



Clinical trial results:

A Phase III Open Label, Multicenter, Extension Study to Assess the Safety and Efficacy of Recombinant Coagulation Factor VIII (rVIII-SingleChain, CSL627) in Subjects with Severe Hemophilia A

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2013-003262-13 |
| Trial protocol | IT GB DE CZ HU ES NL AT PL PT IE |
| Global end of trial date | 19 January 2021 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 22 July 2021 |
| First version publication date | 22 July 2021 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | CSL627_3001 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02172950 |
| 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 | Clin.Trial Registration Coordinator, CSL Behring GmbH, 34 91708 86 00, clinicaltrials@cslbehring.com |
| Scientific contact | Clin.Trial Registration Coordinator, CSL Behring GmbH, 34 91708 86 00, clinicaltrials@cslbehring.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 12 February 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 January 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the safety of long term use of rVIII-SingleChain

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 13 October 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: 11 |
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | Georgia: 5 |
| Country: Number of subjects enrolled | Japan: 7 |
| Country: Number of subjects enrolled | Lebanon: 12 |
| Country: Number of subjects enrolled | Malaysia: 15 |
| Country: Number of subjects enrolled | Philippines: 18 |
| Country: Number of subjects enrolled | South Africa: 22 |
| Country: Number of subjects enrolled | Switzerland: 1 |
| Country: Number of subjects enrolled | Thailand: 10 |
| Country: Number of subjects enrolled | Ukraine: 17 |
| Country: Number of subjects enrolled | United States: 22 |
| Country: Number of subjects enrolled | Netherlands: 12 |
| Country: Number of subjects enrolled | Poland: 36 |
| Country: Number of subjects enrolled | Portugal: 5 |
| Country: Number of subjects enrolled | Romania: 4 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Austria: 6 |
| Country: Number of subjects enrolled | Czechia: 2 |
| Country: Number of subjects enrolled | France: 7 |

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | Hungary: 2 |
| Country: Number of subjects enrolled | Ireland: 5 |
| Country: Number of subjects enrolled | Italy: 9 |
| Worldwide total number of subjects | 246 |
| EEA total number of subjects | 104 |

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) | 17 |
| Children (2-11 years) | 74 |
| Adolescents (12-17 years) | 23 |
| Adults (18-64 years) | 131 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This multicenter, non-randomized, open-label, multiple-arm phase 3 extension study continued to investigate the safety and efficacy of rVIII-SingleChain in PTPs and PUPs with severe hemophilia A (FVIII activity levels < 1%).

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 | CSL627: Previously treated patients (PTPs) |

Arm description: -

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | rVIII-SingleChain |
| Investigational medicinal product code | CSL627 |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

The rVIII-SingleChain drug product is recombinant factor VIII (rFVIII) and was administered by IV injection. The rVIII-SingleChain dose and dosing schedule were determined at the investigator's discretion.

| | |
|------------------|--|
| Arm title | CSL627: Previously untreated patients (PUPs) |
|------------------|--|

Arm description: -

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | rVIII-SingleChain |
| Investigational medicinal product code | CSL627 |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

The rVIII-SingleChain drug product is recombinant factor VIII (rFVIII) and was administered by IV injection. The rVIII-SingleChain dose and dosing schedule were determined at the investigator's discretion.

| Number of subjects in period 1 | CSL627: Previously treated patients (PTPs) | CSL627: Previously untreated patients (PUPs) |
|---------------------------------------|--|--|
| Started | 222 | 24 |
| Completed | 197 | 19 |
| Not completed | 25 | 5 |
| Adverse event, serious fatal | 1 | - |
| Physician decision | 3 | 3 |
| Consent withdrawn by subject | 10 | - |
| Patient relocated overseas | 1 | - |
| Adverse event, non-fatal | 4 | 1 |
| Patient went to other country | 1 | - |
| Patient locating overseas | - | 1 |
| Patient moving | 1 | - |
| Patient traveling | 1 | - |
| Expected protocol violation | 1 | - |
| Lost to follow-up | 1 | - |
| Lack of efficacy | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|--|
| Reporting group title | CSL627: Previously treated patients (PTPs) |
| Reporting group description: - | |
| Reporting group title | CSL627: Previously untreated patients (PUPs) |
| Reporting group description: - | |

| Reporting group values | CSL627: Previously treated patients (PTPs) | CSL627: Previously untreated patients (PUPs) | Total |
|--|--|--|-------|
| Number of subjects | 222 | 24 | 246 |
| 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 | 17 | 17 |
| Children (2-11 years) | 67 | 7 | 74 |
| Adolescents (12-17 years) | 23 | 0 | 23 |
| Adults (18-64 years) | 131 | 0 | 131 |
| From 65-84 years | 1 | 0 | 1 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 22.5 | 1.4 | |
| standard deviation | ± 14.55 | ± 1.18 | - |
| Gender categorical Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 222 | 24 | 246 |

End points

End points reporting groups

| | |
|--------------------------------|--|
| Reporting group title | CSL627: Previously treated patients (PTPs) |
| Reporting group description: - | |
| Reporting group title | CSL627: Previously untreated patients (PUPs) |
| Reporting group description: - | |

Primary: Incidence of inhibitor formation to FVIII in PTPs with 100 Exposure Days (EDs) to CSL627

| | |
|------------------------|--|
| End point title | Incidence of inhibitor formation to FVIII in PTPs with 100 Exposure Days (EDs) to CSL627 ^{[1][2]} |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Up to 5 years | |

Notes:

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

Justification: Descriptive statistics were used for this endpoint.

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

Justification: This endpoint is only for PTPs.

| | | | | |
|-----------------------------|---|--|--|--|
| End point values | CSL627: Previously treated patients (PTPs) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 198 | | | |
| Units: Percent | | | | |
| number (not applicable) | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of PUPs with high-titer inhibitor formation to FVIII with at least 50 EDs to CSL627

| | |
|--|--|
| End point title | Number of PUPs with high-titer inhibitor formation to FVIII with at least 50 EDs to CSL627 ^{[3][4]} |
| End point description: | |
| High-titer inhibitor is defined as an inhibitor titer of ≥ 5 Bethesda units/mL. | |
| End point type | Primary |
| End point timeframe: | |
| Up to 5 years | |

Notes:

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

Justification: Descriptive statistics were used for this endpoint.

[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: This endpoint is only for PUPs.

| End point values | CSL627: Previously untreated patients (PUPs) | | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: Number | | | | |
| number (not applicable) | 5 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percent treatment success for major bleeding episodes in PUPs

| | |
|-----------------|--|
| End point title | Percent treatment success for major bleeding episodes in |
|-----------------|--|

End point description:

Major bleeding episodes treated successfully where treatment success for a bleeding episode is defined as a rating of "excellent" or "good" on the investigator's clinical assessment of hemostatic efficacy 4-point scale "excellent, good, moderate or poor/no response". Major bleeding episodes are defined as bleeding episodes for which a subject is required to seek treatment at the hemophilia center or that threatens the subject's life or loss of limb.

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

End point timeframe:

Up to 5 years

Notes:

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

Justification: Descriptive statistics were used for this endpoint.

[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: This endpoint is only for PUPs.

| End point values | CSL627: Previously untreated patients (PUPs) | | | |
|--|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 23 | | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Number of major bleeds | 1 | | | |
| Percent of major bleeds successfully treated | 100 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Annualized spontaneous bleeding rate in PUPs

| | |
|-----------------|--|
| End point title | Annualized spontaneous bleeding rate in PUPs ^{[7][8]} |
|-----------------|--|

End point description:

The annualized spontaneous bleeding rate for PUPs taking prophylaxis and on-demand treatment regimens.

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

End point timeframe:

Up to 5 years

Notes:

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

Justification: Descriptive statistics were used for this endpoint.

[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: This endpoint is only for PUPs.

| End point values | CSL627: Previously untreated patients (PUPs) | | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 23 | | | |
| Units: Spontaneous bleeds | | | | |
| arithmetic mean (standard deviation) | | | | |
| On-demand (n=12) | 1.90 (± 2.252) | | | |
| Prophylaxis (n=23) | 4.04 (± 6.374) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment success in PTPs

| | |
|-----------------|--|
| End point title | Treatment success in PTPs ^[9] |
|-----------------|--|

End point description:

Percentage of bleeding episodes treated successfully where treatment success for a bleeding episode is defined as a rating of "excellent" or "good" on the investigator's clinical assessment of hemostatic efficacy 4-point scale "excellent, good, moderate or poor/no response".

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

End point timeframe:

Up to 5 years

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: The endpoint is only for PTPs

| End point values | CSL627: Previously treated patients (PTPs) | | | |
|---|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 222 ^[10] | | | |
| Units: percent | | | | |
| number (confidence interval 95%) | | | | |
| Percent of bleeding events successfully treated | 87.1 (75.3 to 93.7) | | | |

Notes:

[10] - Number of treated bleeding events = 2413.

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized bleeding rate in PTPs and PUPs

| | |
|------------------------|---|
| End point title | Annualized bleeding rate in PTPs and PUPs |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 5 years | |

| End point values | CSL627: Previously treated patients (PTPs) | CSL627: Previously untreated patients (PUPs) | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222 ^[11] | 23 ^[12] | | |
| Units: Number of bleeds per year | | | | |
| number (confidence interval 95%) | | | | |
| On-demand | 28.6 (26.8 to 30.6) | 3.4 (2.4 to 4.7) | | |
| Prophylaxis | 2.8 (2.7 to 3.0) | 5.7 (5.1 to 6.4) | | |

Notes:

[11] - On-demand (n=11); Prophylaxis (n=209)

[12] - On-demand (n=10); Prophylaxis (n=23)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of bleeding episodes requiring 1, 2, 3 or > 3 infusions of CSL627 to achieve hemostasis

| | |
|------------------------|--|
| End point title | Percentage of bleeding episodes requiring 1, 2, 3 or > 3 infusions of CSL627 to achieve hemostasis |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 5 years | |

| End point values | CSL627: Previously treated patients (PTPs) | CSL627: Previously untreated patients (PUPs) | | |
|-----------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222 | 24 | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Number of treated bleeds | 2413 | 315 | | |
| 1 infusion | 71.5 | 77.5 | | |
| 2 infusions | 14.8 | 11.4 | | |
| 3 infusions | 6.9 | 5.4 | | |
| >3 infusions | 6.3 | 3.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Hemostatic efficacy of CSL627 for PTPs and PUPs who undergo surgery

| | |
|--|---|
| End point title | Hemostatic efficacy of CSL627 for PTPs and PUPs who undergo surgery |
| End point description: | |
| The investigator will rate the efficacy of the rVIII-SingleChain treatment during surgery based on a hemostatic efficacy four point rating scale of "excellent, good, moderate or poor/no response". | |
| End point type | Secondary |
| End point timeframe: | |
| From the start of surgery through the post-operative recovery (generally up to 14 days after surgery) | |

| End point values | CSL627: Previously treated patients (PTPs) | CSL627: Previously untreated patients (PUPs) | | |
|-----------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 3 | | |
| Units: Number | | | | |
| number (not applicable) | | | | |
| Number of surgeries | 32 | 3 | | |
| Excellent | 28 | 3 | | |

| | | | | |
|------------------|---|---|--|--|
| Good | 4 | 0 | | |
| Moderate | 0 | 0 | | |
| Poor/No response | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of inhibitor formation to FVIII after 10 EDs and after 50 EDs in PTPs

| | |
|-----------------|---|
| End point title | Incidence of inhibitor formation to FVIII after 10 EDs and after 50 EDs in PTPs ^[13] |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 5 years

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: The endpoint is only for PTPs

| End point values | CSL627: Previously treated patients (PTPs) | | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 198 | | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| after 10 EDs | 0 | | | |
| after 50 EDs | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of PTPs and PUPs developing antibodies against CSL627

| | |
|-----------------|--|
| End point title | Percentage of PTPs and PUPs developing antibodies against CSL627 |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 5 years

| End point values | CSL627: Previously treated patients (PTPs) | CSL627: Previously untreated patients (PUPs) | | |
|-----------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222 | 24 | | |
| Units: percent | | | | |
| number (not applicable) | 15.3 | 70.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of PTPs and PUPs developing antibodies to Chinese hamster ovary (CHO) proteins

| | |
|-----------------|---|
| End point title | Percentage of PTPs and PUPs developing antibodies to Chinese hamster ovary (CHO) proteins |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 5 years

| End point values | CSL627: Previously treated patients (PTPs) | CSL627: Previously untreated patients (PUPs) | | |
|-----------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222 | 24 | | |
| Units: percent | | | | |
| number (not applicable) | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of PUPs with high-titer inhibitor formation to FVIII in PUPs after 10 EDs with CSL627

| | |
|-----------------|--|
| End point title | Number of PUPs with high-titer inhibitor formation to FVIII in PUPs after 10 EDs with CSL627 ^[14] |
|-----------------|--|

End point description:

High-titer inhibitor is defined as an inhibitor titer of ≥ 5 Bethesda units/mL.

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

End point timeframe:

Up to 5 years

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: The endpoint is only for PUPs

| End point values | CSL627: Previously untreated patients (PUPs) | | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: Number | | | | |
| number (not applicable) | 4 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of PUPs with low-titer inhibitor formation to FVIII after 10 EDs and after 50 EDs with CSL627

| | |
|-----------------|--|
| End point title | Number of PUPs with low-titer inhibitor formation to FVIII after 10 EDs and after 50 EDs with CSL627 ^[15] |
|-----------------|--|

End point description:

Low-titer inhibitor is defined as an inhibitor titer of less than 5 Bethesda units/mL.

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

End point timeframe:

Up to 5 years

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: The endpoint is only for PUPs

| End point values | CSL627: Previously untreated patients (PUPs) | | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: Number | | | | |
| number (not applicable) | | | | |
| after 10 EDs | 4 | | | |
| after 50 EDs | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of total inhibitor formation to FVIII in PUPs

| | |
|-----------------|---|
| End point title | Incidence of total inhibitor formation to FVIII in PUPs ^[16] |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 5 years

Notes:

[16] - 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: The endpoint is only for PUPs

| | | | | |
|-----------------------------|---|--|--|--|
| End point values | CSL627: Previously untreated patients (PUPs) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: percent | | | | |
| number (not applicable) | 50.0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent treatment success for non-major bleeding episodes in PUPs

| | |
|-----------------|---|
| End point title | Percent treatment success for non-major bleeding episodes in PUPs ^[17] |
|-----------------|---|

End point description:

Percentage of bleeding episodes treated successfully where treatment success for a bleeding episode is defined as a rating of "excellent" or "good" on the investigator's clinical assessment of hemostatic efficacy 4-point scale "excellent, good, moderate or poor/no response". Non-major bleeding episodes are those not requiring treatment at the hemophilia center or not threatening subject's life or loss of limb.

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

End point timeframe:

Up to 5 years

Notes:

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

Justification: The endpoint is only for PUPs

| End point values | CSL627: Previously untreated patients (PUPs) | | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 ^[18] | | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 92.1 (87.0 to 95.3) | | | |

Notes:

[18] - Number of treated bleeding events = 315

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of on-demand infusions of CSL627

| | |
|------------------------|--|
| End point title | Mean number of on-demand infusions of CSL627 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 5 years | |

| End point values | CSL627: Previously treated patients (PTPs) | CSL627: Previously untreated patients (PUPs) | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 12 | | |
| Units: number of infusions | | | | |
| arithmetic mean (standard deviation) | | | | |
| per subject per month | 6.26 (± 4.778) | 1.23 (± 1.296) | | |
| per subject per year | 75.18 (± 57.335) | 14.75 (± 15.547) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean on-demand dose administered of CSL627

| | |
|------------------------|--|
| End point title | Mean on-demand dose administered of CSL627 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 5 years | |

| End point values | CSL627: Previously treated patients (PTPs) | CSL627: Previously untreated patients (PUPs) | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 11 | 12 | | |
| Units: IU/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| per subject per month | 210.39 (\pm 188.106) | 41.93 (\pm 44.643) | | |
| per subject per year | 2524.69 (\pm 2257.278) | 503.16 (\pm 535.712) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean prophylaxis dose administered of CSL627

| | |
|------------------------|--|
| End point title | Mean prophylaxis dose administered of CSL627 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 5 years | |

| End point values | CSL627: Previously treated patients (PTPs) | CSL627: Previously untreated patients (PUPs) | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 211 | 23 | | |
| Units: IU/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| per subject per month | 380.95 (\pm 130.079) | 389.30 (\pm 243.191) | | |
| per subject per year | 4571.35 (\pm 1560.944) | 4671.54 (\pm 2918.288) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean total amount of CSL627 administered during surgery period in

PTPs

| | |
|-----------------|--|
| End point title | Mean total amount of CSL627 administered during surgery period in PTPs ^[19] |
|-----------------|--|

End point description:

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

End point timeframe:

Day of surgery up to 336 hours post-surgery

Notes:

[19] - 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: The endpoint is only for PTPs

| | | | | |
|--------------------------------------|--|--|--|--|
| End point values | CSL627: Previously treated patients (PTPs) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: IU | | | | |
| arithmetic mean (standard deviation) | 51663.0 (± 62033.25) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of PUPs with clinically significant abnormal vital signs values after first infusion of CSL627

| | |
|-----------------|---|
| End point title | Percentage of PUPs with clinically significant abnormal vital signs values after first infusion of CSL627 ^[20] |
|-----------------|---|

End point description:

Vital signs assessments include heart rate, blood pressure, and body temperature. Clinical significance of an abnormality will be assessed by the investigator.

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

End point timeframe:

Up to 6 hours after first infusion

Notes:

[20] - 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: The endpoint is only for PUPs

| | | | | |
|-----------------------------|--|--|--|--|
| End point values | CSL627: Previously untreated patients (PUPs) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: percent | | | | |
| number (not applicable) | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of PUPs with treatment-emergent clinically significant abnormal vital signs values

| | |
|-----------------|---|
| End point title | Percentage of PUPs with treatment-emergent clinically significant abnormal vital signs values ^[21] |
|-----------------|---|

End point description:

Vital signs assessments include heart rate, blood pressure, and body temperature. Clinical significance of an abnormality will be assessed by the investigator.

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

End point timeframe:

Up to 5 years

Notes:

[21] - 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: The endpoint is only for PUPs

| End point values | CSL627: Previously untreated patients (PUPs) | | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: percent | | | | |
| number (not applicable) | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total amount of CSL627 administered during surgery period in PUPs

| | |
|-----------------|---|
| End point title | Total amount of CSL627 administered during surgery period in PUPs ^[22] |
|-----------------|---|

End point description:

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

End point timeframe:

Day of surgery up to 336 hours post-surgery

Notes:

[22] - 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: The endpoint is only for PUPs

| | | | | |
|-----------------------------|---|--|--|--|
| End point values | CSL627: Previously untreated patients (PUPs) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: IU | | | | |
| number (not applicable) | | | | |
| Subject 1 | 15693 | | | |
| Subject 2 | 5631 | | | |
| Subject 3 | 7330 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 5 years

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | CSL627: Previously treated patients (PTPs) |
|-----------------------|--|

Reporting group description: -

| | |
|-----------------------|--|
| Reporting group title | CSL627: Previously untreated patients (PUPs) |
|-----------------------|--|

Reporting group description: -

| Serious adverse events | CSL627: Previously treated patients (PTPs) | CSL627: Previously untreated patients (PUPs) | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 23 / 222 (10.36%) | 14 / 24 (58.33%) | |
| number of deaths (all causes) | 1 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Anti factor VIII antibody positive | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 6 / 24 (25.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inhibiting antibodies positive | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 5 / 24 (20.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Road traffic accident | | | |
| subjects affected / exposed | 2 / 222 (0.90%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal injury | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periprosthetic fracture | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin laceration | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 2 / 24 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound haemorrhage | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 1 / 24 (4.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Shock | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vasospasm | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 1 / 24 (4.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |

| | | | |
|---|-----------------|----------------|--|
| Generalised tonic-clonic seizure subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lennox-Gastaut syndrome subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest pain subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Factor VIII inhibition subjects affected / exposed | 0 / 222 (0.00%) | 1 / 24 (4.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Blindness transient subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Social circumstances | | | |
| Pregnancy of partner subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis erosive | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 1 / 24 (4.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Nephritis | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (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 | | | |
| Haemophilic arthropathy | | | |
| subjects affected / exposed | 3 / 222 (1.35%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Muscle haemorrhage | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendinous contracture | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 1 / 24 (4.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 2 / 222 (0.90%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (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 | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 1 / 24 (4.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acinetobacter infection | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 1 / 24 (4.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 0 / 24 (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 | CSL627: Previously treated patients (PTPs) | CSL627: Previously untreated patients (PUPs) | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 130 / 222 (58.56%) | 23 / 24 (95.83%) | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 2 / 222 (0.90%) | 2 / 24 (8.33%) | |
| occurrences (all) | 2 | 3 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 14 / 222 (6.31%) | 15 / 24 (62.50%) | |
| occurrences (all) | 18 | 44 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 2 / 24 (8.33%) | |
| occurrences (all) | 0 | 4 | |
| Immune system disorders | | | |

| | | | |
|---|--|---|--|
| Allergy to arthropod sting subjects affected / exposed occurrences (all) | 0 / 222 (0.00%) 0 | 2 / 24 (8.33%) 5 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all) Bronchospasm subjects affected / exposed occurrences (all) | 13 / 222 (5.86%) 19 3 / 222 (1.35%) 3 0 / 222 (0.00%) 0 | 6 / 24 (25.00%) 13 2 / 24 (8.33%) 3 2 / 24 (8.33%) 4 | |
| Investigations Coronavirus test positive subjects affected / exposed occurrences (all) Inhibiting antibodies positive subjects affected / exposed occurrences (all) | 0 / 222 (0.00%) 0 0 / 222 (0.00%) 0 | 2 / 24 (8.33%) 2 2 / 24 (8.33%) 2 | |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Head injury subjects affected / exposed occurrences (all) Contusion subjects affected / exposed occurrences (all) | 11 / 222 (4.95%) 12 11 / 222 (4.95%) 11 11 / 222 (4.95%) 13 | 3 / 24 (12.50%) 5 1 / 24 (4.17%) 3 0 / 24 (0.00%) 0 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 20 / 222 (9.01%) 29 | 0 / 24 (0.00%) 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|--|--|---|--|
| Iron deficiency anaemia subjects affected / exposed occurrences (all) | 2 / 222 (0.90%) 3 | 3 / 24 (12.50%) 3 | |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 4 / 222 (1.80%) 4 | 2 / 24 (8.33%) 2 | |
| Gastrointestinal disorders Dental caries subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) | 11 / 222 (4.95%) 11 5 / 222 (2.25%) 5 4 / 222 (1.80%) 5 | 0 / 24 (0.00%) 0 5 / 24 (20.83%) 6 3 / 24 (12.50%) 8 | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all) | 6 / 222 (2.70%) 6 1 / 222 (0.45%) 1 | 3 / 24 (12.50%) 3 3 / 24 (12.50%) 3 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Joint swelling subjects affected / exposed occurrences (all) Haemarthrosis subjects affected / exposed occurrences (all) | 20 / 222 (9.01%) 28 4 / 222 (1.80%) 5 2 / 222 (0.90%) 3 | 1 / 24 (4.17%) 1 2 / 24 (8.33%) 2 2 / 24 (8.33%) 2 | |
| Infections and infestations | | | |

| | | |
|-----------------------------------|-------------------|-----------------|
| Nasopharyngitis | | |
| subjects affected / exposed | 40 / 222 (18.02%) | 9 / 24 (37.50%) |
| occurrences (all) | 73 | 15 |
| Upper respiratory tract infection | | |
| subjects affected / exposed | 25 / 222 (11.26%) | 7 / 24 (29.17%) |
| occurrences (all) | 37 | 18 |
| Influenza | | |
| subjects affected / exposed | 14 / 222 (6.31%) | 4 / 24 (16.67%) |
| occurrences (all) | 16 | 6 |
| Tonsillitis | | |
| subjects affected / exposed | 13 / 222 (5.86%) | 5 / 24 (20.83%) |
| occurrences (all) | 17 | 5 |
| Rhinitis | | |
| subjects affected / exposed | 7 / 222 (3.15%) | 6 / 24 (25.00%) |
| occurrences (all) | 7 | 10 |
| Ear infection | | |
| subjects affected / exposed | 5 / 222 (2.25%) | 5 / 24 (20.83%) |
| occurrences (all) | 8 | 9 |
| Conjunctivitis | | |
| subjects affected / exposed | 6 / 222 (2.70%) | 3 / 24 (12.50%) |
| occurrences (all) | 6 | 4 |
| Bronchitis | | |
| subjects affected / exposed | 5 / 222 (2.25%) | 3 / 24 (12.50%) |
| occurrences (all) | 7 | 3 |
| Varicella | | |
| subjects affected / exposed | 2 / 222 (0.90%) | 6 / 24 (25.00%) |
| occurrences (all) | 2 | 7 |
| Otitis media | | |
| subjects affected / exposed | 3 / 222 (1.35%) | 4 / 24 (16.67%) |
| occurrences (all) | 5 | 5 |
| Viral rhinitis | | |
| subjects affected / exposed | 1 / 222 (0.45%) | 2 / 24 (8.33%) |
| occurrences (all) | 1 | 2 |
| Scarlet fever | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 2 / 24 (8.33%) |
| occurrences (all) | 0 | 2 |

| | | | |
|-----------------------------|-----------------|----------------|--|
| Tinea capitis | | | |
| subjects affected / exposed | 0 / 222 (0.00%) | 2 / 24 (8.33%) | |
| occurrences (all) | 2 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 28 March 2014 | <ul style="list-style-type: none">-Update of section on previous clinical study experience to reflect the start of pediatric Study 3002.-Removal of the overall caregiver / subject assessment of hemostatic efficacy for subjects ≥ 12 to ≤ 65 years of age to provide consistent means of evaluation for pain and symptom relief for all subjects in the study.-Clarification for symptom and pain relief assessments. |
| 05 June 2015 | <ul style="list-style-type: none">-Addition of Arm 3 (PTPs who were not currently participating in a rVIII-SingleChain study).-Addition of confirmed inhibitors as SAEs. |
| 27 January 2017 | <ul style="list-style-type: none">-Addition of final blood sample collection for inhibitor assessment at the EOS Visit for Arm 1 PTPs.-Addition of exploratory objective and 2 associated exploratory endpoints for inhibitor incidence in PTPs.-Extension of the individual subject participation / estimated time to reach the required number of EDs.-Change in number of study sites.-Removal of subject's assessment of bleeding / pain relief. |
| 01 October 2019 | <ul style="list-style-type: none">-Change in number of expected enrolled subjects into Arm 2 PUPs from 50 to 24.-Removal of "at least 50" with respect to number of enrolled subjects.-Change in the inhibitor treatment period from 18 to 24 months.-Clarification for reporting inhibitor relapse SAE.-Clarification in the definition of inhibitor diagnosis.-Change in maximum duration of individual subject participation in the ITI substudy from 24 to 30 months. |
| 26 May 2020 | <ul style="list-style-type: none">-Change in the number of EDs from 150 to 75 EDs that PUPs in Arm 2 needed to complete the study. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported