Clinical trial results:
B-LONG: An Open-label, Multicenter Evaluation of the Safety, Pharmacokinetics, and Efficacy of Recombinant, Long-acting Coagulation Factor IX Fc Fusion Protein (rFIXFc) in the Prevention and Treatment of Bleeding in Previously Treated Subjects With Severe Hemophilia B

Summary

EudraCT number	2009-014295-21
Trial protocol	SE GB DE FR PL BE IT NL
Global end of trial date	29 July 2012

Results information

Result version number	v1 (current)
This version publication date	04 February 2016
First version publication date	20 June 2015

Trial information

Trial identification

Sponsor protocol code	998HB102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01027364
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street , Cambridge, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, Clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, Clinicaltrials@biogen.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	29 July 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study were: to evaluate the safety and tolerability of rFIXFc; to evaluate the efficacy of rFIXFc in all treatment arms; to evaluate the effectiveness of prophylaxis over on-demand (episodic) therapy by comparing the annualized number of bleeding episodes between subjects receiving rFIXFc on each prevention (prophylaxis) regimen and subjects receiving rFIXFc on an episodic regimen. The secondary objectives of the study were: to evaluate and assess the pharmacokinetic (PK) parameter estimates of rFIXFc and rFIX (BeneFIX®) at baseline in the Sequential PK subgroup as well as rFIXFc at Week 26 (±1 week); to evaluate subjects' response to treatment; to evaluate rFIXFc consumption.

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent form and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 January 2010
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: 3
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	China: 7

Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Hong Kong: 7
Country: Number of subjects enrolled	India: 7
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	South Africa: 9
Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	123
EEA total number of subjects	30

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)	0
Adolescents (12-17 years)	11
Adults (18-64 years)	110
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who signed informed consent underwent a screening evaluation up to 8 weeks prior to the first dose of the study treatment.
Of the 12 total subjects started in Arm 4: 6 started in Arm 4; 5 joined from Arm 1; 1 joined from Arm 3.
Of the 11 total subjects completed in Arm 4: 3 completed Arm 4 only, 7 continued to Arm 1; 1 continued to Arm 3.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Arm 1: Weekly Prophylaxis

Arm description:

50 IU/kg rFIXFc via intravenous (IV) injection once every 7 days initially, then at a dose indicated by the subject's baseline PK assessment that ensured a target trough of 1% to 3% above baseline or higher, as clinically indicated. Adjustments to the initial weekly dose of rFIXFc (50 IU/kg) were to be made based on baseline PK assessments, occurrence of spontaneous bleeding episodes, and the trough levels, which were to be monitored at Weeks 4, 16, 26, and 39.

Prior to the first dose of rFIXFc, subjects in the Sequential PK subgroup were to receive a single dose of 50 IU/kg BeneFIX administered IV in the clinic, followed by PK sampling. A single dose of 50 IU/kg rFIXFc was administered following a 120-hour washout from BeneFIX, followed by PK sampling for a baseline PK profiling. At Week 26 (±1 week) subjects were to receive a single dose of 50 IU/kg rFIXFc for repeat PK profiling.

Arm type	Experimental
Investigational medicinal product name	rFIXFc
Investigational medicinal product code	rFIXFc
Other name	Recombinant Factor IX Fc Fusion Protein
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Study site staff was instructed to refer to the Directions for Handling and Administration (DHA) Manual located in the Investigator Site File and/or the Pharmacy Manual for specific instructions on the handling, preparation, administration, and disposal of rFIXFc and BeneFIX.

Investigational medicinal product name	Recombinant Factor IX
Investigational medicinal product code	
Other name	BeneFIX®, Coagulation Factor IX (Recombinant)
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

BeneFIX was to be prepared and administered following the manufacturer's prescribing information.

Arm title	Arm 2: Individualized Interval Prophylaxis

Arm description:

100 IU/kg rFIXFc via IV injection once every 10 days initially, then at an interval derived from the baseline PK assessment that ensured a target trough of 1% to 3% above baseline or higher, as clinically indicated. Adjustments to the initial 10-day interval were to be made based on baseline PK assessments and trough levels, which were monitored at Weeks 4, 16, 26, and 39.

Arm type	Experimental
Investigational medicinal product name	rFIXFc
Investigational medicinal product code	rFIXFc
Other name	Recombinant Factor IX Fc Fusion Protein
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Study site staff was instructed to refer to the DHA Manual located in the Investigator Site File and/or the Pharmacy Manual for specific instructions on the handling, preparation, administration, and disposal of rFIXFc and BeneFIX.

Arm title	Arm 3: Episodic (On Demand)

Arm description:

20 to 100 IU/kg rFIXFc via IV injection, or the dose indicated by the subject's baseline PK to target a plasma level of 20% to 100%, as needed for the treatment of mild to severe bleeding episodes.

Arm type	Experimental
Investigational medicinal product name	rFIXFc
Investigational medicinal product code	rFIXFc
Other name	Recombinant Factor IX Fc Fusion Protein
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Study site staff was instructed to refer to the DHA Manual located in the Investigator Site File and/or the Pharmacy Manual for specific instructions on the handling, preparation, administration, and disposal of rFIXFc and BeneFIX.

Arm title	Arm 4: Perioperative Management

Arm description:

The surgical period and dosing were dependent on the type of surgery the subject underwent. Subjects who started the study in one of the other treatment arms prior to surgery returned to the original treatment arm. Subjects who joined the study in the Surgery arm were assigned to one of the other treatment arms following post-operative rehabilitation.

Arm type	Experimental
Investigational medicinal product name	rFIXFc
Investigational medicinal product code	rFIXFc
Other name	Recombinant Factor IX Fc Fusion Protein
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Study site staff was instructed to refer to the DHA Manual located in the Investigator Site File and/or the Pharmacy Manual for specific instructions on the handling, preparation, administration, and disposal of rFIXFc and BeneFIX.

Number of subjects in period 1	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)
Started	63	29	27
Enrolled in Sequential PK Subgroup	22 [1]	0 [2]	0 [3]
Joined Arm 4 For Surgery Then Returned	5 [4]	0 [5]	1 [6]
Started Arm 4 Then Joined Another Arm	2 [7]	0 [8]	0 [9]
Participated in Arm 4 Only	0 [10]	0 [11]	0 [12]

Completed	59	27	26
Not completed	4	2	1
Consent withdrawn by subject	1	2	-
Adverse event, non-fatal	1	-	1
Lost to follow-up	1	-	-
Protocol deviation	1	-	-

Number of subjects in period 1	Arm 4: Perioperative Management
Started	12
Enrolled in Sequential PK Subgroup	0 [13]
Joined Arm 4 For Surgery Then Returned	6 [14]
Started Arm 4 Then Joined Another Arm	2 [15]
Participated in Arm 4 Only	4 [16]
Completed	11
Not completed	1
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Lost to follow-up	-
Protocol deviation	1

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: Milestones are provided to account for PK Subgroup population and illustrate the crossover of subjects from arm to arm during the study.

[2] - 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: Milestones are provided to account for PK Subgroup population and illustrate the crossover of subjects from arm to arm during the study.

[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: Milestones are provided to account for PK Subgroup population and illustrate the crossover of subjects from arm to arm during the study.

[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: Milestones are provided to account for PK Subgroup population and illustrate the crossover of subjects from arm to arm during the study.

[5] - 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: Milestones are provided to account for PK Subgroup population and illustrate the crossover of subjects from arm to arm during the study.

[6] - 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: Milestones are provided to account for PK Subgroup population and illustrate the crossover of subjects from arm to arm during the study.

[7] - 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: Milestones are provided to account for PK Subgroup population and illustrate the crossover

of subjects from arm to arm during the study.

[8] - 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: Milestones are provided to account for PK Subgroup population and illustrate the crossover of subjects from arm to arm during the study.

[9] - 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: Milestones are provided to account for PK Subgroup population and illustrate the crossover of subjects from arm to arm during the study.

[10] - 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: Milestones are provided to account for PK Subgroup population and illustrate the crossover of subjects from arm to arm during the study.

[11] - 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: Milestones are provided to account for PK Subgroup population and illustrate the crossover of subjects from arm to arm during the study.

[12] - 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: Milestones are provided to account for PK Subgroup population and illustrate the crossover of subjects from arm to arm during the study.

[13] - 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: Milestones are provided to account for PK Subgroup population and illustrate the crossover of subjects from arm to arm during the study.

[14] - 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: Milestones are provided to account for PK Subgroup population and illustrate the crossover of subjects from arm to arm during the study.

[15] - 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: Milestones are provided to account for PK Subgroup population and illustrate the crossover of subjects from arm to arm during the study.

[16] - 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: Milestones are provided to account for PK Subgroup population and illustrate the crossover of subjects from arm to arm during the study.

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1: Weekly Prophylaxis

Reporting group description:

50 IU/kg rFIXFc via intravenous (IV) injection once every 7 days initially, then at a dose indicated by the subject's baseline PK assessment that ensured a target trough of 1% to 3% above baseline or higher, as clinically indicated. Adjustments to the initial weekly dose of rFIXFc (50 IU/kg) were to be made based on baseline PK assessments, occurrence of spontaneous bleeding episodes, and the trough levels, which were to be monitored at Weeks 4, 16, 26, and 39.

Prior to the first dose of rFIXFc, subjects in the Sequential PK subgroup were to receive a single dose of 50 IU/kg BeneFIX administered IV in the clinic, followed by PK sampling. A single dose of 50 IU/kg rFIXFc was administered following a 120-hour washout from BeneFIX, followed by PK sampling for a baseline PK profiling. At Week 26 (±1 week) subjects were to receive a single dose of 50 IU/kg rFIXFc for repeat PK profiling.

Reporting group title	Arm 2: Individualized Interval Prophylaxis

Reporting group description:

100 IU/kg rFIXFc via IV injection once every 10 days initially, then at an interval derived from the baseline PK assessment that ensured a target trough of 1% to 3% above baseline or higher, as clinically indicated. Adjustments to the initial 10-day interval were to be made based on baseline PK assessments and trough levels, which were monitored at Weeks 4, 16, 26, and 39.

Reporting group title	Arm 3: Episodic (On Demand)

Reporting group description:

20 to 100 IU/kg rFIXFc via IV injection, or the dose indicated by the subject's baseline PK to target a plasma level of 20% to 100%, as needed for the treatment of mild to severe bleeding episodes.

Reporting group title	Arm 4: Perioperative Management

Reporting group description:

The surgical period and dosing were dependent on the type of surgery the subject underwent. Subjects who started the study in one of the other treatment arms prior to surgery returned to the original treatment arm. Subjects who joined the study in the Surgery arm were assigned to one of the other treatment arms following post-operative rehabilitation.

Reporting group values	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)
Number of subjects	63	29	27
Age categorical Units: Subjects			
Adolescents (12-17 years)	6	3	2
Adults (18-64 years)	55	26	25
From 65-84 years	2	0	0
Age continuous Units: years			
median	28	33	36
full range (min-max)	12 to 71	12 to 62	14 to 64
Gender categorical Units: Subjects			
Female	0	0	0
Male	63	29	27

Reporting group values	Arm 4: Perioperative Management	Total	
Number of subjects	12	123	

Age categorical Units: Subjects			
Adolescents (12-17 years)	1	11	
Adults (18-64 years)	11	110	
From 65-84 years	0	2	
Age continuous Units: years			
median	34.5		
full range (min-max)	17 to 61	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	12	123	

End points

End points reporting groups

Reporting group title	Arm 1: Weekly Prophylaxis

Reporting group description:

50 IU/kg rFIXFc via intravenous (IV) injection once every 7 days initially, then at a dose indicated by the subject's baseline PK assessment that ensured a target trough of 1% to 3% above baseline or higher, as clinically indicated. Adjustments to the initial weekly dose of rFIXFc (50 IU/kg) were to be made based on baseline PK assessments, occurrence of spontaneous bleeding episodes, and the trough levels, which were to be monitored at Weeks 4, 16, 26, and 39.

Prior to the first dose of rFIXFc, subjects in the Sequential PK subgroup were to receive a single dose of 50 IU/kg BeneFIX administered IV in the clinic, followed by PK sampling. A single dose of 50 IU/kg rFIXFc was administered following a 120-hour washout from BeneFIX, followed by PK sampling for a baseline PK profiling. At Week 26 (±1 week) subjects were to receive a single dose of 50 IU/kg rFIXFc for repeat PK profiling.

Reporting group title	Arm 2: Individualized Interval Prophylaxis

Reporting group description:

100 IU/kg rFIXFc via IV injection once every 10 days initially, then at an interval derived from the baseline PK assessment that ensured a target trough of 1% to 3% above baseline or higher, as clinically indicated. Adjustments to the initial 10-day interval were to be made based on baseline PK assessments and trough levels, which were monitored at Weeks 4, 16, 26, and 39.

Reporting group title	Arm 3: Episodic (On Demand)

Reporting group description:

20 to 100 IU/kg rFIXFc via IV injection, or the dose indicated by the subject's baseline PK to target a plasma level of 20% to 100%, as needed for the treatment of mild to severe bleeding episodes.

Reporting group title	Arm 4: Perioperative Management

Reporting group description:

The surgical period and dosing were dependent on the type of surgery the subject underwent. Subjects who started the study in one of the other treatment arms prior to surgery returned to the original treatment arm. Subjects who joined the study in the Surgery arm were assigned to one of the other treatment arms following post-operative rehabilitation.

Subject analysis set title	Arm 1: Weekly Prophylaxis-BeneFIX
Subject analysis set type	Safety analysis

Subject analysis set description:

Prior to the first dose of rFIXFc, subjects in the Sequential PK subgroup were to receive a single dose of 50 IU/kg BeneFIX administered IV in the clinic, followed by PK sampling. A single dose of 50 IU/kg rFIXFc was administered following a 120-hour washout from BeneFIX, followed by PK sampling for a baseline PK profiling. At Week 26 (±1 week) subjects were to receive a single dose of 50 IU/kg rFIXFc for repeat PK profiling.

Subject analysis set title	Arm 1: Weekly Prophylaxis-rFIXFc
Subject analysis set type	Safety analysis

Subject analysis set description:

Prior to the first dose of rFIXFc, subjects in the Sequential PK subgroup were to receive a single dose of 50 IU/kg BeneFIX administered IV in the clinic, followed by PK sampling. A single dose of 50 IU/kg rFIXFc was administered following a 120-hour washout from BeneFIX, followed by PK sampling for a baseline PK profiling. At Week 26 (±1 week) subjects were to receive a single dose of 50 IU/kg rFIXFc for repeat PK profiling.

Subject analysis set title	Total
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects from Arms 1-4

Subject analysis set title	Pre-study Regimen: Prophylaxis (Arms 1 and 2 Pooled)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects from the Weekly or Individualized Interval Prophylaxis Arms (Arms 1 or 2) who had a prophylaxis pre-study regimen.

Subject analysis set title	Pre-study Regimen: On Demand (Arms 1 and 2 Pooled)

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects from the Weekly or Individualized Interval Prophylaxis Arms (Arms 1 or 2) who had an on-demand pre-study regimen.

Subject analysis set title	Arm 1: Weekly Prophylaxis - Sequential PK Subgroup
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Prior to the first dose of rFIXFc, subjects in the Sequential PK subgroup were to receive a single dose of 50 IU/kg BeneFIX administered IV in the clinic, followed by PK sampling. A single dose of 50 IU/kg rFIXFc was administered following a 120-hour washout from BeneFIX, followed by PK sampling for a baseline PK profiling. At Week 26 (±1 week) subjects were to receive a single dose of 50 IU/kg rFIXFc for repeat PK profiling.

All subjects in Arm 1 received 50 IU/kg rFIXFc via intravenous (IV) injection once every 7 days initially, then at a dose indicated by the subject's baseline pharmacokinetic (PK) assessment that ensured a target trough of 1% to 3% above baseline or higher, as clinically indicated. Adjustments to the initial weekly dose of rFIXFc (50 IU/kg) were to be made based on baseline PK assessments, occurrence of spontaneous bleeding episodes, and the trough levels, which were to be monitored at Weeks 4, 16, 26, and 39.

Subject analysis set title	Arm 1: Sequential PK Subgroup: BeneFIX
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Prior to the first dose of rFIXFc, subjects in the Sequential PK subgroup were to receive a single dose of 50 IU/kg BeneFIX administered IV in the clinic, followed by PK sampling. A single dose of 50 IU/kg rFIXFc was administered following a 120-hour washout from BeneFIX, followed by PK sampling for a baseline PK profiling. At Week 26 (±1 week) subjects were to receive a single dose of 50 IU/kg rFIXFc for repeat PK profiling.

All subjects in Arm 1 received 50 IU/kg rFIXFc via intravenous (IV) injection once every 7 days initially, then at a dose indicated by the subject's baseline pharmacokinetic (PK) assessment that ensured a target trough of 1% to 3% above baseline or higher, as clinically indicated. Adjustments to the initial weekly dose of rFIXFc (50 IU/kg) were to be made based on baseline PK assessments, occurrence of spontaneous bleeding episodes, and the trough levels, which were to be monitored at Weeks 4, 16, 26, and 39.

Subject analysis set title	Arm 1: Sequential PK Subgroup: rFIXFc Day 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Prior to the first dose of rFIXFc, subjects in the Sequential PK subgroup were to receive a single dose of 50 IU/kg BeneFIX administered IV in the clinic, followed by PK sampling. A single dose of 50 IU/kg rFIXFc was administered following a 120-hour washout from BeneFIX, followed by PK sampling for a baseline PK profiling. At Week 26 (±1 week) subjects were to receive a single dose of 50 IU/kg rFIXFc for repeat PK profiling.

All subjects in Arm 1 received 50 IU/kg rFIXFc via intravenous (IV) injection once every 7 days initially, then at a dose indicated by the subject's baseline pharmacokinetic (PK) assessment that ensured a target trough of 1% to 3% above baseline or higher, as clinically indicated. Adjustments to the initial weekly dose of rFIXFc (50 IU/kg) were to be made based on baseline PK assessments, occurrence of spontaneous bleeding episodes, and the trough levels, which were to be monitored at Weeks 4, 16, 26, and 39.

Subject analysis set title	Arm 1: Sequential PK Subgroup: rFIXFc Week 26
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Prior to the first dose of rFIXFc, subjects in the Sequential PK subgroup were to receive a single dose of 50 IU/kg BeneFIX administered IV in the clinic, followed by PK sampling. A single dose of 50 IU/kg rFIXFc was administered following a 120-hour washout from BeneFIX, followed by PK sampling for a baseline PK profiling. At Week 26 (±1 week) subjects were to receive a single dose of 50 IU/kg rFIXFc for repeat PK profiling.

All subjects in Arm 1 received 50 IU/kg rFIXFc via intravenous (IV) injection once every 7 days initially, then at a dose indicated by the subject's baseline pharmacokinetic (PK) assessment that ensured a target trough of 1% to 3% above baseline or higher, as clinically indicated. Adjustments to the initial weekly dose of rFIXFc (50 IU/kg) were to be made based on baseline PK assessments, occurrence of spontaneous bleeding episodes, and the trough levels, which were to be monitored at Weeks 4, 16, 26, and 39.

Subject analysis set title	Arm 1: Sequential PK Subgroup: rFIXFc Week 52
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Prior to the first dose of rFIXFc, subjects in the Sequential PK subgroup were to receive a single dose of 50 IU/kg BeneFIX administered IV in the clinic, followed by PK sampling. A single dose of 50 IU/kg rFIXFc was administered following a 120-hour washout from BeneFIX, followed by PK sampling for a baseline PK profiling. At Week 26 (±1 week) subjects were to receive a single dose of 50 IU/kg rFIXFc for repeat PK profiling.

All subjects in Arm 1 received 50 IU/kg rFIXFc via intravenous (IV) injection once every 7 days initially, then at a dose indicated by the subject's baseline pharmacokinetic (PK) assessment that ensured a target trough of 1% to 3% above baseline or higher, as clinically indicated. Adjustments to the initial weekly dose of rFIXFc (50 IU/kg) were to be made based on baseline PK assessments, occurrence of spontaneous bleeding episodes, and the trough levels, which were to be monitored at Weeks 4, 16, 26, and 39.

Primary: Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities

End point title	Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities[1][2]

End point description:

Clinical laboratory evaluations included hematology and blood chemistry. Table does not include laboratory tests evaluated during the surgical/rehabilitation period. Because the perioperative management period represents a unique clinical situation, safety data obtained during the surgical/rehabilitation period for subjects in Arm 4 were included in listings and reviewed separately. Review of the listing was sufficient to assess this endpoint. ULN=upper limit of normal. Safety Analysis Set: subjects who received at least 1 dose of BeneFIX or rFIXFc.

End point type	Primary

End point timeframe:

up to 52 weeks ± 1 week

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: Per protocol, descriptive statistics were collected for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: For this study, a table was not generated for potentially clinically significant laboratory abnormalities for subjects in the perioperative management/surgical arm (Arm 4).

End point values	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63[3]	29[4]	27[5]	
Units: subjects				
White Blood Cells <3.0*10^9/L; n=62, 28, 27	2	0	2	
White Blood Cells >=16*10^9/L; n=62, 28, 27	0	0	0	
Lymphocytes <0.8*10^9/L; n=60, 28, 26	1	2	3	
Lymphocytes >12*10^9/L; n=60, 28, 26	0	0	0	
Neutrophils <1.5*10^9/L; n=60, 28, 26	2	0	1	
Neutrophils >13.5*10^9/L; n=60, 28, 26	0	0	0	
Monocytes >2.5*10^9/L; n=60, 28, 26	0	0	0	
Eosinophils >1.6*10^9/L; n=60, 28, 26	0	0	0	
Basophils >1.6*10^9/L; n=60, 28, 26	0	0	0	

Red Blood Cells <=3.5*10^12/L; n=62, 28, 27	1	0	0	
Red Blood Cells >=6.4*10^12/L; n=62, 28, 27	0	0	0	
Hemoglobin <=115 g/L; n=62, 28, 27	1	0	0	
Hemoglobin >=190 g/L; n=62, 28, 27	0	0	0	
Hematocrit <=37%; n=62, 28, 27	4	0	2	
Hematocrit >=60%; n=62, 28, 27	0	0	0	
Platelets <=75*10^9/L; n=62, 28, 27	0	0	1	
Platelets >=700*10^9/L; n=62, 28, 27	0	0	0	
Alanine Aminotransferase >=3*ULN; n=62, 28, 27	0	0	2	
Aspartate Aminotransferase >=3*ULN; n=62, 28, 27	2	1	1	
Alkaline Phosphatase >=3*ULN; n=62, 28, 27	0	0	0	
Total Bilirubin >=34.2 µmol/L; n=62, 28, 27	1	0	0	
Blood Urea Nitrogen >=10.7 mmol/L; n=62, 28, 27	1	0	0	
Creatinine >=176.8 µmol/L; n=62, 28, 27	1	0	0	
Sodium <=126 mmol/L; n=62, 28, 27	0	0	0	
Sodium >=156 mmol/L; n=62, 28, 27	0	0	0	
Potassium <=3 mmol/L; n=62, 28, 27	0	0	0	
Potassium >=6 mmol/L; n=62, 28, 27	0	0	0	
Chloride <=90 mmol/L; n=62, 28, 27	0	0	0	
Chloride >=118 mmol/L; n=62, 28, 27	0	0	0	
Phosphate <=0.55 mmol/L n=62, 28, 27	0	0	1	
Phosphate >=1.71 mmol/L; n=62, 28, 27	1	1	0	
Glucose <=2.22 mmol/L; n=62, 28, 27	0	0	0	
Glucose >=9.71 mmol/L; n=62, 28, 27	4	1	0	
Albumin <=25 g/L; n=62, 28, 27	0	0	0	
Total Protein <=45 g/L; n=62, 28, 27	0	0	0	
Total Protein >=100 g/L; n=62, 28, 27	0	0	0	

Notes:

[3] - n=the number of subjects with at least one post-baseline value.

[4] - n=the number of subjects with at least one post-baseline value.

[5] - n=the number of subjects with at least one post-baseline value.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)[6][7]

End point description:

AE=any untoward medical occurrence that did not necessarily have a causal relationship with this treatment, and could be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study product, whether related or not. TE=event present prior to receiving the first injection of BeneFIX or rFIXFc that subsequently worsened in severity or not present prior to receiving the first injection but subsequently appeared before last visit on study. Serious AE (SAE)=AE

resulting in death, immediate risk of death, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital/anomaly/birth defect, or any other medically important event. Related=related, possibly related, and relationship missing. Data include AEs emergent during the surgical/rehabilitation period; AE data are included in each treatment arm only for the time each subject was enrolled in that arm.

End point type	Primary

End point timeframe:

up to 52 weeks + 30 days ± 1 week

Notes:

[6] - 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: Per protocol, descriptive statistics were collected for this endpoint.

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)	Arm 4: Perioperative Management	Arm 1: Weekly Prophylaxis-BeneFIX
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29[8]	27[9]	12[10]	23[11]
Units: subjects				
>=1 TEAE	23	20	10	2
>=1 Related TEAE	4	1	0	0
>=1 TESAE	4	4	3	0
>=1 Related TESAE	1	0	0	0

Notes:

[8] - Safety Analysis Set: subjects who received at least 1 dose of BeneFIX or rFIXFc.

[9] - Safety Analysis Set: subjects who received at least 1 dose of BeneFIX or rFIXFc.

[10] - Safety Analysis Set: subjects who received at least 1 dose of BeneFIX or rFIXFc.

[11] - Safety Analysis Set: subjects who received at least 1 dose of BeneFIX or rFIXFc.

End point values	Arm 1: Weekly Prophylaxis-rFIXFc			
Subject group type	Subject analysis set			
Number of subjects analysed	63[12]			
Units: subjects				
>=1 TEAE	45			
>=1 Related TEAE	5			
>=1 TESAE	5			
>=1 Related TESAE	0			

Notes:

[12] - Safety Analysis Set: subjects who received at least 1 dose of BeneFIX or rFIXFc.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Non-serious Treatment-emergent Adverse Events (TEAEs) During the Surgical / Rehabilitation Period

End point title	Number of Subjects With Non-serious Treatment-emergent Adverse Events (TEAEs) During the Surgical / Rehabilitation

	Period[13][14]

End point description:

Please see the endpoint "Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)" for definitions of AEs and TEAEs. Subjects are counted once if they report multiple events in the same system organ class (SOC) or preferred term (PT). Coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.0 dictionary. The following SOCs are abbreviated in the table: Immune System (IS); Injury, Poisoning, and Procedural (IPP); Metabolism and Nutrition (MN); Musculoskeletal and Connective Tissue (MCT); Respiratory, Thoracic and Mediastinal (RTM); Skin and Subcutaneous Tissue (SST). Safety Analysis Set: subjects who received at least 1 dose of BeneFIX or rFIXFc. A subject may have been in more than one group (i.e., subjects in Arm 4 who were also in Arm 1, 2, or 3; please see Subject Disposition for details).

End point type	Primary

End point timeframe:

up to 52 weeks + 30 days ± 1 week

Notes:

[13] - 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: Per protocol, descriptive statistics were collected for this endpoint.

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 4: Perioperative Management			
Subject group type	Reporting group			
Number of subjects analysed	12[15]			
Units: subjects				
SOC: Blood/Lymphatic System Disorders; PT: Anaemia	2			
SOC: Ear and Labyrinth Disorders; PT: Vertigo	1			
SOC: Gastrointestinal Disorders; PT: Constipation	1			
SOC: Gastrointestinal Disorders; PT: Nausea	1			
SOC: Gastrointestinal Disorders; PT: Vomiting	1			
SOC: General Disorders; PT: Asthenia	1			
SOC: General Disorders; PT: Infusion Site Pain	1			
SOC: IS Disorders; PT: Drug Hypersensitivity	1			
SOC: Infections/Infestations; PT: Cellulitis	1			
SOC: IPP Complications; PT: Incision Site Pain	1			
SOC: IPP Complications; PT: Procedural Pain	1			
SOC: IPP Complications; PT: Wound Complication	1			
SOC: Investigations; PT: Weight Increased	1			
SOC: MN Disorders; PT: Decreased Appetite	1			
SOC: MCT Disorders; PT: Muscle Spasms	1			

SOC: Nervous System Disorders; PT: Dizziness	2			
SOC: Nervous System Disorders; PT: Headache	1			
SOC: Nervous System (NS) Disorders; PT: Neuralgia	1			
SOC: NS Disorders; PT: Neuropathy Peripheral	1			
SOC: Psychiatric Disorders; PT: Anxiety	1			
SOC: Psychiatric Disorders; PT: Insomnia	1			
SOC: RTM Disorders; PT: Dyspnoea	1			
SOC: RTM Disorders; Oropharyngeal Pain	1			
SOC: SST Disorders; PT: Hyperhidrosis	1			
SOC: Vascular Disorders; PT: Hypertension	1			
SOC: Vascular Disorders; PT: Hypotension	1			

Notes:

[15] - Number of subjects with at least 1 TEAE analyzed=8

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-emergent Serious Adverse Events (TESAEs) During the Surgical / Rehabilitation Period

End point title	Number of Subjects With Treatment-emergent Serious Adverse Events (TESAEs) During the Surgical / Rehabilitation Period[16][17]

End point description:

SAE=AE resulting in death, immediate risk of death, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital/anomaly/birth defect, or any other medically important event. TESAE=SAE present prior to receiving the first injection of BeneFIX or rFIXFc that subsequently worsened in severity or was not present prior to receiving the first injection but subsequently appeared before last visit on study. Subjects are counted once if they report multiple events in the same system organ class (SOC) or preferred term (PT). Coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.0 dictionary. The following SOC is abbreviated in the table: Injury, Poisoning, and Procedural (IPP). Safety Analysis Set: subjects who received at least 1 dose of BeneFIX or rFIXFc. A subject may have been in more than one group (i.e., subjects in Arm 4 who were also in Arm 1, 2, or 3).

End point type	Primary

End point timeframe:

up to 52 weeks + 30 days ± 1 week

Notes:

[16] - 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: Per protocol, descriptive statistics were collected for this endpoint.

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 4: Perioperative Management			
Subject group type	Reporting group			
Number of subjects analysed	12[18]			
Units: subjects				
SOC: Cardiac Disorders; PT: Tachycardia	1			
SOC: Infections/Infestations; PT: Bacterial Sepsis	1			
SOC: Infections/Infestations; PT: Pilondial Cyst	1			
SOC: Infections/Infestations; PT: Tooth Abscess	1			
SOC: IPP Complications; PT: Limb Crushing Injury	1			

Notes:

[18] - Number of subjects with at least 1 TESAE analyzed=3

Statistical analyses

No statistical analyses for this end point

Primary: Incidence Rate of FIX Inhibitor Development

End point title	Incidence Rate of FIX Inhibitor Development[19]

End point description:

An inhibitor test result ≥0.6 Bethesda units (BU)/mL, identified and confirmed by re-testing of a second sample obtained within 2 to 4 weeks, was considered positive. Both tests were to be performed using the Nijmegen-modified Bethesda Assay by the central laboratory. The incidence rates along with the 95% confidence interval (CI) were summarized for all titers for subjects with 50 or more exposure days (EDs) to rFIXFc and a valid inhibitor test after the 50th exposure. In addition, the incidence rates for all subjects regardless of their EDs to rFIXFc were also summarized. The 95% CI was calculated using Clopper-Pearson exact method. Safety Analysis Set: subjects who received at least 1 dose of of rFIXFc and who had a valid inhibitor test.

End point type	Primary

End point timeframe:

up to 52 weeks ± 1 week

Notes:

[19] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)	Arm 4: Perioperative Management
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63[20]	27[21]	27[22]	4[23]
Units: percentage of subjects				
number (confidence interval 95%)				
Subjects with ≥50 EDs to rFIXFc; n=52, 2, 0, 1, 55	0 (0 to 6.85)	0 (0 to 84.19)	0 (0 to 0)	0 (0 to 97.5)
All subjects; n=63, 27, 27, 4, 121	0 (0 to 5.69)	0 (0 to 12.77)	0 (0 to 12.77)	0 (0 to 60.24)

Notes:

[20] - n=number of subjects with given number of EDs who had a valid inhibitor test.

[21] - n=number of subjects with given number of EDs who had a valid inhibitor test.

[22] - For "Subjects with ≥50 EDs to rFIXFc," the 95% CI= NA (not applicable), since n=0 in this arm.

[23] - n=number of subjects with given number of EDs who had a valid inhibitor test.

End point values	Total			
Subject group type	Subject analysis set			
Number of subjects analysed	121[24]			
Units: percentage of subjects				
number (confidence interval 95%)				
Subjects with ≥50 EDs to rFIXFc; n=52, 2, 0, 1, 55 All subjects; n=63, 27, 27, 4, 121	0 (0 to 6.49) 0 (0 to 3)			

Notes:

[24] - n=number of subjects with given number of EDs who had a valid inhibitor test.

Statistical analyses

No statistical analyses for this end point

Primary: Annualized Bleeding Rate

End point title	Annualized Bleeding Rate[25][26]

End point description:

Annualized bleeding episodes = (number of bleeding episodes / number of days in the respective period)*365.25. In Arms 1 and 2, the efficacy period (EP) started with date and time of first prophylactic dose following a completed PK sampling period and ended with last dose administered (for prophylaxis or a bleeding episode). In Arm 3, the EP started following last PK sampling timepoint and ended with either date of last contact or date of last entry into the eDiary, whichever was later. The EP was interrupted for the repeat PK period in Arm 1 (sequential PK subgroup) and for all surgical/rehabilitation periods (for both major and minor surgeries) in all 3 arms. A bleeding episode started from the first sign of a bleed, and ended 72 hours after the last treatment for the bleeding, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, were considered the same bleeding episode.

End point type	Primary

End point timeframe:

up to 52 weeks ± 1 week (efficacy period as defined in description)

Notes:

[25] - 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: Per protocol, descriptive statistics were collected for this endpoint.

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61[27]	26[28]	27[29]	
Units: episodes per participant per year				
median (inter-quartile range (Q1-Q3))	2.95 (1.01 to 4.35)	1.38 (0 to 3.43)	17.69 (10.77 to 23.24)	

Notes:

[27] - Full Analysis Set: subjects who received at least 1 dose of rFIXFc.

[28] - Full Analysis Set: subjects who received at least 1 dose of rFIXFc.

[29] - Full Analysis Set: subjects who received at least 1 dose of rFIXFc.

Statistical analyses

No statistical analyses for this end point

Primary: Comparison of Annualized Bleeding Rates

End point title	Comparison of Annualized Bleeding Rates[30]

End point description:

Estimated with a factor for arm, based on whole study duration for all subjects. Annualized bleeding episodes = (number of bleeding episodes / number of days in the respective period)*365.25. In Arms 1 and 2, the EP started with date and time of first prophylactic dose following a completed PK sampling period and ended with last dose administered (for prophylaxis or a bleeding episode). In Arm 3, the EP started following last PK sampling timepoint and ended with either date of last contact or date of last entry into the eDiary, whichever was later. The EP was interrupted for the repeat PK period in Arm 1 and for all surgical/rehabilitation periods in all 3 arms. A bleeding episode started from the first sign of a bleed, and ended 72 hours after the last treatment for the bleeding, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, were considered the same bleeding episode.

End point type	Primary

End point timeframe:

up to 52 weeks ± 1 week (efficacy period as defined in description)

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61[31]	26[32]	27[33]	
Units: episodes per subject per year				
number (confidence interval 95%)	3.12 (2.46 to 3.95)	2.4 (1.67 to 3.47)	18.67 (14.01 to 24.89)	

Notes:

[31] - Full Analysis Set: subjects who received at least 1 dose of rFIXFc.

[32] - Full Analysis Set: subjects who received at least 1 dose of rFIXFc.

[33] - Full Analysis Set: subjects who received at least 1 dose of rFIXFc.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm 3: Episodic (On Demand) v Arm 1: Weekly Prophylaxis

Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	< 0.001 [35]
Method	negative binomial model
Parameter estimate	Bleeding Rate Ratio
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.24

Notes:

[34] - The null hypothesis for the primary endpoint is no difference between any prevention regimen and the on-demand regimen. The sample size of this study was mainly based on clinical rather than statistical considerations. However it was projected to have > 95% power at the 2-sided 0.05 level of significance, based upon this hypothesis test.

[35] - A hierarchical approach was applied to the comparison of the annualized bleeding rates between the prophylaxis arms and the episodic arm.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Arm 3: Episodic (On Demand) v Arm 2: Individualized Interval Prophylaxis
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	< 0.001 [37]
Method	negative binomial model
Parameter estimate	Bleeding Rate Ratio
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.2

Notes:

[36] - The null hypothesis for the primary endpoint is no difference between any prevention regimen and the on-demand regimen. The sample size of this study was mainly based on clinical rather than statistical considerations. However it was projected to have > 95% power at the 2-sided 0.05 level of significance, based upon this hypothesis test.

[37] - A hierarchical approach was applied to the comparison of the annualized bleeding rates between the prophylaxis arms and the episodic arm.

Secondary: Subject Assessment of Response to Injections to Treat a Bleeding Episode

End point title	Subject Assessment of Response to Injections to Treat a Bleeding Episode[38]

End point description:

Subject's assessment of the response to the first rFIXFc injection for each bleeding episode. Percentages were based on the number of bleeding episodes for which a response was provided for the first injection, using the following 4-point scale: excellent; good; moderate; no response. Full Analysis Set: subjects who received at least 1 dose of rFIXFc and had a bleeding episode; subjects with a non-evaluable bleeding episode are counted in the 'number of subjects analyzed,' but not the percentages.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47[39]	15[40]	27[41]	
Units: percentage of responses				
number (not applicable)				
Excellent or Good	78.8	74.6	87.1	
Excellent	35.3	31.7	37.3	
Good	43.6	42.9	49.7	
Moderate	18.6	22.2	11.9	
No Response	2.6	3.2	1	

Notes:

[39] - Number of bleeding episodes analyzed=156

[40] - Number of bleeding episodes analyzed=63

[41] - Number of bleeding episodes analyzed=394

Statistical analyses

No statistical analyses for this end point

Secondary: Physicians' Global Assessments of Subjects' Response to Treatment With rFIXFc

End point title	Physicians' Global Assessments of Subjects' Response to Treatment With rFIXFc[42]

End point description:

Physicians assessed each subject's response to rFIXFc using a 4-point scale: excellent; effective; partially effective; ineffective. Percentage of the total count of scale responses for all subjects is presented. Multiple responses per subject are counted. Full Analysis Set: subjects who received at least 1 dose of rFIXFc, had evaluable efficacy assessments, and had nonmissing observations at time point.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61[43]	26[44]	27[45]	
Units: percentage of responses				
number (not applicable)				
Excellent	74.5	73.2	58.3	

Effective	24.3	26	39.6	
Partially Effective	1.1	0.8	2.1	
Ineffective	0	0	0	

Notes:

[43] - Number of responses analyzed=267

[44] - Number of responses analyzed=123

[45] - Number of responses analyzed=96

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rFIXFc Consumption Per Subject

End point title	Annualized rFIXFc Consumption Per Subject[46]

End point description:

Consumption is calculated for the EP. In Arms 1 and 2, the EP started with date and time of first prophylactic dose following a completed PK sampling period and ended with last dose administered (for prophylaxis or a bleeding episode). In Arm 3, the EP started following last PK sampling timepoint and ended with either date of last contact or date of last entry into the eDiary, whichever was later. The EP was interrupted for the repeat PK period in Arm 1 (sequential PK subgroup) and for all surgical/rehabilitation periods (for both major and minor surgeries) in all 3 arms. Overall units (IU/kg) of annualized rFIXFc consumption = [Total rFIXFc IU/kg received during the EP / number of days in EP]*365.25. Full Analysis Set: subjects who received at least 1 dose of rFIXFc with evaluable data in the EP. 'Overall' n=all subjects in the Full Analysis Set (FAS) with evaluable data in the EP. 'Last 3 months on Study' n=all subjects in the FAS with evaluable data and >=6 months on study.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week (efficacy period as defined in description)

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	26	27	
Units: IU/kg rFIXFc per subject per year				
arithmetic mean (standard deviation)				
Overall; n=61, 26, 27	2686.94 (± 825.969)	3371.92 (± 649.69)	936.7 (± 481.764)	
Last 3 months on study; n=58, 26, 27	2467.32 (± 978.529)	3497.78 (± 957.377)	957.73 (± 699.64)	

Statistical analyses

No statistical analyses for this end point

Secondary: Average Weekly Dose For the Fixed Weekly Interval Prophylaxis Arm

End point title	Average Weekly Dose For the Fixed Weekly Interval

	Prophylaxis Arm[47]

End point description:

Average weekly dose=(total IU/kg of all eligible prophylactic doses in the included intervals/total number of days in the included intervals)*7. Eligible dose=the first of the 2 doses defining the interval. Subjects could have multiple prophylactic dose changes. Prophylactic dosing=from first prophylactic injection received for rFIXFc to the last prophylactic injection on study. Intervals between 2 prophylactic doses separated by a bleed/surgery/PK visit were not included. In Arm 1, the EP started with date and time of first prophylactic dose following a completed PK sampling period and ended with last dose administered (for prophylaxis or a bleeding episode). The EP was interrupted for the repeat PK period in Arm 1 (sequential PK subgroup) and for all surgical/rehabilitation periods (for both major and minor surgeries). FAS: subjects who received at least 1 dose of rFIXFc with evaluable data in the EP. See previous endpoint for definitions of 'Overall' and 'Last 3 months on study.'

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week (efficacy period as defined in description).

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 1: Weekly Prophylaxis			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: IU/kg				
arithmetic mean (standard deviation)				
Overall; n=61	46.26 (± 11.304)			
Last 3 months on study; n=58	43.1 (± 15.395)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average Dosing Interval For the Individualized Interval Prophylaxis Arm

End point title	Average Dosing Interval For the Individualized Interval Prophylaxis Arm[48]

End point description:

Average dosing interval = sum of days in the included dosing intervals divided by the number of included intervals. Subjects could have multiple prophylactic dose interval changes. Prophylactic dosing = from first prophylactic injection received for rFIXFc to the last prophylactic injection on study. Intervals between 2 prophylactic doses separated by a bleed/surgery/PK visit were not included. In Arm 2, the EP started with date and time of first prophylactic dose following a completed PK sampling period and ended with last dose administered (for prophylaxis or a bleeding episode). The EP was interrupted for all surgical/rehabilitation periods (for both major and minor surgeries). Full Analysis Set: subjects in Arm 2 who received at least 1 dose of rFIXFc with >=6 months on study and evaluable data.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week (efficacy period as defined in description)

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint,

per protocol.

End point values	Arm 2: Individualized Interval Prophylaxis			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: days				
median (inter-quartile range (Q1-Q3))				
Overall	12.53 (10.38 to 13.37)			
Last 3 months on study	14 (11.29 to 14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rate by Type of Bleed (Spontaneous and Traumatic)

End point title	Annualized Bleeding Rate by Type of Bleed (Spontaneous and Traumatic)[49]

End point description:

Annualized bleeding episodes = (number of bleeding episodes/number of days in EP)*365.25. Please see the definition of the EP in the Annualized Bleeding Rate Primary Endpoint Description. The EP was interrupted for the repeat PK period in Arm 1 (sequential PK subgroup) and for all surgical/rehabilitation periods (for both major and minor surgeries) in all 3 arms. A bleeding episode started from the first sign of a bleed, and ended 72 hours after the last treatment for the bleeding, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, were considered the same bleeding episode. Any bleeding at a different location was a separate bleeding episode regardless of time from the last injection. Full Analysis Set: subjects who received at least 1 dose of rFIXFc with evaluable data.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week (efficacy period as defined in description)

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	26	27	
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))				
Spontaneous	1.04 (0 to 2.19)	0.88 (0 to 2.3)	11.78 (2.62 to 19.78)	

Traumatic	0.99 (0 to 2.13)	0 (0 to 0.78)	2.21 (0 to 6.81)	
Unknown	0 (0 to 0)	0 (0 to 0)	0 (0 to 1.34)	

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rate by Location of Bleed (Joint, Muscle, Internal, Skin/Mucosa)

End point title	Annualized Bleeding Rate by Location of Bleed (Joint, Muscle, Internal, Skin/Mucosa)[50]

End point description:

Annualized bleeding episodes = (number of bleeding episodes/number of days in EP)*365.25. Please see the definition of the EP in the Annualized Bleeding Rate Primary Endpoint Description. The EP was interrupted for the repeat PK period in Arm 1 (sequential PK subgroup) and for all surgical/rehabilitation periods (for both major and minor surgeries) in all 3 arms. A bleeding episode started from the first sign of a bleed, and ended 72 hours after the last treatment for the bleeding, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, were considered the same bleeding episode. Any bleeding at a different location was a separate bleeding episode regardless of time from the last injection. Full Analysis Set: subjects who received at least 1 dose of rFIXFc with evaluable data.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week (efficacy period as defined in description)

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	26	27	
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))				
Joint	1.11 (0 to 4.01)	0.36 (0 to 3.24)	13.58 (6.13 to 21.61)	
Muscle	0 (0 to 1.04)	0 (0 to 0)	3.96 (1.02 to 6.79)	
Internal	0 (0 to 0)	0 (0 to 0)	0 (0 to 1.31)	
Skin/Mucosa	0 (0 to 0)	0 (0 to 0)	0 (0 to 1.14)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days From Last Injection to Treat a New Bleeding Episode

End point title	Number of Days From Last Injection to Treat a New Bleeding Episode[51]

End point description:

Please see the definition of the EP in the Annualized Bleeding Rate Primary Endpoint Description. The EP was interrupted for the repeat PK period in Arm 1 (sequential PK subgroup) and for all surgical/rehabilitation periods (for both major and minor surgeries) in all 3 arms. A follow-up injection administered >72 hours after the most recent injection given to treat a bleed was considered a new bleed at the same location and was classified as type=Unknown (bleeding episodes of this type were not evaluable). The first bleed for each subject could not be included in this analysis since there was no previous bleed from which to measure time. The number of days from the last injection to treat a bleed to a new bleeding episode was analyzed across all evaluable bleeding episodes per subject. Full Analysis Set: subjects who received at least 1 dose of rFIXFc and had at least 1 evaluable bleeding episode.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week (efficacy period as defined in description)

Notes:

[51] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35[52]	13[53]	27[54]	
Units: days				
median (inter-quartile range (Q1-Q3))				
Per Bleeding Episode	40.78 (14.1 to 78.63)	39.48 (26.05 to 84.82)	13.42 (8 to 22.83)	
Per Subject	59.52 (37.39 to 88.78)	76.13 (51.38 to 98.29)	19.67 (15.61 to 32.86)	

Notes:

[52] - Number of evaluable bleeding episodes analyzed=110

[53] - Number of evaluable bleeding episodes analyzed=45

[54] - Number of evaluable bleeding episodes analyzed=359

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Injections Required for Resolution of a Bleeding Episode

End point title	Number of Injections Required for Resolution of a Bleeding Episode[55]

End point description:

Please see the definition of theEP in the Annualized Bleeding Rate Primary Endpoint Description. The EP was interrupted for the repeat PK period in Arm 1 and for all surgical/rehabilitation periods in all 3 arms. A bleeding episode started from the first sign of a bleed, and ended 72 hours after the last treatment for the bleeding, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, were considered the same bleeding episode. All injections given from the initial sign of a bleed until the last date/ time within the bleed window are counted. The resolution of a bleed is defined as no sign of bleeding following injection for the bleed. Full Analysis Set: subjects who received at least 1 dose of rFIXFc and had at least 1 bleeding episode.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week (efficacy period as defined in description)

Notes:

[55] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47[56]	15[57]	27[58]	
Units: injections				
median (inter-quartile range (Q1-Q3))				
Per Bleeding Episode	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
Per Subject	1 (1 to 1.25)	1.09 (1 to 1.33)	1.04 (1 to 1.08)	

Notes:

[56] - Number of bleeding episodes analyzed=167

[57] - Number of bleeding episodes analyzed=67

[58] - Number of bleeding episodes analyzed=402

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Injections Required for Resolution of a Bleeding Episode by Location of Bleed

End point title	Number of Injections Required for Resolution of a Bleeding Episode by Location of Bleed[59]

End point description:

Please see the definition of the EP in the Annualized Bleeding Rate Primary Endpoint Description. The EP was interrupted for the repeat PK period in Arm 1 (sequential PK subgroup) and for all surgical/rehabilitation periods (for both major and minor surgeries) in all 3 arms. Please see the definition of a bleeding episode in the previous endpoint (Number of Injections Required for Resolution of a Bleeding Episode). All injections given from the initial sign of a bleed until the last date/time within the bleed window were counted. The resolution of a bleed was defined as no sign of bleeding following injection for the bleed. Bleeding episodes that presented in multiple locations are included as a single event in the overall summary for the number of injections to resolve that bleeding episode but are included in summaries for each location. Full Analysis Set: subjects who received at least 1 dose of rFIXFc, had a bleeding episode, and had evaluable efficacy assessments.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week (efficacy period as defined in description)

Notes:

[59] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47[60]	15[61]	27[62]	
Units: injections				

median (inter-quartile range (Q1-Q3))				
Joint; n=125, 52, 314	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
Muscle; n=35, 10, 90	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
Internal; n=9, 3, 11	1 (1 to 2)	2 (1 to 2)	1 (1 to 2)	
Skin/Mucosa; n=11, 4, 21	1 (1 to 2)	1 (1 to 1)	1 (1 to 1)	

Notes:

[60] - n=total number of bleeding episodes at given location

[61] - n=total number of bleeding episodes at given location

[62] - n=total number of bleeding episodes at given location

Statistical analyses

No statistical analyses for this end point

Secondary: Total Dose Per Injection Required for Resolution of a Bleeding Episode by Location of Bleed

End point title	Total Dose Per Injection Required for Resolution of a Bleeding Episode by Location of Bleed[63]

End point description:

For each bleeding episode at one location, the total dose is the sum of the doses (IU/kg) administered across all injections given to treat that bleeding episode. Please see the definition of the EP in the Annualized Bleeding Rate Primary Endpoint Description. The EP was interrupted for the repeat PK period in Arm 1 (sequential PK subgroup) and for all surgical/rehabilitation periods (for both major and minor surgeries) in all 3 arms. Please see the definition of a bleeding episode in a previous endpoint (Number of Injections Required for Resolution of a Bleeding Episode). Bleeding episodes that presented in multiple locations are included as a single event in the overall summary for dose administered to resolve that bleeding episode but are included in the individual summaries for each location. Full Analysis Set: subjects who received at least 1 dose of rFIXFc, had a bleeding episode, and had complete information on the dose administered to treat a bleeding episode.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week (efficacy period as defined in description)

Notes:

[63] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47[64]	15[65]	27[66]	
Units: IU/kg				
median (inter-quartile range (Q1-Q3))				
Joint; n=124, 52, 313	50.14 (31.65 to 61.64)	45.29 (35.71 to 97.41)	46.73 (33.33 to 60.79)	
Muscle; n=35, 10, 90	55.56 (46.89 to 88.16)	67.17 (33.63 to 87.46)	46.57 (33.33 to 60.79)	
Internal; n=9, 3, 11	48.72 (41.67 to 125)	70.26 (33.63 to 131.72)	46.73 (33.33 to 61.07)	
Skin/Mucosa; n=11, 4, 21	46.89 (38.67 to 79.55)	48.48 (34.5 to 79.69)	22.22 (20.83 to 36.36)	

Notes:

[64] - n=total number of bleeding episodes at this location

[65] - n=total number of bleeding episodes at this location

[66] - n=total number of bleeding episodes at this location

Statistical analyses

No statistical analyses for this end point

Secondary: Hemophilia-Specific Quality of Life Index for Adults (Haem-A-QoL) Questionnaire: Change From Baseline to Week 26

End point title	Hemophilia-Specific Quality of Life Index for Adults (Haem-A-QoL) Questionnaire: Change From Baseline to Week 26

End point description:

The Haem-A-QoL consists of items pertaining to 10 domains specific to living with hemophilia and was administered to adult subjects (> 17 years). The areas covered by this instrument are: physical health, feeling, view of yourself, sports/leisure, school/work, dealing with hemophilia, and treatment (all 7 domains, during the last month) and future, family planning, and outlook for the future (all 3 domains, recently). Changes from baseline for the Haem-A-QoL questionnaire are summarized by prestudy treatment regimen (pooled for Arms 1 and 2). Lower scores represent better quality of life (QoL); therefore, a negative change from baseline represents improvement during the course of the study. Scores on a scale range between 0 and 100. Full Analysis Set: subjects in the 2 prophylaxis arms (Arms 1 and 2) over 17 years of age who received at least 1 dose of rFIXFc and had an assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Pre-study Regimen: Prophylaxis (Arms 1 and 2 Pooled)	Pre-study Regimen: On Demand (Arms 1 and 2 Pooled)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27[67]	31[68]		
Units: units				
median (full range (min-max))				
Total Score; n=27, 26	-6.82 (-22.8 to 6.1)	-6.25 (-25.5 to 12.8)		
Physical Health; n=27, 31	-10 (-45 to 20)	-15 (-60 to 15)		
Feeling; n=27, 31	0 (-43.8 to 50)	0 (-43.8 to 62.5)		
View of Yourself; n=27, 30	-5 (-25 to 15)	-5 (-35 to 25)		
Sports and Leisure; n=22, 21	-7.5 (-70 to 25)	-20 (-40 to 35)		
Work and School; n=22, 25	0 (-31.3 to 52.1)	-6.25 (-31.3 to 18.8)		
Dealing with Hemophilia; n=27, 31	0 (-100 to 100)	-8.33 (-66.7 to 75)		
Treatment; n=27, 31	-6.25 (-18.8 to 18.8)	0 (-53.1 to 37.5)		
Future; n=26, 30	-5 (-25 to 10)	0 (-30 to 20)		
Family Planning; n=15, 13	0 (-29.2 to 12.5)	0 (-43.8 to 25)		

Partnership and Sexuality; n=26, 30	0 (-50 to 66.7)	0 (-25 to 25)		

Notes:

[67] - n=subjects who had specified assessment at given timepoint

[68] - n=subjects who had specified assessment at given timepoint

Statistical analyses

No statistical analyses for this end point

Secondary: Haem-A-QoL Questionnaire for Adults: Change From Baseline to Week 52

End point title	Haem-A-QoL Questionnaire for Adults: Change From Baseline to Week 52

End point description:

The Haem-A-QoL consists of items pertaining to 10 domains specific to living with hemophilia and was administered to adult subjects (> 17 years). The areas covered by this instrument are: physical health, feeling, view of yourself, sports/leisure, school/work, dealing with hemophilia, and treatment (all 7 domains, during the last month) and future, family planning, and outlook for the future (all 3 domains, recently). Changes from baseline for the Haem-A-QoL questionnaire are summarized by prestudy treatment regimen (pooled for Arms 1 and 2). Lower scores represent better QoL; therefore, a negative change from baseline represents improvement during the course of the study. Scores on a scale range between 0 and 100. Full Analysis Set: subjects in the 2 prophylaxis arms (Arms 1 and 2) over 17 years of age who received at least 1 dose of rFIXFc and had an assessment.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Pre-study Regimen: Prophylaxis (Arms 1 and 2 Pooled)	Pre-study Regimen: On Demand (Arms 1 and 2 Pooled)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27[69]	24[70]		
Units: units on a scale				
median (full range (min-max))				
Total Score; n=25, 19	-4.35 (-24.4 to 9.6)	-6.06 (-31 to 1)		
Physical Health; n=26, 23	-10 (-45 to 20)	-15 (-60 to 0)		
Feeling; n=26, 23	0 (-37.5 to 75)	0 (-50 to 18.8)		
View of Yourself; n=26, 24	-7.5 (-45 to 20)	-5 (-35 to 15)		
Sports and Leisure; n=20, 16	-0.62 (-55 to 27.5)	-17.5 (-55 to 17.5)		
Work and School; n=22, 20	0 (-31.3 to 25)	-3.13 (-41.7 to 25)		
Dealing with Hemophilia; n=27, 24	0 (-66.7 to 33.3)	4.17 (-66.7 to 66.7)		
Treatment; n=27, 24	-6.25 (-30.8 to 15.6)	-4.69 (-34.4 to 34.4)		
Future; n=26, 23	-5 (-40 to 20)	-5 (-40 to 15)		
Family Planning; n=14, 11	0 (-25 to 33.3)	0 (-12.5 to 12.5)		

Notes:

[69] - n=subjects who had specified assessment at given timepoint

[70] - n=subjects who had specified assessment at given timepoint

Statistical analyses

No statistical analyses for this end point

Secondary: Hemophilia-Specific Quality of Life Index for Children (Haemo-QoL) Questionnaire: Change From Baseline to Week 26 and Week 52

End point title	Hemophilia-Specific Quality of Life Index for Children (Haemo-QoL) Questionnaire: Change From Baseline to Week 26 and Week 52

End point description:

The Haemo-QoL, a QoL assessment instrument for children and adolescents with hemophilia, was administered to subjects from 13- to 17-years-old. This instrument assesses domains specific to living with hemophilia. For the Haemo-QoL, higher scores indicate a worse QoL. Scores range between 0 and 100.

End point type	Secondary

End point timeframe:

Baseline, Week 26, Week 52

End point values	Pre-study Regimen: Prophylaxis (Arms 1 and 2 Pooled)	Pre-study Regimen: On Demand (Arms 1 and 2 Pooled)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[71]	0[72]		
Units: units on a scale				
median (full range (min-max))	(to)	(to)		

Notes:

[71] - No summary analysis was done due to the small number of subjects completing the questionnaire.

[72] - No summary analysis was done due to the small number of subjects completing the questionnaire.

Statistical analyses

No statistical analyses for this end point

Secondary: Investigators'/Surgeons' Assessment of Subjects' Response to rFIXFc for Major Surgery

End point title	Investigators'/Surgeons' Assessment of Subjects' Response to rFIXFc for Major Surgery[73]

End point description:

Based on the first assessment of hemostasis by the surgeon/investigator 24 hours or later post-surgery. Scaled responses: Excellent = 1, Good = 2, Fair = 3, Poor/none = 4. Subjects in Arm 4 who received at least 1 dose of rFIXFc.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week

Notes:

[73] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 4: Perioperative Management			
Subject group type	Reporting group			
Number of subjects analysed	12[74]			
Units: responses				
Excellent or Good	14			
Excellent	13			
Good	1			
Fair	0			
Poor/None	0			

Notes:

[74] - Number of major surgeries analyzed=14

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Injections Required to Maintain Hemostasis During Major Surgery

End point title	Number of Injections Required to Maintain Hemostasis During Major Surgery[75]

End point description:

The number of injections to maintain hemostasis during surgery includes all injections for surgery purposes including the loading dose to the end date/time of surgery. Subjects in Arm 4 who received at least 1 dose of rFIXFc.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week

Notes:

[75] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 4: Perioperative Management			
Subject group type	Reporting group			
Number of subjects analysed	12[76]			
Units: injections				
median (full range (min-max))	1 (1 to 4)			

Notes:

[76] - Number of major surgeries analyzed=14

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Per Injection and Total Dose Required to Maintain Hemostasis During Major Surgery

End point title	Dose Per Injection and Total Dose Required to Maintain Hemostasis During Major Surgery[77]

End point description:

Mean dose per injection is the average dose for all injections (including loading dose) needed to maintain hemostasis during surgery. Total dose is the sum across all injections (including loading dose) needed to maintain hemostasis during surgery. Subjects in Arm 4 who received at least 1 dose of rFIXFc.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week

Notes:

[77] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 4: Perioperative Management			
Subject group type	Reporting group			
Number of subjects analysed	12[78]			
Units: IU/kg				
median (full range (min-max))				
Dose per Injection Total Dose	90.91 (49.4 to 142.3) 102.59 (49.4 to 264.5)			

Notes:

[78] - Number of major surgeries analyzed=14

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Total Blood Loss During Major Surgery

End point title	Estimated Total Blood Loss During Major Surgery[79]

End point description:

Subjects in Arm 4 who received at least 1 dose of rFIXFc.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week

Notes:

[79] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 4: Perioperative Management			
Subject group type	Reporting group			
Number of subjects analysed	12[80]			
Units: mL				
median (full range (min-max))	65.5 (0 to 300)			

Notes:

[80] - Number of major surgeries analyzed=14

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Transfusions Required Per Surgery

End point title	Number of Transfusions Required Per Surgery[81]

End point description:

Number of blood component transfusions during a single surgery. Subjects in Arm 4 who received at least 1 dose of rFIXFc.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week

Notes:

[81] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 4: Perioperative Management			
Subject group type	Reporting group			
Number of subjects analysed	12[82]			
Units: surgeries				
0 transfusions	12			
1 transfusion	0			
2 transfusions	1			
3 transfusions	0			
> 3 transfusions	1			

Notes:

[82] - Number of major surgeries analyzed=14

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax)

End point title	Maximum Concentration (Cmax)

End point description:

Maximum concentration during a dosing interval. Assessment of FIX activity with BeneFIX was conducted following a required 120-hour (5-day) washout period, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 72 (±3) hours, and 96 (±3) hours (4 days) from the start of the injection. Assessment of FIX

activity and rFIXFc concentration was conducted following the initial dose of rFIXFc (after a required 120-hour [5-day] washout period) and at Week 26, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 96 (±3) hours (4 days), 144 (±3) hours (6 days), 168 (±3) hours (7 days), 192 (±3) hours (8 days), and 240 (±3) hours (10 days) from the start of the injection.

End point type	Secondary

End point timeframe:

See Measure Description for complete time frame. Each subject was to complete PK sampling up to, and including, the 96-hour (4-day) timepoint for BeneFIX PK assessment and the 240-hour (10-day) timepoint for rFIXFc PK assessment.

End point values	Arm 1: Weekly Prophylaxis - Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	22[83]			
Units: IU/dL				
geometric mean (confidence interval 95%)				
rFIXFc Baseline	40.81 (33.6 to 49.58)			
BeneFIX	43.08 (36.69 to 50.59)			

Notes:

[83] - Subjects in Sequential PK Subgroup with evaluable PK profiles for both BeneFIX and baseline rFIXFc.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve (AUC) per Dose

End point title	Area Under the Curve (AUC) per Dose

End point description:

Dose normalized area under the drug concentration-time curve. Assessment of FIX activity with BeneFIX was conducted following a required 120-hour (5-day) washout period, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 72 (±3) hours, and 96 (±3) hours (4 days) from the start of the injection. Assessment of FIX activity and rFIXFc concentration was conducted following the initial dose of rFIXFc (after a required 120-hour [5-day] washout period) and at Week 26, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 96 (±3) hours (4 days), 144 (±3) hours (6 days), 168 (±3) hours (7 days), 192 (±3) hours (8 days), and 240 (±3) hours (10 days) from the start of the injection.

End point type	Secondary

End point timeframe:

See Measure Description for complete time frame. Each subject was to complete PK sampling up to, and including, the 96-hour (4-day) timepoint for BeneFIX PK assessment and the 240-hour (10-day) timepoint for rFIXFc PK assessment.

End point values	Arm 1: Weekly Prophylaxis - Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	22[84]			
Units: IU*h/dL per IU/kg				
geometric mean (confidence interval 95%)				
rFIXFc Baseline	31.32 (27.88 to 35.18)			
BeneFIX	15.77 (14.02 to 17.74)			

Notes:

[84] - Subjects in Sequential PK Subgroup with evaluable PK profiles for both BeneFIX and baseline rFIXFc.

Statistical analyses

No statistical analyses for this end point

Secondary: Half Life (t1/2) Alpha and t1/2 Beta

End point title	Half Life (t1/2) Alpha and t1/2 Beta

End point description:

Time required for the concentration of the drug to reach half of its original value. Alpha and beta t1/2 indicate distribution and elimination half-life in a two-compartment PK model. Assessment of FIX activity with BeneFIX was conducted following a required 120-hour (5-day) washout period, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 72 (±3) hours, and 96 (±3) hours (4 days) from the start of the injection. Assessment of FIX activity and rFIXFc concentration was conducted following the initial dose of rFIXFc (after a required 120-hour [5-day] washout period) and at Week 26, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 96 (±3) hours (4 days), 144 (±3) hours (6 days), 168 (±3) hours (7 days), 192 (±3) hours (8 days), and 240 (±3) hours (10 days) from the start of the injection.

End point type	Secondary

End point timeframe:

See Measure Description for complete time frame. Each subject was to complete PK sampling up to, and including, the 96-hour (4-day) timepoint for BeneFIX PK assessment and the 240-hour (10-day) timepoint for rFIXFc PK assessment.

End point values	Arm 1: Weekly Prophylaxis - Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	22[85]			
Units: hours				
geometric mean (confidence interval 95%)				
rFIXFc Baseline: t1/2 alpha	5.0279 (3.2032 to 7.8919)			
BeneFIX: t1/2 alpha	2.4113 (1.6183 to 3.593)			
rFIXFc Baseline: t1/2 beta	82.12 (71.39 to 94.46)			

BeneFIX: t1/2 beta	33.77 (29.13 to 39.15)			

Notes:

[85] - Subjects in the Sequential PK Subgroup with evaluable PK profiles for BeneFIX and baseline rFIXFc.

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CL)

End point title	Clearance (CL)

End point description:

The measure of the efficiency of the body to remove the drug and the unit is the volume of the plasma or blood cleared of drug per unit time. Assessment of FIX activity with BeneFIX was conducted following a required 120-hour (5-day) washout period, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 72 (±3) hours, and 96 (±3) hours (4 days) from the start of the injection. Assessment of FIX activity and rFIXFc concentration was conducted following the initial dose of rFIXFc (after a required 120-hour [5-day] washout period) and at Week 26, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 96 (±3) hours (4 days), 144 (±3) hours (6 days), 168 (±3) hours (7 days), 192 (±3) hours (8 days), and 240 (±3) hours (10 days) from the start of the injection.

End point type	Secondary

End point timeframe:

See Measure Description for complete time frame. Each subject was to complete PK sampling up to, and including, the 96-hour (4-day) timepoint for BeneFIX PK assessment and the 240-hour (10-day) timepoint for rFIXFc PK assessment.

End point values	Arm 1: Weekly Prophylaxis - Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	22[86]			
Units: mL/h/kg				
geometric mean (confidence interval 95%)				
rFIXFc Baseline	3.193 (2.843 to 3.587)			
BeneFIX	6.34 (5.637 to 7.131)			

Notes:

[86] - Subjects in Sequential PK Subgroup with evaluable PK profiles for both BeneFIX and baseline rFIXFc.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time (MRT)

End point title	Mean Residence Time (MRT)

End point description:

The average time for all the drug molecules to reside in the body. Assessment of FIX activity with

BeneFIX was conducted following a required 120-hour (5-day) washout period, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 72 (±3) hours, and 96 (±3) hours (4 days) from the start of the injection. Assessment of FIX activity and rFIXFc concentration was conducted following the initial dose of rFIXFc (after a required 120-hour [5-day] washout period) and at Week 26, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 96 (±3) hours (4 days), 144 (±3) hours (6 days), 168 (±3) hours (7 days), 192 (±3) hours (8 days), and 240 (±3) hours (10 days) from the start of the injection.

End point type	Secondary

End point timeframe:

See Measure Description for complete time frame. Each participant was to complete PK sampling up to, and including, the 96-hour (4-day) timepoint for BeneFIX PK assessment and the 240-hour (10-day) timepoint for rFIXFc PK assessment.

End point values	Arm 1: Weekly Prophylaxis - Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	22[87]			
Units: hours				
geometric mean (confidence interval 95%)				
rFIXFc Baseline	98.6 (88.16 to 110.29)			
BeneFIX	41.19 (35.98 to 47.15)			

Notes:

[87] - Subjects in Sequential PK Subgroup with evaluable PK profiles for both BeneFIX and baseline rFIXFc.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume in Steady State (Vss)

End point title	Volume in Steady State (Vss)

End point description:

Volume of distribution at steady state. Assessment of FIX activity with BeneFIX was conducted following a required 120-hour (5-day) washout period, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 72 (±3) hours, and 96 (±3) hours (4 days) from the start of the injection. Assessment of FIX activity and rFIXFc concentration was conducted following the initial dose of rFIXFc (after a required 120-hour [5-day] washout period) and at Week 26, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 96 (±3) hours (4 days), 144 (±3) hours (6 days), 168 (±3) hours (7 days), 192 (±3) hours (8 days), and 240 (±3) hours (10 days) from the start of the injection.

End point type	Secondary

End point timeframe:

See Measure Description for complete time frame. Each subject was to complete PK sampling up to, and including, the 96-hour (4-day) timepoint for BeneFIX PK assessment and the 240-hour (10-day) timepoint for rFIXFc PK assessment.

End point values	Arm 1: Weekly Prophylaxis - Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	22[88]			
Units: mL/kg				
geometric mean (confidence interval 95%)				
rFIXFc Baseline	314.8 (277.8 to 356.8)			
BeneFIX	261.1 (222.9 to 305.9)			

Notes:

[88] - Subjects in Sequential PK Subgroup with evaluable PK profiles for both BeneFIX and baseline rFIXFc.

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental Recovery

End point title	Incremental Recovery

End point description:

IU/dL rise in plasma per IU/kg drug administered. Assessment of FIX activity with BeneFIX was conducted following a required 120-hour (5-day) washout period, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 72 (±3) hours, and 96 (±3) hours (4 days) from the start of the injection. Assessment of FIX activity and rFIXFc concentration was conducted following the initial dose of rFIXFc (after a required 120-hour [5-day] washout period) and at Week 26, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 96 (±3) hours (4 days), 144 (±3) hours (6 days), 168 (±3) hours (7 days), 192 (±3) hours (8 days), and 240 (±3) hours (10 days) from the start of the injection.

End point type	Secondary

End point timeframe:

See Measure Description for complete time frame. Each subject was to complete PK sampling up to, and including, the 96-hour (4-day) timepoint for BeneFIX PK assessment and the 240-hour (10-day) timepoint for rFIXFc PK assessment.

End point values	Arm 1: Weekly Prophylaxis - Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	22[89]			
Units: IU/dL per IU/kg				
geometric mean (confidence interval 95%)				
rFIXFc Baseline	0.9211 (0.771 to 1.1004)			
BeneFIX	0.9451 (0.8149 to 1.0961)			

Notes:

[89] - Subjects in Sequential PK Subgroup with evaluable PK profiles for both BeneFIX and baseline rFIXFc.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to 1% and 3% FIX Activity

End point title	Time to 1% and 3% FIX Activity

End point description:

Time to reach 1 or 3 IU/dL (%) after a single dose. Assessment of FIX activity with BeneFIX was conducted following a required 120-hour (5-day) washout period, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 72 (±3) hours, and 96 (±3) hours (4 days) from the start of the injection. Assessment of FIX activity and rFIXFc concentration was conducted following the initial dose of rFIXFc (after a required 120-hour [5-day] washout period) and at Week 26, at these timepoints: predose, 10 (±2) minutes, 1 hour (±15 minutes), 3 hours (±15 minutes), 6 hours (±15 minutes), 24 (±2) hours, 48 (±2) hours, 96 (±3) hours (4 days), 144 (±3) hours (6 days), 168 (±3) hours (7 days), 192 (±3) hours (8 days), and 240 (±3) hours (10 days) from the start of the injection.

End point type	Secondary

End point timeframe:

See Measure Description for complete time frame. Each subject was to complete PK sampling up to, and including, the 96-hour (4-day) timepoint for BeneFIX PK assessment and the 240-hour (10-day) timepoint for rFIXFc PK assessment.

End point values	Arm 1: Weekly Prophylaxis - Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	22[90]			
Units: days				
geometric mean (confidence interval 95%)				
rFIXFc Baseline: 1% Activity	11.224 (10.2 to 12.35)			
BeneFIX: 1% Activity	5.087 (4.579 to 5.651)			
rFIXFc Baseline: 3% Activity	5.767 (5.066 to 6.565)			
BeneFIX: 3% Activity	2.832 (2.568 to 3.123)			

Notes:

[90] - Subjects in Sequential PK Subgroup with evaluable PK profiles for both BeneFIX and baseline rFIXFc.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Relevant Abnormalities or Relevant

Changes from Baseline in Vital Signs

End point title	Number of Subjects With Clinically Relevant Abnormalities or Relevant Changes from Baseline in Vital Signs[91]

End point description:

Number of subjects with clinically relevant abnormalities or relevant changes from baseline in temperature, pulse (beats per minute [bpm]), systolic blood pressure (SBP), and diastolic blood pressure (DBP) are presented. Baseline (BL) is defined as the last non-missing evaluable assessment taken prior and closest to the first rFIXFc dose. Because the perioperative management period represents a unique clinical situation, safety data obtained during the surgical/rehabilitation period for subjects in Arm 4 were included in listings and reviewed separately. Review of the listing was sufficient to assess this endpoint. Safety Analysis Set: subjects who received at least 1 dose of BeneFIX or rFIXFc; a table was not generated for subjects in the perioperative management/surgical arm (Arm 4). n=subjects with a baseline and at least 1 post-baseline vital sign assessment.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 1 week

Notes:

[91] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data include all relevant reporting groups and/or subject analysis sets for this endpoint, per protocol.

End point values	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	29	27	
Units: subjects				
Temperature: >38°C and ≥1°C from BL, n=61,28,24	0	0	0	
Pulse: >120 bpm or >20 bpm from BL, n=62,28,24	1	2	0	
Pulse: <50 bpm or >20 bpm from BL, n=62,28,24	2	1	0	
SBP: >180 mm Hg or >40 mm Hg from BL, n=62,28,24	0	1	0	
SBP: <90 mm Hg or >30 mm Hg from BL, n=62,28,24	4	1	0	
DBP: >105 mm Hg or >30 mm Hg from BL, n=62,28,24	3	0	0	
DBP: <50 mm Hg or >20 mm Hg from BL, n=62,28,24	5	4	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Coagulation Parameter: Change From Pre-dose Values in Prothrombin Split Fragments 1+ 2 (F 1+2)

End point title	Coagulation Parameter: Change From Pre-dose Values in Prothrombin Split Fragments 1+ 2 (F 1+2)

End point description:

Maximum value post-dosing is defined as maximum value over the 1-, 6-, and 24-hour evaluations. The Sequential PK subgroup consisted of all subjects who had evaluable PK profiles for both BeneFIX and baseline rFIXFc, and/or evaluable PK profiles for both baseline and repeat rFIXFc at Week 26 (±1 week).

n=subjects with an assessment at given time point.

End point type	Secondary

End point timeframe:

Pre-dose, 1 hour post-dose, 6 hours post-dose, and 24 hours post-dose at baseline (120 hours before Day 1, for BeneFIX), Day 1, Week 26, and Week 52 (for rFIXFc)

End point values	Arm 1: Sequential PK Subgroup: BeneFIX	Arm 1: Sequential PK Subgroup: rFIXFc Day 1	Arm 1: Sequential PK Subgroup: rFIXFc Week 26	Arm 1: Sequential PK Subgroup: rFIXFc Week 52
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	23	23	23[92]
Units: pmol/L				
arithmetic mean (standard deviation)				
Pre-dosing Value; n=23, 23, 20, 19	134.1 (± 64.93)	130 (± 57.55)	131.6 (± 42.43)	176.7 (± 112.36)
Change at 1 Hour Post-dosing; n=23, 22, 20, 0	73.4 (± 171.68)	8.6 (± 39.14)	1.3 (± 51.64)	0 (± 0)
Change at 6 Hours Post-dosing; n=23, 22, 20, 0	7.8 (± 55.45)	8.3 (± 38.66)	-4.4 (± 45.95)	0 (± 0)
Change at 24 Hours Post-dosing; n=23, 22, 18, 0	-3.7 (± 34.39)	9.8 (± 45.62)	1.7 (± 27.14)	0 (± 0)
Maximum Post-dosing Change; n=23, 23, 19, 0	83 (± 168.71)	30.9 (± 48.52)	20.4 (± 49.38)	0 (± 0)

Notes:

[92] - 0 values are actually NA for n=0 categories.

Statistical analyses

No statistical analyses for this end point

Secondary: Coagulation Parameter: Change From Pre-dose Values in Thrombin-antithrombin (TAT) Complex

End point title	Coagulation Parameter: Change From Pre-dose Values in Thrombin-antithrombin (TAT) Complex

End point description:

Maximum value post-dosing is defined as maximum value over the 1-, 6-, and 24-hour evaluations. The Sequential PK subgroup consisted of all subjects who had evaluable PK profiles for both BeneFIX and baseline rFIXFc, and/or evaluable PK profiles for both baseline and repeat rFIXFc at Week 26 (±1 week). n=subjects with an assessment at given time point.

End point type	Secondary

End point timeframe:

Pre-dose, 1 hour post-dose, 6 hours post-dose, and 24 hours post-dose at baseline (120 hours before Day 1, for BeneFIX), Day 1, Week 26, and Week 52 (for rFIXFc)

End point values	Arm 1: Sequential PK Subgroup: BeneFIX	Arm 1: Sequential PK Subgroup: rFIXFc Day 1	Arm 1: Sequential PK Subgroup: rFIXFc Week 26	Arm 1: Sequential PK Subgroup: rFIXFc Week 52
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	23	23	23[93]
Units: ng/mL				
arithmetic mean (standard deviation)				
Pre-dosing Value; n=23, 23, 20, 19	2.87 (± 2.891)	2.87 (± 2.23)	3.11 (± 4.075)	4.28 (± 7.588)
Change at 1 Hour Post-dosing; n=23, 22, 20, 0	6.67 (± 15.491)	1.05 (± 4.019)	0.11 (± 5.813)	0 (± 0)
Change at 6 Hours Post-dosing; n=23, 22, 20, 0	1.91 (± 7.303)	1.07 (± 4.686)	-0.09 (± 5.763)	0 (± 0)
Change at 24 Hours Post-dosing; n=23, 22, 18, 0	-0.58 (± 2.968)	0.81 (± 6.095)	-1.1 (± 4.308)	0 (± 0)
Maximum Post-dosing Change; n=23, 23, 19, 0	7.42 (± 15.416)	3.63 (± 7)	0.32 (± 5.969)	0 (± 0)

Notes:

[93] - 0 values are actually NA for n=0 categories.

Statistical analyses

No statistical analyses for this end point

Secondary: Coagulation Parameter: Change From Pre-dose Values in D-dimer

End point title	Coagulation Parameter: Change From Pre-dose Values in D-dimer

End point description:

Maximum value post-dosing is defined as maximum value over the 1-, 6-, and 24-hour evaluations. The Sequential PK subgroup consisted of all subjects who had evaluable PK profiles for both BeneFIX and baseline rFIXFc, and/or evaluable PK profiles for both baseline and repeat rFIXFc at Week 26 (±1 week). n=subjects with an assessment at given time point.

End point type	Secondary

End point timeframe:

Pre-dose, 1 hour post-dose, 6 hours post-dose, and 24 hours post-dose at baseline (120 hours before Day 1, for BeneFIX), Day 1, Week 26, and Week 52 (for rFIXFc)

End point values	Arm 1: Sequential PK Subgroup: BeneFIX	Arm 1: Sequential PK Subgroup: rFIXFc Day 1	Arm 1: Sequential PK Subgroup: rFIXFc Week 26	Arm 1: Sequential PK Subgroup: rFIXFc Week 52
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	23	23	23[94]
Units: ng/mL				
arithmetic mean (standard deviation)				
Pre-dosing Value; n=23, 22, 20, 19	153 (± 119.37)	176.2 (± 165.48)	120.5 (± 73.38)	134.7 (± 151.36)
Change at 1 Hour Post-dosing; n=23, 21, 20, 0	35.9 (± 101.8)	89.6 (± 509.24)	-5.9 (± 28.18)	0 (± 0)
Change at 6 Hours Post-dosing; n=23, 21, 20, 0	47.6 (± 259.7)	-39.6 (± 134.42)	-9.4 (± 16.84)	0 (± 0)
Change at 24 Hours Post-dosing; n=23, 21, 18, 0	20 (± 85.93)	-31 (± 138.22)	-8.2 (± 26.06)	0 (± 0)

Maximum Post-dosing Change; n=23, 22, 19, 0	95.7 (± 266.98)	100.6 (± 494.7)	4.8 (± 16.1)	0 (± 0)

Notes:

[94] - 0 values are actually NA for n=0 categories.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to 52 weeks + 30 days ± 1 week

Adverse event reporting additional description:

As the perioperative management period represents a unique clinical situation, safety data obtained during the surgical/rehabilitation period for Arm 4 subjects were analyzed separately per the Analysis Plan, and not included within the Arms 1-3 analysis. See Endpoints 3 and 4 for AE/SAE data for the surgical/rehabilitation period, Arm 4.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Arm 1: Weekly Prophylaxis

Reporting group description:

50 IU/kg rFIXFc via intravenous (IV) injection once every 7 days initially, then at a dose indicated by the subject's baseline pharmacokinetic (PK) assessment that ensured a target trough of 1% to 3% above baseline or higher, as clinically indicated. Adjustments to the initial weekly dose of rFIXFc (50 IU/kg) were to be made based on baseline PK assessments, occurrence of spontaneous bleeding episodes, and the trough levels, which were to be monitored at Weeks 4, 16, 26, and 39.

Prior to the first dose of rFIXFc, subjects in the Sequential PK subgroup were to receive a single dose of 50 IU/kg BeneFIX administered IV in the clinic, followed by PK sampling. A single dose of 50 IU/kg rFIXFc was administered following a 120-hour washout from BeneFIX, followed by PK sampling for a baseline PK profiling. At Week 26 (±1 week) subjects were to receive a single dose of 50 IU/kg rFIXFc for repeat PK profiling.

Reporting group title	Arm 2: Individualized Interval Prophylaxis

Reporting group description:

100 IU/kg rFIXFc via IV injection once every 10 days initially, then at an interval derived from the baseline PK assessment that ensured a target trough of 1% to 3% above baseline or higher, as clinically indicated. Adjustments to the initial 10-day interval were to be made based on baseline PK assessments and trough levels, which were monitored at Weeks 4, 16, 26, and 39.

Reporting group title	Arm 3: Episodic (On Demand)

Reporting group description:

20 to 100 IU/kg rFIXFc via IV injection, or the dose indicated by the subject's baseline PK to target a plasma level of 20% to 100%, as needed for the treatment of mild to severe bleeding episodes

Serious adverse events	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 63 (7.94%)	4 / 29 (13.79%)	4 / 27 (14.81%)
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 / 63 (0.00%)	1 / 29 (3.45%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 63 (1.59%)	0 / 29 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	1 / 63 (1.59%)	0 / 29 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 63 (0.00%)	1 / 29 (3.45%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Obstructive uropathy			
subjects affected / exposed	0 / 63 (0.00%)	1 / 29 (3.45%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 29 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 29 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 29 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 63 (0.00%)	1 / 29 (3.45%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm 1: Weekly Prophylaxis	Arm 2: Individualized Interval Prophylaxis	Arm 3: Episodic (On Demand)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 63 (46.03%)	17 / 29 (58.62%)	11 / 27 (40.74%)
Investigations			
Weight increased			
subjects affected / exposed	1 / 63 (1.59%)	0 / 29 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Injury, poisoning and procedural complications			

Laceration			
subjects affected / exposed	1 / 63 (1.59%)	2 / 29 (6.90%)	0 / 27 (0.00%)
occurrences (all)	1	2	0
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 63 (4.76%)	2 / 29 (6.90%)	1 / 27 (3.70%)
occurrences (all)	3	4	2
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 63 (3.17%)	2 / 29 (6.90%)	2 / 27 (7.41%)
occurrences (all)	2	2	2
Dizziness			
subjects affected / exposed	3 / 63 (4.76%)	2 / 29 (6.90%)	0 / 27 (0.00%)
occurrences (all)	4	3	0
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 63 (0.00%)	2 / 29 (6.90%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 63 (1.59%)	2 / 29 (6.90%)	0 / 27 (0.00%)
occurrences (all)	1	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 63 (0.00%)	0 / 29 (0.00%)	3 / 27 (11.11%)
occurrences (all)	0	0	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 63 (9.52%)	2 / 29 (6.90%)	0 / 27 (0.00%)
occurrences (all)	8	2	0
Musculoskeletal pain			
subjects affected / exposed	2 / 63 (3.17%)	2 / 29 (6.90%)	0 / 27 (0.00%)
occurrences (all)	2	2	0
Back pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 29 (3.45%)	2 / 27 (7.41%)
occurrences (all)	0	1	3
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	13 / 63 (20.63%)	4 / 29 (13.79%)	1 / 27 (3.70%)
occurrences (all)	23	6	2
Influenza			
subjects affected / exposed	5 / 63 (7.94%)	0 / 29 (0.00%)	4 / 27 (14.81%)
occurrences (all)	5	0	6
Upper respiratory tract infection			
subjects affected / exposed	4 / 63 (6.35%)	2 / 29 (6.90%)	1 / 27 (3.70%)
occurrences (all)	5	2	1
Sinusitis			
subjects affected / exposed	3 / 63 (4.76%)	2 / 29 (6.90%)	0 / 27 (0.00%)
occurrences (all)	3	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2010	The following primary changes were made: - Additional guidance was provided for adjusting dosing regimens for subjects in Arms 1 and 2 during the period of time between when the first dose was administered and until the PK data became available for guiding further adjustments to the regimen. -Additional guidance was added for those subjects in whom breakthrough bleeding occurred while trough levels remained within the specific 1% to 3% range above baseline. - The Schedule of Events for Arm 4, Surgery, was clarified.
01 September 2010	The following primary changes were made: - Primary objectives were added to evaluate: -Efficacy in Arm 3 and Arm 4 - Efficacy of prophylaxis over episodic therapy based on the annualized number of bleeding episodes - Language in primary endpoint evaluating the number of breakthrough bleeding episodes annualized over the study period for Arms 1, 2, and 3 was revised. - The secondary endpoints in Arm 4 for response using a 4-point scale, hemostasis maintenance and other parameters were made primary endpoints. - Exploratory endpoints for global hemostasis and health economics were added. - The initial dose for Arm 1 was changed from 40 IU/kg to 50 IU/kg. - All 4-day washout periods were increased to 5 days. - Maximum dose was defined as 100 IU/kg for subjects not undergoing surgery. - PK timepoints were redefined. - Requirements to open Arm 4 to enrollment were changed to 10 subjects, instead of 15, when sufficient PK and efficacy data had been collected from Arms 1, 2, or 3 with no safety concerns. - Additional clarifications were provided, and a more objective definition of major surgery, utilizing more recent publications for definition of target joint and Physician’s Global Assessment, was selected.

07 February 2011	The following primary changes were made: - Overall study sample size was increased from 75 to 100 subjects to ensure that 50 EDs occurred for at least 70 subjects in Arms 1 and 2. - Washout periods and minimum PK sampling periods were clarified. - Management of subjects who were unable to complete washout and/or blood sampling periods was clarified. - Study procedures were clarified for screening, physical examination, joint assessment, vital signs following dosing in clinic, weight and height measurements, follow-up injections, and the possible need for unscheduled visits. - Definitions of minor and major bleeding episodes and management of bleeding episodes were clarified. - The description and the scale used in the assessments of response to bleeding, the Physician's Global Assessment, and assessment of response to surgery were revised.
31 May 2012	The following primary change was made: - An additional interim analysis was added, to be conducted when 34 subjects had been tested for inhibitor after reaching 50 EDs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24304002