



Clinical trial results:

A Phase 3b Open-label, Multicenter, Safety and Efficacy Extension Study of a Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2012-005489-37 |
| Trial protocol | DE IT CZ BG ES AT |
| Global end of trial date | 02 June 2021 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 26 November 2021 |
| First version publication date | 26 November 2021 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | CSL654_3003 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02053792 |
| 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 Coordinator, CSL Behring GmbH, 049 642139 3304, clinicaltrials@cslbehring.com |
| Scientific contact | Clinical Trial Coordinator, CSL Behring GmbH, 049 642139 3304, 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? | Yes |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 29 June 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 June 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of rIX-FP as measured by new cases of inhibitors against FIX in subjects with severe hemophilia B.

Protection of trial subjects:

If a subject is withdrawn from the study or further participation is declined, they will continue to have access to medical care and will be treated as per routine medical practice.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 06 February 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: 5 |
| Country: Number of subjects enrolled | Philippines: 2 |
| Country: Number of subjects enrolled | United States: 6 |
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | Israel: 15 |
| Country: Number of subjects enrolled | Japan: 9 |
| Country: Number of subjects enrolled | Malaysia: 2 |
| Country: Number of subjects enrolled | South Africa: 2 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | Austria: 5 |
| Country: Number of subjects enrolled | Bulgaria: 4 |
| Country: Number of subjects enrolled | Czechia: 3 |
| Country: Number of subjects enrolled | France: 14 |
| Country: Number of subjects enrolled | Germany: 11 |
| Country: Number of subjects enrolled | Italy: 12 |
| Worldwide total number of subjects | 97 |
| EEA total number of subjects | 55 |

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) | 13 |
| Children (2-11 years) | 25 |
| Adolescents (12-17 years) | 5 |
| Adults (18-64 years) | 54 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Approximately 115 male PTPs and PUPs with hemophilia B were planned to be enrolled, including all eligible PTPs from CSLB-sponsored rIX-FP lead-in studies, approximately 10 PTPs who required major, nonemergency surgery, and approximately 20 PUPs.

Period 1

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

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | CSL654 (PTPs) |

Arm description:

Previously treated patients (PTPs) will administer CSL654 (rIX-FP) by intravenous infusion as routine prophylaxis, prevention, and on-demand treatment during a treatment period of approximately 5 years or the time it took to reach 100 EDs.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Recombinant fusion protein linking coagulation factor IX with albumin |
| Investigational medicinal product code | CSL654 |
| Other name | rIX-FP |
| Pharmaceutical forms | Powder and solvent for solution for injection/infusion |
| Routes of administration | Intravenous use, Subcutaneous use |

Dosage and administration details:

Previously treated patients (PTPs) will administer rIX-FP by intravenous infusion as routine prophylaxis, prevention, and on-demand treatment during a treatment period of approximately 5 years. The dose of rIX-FP administered will be based on the subject's previous rIX-FP use and/or pharmacokinetic data.

| | |
|------------------|---------------|
| Arm title | CSL654 (PUPs) |
|------------------|---------------|

Arm description:

Previously untreated patients (PUPs) administered CSL654 (rIX-FP) intravenously as weekly prophylaxis and/or on-demand treatment during the first 12 months, and as weekly routine prophylaxis thereafter up to 3 years or the time it takes to achieve 50 EDs..

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

Dosage and administration details:

Subjects will administer rIX-FP by intravenous infusion as routine prophylaxis, prevention, and on-demand treatment during a treatment period of approximately 3 years. The dose of rIX-FP administered will be based on the subject's previous rIX-FP use and/or pharmacokinetic data.

| Number of subjects in period 1 | CSL654 (PTPs) | CSL654 (PUPs) |
|---------------------------------------|---------------|---------------|
| Started | 83 | 14 |
| Completed | 77 | 10 |
| Not completed | 6 | 4 |
| Adverse event, serious fatal | 1 | - |
| Consent withdrawn by subject | 2 | 2 |
| Physician decision | - | 1 |
| Unknown | 2 | 1 |
| Lack of efficacy | 1 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | CSL654 (PTPs) |
|-----------------------|---------------|

Reporting group description:

Previously treated patients (PTPs) will administer CSL654 (rIX-FP) by intravenous infusion as routine prophylaxis, prevention, and on-demand treatment during a treatment period of approximately 5 years or the time it took to reach 100 EDs.

| | |
|-----------------------|---------------|
| Reporting group title | CSL654 (PUPs) |
|-----------------------|---------------|

Reporting group description:

Previously untreated patients (PUPs) administered CSL654 (rIX-FP) intravenously as weekly prophylaxis and/or on-demand treatment during the first 12 months, and as weekly routine prophylaxis thereafter up to 3 years or the time it takes to achieve 50 EDs..

| Reporting group values | CSL654 (PTPs) | CSL654 (PUPs) | Total |
|--|---------------|---------------|-------|
| Number of subjects | 83 | 14 | 97 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 13 | 13 |
| Children (2-11 years) | 24 | 1 | 25 |
| Adolescents (12-17 years) | 5 | 0 | 5 |
| Adults (18-64 years) | 54 | 0 | 54 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 27.7 | 1.3 | |
| standard deviation | ± 17.81 | ± 3.11 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 83 | 14 | 97 |

End points

End points reporting groups

| | |
|--|---------------|
| Reporting group title | CSL654 (PTPs) |
| Reporting group description: Previously treated patients (PTPs) will administer CSL654 (rIX-FP) by intravenous infusion as routine prophylaxis, prevention, and on-demand treatment during a treatment period of approximately 5 years or the time it took to reach 100 EDs. | |
| Reporting group title | CSL654 (PUPs) |
| Reporting group description: Previously untreated patients (PUPs) administered CSL654 (rIX-FP) intravenously as weekly prophylaxis and/or on-demand treatment during the first 12 months, and as weekly routine prophylaxis thereafter up to 3 years or the time it takes to achieve 50 EDs.. | |

Primary: Total number of subjects who develop inhibitors against factor IX (FIX)

| | |
|---|--|
| End point title | Total number of subjects who develop inhibitors against factor IX (FIX) ^[1] |
| End point description: | |
| End point type | Primary |
| End point timeframe: For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs). For PUPs: up to 3 years or the time it takes to achieve 50 EDs. | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Descriptive statistics used | |

| End point values | CSL654 (PTPs) | CSL654 (PUPs) | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 83 | 12 | | |
| Units: subjects | | | | |
| number (not applicable) | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Incremental recovery of 50 IU/kg CSL654 in previously untreated patients (PUPs)

| | |
|--|---|
| End point title | Incremental recovery of 50 IU/kg CSL654 in previously untreated patients (PUPs) ^{[2][3]} |
| End point description: | |
| End point type | Primary |
| End point timeframe: 30 minutes after CSL654 infusion | |

Notes:

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

Justification: Descriptive statistics used because study is per guideline and not powered for this endpoint.

[3] - 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: Only PUPs for this endpoint

| End point values | CSL654 (PUPs) | | | |
|--------------------------------------|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 8 | | | |
| Units: (IU/dL)/(IU/kg) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Uncorrected FIX Activity | 1.295 (± 0.3578) | | | |
| Baseline-corrected FIX Activity | 1.231 (± 0.3729) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total Annualized Bleeding Rate (ABR) by Prophylaxis Regimen (PTPs)

| | |
|-----------------|---|
| End point title | Total Annualized Bleeding Rate (ABR) by Prophylaxis Regimen (PTPs) ^[4] |
|-----------------|---|

End point description:

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

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

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: Descriptive statistics derived only for PTPs

| End point values | CSL654 (PTPs) | | | |
|--------------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 83 ^[5] | | | |
| Units: Bleeds/Year/Subject | | | | |
| arithmetic mean (standard deviation) | | | | |
| 7-Day Regimen (n=41) | 2.89 (± 3.115) | | | |
| 10-Day Regimen (n=23) | 2.72 (± 2.827) | | | |
| 14-Day Regimen (n=48) | 2.72 (± 3.395) | | | |
| 21-Day Regimen (n=11) | 1.19 (± 1.572) | | | |

Notes:

[5] - Subjects may be assigned under multiple regimens, but will be counted only once in any given regimen

Statistical analyses

No statistical analyses for this end point

Secondary: Spontaneous ABR by Prophylaxis Regimen (PTPs)

End point title Spontaneous ABR by Prophylaxis Regimen (PTPs)^[6]

End point description:

End point type Secondary

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

Notes:

[6] - 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: Only PTPs for this endpoint

| End point values | CSL654 (PTPs) | | | |
|--------------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 83 ^[7] | | | |
| Units: Bleeds/Year/Subject | | | | |
| arithmetic mean (standard deviation) | | | | |
| 7-Day Regimen (n=41) | 0.95 (± 1.672) | | | |
| 10-Day Regimen (n=23) | 0.98 (± 1.689) | | | |
| 14-Day Regimen (n=48) | 1.32 (± 2.205) | | | |
| 21-Day Regimen (n=11) | 0.60 (± 1.408) | | | |

Notes:

[7] - Subjects may be assigned under multiple regimens, but will be counted only once in any given regimen

Statistical analyses

No statistical analyses for this end point

Secondary: Total ABR for On-demand Regimen vs. 14-Day Regimen (PTPs)

End point title Total ABR for On-demand Regimen vs. 14-Day Regimen

End point description:

End point type Secondary

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

Notes:

[8] - 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: Only PTPs for this endpoint

| End point values | CSL654 (PTPs) | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 | | | |
| Units: Bleeds/Year/Subject | | | | |
| arithmetic mean (standard deviation) | | | | |
| On-demand Regimen (n=14) | 17.51 (± 7.130) | | | |
| 14-Day Regimen (n=14) | 3.01 (± 4.204) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Spontaneous ABR for On-demand Regimen vs. 14-Day Regimen (PTPs)

| | |
|-----------------|--|
| End point title | Spontaneous ABR for On-demand Regimen vs. 14-Day Regimen (PTPs) ^[9] |
|-----------------|--|

End point description:

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

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

Notes:

[9] - 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: Only PTPs for this endpoint

| End point values | CSL654 (PTPs) | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 | | | |
| Units: Bleeds/Year/Subject | | | | |
| arithmetic mean (standard deviation) | | | | |
| On-demand Regimen (n=14) | 13.17 (± 5.873) | | | |
| 14-Day Regimen (n=14) | 1.93 (± 3.363) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: CSL654 consumed per month per subject during routine prophylaxis treatment

| | |
|-----------------|--|
| End point title | CSL654 consumed per month per subject during routine prophylaxis treatment |
|-----------------|--|

End point description:

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

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs). For PUPs: up to 3 years or the time it takes to achieve 50 EDs.

| End point values | CSL654 (PTPs) | CSL654 (PUPs) | | |
|--------------------------------------|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 83 | 12 | | |
| Units: IU/kg | | | | |
| arithmetic mean (standard deviation) | 181.8 (± 35.16) | 188.53 (± 24.096) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with at least one treatment emergent adverse event (TEAE) and the percentage of participants with at least one CSL654-related TEAE

| | |
|-----------------|---|
| End point title | Percentage of participants with at least one treatment emergent adverse event (TEAE) and the percentage of participants with at least one CSL654-related TEAE |
|-----------------|---|

End point description:

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

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs). For PUPs: up to 3 years or the time it takes to achieve 50 EDs.

| End point values | CSL654 (PTPs) | CSL654 (PUPs) | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 83 | 12 | | |
| Units: Percent | | | | |
| number (not applicable) | | | | |
| AEs | 89.2 | 91.7 | | |
| Related AEs | 1.2 | 16.7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Investigator's Overall Clinical Assessment of Hemostatic Efficacy for the Treatment of Major Bleeding Events with CSL654 (PUPs)

| | |
|-----------------|---|
| End point title | Number of Participants with Investigator's Overall Clinical Assessment of Hemostatic Efficacy for the Treatment of Major Bleeding Events with CSL654 (PUPs) ^[10] |
|-----------------|---|

End point description:

The investigator will rate the efficacy of the CSL654 treatment based on a hemostatic efficacy four point rating scale of "excellent, good, moderate or poor/no response"

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

End point timeframe:

Up to 3 years or the time it takes to achieve 50 EDs

Notes:

[10] - 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: Only PUPs for this endpoint

| End point values | CSL654 (PUPs) | | | |
|-----------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[11] | | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Excellent | | | | |
| Good | | | | |
| Moderate | | | | |
| Poor/No response | | | | |

Notes:

[11] - No major bleeding events were reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Total ABR for Subjects ≥ 12 years: 7-Day Regimen vs. 14-Day Regimen (PTPs)

| | |
|-----------------|---|
| End point title | Total ABR for Subjects ≥ 12 years: 7-Day Regimen vs. 14-Day Regimen (PTPs) ^[12] |
|-----------------|---|

End point description:

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

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

Notes:

[12] - 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: Only PTPs for this endpoint

| End point values | CSL654 (PTPs) | | | |
|--------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 | | | |
| Units: Bleeds/Year/Subject | | | | |
| arithmetic mean (standard deviation) | | | | |
| 7-Day Regimen | 1.12 (\pm 1.697) | | | |
| 14-Day Regimen | 2.19 (\pm 3.000) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Spontaneous ABR for Subjects ≥ 12 years: 7-Day Regimen vs. 14-Day Regimen (PTPs)

| | |
|-----------------|---|
| End point title | Spontaneous ABR for Subjects ≥ 12 years: 7-Day Regimen vs. 14-Day Regimen (PTPs) ^[13] |
|-----------------|---|

End point description:

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

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

Notes:

[13] - 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: Only PTPs for this endpoint

| End point values | CSL654 (PTPs) | | | |
|--------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 | | | |
| Units: Bleeds/Year/Subject | | | | |
| arithmetic mean (standard deviation) | | | | |
| 7-Day Regimen | 0.49 (\pm 1.135) | | | |
| 14-Day Regimen | 1.33 (\pm 2.349) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total ABR for Subjects ≥ 12 years: 7-Day Regimen vs. (10 or 14)-Day Regimen (PTPs)

| | |
|-----------------|---|
| End point title | Total ABR for Subjects ≥ 12 years: 7-Day Regimen vs. (10 or 14)-Day Regimen (PTPs) ^[14] |
|-----------------|---|

End point description:

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

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

Notes:

[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: Only PTPs for this endpoint

| End point values | CSL654 (PTPs) | | | |
|--------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: Bleeds/Year/Subject | | | | |
| arithmetic mean (standard deviation) | | | | |
| 7-Day Regimen | 1.31 (\pm 1.868) | | | |

| | | | | |
|------------------------|---------------------|--|--|--|
| (10 or 14)-Day Regimen | 2.01 (\pm 2.700) | | | |
|------------------------|---------------------|--|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Spontaneous ABR for Subjects ≥ 12 years: 7-Day Regimen vs. (10 or 14)-Day Regimen (PTPs)

| | |
|-----------------|---|
| End point title | Spontaneous ABR for Subjects ≥ 12 years: 7-Day Regimen vs. (10 or 14)-Day Regimen (PTPs) ^[15] |
|-----------------|---|

End point description:

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

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

Notes:

[15] - 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: Only PTPs for this endpoint

| End point values | CSL654 (PTPs) | | | |
|--------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: Bleeds/Year/Subject | | | | |
| arithmetic mean (standard deviation) | | | | |
| 7-Day Regimen | 0.57 (\pm 1.192) | | | |
| (10 or 14)-Day Regimen | 1.05 (\pm 2.022) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs). For PUPs: up to 3 years or the time it takes to achieve 50 EDs.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | CSL654 (PTPs) |
|-----------------------|---------------|

Reporting group description:

Subjects will administer CSL654 (rIX-FP) by intravenous infusion as routine prophylaxis, prevention, and on-demand treatment during a treatment period of approximately 5 years.

| | |
|-----------------------|---------------|
| Reporting group title | CSL654 (PUPs) |
|-----------------------|---------------|

Reporting group description:

For previously untreated patients, subjects will administer CSL654 (rIX-FP) intravenously as weekly prophylaxis and/or on-demand treatment during the first 12 months, and as weekly routine prophylaxis thereafter.

| Serious adverse events | CSL654 (PTPs) | CSL654 (PUPs) | |
|---|------------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 17 / 83 (20.48%) | 5 / 12 (41.67%) | |
| number of deaths (all causes) | 1 | 0 | |
| number of deaths resulting from adverse events | 1 | 0 | |
| Investigations | | | |
| Serum ferritin decreased | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anti factor IX antibody increased | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Contusion | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extradural Haematoma | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle injury | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral Ischaemia | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Haemorrhage intracranial subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Iron deficiency anaemia subjects affected / exposed | 2 / 83 (2.41%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Haemorrhoids subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine polyp subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Haemarthrosis | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemophilic arthropathy | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint Swelling | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess Jaw | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Peritonsillar abscess | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | CSL654 (PTPs) | CSL654 (PUPs) | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 69 / 83 (83.13%) | 11 / 12 (91.67%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 5 / 83 (6.02%) | 0 / 12 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 15 / 83 (18.07%) | 6 / 12 (50.00%) | |
| occurrences (all) | 24 | 9 | |
| Catheter site bruise | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Influenza like illness | | | |

| | | | |
|---|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 1 / 12 (8.33%) 3 | |
| Selective IgA immunodeficiency subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 6 / 83 (7.23%) 7 | 2 / 12 (16.67%) 2 | |
| Psychiatric disorders Irritability subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) | 7 / 83 (8.43%) 12 | 2 / 12 (16.67%) 6 | |
| Laceration subjects affected / exposed occurrences (all) | 6 / 83 (7.23%) 7 | 2 / 12 (16.67%) 2 | |
| Fall subjects affected / exposed occurrences (all) | 4 / 83 (4.82%) 4 | 4 / 12 (33.33%) 6 | |
| Head injury subjects affected / exposed occurrences (all) | 3 / 83 (3.61%) 4 | 3 / 12 (25.00%) 5 | |
| Mouth injury subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 2 / 12 (16.67%) 2 | |
| Arthropod bite subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 1 / 12 (8.33%) 3 | |

| | | | |
|---|---|---|--|
| Accident subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Skin abrasion subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Soft tissue injury subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Tongue injury subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Congenital, familial and genetic disorders Factor VII deficiency subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) Tongue biting subjects affected / exposed occurrences (all) | 11 / 83 (13.25%) 21 0 / 83 (0.00%) 0 | 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 | |
| Gastrointestinal disorders Dental caries subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) | 10 / 83 (12.05%) 12 6 / 83 (7.23%) 6 5 / 83 (6.02%) 6 4 / 83 (4.82%) 5 | 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 2 / 12 (16.67%) 3 | |

| | | | |
|---|------------------|-----------------|--|
| Teething | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 2 | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Gingival disorder | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 1 / 12 (8.33%) | |
| occurrences (all) | 3 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 2 / 12 (16.67%) | |
| occurrences (all) | 5 | 4 | |
| Dermatitis diaper | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 2 | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 2 | |
| Ingrowing nail | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Nail bed inflammation | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 25 / 83 (30.12%) | 0 / 12 (0.00%) | |
| occurrences (all) | 35 | 0 | |
| Pain in extremity | | | |

| | | | |
|-----------------------------------|------------------|-----------------|--|
| subjects affected / exposed | 8 / 83 (9.64%) | 0 / 12 (0.00%) | |
| occurrences (all) | 10 | 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 6 / 83 (7.23%) | 0 / 12 (0.00%) | |
| occurrences (all) | 8 | 0 | |
| Soft tissue swelling | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 5 | |
| Haemophilic arthropathy | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 1 / 12 (8.33%) | |
| occurrences (all) | 3 | 1 | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 15 / 83 (18.07%) | 3 / 12 (25.00%) | |
| occurrences (all) | 25 | 14 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 10 / 83 (12.05%) | 1 / 12 (8.33%) | |
| occurrences (all) | 10 | 1 | |
| Influenza | | | |
| subjects affected / exposed | 6 / 83 (7.23%) | 1 / 12 (8.33%) | |
| occurrences (all) | 6 | 2 | |
| Sinusitis | | | |
| subjects affected / exposed | 5 / 83 (6.02%) | 0 / 12 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Tonsillitis | | | |
| subjects affected / exposed | 5 / 83 (6.02%) | 0 / 12 (0.00%) | |
| occurrences (all) | 8 | 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 83 (4.82%) | 2 / 12 (16.67%) | |
| occurrences (all) | 8 | 6 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 83 (4.82%) | 3 / 12 (25.00%) | |
| occurrences (all) | 6 | 7 | |

| | | |
|-----------------------------|----------------|-----------------|
| Ear infection | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 1 / 12 (8.33%) |
| occurrences (all) | 3 | 2 |
| Rhinitis | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 2 / 12 (16.67%) |
| occurrences (all) | 3 | 2 |
| Viral infection | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 2 |
| Pharyngitis streptococcal | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 3 |
| Hand-foot-and-mouth disease | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 2 |
| Otitis media | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 2 |
| Croup infectious | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 |
| Eye infection | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 |
| Eyelid boil | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 |
| Gastrointestinal infection | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 |
| Otitis media chronic | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 |
| Otitis media viral | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 |

| | | | |
|---------------------------------------|----------------|----------------|--|
| Paronychia | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Streptococcal infection | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 17 September 2013 | <ol style="list-style-type: none"> 1. Addition of a third group of subjects (Arm 3) to the study design. Arm 3 comprises subjects who have not previously completed a CSL-sponsored rIX-FP lead-in study and who are scheduled to have a major non-emergency surgery within 8 weeks from the start of the initial pharmacokinetic rIX-FP (100 IU/kg) evaluation period. 2. Change in the sample size from 85 to 95. 3. Clarification that the exploratory objective relating to quality of life is limited to subjects from the CSL654_3002 lead-in study. 4. Minor corrections and clarifications, including word modifications and administrative changes. |
| 03 June 2014 | <p>- Per agreement with The Paediatric Committee (PDCO) /European Medicines Agency, study in previously untreated patients (PUPs) is added into this study.</p> <ol style="list-style-type: none"> 1. To add PUPs with severe hemophilia B (FIX activity $\leq 2\%$) who have never been treated with FIX clotting factor products (except previous exposure to blood components) as study Arm 4. 2. Change in the sample size from 95 to 115, to include at least 20 PUPs. 3. Independent Data Monitoring Committee is being utilized to provide an independent evaluation of the study. |
| 14 October 2015 | <p>Addition of substudy to assess the pharmacokinetics and safety following subcutaneous administration of rIX-FP in hemophilia B subjects. This substudy will comprise subjects who are currently enrolled in the main study protocol CSL654_3003.</p> |
| 02 December 2016 | <ol style="list-style-type: none"> 1. Main study: Addition of the ABR for total treated bleeding episodes to the comparisons between prophylaxis regimens for subjects from Study CSL654_3001. Addition of multiple testing procedure to control the overall Type I error rate for ABR and spontaneous annual bleeding rate (AsBR) comparisons between prophylaxis regimens. 2. Main study: Update of overall study duration and study participation of Arms 1, 2 and 3 subjects to approximately 5 years, and addition of visits beyond 36 months. 3. Main study and subcutaneous (SC) substudy: Addition of final analyses of the a) previously treated patient (PTP) data when all PTPs have completed the study and b) SC substudy data when all subjects have completed the SC substudy. 4. Main study: Minor corrections and clarifications, including word modifications and administrative changes throughout the document. 5. SC substudy: Change in SC dosing in Cohort 3 from single to repeated SC dosing (including home treatment). 6. SC substudy: Addition of optional Cohort 4 for repeated SC dosing that will be opened if additional data are needed to inform further clinical development. 7. SC substudy: Addition of details regarding local tolerability assessments. 8. SC substudy: Addition of SC substudy information to the main study protocol where relevant (eg, objectives and endpoints). |
| 03 February 2020 | <ol style="list-style-type: none"> 1. Adjustment of number of PUPs from "at least 20" to "at least 13" to reflect PDCO opinion to allow early termination of PUP enrolment. 2. As study has been completed for PTPs, adjustment of number of PTPs in final PTP analysis (N=83). 3. Adjustment of overall number of subjects to reflect 1 and 2. 4. The frequency of the CSL Safety Management Team meetings has been updated from approximately every 6 months to approximately every 3 months, to reflect an internal process change. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported