



## Clinical trial results:

### A Phase II/III Open-label, Multicenter, Safety and Efficacy Study of a Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-002415-28 |
| Trial protocol           | DE AT ES IT BG |
| Global end of trial date | 21 July 2014   |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1               |
| This version publication date  | 13 July 2016     |
| First version publication date | 04 February 2015 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | CSL654_3001 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01496274 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | CSL Behring GmbH  |
| Sponsor organisation address | Emil-von-Behring-Str. 76, Marburg, Germany, 35041                             |
| Public contact               | Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.com |
| Scientific contact           | Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.com |

Notes:

#### Paediatric regulatory details

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-001107-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? | No                  |

Notes:

## Results analysis stage

|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 18 August 2014 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 21 July 2014   |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of the study are to evaluate the efficacy of rIX-FP in preventing bleeding episodes (prophylaxis) and safety of rIX-FP with respect to the development of inhibitors to FIX in patients with severe hemophilia B.

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, and standard operating procedures for clinical research and development at CSL Behring (CSLB).

The study protocol and all amendments were approved by the Independent Ethics Committee(s) (IECs) / Institutional Review Board(s) (IRBs) of the participating centers.

Before undergoing screening procedures for possible enrollment into the study, subjects were informed, in an understandable form, about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's written informed consent to participate in the study.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 23 February 2012 |
| 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 | Spain: 5              |
| Country: Number of subjects enrolled | Austria: 1            |
| Country: Number of subjects enrolled | Bulgaria: 6           |
| Country: Number of subjects enrolled | France: 8             |
| Country: Number of subjects enrolled | Germany: 8            |
| Country: Number of subjects enrolled | Italy: 7              |
| Country: Number of subjects enrolled | Israel: 11            |
| Country: Number of subjects enrolled | Japan: 10             |
| Country: Number of subjects enrolled | Russian Federation: 1 |
| Country: Number of subjects enrolled | United States: 6      |
| Worldwide total number of subjects   | 63                    |
| EEA total number of subjects         | 35                    |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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)                 | 7  |
| Adults (18-64 years)                      | 56 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled from 30 sites in 10 countries.

### Pre-assignment

Screening details:

A total of 69 subjects provided informed consent and were screened for study participation. Of these, 63 subjects were enrolled and treated with rIX-FP.

### Period 1

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

### Arms

|                              |             |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes         |
| <b>Arm title</b>             | Prophylaxis |

Arm description:

Routine weekly prophylaxis and episodic treatment for bleeding episodes. An individualized dosing interval may be tested in sub-group subjects during the 2nd part of the trial.

Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | rIX-FP   |
| Investigational medicinal product code | CSL654 or rIX-FP   |
| Other name                             |  |
| Pharmaceutical forms                   | Powder for concentrate for solution for injection/infusion |
| Routes of administration               | Intravenous use  |

Dosage and administration details:

Recombinant IX-FP (rIX-FP) is a fusion protein linking coagulation factor IX with albumin, and will be administered by intravenous administration.

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | On-demand |
|------------------|-----------|

Arm description:

Episodic treatment for bleeding episodes for up to 26 weeks then switch to routine weekly prophylaxis for the remainder of the study.

Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | rIX-FP   |
| Investigational medicinal product code | CSL654 or rIX-FP   |
| Other name                             |  |
| Pharmaceutical forms                   | Powder for concentrate for solution for injection/infusion |
| Routes of administration               | Intravenous use  |

Dosage and administration details:

Recombinant IX-FP (rIX-FP) is a fusion protein linking coagulation factor IX with albumin, and will be administered by intravenous administration.

| <b>Number of subjects in period 1</b> | Prophylaxis | On-demand |
|---------------------------------------|-------------|-----------|
| Started                               | 40          | 23        |
| Completed                             | 37          | 18        |
| Not completed                         | 3           | 5         |
| Consent withdrawn by subject          | 2           | -         |
| Adverse event, non-fatal              | 1           | 1         |
| Protocol violation                    | -           | 1         |
| Lost to follow-up                     | -           | 3         |

## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Prophylaxis |
|-----------------------|-------------|

Reporting group description:

Routine weekly prophylaxis and episodic treatment for bleeding episodes. An individualized dosing interval may be tested in sub-group subjects during the 2nd part of the trial.

Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention.

|                       |           |
|-----------------------|-----------|
| Reporting group title | On-demand |
|-----------------------|-----------|

Reporting group description:

Episodic treatment for bleeding episodes for up to 26 weeks then switch to routine weekly prophylaxis for the remainder of the study.

Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention.

| Reporting group values                                | Prophylaxis | On-demand | Total |
|---|-------------|-----------|-------|
| Number of subjects                                    | 40          | 23        | 63    |
| Age categorical                                       |             |           |       |
| Units: Subjects                                       |             |           |       |
| In utero  | 0           | 0         | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0           | 0         | 0     |
| Newborns (0-27 days)                                  | 0           | 0         | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0           | 0         | 0     |
| Children (2-11 years)                                 | 0           | 0         | 0     |
| Adolescents (12-17 years)                             | 7           | 0         | 7     |
| Adults (18-64 years)                                  | 33          | 23        | 56    |
| From 65-84 years                                      | 0           | 0         | 0     |
| 85 years and over                                     | 0           | 0         | 0     |
| Gender categorical                                    |             |           |       |
| Units: Subjects                                       |             |           |       |
| Female  | 0           | 0         | 0     |
| Male  | 40          | 23        | 63    |

## End points

### End points reporting groups

|  |                                    |
|--|------------------------------------|
| Reporting group title  | Prophylaxis                        |
| Reporting group description:<br>Routine weekly prophylaxis and episodic treatment for bleeding episodes. An individualized dosing interval may be tested in sub-group subjects during the 2nd part of the trial.<br><br>Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention. |                                    |
| Reporting group title  | On-demand                          |
| Reporting group description:<br>Episodic treatment for bleeding episodes for up to 26 weeks then switch to routine weekly prophylaxis for the remainder of the study.<br><br>Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention.  |                                    |
| Subject analysis set title   | Safety Population                  |
| Subject analysis set type  | Sub-group analysis                 |
| Subject analysis set description:<br>The Safety population consisted of subjects who received at least 1 dose of rIX-FP during the study.  |                                    |
| Subject analysis set title   | On-demand Arm, on-demand regimen   |
| Subject analysis set type  | Sub-group analysis                 |
| Subject analysis set description:<br>Participants in the On-demand Arm, when receiving episodic treatment for bleeding episodes (on-demand regimen).   |                                    |
| Subject analysis set title   | On-demand Arm, prophylaxis regimen |
| Subject analysis set type  | Sub-group analysis                 |
| Subject analysis set description:<br>Participants in the On-demand Arm, when receiving routine weekly prophylaxis (prophylaxis regimen).   |                                    |
| Subject analysis set title   | Prophylaxis Arm, 7-day regimen     |
| Subject analysis set type  | Sub-group analysis                 |
| Subject analysis set description:<br>Subjects received prophylactic rIX-FP on a weekly basis.  |                                    |
| Subject analysis set title   | Prophylaxis Arm, 10-day regimen    |
| Subject analysis set type  | Sub-group analysis                 |
| Subject analysis set description:<br>Subjects received prophylactic rIX-FP every 10 days.  |                                    |
| Subject analysis set title   | Prophylaxis Arm, 14-day regimen    |
| Subject analysis set type  | Sub-group analysis                 |
| Subject analysis set description:<br>Subjects received prophylactic rIX-FP every 14 days.  |                                    |
| Subject analysis set title   | PK - Prophylaxis Arm               |
| Subject analysis set type  | Sub-group analysis                 |
| Subject analysis set description:<br>Subjects included in the Pharmacokinetic (PK) population from the prophylaxis arm who received at least 1 dose of rIX-FP at 50 IU/kg. Data are presented for subjects from the PK population who had a sufficient number of analyzable PK samples for evaluation of the PK profile of rIX-FP.                               |                                    |
| Subject analysis set title   | PK - On-demand Arm                 |
| Subject analysis set type  | Sub-group analysis                 |
| Subject analysis set description:<br>Subjects included in the PK population from the on-demand arm who received at least 1 dose of rIX-FP at 50 IU/kg. Data are presented for subjects from the PK population who had a sufficient number of analyzable PK samples for evaluation of the PK profile of rIX-FP.   |                                    |

|   |                     |
|---|---------------------|
| Subject analysis set title  | Surgical population |
| Subject analysis set type   | Sub-group analysis  |
| Subject analysis set description:   |                     |
| The Surgical population consisted of 3 subjects in the prophylaxis arm and 1 subject in the on demand arm who received at least 1 dose of rIX FP for a major or minor surgical procedure. |                     |

### Primary: Number of subjects developing inhibitors against factor IX (FIX)

|  |   |
|--|---|
| End point title  | Number of subjects developing inhibitors against factor IX (FIX) <sup>[1]</sup> |
| End point description:   |   |
| The number of participants developing inhibitors against factor IX (FIX) along with the 95% Clopper-Pearson confidence interval, are summarized for subjects with 50 or more exposure days (EDs) to rIX-FP, and for all participants in the study. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| Up to 27.7 months (maximum)  |   |

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: No statistical analyses were conducted for this end point.

| End point values                                   | Safety Population    |  |  |  |
|--|----------------------|--|--|--|
| Subject group type                                 | Subject analysis set |  |  |  |
| Number of subjects analysed                        | 63                   |  |  |  |
| Units: Participants                                |                      |  |  |  |
| number (confidence interval 95%)                   |                      |  |  |  |
| Participants with $\geq 50$ EDs to rIX-FP (n = 49) | 0 (0 to 7.3)         |  |  |  |
| All participants (n = 63)                          | 0 (0 to 5.7)         |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Change in frequency of spontaneous bleeding events between on-demand and prophylaxis treatments (annualized)

|  |  |
|--|--|
| End point title  | Change in frequency of spontaneous bleeding events between on-demand and prophylaxis treatments (annualized) |
| End point description:   |  |
| Subjects in the on-demand arm received on-demand dosing with rIX-FP for up to 26 weeks (on-demand regimen), and then received weekly prophylaxis with rIX-FP for the remainder of the study (prophylaxis regimen). The effectiveness of prophylaxis in comparison to on-demand therapy was investigated by comparing the same subject's annualized spontaneous bleeding rate (AsBR) during the on-demand regimen and during the prophylaxis regimen. |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| Up to 26 weeks for on-demand regimen, and between 1 and 17 months for prophylaxis regimen.   |  |



| End point values                      | On-demand Arm, on-demand regimen | On-demand Arm, prophylaxis regimen |  |  |
|---------------------------------------|----------------------------------|------------------------------------|--|--|
| Subject group type                    | Subject analysis set             | Subject analysis set               |  |  |
| Number of subjects analysed           | 19                               | 19                                 |  |  |
| Units: bleeds/year/subject            |                                  |                                    |  |  |
| median (inter-quartile range (Q1-Q3)) | 15.43 (7.98 to 17.96)            | 0 (0 to 0.96)                      |  |  |

## Statistical analyses

| Statistical analysis title   | Percent reduction in AsBR   |
|--|---|
| Statistical analysis description:<br>Matched pairs design with 19 subjects and 2 observations per subject. |   |
| Comparison groups  | On-demand Arm, prophylaxis regimen v On-demand Arm, on-demand regimen |
| Number of subjects included in analysis  | 38  |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority <sup>[2]</sup>  |
| P-value  | < 0.0001 <sup>[3]</sup>   |
| Method   | Wilcoxon signed-rank test   |

Notes:

[2] - A test of null hypothesis that the ratio of AsBR (prophylaxis regimen/on-demand regimen) was  $\geq 0.50$  was conducted at the 1-sided 0.025 level.

[3] - P value is based on a Wilcoxon signed-rank test of  $H_0$ : AsBR ratio (prophylaxis regimen/on-demand regimen)  $\geq 0.50$ . The ratio was based on the original scale.

## Secondary: Number of subjects developing antibodies against rIX-FP

|   |   |
|---|---|
| End point title   | Number of subjects developing antibodies against rIX-FP |
| End point description:  |   |
| End point type  | Secondary   |
| End point timeframe:<br>For the duration of the study; median 20.27 months. |   |

| End point values            | Safety Population    |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 63                   |  |  |  |
| Units: participants         | 0                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: rIX-FP consumed per month while maintaining assigned prophylactic

**treatment interval during routine prophylaxis.**

|                 |  |
|-----------------|--|
| End point title | rIX-FP consumed per month while maintaining assigned prophylactic treatment interval during routine prophylaxis. |
|-----------------|--|

End point description:

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

End point timeframe:

For Prophylaxis Arm 7-, 10- and 14-day regimens, median 269, 240 and 386 days respectively. For On-demand Arm, prophylaxis regimen, median 316 days.

| End point values                     | On-demand Arm, prophylaxis regimen | Prophylaxis Arm, 7-day regimen | Prophylaxis Arm, 10-day regimen | Prophylaxis Arm, 14-day regimen |
|--------------------------------------|------------------------------------|--------------------------------|---------------------------------|---------------------------------|
| Subject group type                   | Subject analysis set               | Subject analysis set           | Subject analysis set            | Subject analysis set            |
| Number of subjects analysed          | 19                                 | 40                             | 7                               | 21                              |
| Units: IU/kg/month                   |                                    |                                |                                 |                                 |
| arithmetic mean (standard deviation) | 191.68 ( $\pm$ 36.33)              | 202.68 ( $\pm$ 47.92)          | 201.5 ( $\pm$ 42.56)            | 157.44 ( $\pm$ 16.34)           |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Incremental recovery of rIX-FP**

|                 |                                |
|-----------------|--------------------------------|
| End point title | Incremental recovery of rIX-FP |
|-----------------|--------------------------------|

End point description:

Pharmacokinetic (PK) data are presented for a single 50 IU/kg dose of rIX-FP.

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

End point timeframe:

336 hours

| End point values                     | PK - Prophylaxis Arm | PK - On-demand Arm   |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 27                   | 18                   |  |  |
| Units: (IU/dL)/(IU/kg)               |                      |                      |  |  |
| arithmetic mean (standard deviation) | 1.29 ( $\pm$ 0.33)   | 1.24 ( $\pm$ 0.25)   |  |  |

**Statistical analyses**

No statistical analyses for this end point

### Secondary: The frequency of related adverse events

|                 |   |
|-----------------|---|
| End point title | The frequency of related adverse events |
|-----------------|---|

End point description:

The percentage of participants experiencing treatment-related adverse-events (TEAEs).

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

End point timeframe:

For the duration of the study; median 20.27 months.

| End point values                  | Prophylaxis     | On-demand       | Safety Population    |  |
|-----------------------------------|-----------------|-----------------|----------------------|--|
| Subject group type                | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed       | 40              | 23              | 63                   |  |
| Units: percentage of participants |                 |                 |                      |  |
| number (not applicable)           |                 |                 |                      |  |
| Related TEAE                      | 10              | 4.3             | 7.9                  |  |
| Not related TEAE                  | 87.5            | 78.3            | 84.1                 |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of bleeding episodes requiring one or $\leq$ two injections of rIX-FP

|                 |   |
|-----------------|---|
| End point title | Proportion of bleeding episodes requiring one or $\leq$ two injections of rIX-FP <sup>[4]</sup> |
|-----------------|---|

End point description:

Number of injections required to achieve hemostasis expressed as a percentage of the bleeding episodes requiring treatment. The number of bleeding episodes requiring treatment were 101, 220 and 37 in the Prophylaxis Arm, On-demand Arm (On-demand Regimen) and On-demand Arm (Prophylaxis Regimen), respectively.

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

End point timeframe:

For the duration of the study; median 20.27 months.

Notes:

[4] - 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 for the On-demand Arm are provided for the two On-demand sub-group regimens (On-demand regimen and prophylaxis regimen), rather than for the overall On-demand Arm.

| End point values                       | Prophylaxis     | On-demand Arm, on-demand regimen | On-demand Arm, prophylaxis regimen |  |
|--|-----------------|----------------------------------|------------------------------------|--|
| Subject group type                     | Reporting group | Subject analysis set             | Subject analysis set               |  |
| Number of subjects analysed            | 40              | 23                               | 19                                 |  |
| Units: percentage of bleeding episodes |                 |                                  |                                    |  |
| number (not applicable)                |                 |                                  |                                    |  |

|                   |      |      |      |  |
|-------------------|------|------|------|--|
| 1 injection       | 92.1 | 94.5 | 91.9 |  |
| 1 or 2 injections | 100  | 98.6 | 94.6 |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Investigator's overall clinical assessment of hemostatic efficacy for treatment of bleeding episodes, based on a four point ordinal scales (excellent, good, moderate, poor/no response)

|                 |  |
|-----------------|--|
| End point title | Investigator's overall clinical assessment of hemostatic efficacy for treatment of bleeding episodes, based on a four point ordinal scales (excellent, good, moderate, poor/no response) |
|-----------------|--|

End point description:

Number of bleeding episodes requiring treatment that resulted in hemostatic efficacy of excellent, good, moderate, poor/no response, according to the Investigator's clinical assessment of hemostatic efficacy, expressed as a percentage of the bleeding episodes requiring treatment. The number of bleeding episodes requiring treatment were 101 and 257 in the Prophylaxis Arm and On-demand Arm, respectively.

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

End point timeframe:

For the duration of the study; median 20.27 months.

| End point values                       | Prophylaxis     | On-demand       |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                     | Reporting group | Reporting group |  |  |
| Number of subjects analysed            | 40              | 23              |  |  |
| Units: percentage of bleeding episodes |                 |                 |  |  |
| number (not applicable)                |                 |                 |  |  |
| Excellent                              | 71.3            | 87.5            |  |  |
| Good                                   | 20.8            | 7.4             |  |  |
| Moderate                               | 3               | 2.3             |  |  |
| Poor/No response                       | 0               | 0.4             |  |  |
| Missing                                | 5               | 2.3             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Half-life (t<sub>1/2</sub>) of a single dose of rIX-FP

|                 |  |
|-----------------|--|
| End point title | Half-life (t <sub>1/2</sub> ) of a single dose of rIX-FP |
|-----------------|--|

End point description:

PK data are presented for a single 50 IU/kg dose of rIX-FP.

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

End point timeframe:

336 hours

| End point values                     | PK - Prophylaxis Arm  | PK - On-demand Arm   |  |  |
|--------------------------------------|-----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set  | Subject analysis set |  |  |
| Number of subjects analysed          | 26                    | 17                   |  |  |
| Units: hour                          |                       |                      |  |  |
| arithmetic mean (standard deviation) | 104.77 ( $\pm$ 22.73) | 96.88 ( $\pm$ 20.94) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area under the curve (AUC)

|   |                            |
|---|----------------------------|
| End point title   | Area under the curve (AUC) |
| End point description:<br>AUC to the last sample with quantifiable drug concentration (AUClast) of a single dose of rIX-FP. PK data are presented for a single 50 IU/kg dose of rIX-FP. |                            |
| End point type  | Secondary                  |
| End point timeframe:<br>336 hours   |                            |

| End point values                     | PK - Prophylaxis Arm     | PK - On-demand Arm   |  |  |
|--------------------------------------|--------------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set     | Subject analysis set |  |  |
| Number of subjects analysed          | 27                       | 18                   |  |  |
| Units: IU*hr/dL                      |                          |                      |  |  |
| arithmetic mean (standard deviation) | 6534.15 ( $\pm$ 1856.96) | 5963.3 ( $\pm$ 1893) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clearance of a single dose of rIX-FP

|   |                                      |
|---|--------------------------------------|
| End point title   | Clearance of a single dose of rIX-FP |
| End point description:<br>PK data are presented for a single 50 IU/kg dose of rIX-FP. |                                      |
| End point type  | Secondary                            |

End point timeframe:

336 hours

| End point values                     | PK - Prophylaxis Arm | PK - On-demand Arm   |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 26                   | 17                   |  |  |
| Units: mL/hr                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 50.19 ( $\pm$ 12.92) | 59 ( $\pm$ 19.37)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Investigator's (or surgeon's) overall clinical assessment of hemostatic efficacy for surgical prophylaxis, based on a four point ordinal scale (excellent, good, moderate, poor/no response)

|                 |  |
|-----------------|--|
| End point title | Investigator's (or surgeon's) overall clinical assessment of hemostatic efficacy for surgical prophylaxis, based on a four point ordinal scale (excellent, good, moderate, poor/no response) |
|-----------------|--|

End point description:

Number of surgical events treated prophylactically with rIX-FP that resulted in hemostatic efficacy of excellent, good, moderate, poor/no response, according to the Investigator's (surgeon's) overall assessment of hemostatic efficacy for surgical prophylaxis. There were six surgical events overall.

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

End point timeframe:

Up to 14 days after surgery

| End point values            | Surgical population  |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 4                    |  |  |  |
| Units: events               |                      |  |  |  |
| Excellent                   | 6                    |  |  |  |
| Good                        | 0                    |  |  |  |
| Moderate                    | 0                    |  |  |  |
| Poor / No response          | 0                    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Annualized spontaneous bleeding events compared between 7 day prophylactic and extended regimens**

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|                 |  |
|-----------------|--|
| End point title | Annualized spontaneous bleeding events compared between 7 day prophylactic and extended regimens |
|-----------------|--|

End point description:

Median number of spontaneous bleeds per year per subject comparing 7-, 10- and 14- day prophylactic regimens.

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

End point timeframe:

During treatment, between median 240 and 386 days per subject.

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| End point values                      | Prophylaxis Arm, 7-day regimen | Prophylaxis Arm, 10-day regimen | Prophylaxis Arm, 14-day regimen |  |
|---------------------------------------|--------------------------------|---------------------------------|---------------------------------|--|
| Subject group type                    | Subject analysis set           | Subject analysis set            | Subject analysis set            |  |
| Number of subjects analysed           | 38                             | 7                               | 21                              |  |
| Units: bleeds/year/subject            |                                |                                 |                                 |  |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 0)                     | 0 (0 to 0)                      | 0 (0 to 1)                      |  |

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

For the duration of the study, up to 27.7 months.

Adverse event reporting additional description:

The Safety analysis population consisted of subjects who received at least 1 dose of rIX-FP during the study. Adverse Event data are treatment-emergent data unless otherwise noted.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 14.1 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Prophylaxis |
|-----------------------|-------------|

Reporting group description:

Routine weekly prophylaxis and episodic treatment for bleeding episodes. An individualized dosing interval may be tested in sub-group subjects during the 2nd part of the trial.

Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention.

|                       |           |
|-----------------------|-----------|
| Reporting group title | On-demand |
|-----------------------|-----------|

Reporting group description:

Episodic treatment for bleeding episodes for up to 26 weeks then switch to routine weekly prophylaxis for the remainder of the study.

Subjects may participate in a surgical 'sub-study' in which rIX-FP may be administered prior to, during and after surgical intervention.

| Serious adverse events                            | Prophylaxis  | On-demand      |  |
|---|--|----------------|--|
| Total subjects affected by serious adverse events |  |                |  |
| subjects affected / exposed                       | 1 / 40 (2.50%)   | 2 / 23 (8.70%) |  |
| number of deaths (all causes)                     | 0  | 0              |  |
| number of deaths resulting from adverse events    | 0  | 0              |  |
| Nervous system disorders                          |  |                |  |
| ACQUIRED EPILEPTIC APHASIA                        |  |                |  |
| subjects affected / exposed                       | 0 / 40 (0.00%)   | 1 / 23 (4.35%) |  |
| occurrences causally related to treatment / all   | 0 / 0  | 0 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0  | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders   |  |                |  |
| SYNOVITIS   |  |                |  |
| subjects affected / exposed                       | 0 / 40 (0.00%)   | 1 / 23 (4.35%) |  |
| occurrences causally related to treatment / all   | 0 / 0  | 0 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0  | 0 / 0          |  |
| PAIN IN EXTREMITY                                 | Additional description: This SAE was not treatment-emergent. |                |  |



|   |  |                |  |
|---|--|----------------|--|
| subjects affected / exposed                     | 1 / 40 (2.50%)   | 0 / 23 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| MUSCLE HAEMORRHAGE                              | Additional description: This SAE was not treatment-emergent. |                |  |
| subjects affected / exposed                     | 1 / 40 (2.50%)   | 0 / 23 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |

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

| Non-serious adverse events                            | Prophylaxis      | On-demand        |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 30 / 40 (75.00%) | 14 / 23 (60.87%) |  |
| Injury, poisoning and procedural complications        |                  |                  |  |
| LIMB INJURY   |                  |                  |  |
| subjects affected / exposed                           | 5 / 40 (12.50%)  | 1 / 23 (4.35%)   |  |
| occurrences (all)                                     | 5                | 1                |  |
| CONTUSION   |                  |                  |  |
| subjects affected / exposed                           | 3 / 40 (7.50%)   | 1 / 23 (4.35%)   |  |
| occurrences (all)                                     | 5                | 3                |  |
| LACERATION  |                  |                  |  |
| subjects affected / exposed                           | 1 / 40 (2.50%)   | 2 / 23 (8.70%)   |  |
| occurrences (all)                                     | 1                | 2                |  |
| Nervous system disorders                              |                  |                  |  |
| HEADACHE  |                  |                  |  |
| subjects affected / exposed                           | 11 / 40 (27.50%) | 4 / 23 (17.39%)  |  |
| occurrences (all)                                     | 26               | 8                |  |
| DIZZINESS   |                  |                  |  |
| subjects affected / exposed                           | 4 / 40 (10.00%)  | 0 / 23 (0.00%)   |  |
| occurrences (all)                                     | 5                | 0                |  |
| Gastrointestinal disorders                            |                  |                  |  |
| DIARRHOEA   |                  |                  |  |
| subjects affected / exposed                           | 2 / 40 (5.00%)   | 3 / 23 (13.04%)  |  |
| occurrences (all)                                     | 2                | 4                |  |
| TOOTHACHE   |                  |                  |  |

|  |   |  |  |
|--|---|--|--|
| subjects affected / exposed<br>occurrences (all)   | 4 / 40 (10.00%)<br>4  | 1 / 23 (4.35%)<br>1  |  |
| Respiratory, thoracic and mediastinal disorders<br>COUGH<br>subjects affected / exposed<br>occurrences (all)   | 3 / 40 (7.50%)<br>3   | 0 / 23 (0.00%)<br>0  |  |
| Skin and subcutaneous tissue disorders<br>ACNE<br>subjects affected / exposed<br>occurrences (all)   | 3 / 40 (7.50%)<br>3   | 0 / 23 (0.00%)<br>0  |  |
| Musculoskeletal and connective tissue disorders<br>ARTHRALGIA<br>subjects affected / exposed<br>occurrences (all)<br><br>BACK PAIN<br>subjects affected / exposed<br>occurrences (all)<br><br>SYNOVITIS<br>subjects affected / exposed<br>occurrences (all)<br><br>PAIN IN EXTREMITY<br>subjects affected / exposed<br>occurrences (all)<br><br>JOINT SWELLING<br>subjects affected / exposed<br>occurrences (all)<br><br>TENDONITIS<br>subjects affected / exposed<br>occurrences (all) | 9 / 40 (22.50%)<br>19<br><br>4 / 40 (10.00%)<br>5<br><br>3 / 40 (7.50%)<br>6<br><br>3 / 40 (7.50%)<br>4<br><br>3 / 40 (7.50%)<br>3<br><br>3 / 40 (7.50%)<br>3 | 0 / 23 (0.00%)<br>0<br><br>2 / 23 (8.70%)<br>3<br><br>0 / 23 (0.00%)<br>0<br><br>0 / 23 (0.00%)<br>0<br><br>0 / 23 (0.00%)<br>0<br><br>0 / 23 (0.00%)<br>0 |  |
| Infections and infestations<br>NASOPHARYNGITIS<br>subjects affected / exposed<br>occurrences (all)<br><br>INFLUENZA<br>subjects affected / exposed<br>occurrences (all)  | 10 / 40 (25.00%)<br>27<br><br>4 / 40 (10.00%)<br>7  | 6 / 23 (26.09%)<br>11<br><br>3 / 23 (13.04%)<br>3  |  |

|                                      |                 |                |  |
|--------------------------------------|-----------------|----------------|--|
| UPPER RESPIRATORY TRACT<br>INFECTION |                 |                |  |
| subjects affected / exposed          | 5 / 40 (12.50%) | 0 / 23 (0.00%) |  |
| occurrences (all)                    | 7               | 0              |  |
| BRONCHITIS                           |                 |                |  |
| subjects affected / exposed          | 4 / 40 (10.00%) | 1 / 23 (4.35%) |  |
| occurrences (all)                    | 4               | 1              |  |
| PHARYNGITIS                          |                 |                |  |
| subjects affected / exposed          | 3 / 40 (7.50%)  | 2 / 23 (8.70%) |  |
| occurrences (all)                    | 3               | 2              |  |
| GASTROENTERITIS                      |                 |                |  |
| subjects affected / exposed          | 3 / 40 (7.50%)  | 0 / 23 (0.00%) |  |
| occurrences (all)                    | 4               | 0              |  |
| ACUTE TONSILLITIS                    |                 |                |  |
| subjects affected / exposed          | 0 / 40 (0.00%)  | 2 / 23 (8.70%) |  |
| occurrences (all)                    | 0               | 2              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 30 November 2011 | Protocol Amendment 1 was issued before the enrollment of the first subject. Key changes to the protocol included: <ul style="list-style-type: none"><li>- Re-assigning a secondary endpoint to be a primary endpoint</li><li>- Adding an efficacy evaluation algorithm for the Investigator rating of bleeding episodes for clarification</li><li>- Updating treatment groups and assigned doses</li><li>- Adding the criteria for dose adjustment and treatment regimen switching, as well as an algorithm for the new dose interval</li><li>- Updating the statistical methodology section</li></ul>   |
| 18 October 2012  | Protocol amendment 2 included the following key changes: <ul style="list-style-type: none"><li>- Added that, for on-demand treatment (Arm 2), a subject's prophylaxis dose could only be adjusted during the first 4 weeks, and that the dose prescribed after 4 weeks of prophylaxis treatment was to be maintained for the rest of the study.</li><li>- Updated the statistical methodology section with analysis population definitions, additional secondary and exploratory endpoints, and additional details on statistical methods</li><li>- Added the comparison of mean annualized bleeding rates between different prophylaxis regimens as one of the secondary endpoints</li></ul>  |
| 27 February 2014 | Protocol Amendment 3 included the following key changes: <ul style="list-style-type: none"><li>- The bleeding episodes that occurred during the 4-week run-in period of prophylaxis therapy for subjects in Arm 2 (on-demand) were no longer to be excluded from analyses of the 26-week treatment period, and the total duration of treatment for Arm 2 was reduced from 30 weeks to 26 weeks, but a minimum of 12 weeks</li><li>- Added additional statistical methods to clarify how missing data were handled during the primary efficacy analysis</li><li>- Clarified that the test proposed for the comparison between the 7-day and the 10-day or 14-day prophylaxis regimens was referred to as a non-inferiority test</li></ul> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported