

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

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

Results information

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

Trial information**Trial identification**

| | |
|-----------------------|----------|
| Sponsor protocol code | 998HB303 |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000914-PIP01-10 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 04 October 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 August 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Australia: 1 |
| Country: Number of subjects enrolled | New Zealand: 1 |
| Country: Number of subjects enrolled | United States: 11 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | Poland: 3 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Country: Number of subjects enrolled | Denmark: 1 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Ireland: 3 |
| Country: Number of subjects enrolled | Italy: 2 |
| Worldwide total number of subjects | 33 |
| EEA total number of subjects | 20 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 31 |
| Children (2-11 years) | 2 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 28 active centres in 11 countries between 13-Nov-2014 to 23-Jul-2018.

Pre-assignment

Screening details:

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

Period 1

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

Arms

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

Arm description:

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

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

Dosage and administration details:

Subjects received rFIXFc as an IV injection

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

Notes:

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

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

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall study |
|-----------------------|---------------|

Reporting group description:

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

| Reporting group values | Overall study | Total | |
|------------------------------------|---------------|-------|--|
| Number of subjects | 33 | 33 | |
| Age categorical Units: Subjects | | | |

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

End points

End points reporting groups

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

Reporting group description:

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

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

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

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 3 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Up to 3 years

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

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Number of Spontaneous Joint Bleeding Episodes

| | |
|-----------------|--|
| End point title | Annualized Number of Spontaneous Joint Bleeding Episodes |
|-----------------|--|

End point description:

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

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

End point timeframe:

Up to 3 years

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Up to 3 years

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Exposure Days (EDs)

| | |
|--|-------------------------------------|
| End point title | Total Number of Exposure Days (EDs) |
| End point description: | |
| An ED was defined as a 24-hour period in which a subject received one or more doses of rFIXFc injections, with the time of the first injection of rFIXFc defined as the start of the ED. Subjects who did not have a particular injection type are counted as having zero injections for that type. Analysis performed on safety analysis set. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 3 years | |

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | Total Annualized rFIXFc Consumption per Subject for the Prevention and Treatment of Bleeding Episodes |
| End point description: | |
| Total annualized rFIXFc consumption (in IU/kg) was calculated for each subject as: Annualized consumption = (Total IU/kg of rFIXFc during efficacy period (EP) divided by total number of days during EP)*365.25. EP reflects the sum of all intervals of time during which subjects were treated with rFIXFc | |

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

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

End point timeframe:

Up to 3 years

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Up to 3 years

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Up to 3 years

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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|------------------------|--|
| End point title | Change From Baseline in rFIXFc Incremental Recovery (IR) |
| End point description: | Blood samples were taken at trough and Cmax for assessment of incremental recovery, measured by the one-stage clotting assay. IR (International Units per decilitre [IU/dL] per IU/kg) = (Cmax for FIX activity – Pre-dose FIX activity) (IU/dL)/ Actual dose (IU/kg), where Cmax (maximum concentration) is 30 minute FIX activity post-dose and FIX activity less than (<)0.5 IU/dL was set to 0 IU/dL for calculation of IR. Analysis performed on FAS. Here 'n' signifies number of FAS subjects with available data for each visit. |
| End point type | Secondary |
| End point timeframe: | Baseline, Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, and 144 |

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 22.0 |

Reporting groups

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

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported