02PED (<6 years old age cohort)]	rFIXFc [9HB02PED (6 - <12 years old age cohort)]	rFIXFc [Subjects from 998HB102]	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	14	93	
Units: days				
median (full range (min-max))				
Weekly Prophylaxis (n= 13, 10, 51)	55.00 (8.0 to 176.0)	165.00 (3.0 to 202.0)	169.00 (4.0 to 327.0)	
Individualized Prophylaxis (n= 0, 5, 31)	99999 (99999 to 99999)	54.00 (4.0 to 141.0)	110.00 (9.0 to 369.0)	
Personalized Prophylaxis (n= 1, 1, 17)	157.00 (157.00 to 157.00)	90.00 (90.00 to 90.00)	146.00 (7.0 to 431.0)	
Episodic (n= 0, 0, 15)	99999 (99999 to 99999)	99999 (99999 to 99999)	52.00 (0.0 to 164.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rFIXFc Consumption per Kilogram per Subject per Year

End point title	Annualized rFIXFc Consumption per Kilogram per Subject per Year
-----------------	---

End point description:

Annualized consumption = (total IU/kg of study treatment received during the efficacy period / total number of days during the efficacy period) multiplied by 365.25. FAS included all subjects who received at least 1 dose of rFIXFc. Here, "n" indicates number of subject analyzed in specified treatment regimen. "99999" indicates that the data was not analyzed for the arm in the specified category.

End point type	Secondary
----------------	-----------

End point timeframe:

Approximately 5 years

End point values	rFIXFc [9HB02PED (<6 years old age cohort)]	rFIXFc [9HB02PED (6 - <12 years old age cohort)]	rFIXFc [Subjects from 998HB102]	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	14	93	
Units: dose per kilogram per subject per year				
median (inter-quartile range (Q1-Q3))				
Weekly Prophylaxis (n= 13, 10, 51)	3382.5 (2930.9 to 3667.4)	3212.0 (2838.5 to 3344.4)	2598.0 (2129.8 to 3370.9)	
Individualized Prophylaxis (n= 0, 5, 31)	99999 (99999 to 99999)	3700.7 (3689.2 to 3716.5)	2894.8 (2520.0 to 4023.5)	
Personalized Prophylaxis (n= 1, 1, 16)	3331.7 (3331.7 to 3331.7)	8931.2 (8931.2 to 8931.2)	3671.2 (2394.8 to 5563.3)	

Episodic (n= 0, 0, 15)	99999 (99999 to 99999)	99999 (99999 to 99999)	595.6 (363.8 to 1024.5)	
------------------------	------------------------	------------------------	-------------------------	--

Statistical analyses

No statistical analyses for this end point

Secondary: Physicians' Global Assessment of Response to Treatment With rFIXFc Using a 4-Point Scale

End point title	Physicians' Global Assessment of Response to Treatment With rFIXFc Using a 4-Point Scale
End point description:	
Subjects were assessed for response to their rFIXFc regimen using the following 4-point scale: Excellent: bleeding episodes responded to less than or equal to (\leq) the usual number of injections or \leq the usual dose of rFIXFc, or the rate of breakthrough bleeding during prophylaxis was \leq that usually observed; Effective: most bleeding episodes responded to the same number of injections and dose, but some required more injections or higher doses, or there was a minor increase in the rate of breakthrough; Partially Effective: bleeding episodes most often required more injections and/or higher doses than expected, or adequate breakthrough bleeding prevention during prophylaxis required more frequent injections and/or higher doses and Ineffective: routine failure to control hemostasis or hemostatic control require additional agents. FAS included all subjects who received at least 1 dose of rFIXFc. The results were reported based on the efficacy period for overall treatment regimen.	
End point type	Secondary
End point timeframe:	
Approximately 5 years	

End point values	rFIXFc [Subjects from 9HB02PED]	rFIXFc [Subjects from 998HB102]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	93		
Units: percentage of visits				
number (not applicable)				
Excellent	86.8	76.3		
Effective	12.6	22.6		
Partially Effective	0.7	1.1		
Ineffective	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Excellent or Good Response to Treatment Using a 4-Point Scale

End point title	Percentage of Subjects with Excellent or Good Response to Treatment Using a 4-Point Scale
-----------------	---

End point description:

Using eDiary, subject received rating for treatment response to any bleeding episode (BE) using 4-point scale-Excellent: Abrupt pain relief and/or improvement in signs of bleeding within approximately (approx.) 8 hours (h) after initial injection (inj.); Good: Definite pain relief and/or improvement in signs of bleeding within approx. 8h after an injection, but possibly requiring more than 1 injection after 24–48h for complete resolution; Moderate: Probable/slight beneficial effect within 8h after initial injection and requires more than 1 injection and None: No improvement, or condition worsens within approx. 8h after initial injection. This assessment was to be made approx. 8 to 12h from time the injection was given to treat BE and prior to any additional doses of rFIXFc given for same bleeding episode. FAS population included. "n"=number of subject analyzed in specified treatment regimen during efficacy period. "99999"=data was not analyzed for the arm in the specified category.

End point type	Secondary
----------------	-----------

End point timeframe:

Approximately 5 years

End point values	rFIXFc [9HB02PED (<6 years old age cohort)]	rFIXFc [9HB02PED (6 - <12 years old age cohort)]	rFIXFc [Subjects from 998HB102]	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	14	93	
Units: % of first inj. with evaluations for BE				
number (not applicable)				
Weekly Prophylaxis (n= 13, 10, 51)	81.1	82.5	74.2	
Individualized Prophylaxis (n= 0, 5, 31)	99999	80.6	87.0	
Personalized Prophylaxis (n= 1, 1, 16)	0	50.0	75.8	
Episodic (n= 0, 0, 15)	99999	99999	97.1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of ICF through follow-up [14 (+7) days after the last dose of rFIXFc] or final visit/early termination visit (approximately 5 years)

Adverse event reporting additional description:

The Safety Analysis Set consisted of subjects who received at least 1 dose of rFIXFc in study. AEs emergent during major surgical/rehabilitation periods are excluded.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	15.0
--------------------	------

Reporting groups

Reporting group title	rFIXFc [Subjects from 9HB02PED]
-----------------------	---------------------------------

Reporting group description:

Weekly prophylaxis (P): Subjects received 20 IU/kg to 100 IU/kg rFIXFc once weekly during weekly prophylaxis. Dose was based on the subject's clinical profile observed in the parent rFIXFc study and the individual pharmacokinetic profile, trough, and/or peak (recovery) values. Individualized P: 100 IU/kg rFIXFc every 8 to 16 days, or twice a month in individualized prophylaxis. Personalized P: included addition of prevention doses prior to strenuous activity; targeting a FIX trough level of greater than (>) 5%, if warranted by the bleeding history and/or activity level or dosing twice a week (25 IU/kg, twice weekly, versus 50 IU/kg, once weekly) for subjects who may have better control with such a regimen. Subjects who reached the age of 12 during the study could also choose to switch to the episodic treatment group, with dosing based on subject's clinical condition and type and severity of bleeding event; no subjects had entered the episodic treatment group as of the end of study.

Reporting group title	rFIXFc [Subjects from 998HB102]
-----------------------	---------------------------------

Reporting group description:

Weekly prophylaxis: Subjects received 20 IU/kg to 100 IU/kg rFIXFc once weekly during weekly prophylaxis. Dose was based on the subject's clinical profile observed in the parent rFIXFc study and the individual pharmacokinetic profile, trough, and/or peak (recovery) values. Individual prophylaxis: Subjects received 100 IU/kg rFIXFc every 8 to 16 days, or twice a month in individualized prophylaxis. Personalized Prophylaxis: Personalized prophylaxis included addition of prevention doses prior to strenuous activity; targeting a FIX trough level of greater than (>) 5 percent (%), if warranted by the bleeding history and/or activity level or dosing twice a week (25 IU/kg, twice weekly, versus 50 IU/kg, once weekly) for subjects who may have better control with such a regimen. Episodic (On Demand): The individual dose of rFIXFc to treat bleeding episodes was based on subject's clinical condition, type and severity of the bleeding event.

Reporting group title	Overall rFIXFc
-----------------------	----------------

Reporting group description: -

Serious adverse events	rFIXFc [Subjects from 9HB02PED]	rFIXFc [Subjects from 998HB102]	Overall rFIXFc
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 27 (18.52%)	31 / 93 (33.33%)	36 / 120 (30.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic neoplasm malignant			

subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Posterior interosseous syndrome			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Knee arthroplasty			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillectomy			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Victim of crime			

subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extradural haematoma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	3 / 27 (11.11%)	4 / 93 (4.30%)	7 / 120 (5.83%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body			
subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Head injury			
subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 27 (0.00%)	2 / 93 (2.15%)	2 / 120 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haematoma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			

subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Necrotising retinitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 27 (0.00%)	2 / 93 (2.15%)	2 / 120 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			

subjects affected / exposed	0 / 27 (0.00%)	2 / 93 (2.15%)	2 / 120 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	0 / 27 (0.00%)	2 / 93 (2.15%)	2 / 120 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilic arthropathy			
subjects affected / exposed	0 / 27 (0.00%)	4 / 93 (4.30%)	4 / 120 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Slipping rib syndrome			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Anal abscess			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 27 (0.00%)	3 / 93 (3.23%)	3 / 120 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis C			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orchitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal cyst			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			

subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 1	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	rFIXFc [Subjects from 9HB02PED]	rFIXFc [Subjects from 998HB102]	Overall rFIXFc
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 27 (85.19%)	66 / 93 (70.97%)	89 / 120 (74.17%)
Investigations			
Serum ferritin decreased			
subjects affected / exposed	2 / 27 (7.41%)	0 / 93 (0.00%)	2 / 120 (1.67%)
occurrences (all)	2	0	2
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	2 / 27 (7.41%)	1 / 93 (1.08%)	3 / 120 (2.50%)
occurrences (all)	2	2	4
Fall			
subjects affected / exposed	7 / 27 (25.93%)	4 / 93 (4.30%)	11 / 120 (9.17%)
occurrences (all)	9	15	24
Head injury			
subjects affected / exposed	2 / 27 (7.41%)	2 / 93 (2.15%)	4 / 120 (3.33%)
occurrences (all)	2	2	4
Joint dislocation			
subjects affected / exposed	2 / 27 (7.41%)	0 / 93 (0.00%)	2 / 120 (1.67%)
occurrences (all)	2	0	2
Joint injury			
subjects affected / exposed	2 / 27 (7.41%)	2 / 93 (2.15%)	4 / 120 (3.33%)
occurrences (all)	3	3	6
Laceration			

subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	5 / 93 (5.38%) 5	8 / 120 (6.67%) 8
Ligament sprain subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	4 / 93 (4.30%) 4	6 / 120 (5.00%) 6
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	7 / 93 (7.53%) 7	7 / 120 (5.83%) 7
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 6	15 / 93 (16.13%) 17	18 / 120 (15.00%) 23
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	6 / 27 (22.22%) 9	5 / 93 (5.38%) 6	11 / 120 (9.17%) 15
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 6	3 / 93 (3.23%) 4	7 / 120 (5.83%) 10
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	4 / 93 (4.30%) 4	6 / 120 (5.00%) 6
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	7 / 93 (7.53%) 8	8 / 120 (6.67%) 9
Gingival bleeding subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 93 (0.00%) 0	2 / 120 (1.67%) 2
Nausea subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	5 / 93 (5.38%) 6	5 / 120 (4.17%) 6
Toothache			

subjects affected / exposed	0 / 27 (0.00%)	5 / 93 (5.38%)	5 / 120 (4.17%)
occurrences (all)	0	6	6
Vomiting			
subjects affected / exposed	5 / 27 (18.52%)	7 / 93 (7.53%)	12 / 120 (10.00%)
occurrences (all)	5	8	13
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 27 (11.11%)	5 / 93 (5.38%)	8 / 120 (6.67%)
occurrences (all)	3	6	9
Epistaxis			
subjects affected / exposed	5 / 27 (18.52%)	0 / 93 (0.00%)	5 / 120 (4.17%)
occurrences (all)	6	0	6
Nasal congestion			
subjects affected / exposed	5 / 27 (18.52%)	0 / 93 (0.00%)	5 / 120 (4.17%)
occurrences (all)	5	0	5
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 27 (0.00%)	5 / 93 (5.38%)	5 / 120 (4.17%)
occurrences (all)	0	5	5
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 27 (0.00%)	5 / 93 (5.38%)	5 / 120 (4.17%)
occurrences (all)	0	7	7
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 27 (14.81%)	10 / 93 (10.75%)	14 / 120 (11.67%)
occurrences (all)	4	13	17
Pain in extremity			
subjects affected / exposed	2 / 27 (7.41%)	1 / 93 (1.08%)	3 / 120 (2.50%)
occurrences (all)	2	1	3
Infections and infestations			
Ear infection			
subjects affected / exposed	3 / 27 (11.11%)	1 / 93 (1.08%)	4 / 120 (3.33%)
occurrences (all)	3	2	5
Hepatitis c			

subjects affected / exposed	0 / 27 (0.00%)	5 / 93 (5.38%)	5 / 120 (4.17%)
occurrences (all)	0	5	5
Influenza			
subjects affected / exposed	1 / 27 (3.70%)	8 / 93 (8.60%)	9 / 120 (7.50%)
occurrences (all)	1	9	10
Lower respiratory tract infection			
subjects affected / exposed	3 / 27 (11.11%)	1 / 93 (1.08%)	4 / 120 (3.33%)
occurrences (all)	5	1	6
Nasopharyngitis			
subjects affected / exposed	3 / 27 (11.11%)	14 / 93 (15.05%)	17 / 120 (14.17%)
occurrences (all)	4	18	22
Paronychia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 93 (0.00%)	2 / 120 (1.67%)
occurrences (all)	2	0	2
Sinusitis			
subjects affected / exposed	1 / 27 (3.70%)	5 / 93 (5.38%)	6 / 120 (5.00%)
occurrences (all)	2	6	8
Tonsillitis			
subjects affected / exposed	2 / 27 (7.41%)	0 / 93 (0.00%)	2 / 120 (1.67%)
occurrences (all)	3	0	3
Upper respiratory tract infection			
subjects affected / exposed	2 / 27 (7.41%)	6 / 93 (6.45%)	8 / 120 (6.67%)
occurrences (all)	3	7	10
Varicella			
subjects affected / exposed	2 / 27 (7.41%)	1 / 93 (1.08%)	3 / 120 (2.50%)
occurrences (all)	2	1	3
Viral infection			
subjects affected / exposed	2 / 27 (7.41%)	3 / 93 (3.23%)	5 / 120 (4.17%)
occurrences (all)	2	3	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2011	The primary reason for this amendment was to clarify the duration and planned end of the study.
20 June 2012	The main reasons for this amendment were: to include various clarifications to the protocol (including a Protocol Clarification Letter), correction of errors, and additions to enhance understanding of the protocol, e.g., in Section 5.3.3 the list of assessments to be performed at the Last Postoperative Visit for subjects who entered the extension study following major surgery in Study 9HB02PED was added; addition of information on dispensation of study treatment between study visits to maintain adequate drug supplies for the subject's study treatment.
13 November 2013	The main reason of this amendment were: to amend dose regimen to be appropriate for subjects <12 years of age to accommodate the transition of subjects from the pediatric study (9HB02PED) to this study (Study 9HB01EXT); ·specify that subjects will be followed through at least 100 EDs; update of statistical section; modification of text to note that major surgeries are to be classified as SAEs; addition of anti-rFIXFc antibody assessment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported