



## Clinical trial results:

### A Phase III Open-label Pharmacokinetic, Efficacy and Safety Study of rVIII-SingleChain in a Pediatric Population with Severe Hemophilia A Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2012-001336-65                |
| Trial protocol           | HU DE ES NL IT PT PL AT IE FR |
| Global end of trial date | 24 August 2015                |

#### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 06 April 2017   |
| First version publication date | 09 September 2016   |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set</li><li>Minor clarifications made</li></ul> |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | CSL627_3002 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02093897 |
| 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,<br>clinicaltrials@cslbehring.com |
| Scientific contact           | Clin.Trial Registration Coordinator, CSL Behring GmbH,<br>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-001215-PIP01-11 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No                  |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No                  |

Notes:

## Results analysis stage

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 21 September 2015 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 24 August 2015    |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of recombinant single-chain FVIII (rVIII-SingleChain) in the treatment of major and minor bleeding episodes based on the investigator's 4-point assessment scale.

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, standard operating procedures for clinical research and development at CSL Behring and any other relevant procedures and applicable international and national regulatory requirements. The study protocol and all amendments were approved by the Independent Ethics Committee / Institutional Review Board of the participating centers. Before undergoing Screening procedures for possible enrollment into the study, the subjects' legally acceptable representative was informed, in an understandable form, about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's legally acceptable representative written informed consent to participate in the study. The investigator could cease study treatment and withdraw the subject, or the subject could withdraw himself from participation in the study at any time. If a subject was withdrawn from the study or further participation was declined, the subject would continue to have access to medical care and would be treated according to routine medical practice, but would no longer receive the investigational medicinal product.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 26 March 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: 3     |
| Country: Number of subjects enrolled | Georgia: 5       |
| Country: Number of subjects enrolled | Lebanon: 6       |
| Country: Number of subjects enrolled | Malaysia: 4      |
| Country: Number of subjects enrolled | Philippines: 8   |
| Country: Number of subjects enrolled | Romania: 1       |
| Country: Number of subjects enrolled | Switzerland: 1   |
| Country: Number of subjects enrolled | Thailand: 10     |
| Country: Number of subjects enrolled | Turkey: 8        |
| Country: Number of subjects enrolled | Ukraine: 6       |
| Country: Number of subjects enrolled | United States: 4 |
| Country: Number of subjects enrolled | Netherlands: 6   |
| Country: Number of subjects enrolled | Poland: 2        |

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Portugal: 2 |
| Country: Number of subjects enrolled | Spain: 2    |
| Country: Number of subjects enrolled | Austria: 3  |
| Country: Number of subjects enrolled | France: 7   |
| Country: Number of subjects enrolled | Germany: 5  |
| Country: Number of subjects enrolled | Italy: 1    |
| Worldwide total number of subjects   | 84          |
| EEA total number of subjects         | 29          |

Notes:

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### 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)  | 2  |
| Children (2-11 years)                     | 82 |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

This multicenter, multinational study enrolled subjects at 37 participating study centers in Australia, Europe, Georgia, Lebanon, Malaysia, Philippines, Switzerland, Thailand, Turkey, Ukraine, and the United States.

### Pre-assignment

Screening details:

Screening took place 4 to 28 days prior to first dose of study product (rVIII-SingleChain). A total of 88 subjects were screened, 4 of these did not fulfill all eligibility criteria and were therefore screening failures.

### Period 1

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

### Arms

|           |                   |
|-----------|-------------------|
| Arm title | rVIII-SingleChain |
|-----------|-------------------|

Arm description:

Subjects were assigned to either an on-demand or prophylaxis regimen and received rVIII-SingleChain as an intravenous (IV) infusion. Subjects assigned to a prophylaxis regimen were treated with 15 to 50 IU/kg of rVIII-SingleChain every second day or 2 to 3 times per week, or at the investigator's discretion, based on available PK data, the FVIII treatment regimen used before enrollment and/or the subject's bleeding phenotype. The dose for on-demand treatment of a bleeding episode was based on the recommendations of the World Federation of Hemophilia (WFH), with a minimum dose of 15 IU/kg. All subjects were to be treated for a minimum of 50 EDs. For the PK evaluation, the subjects received a single IV dose of 50 IU/kg of rVIII-SingleChain on Day 1 at the start of the PK evaluation period. A total of 5313 CSL627 infusions were administered to 84 subjects during the study. As planned, groups were closed and subjects discontinued when 25 subjects reached 50 EDs per group.

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

Dosage and administration details:

Subjects were assigned to either an on-demand or prophylaxis regimen and received rVIII-SingleChain as an intravenous (IV) infusion. Subjects assigned to a prophylaxis regimen were treated with 15 to 50 IU/kg of rVIII-SingleChain every second day or 2 to 3 times per week, or at the investigator's discretion, based on available PK data, the FVIII treatment regimen used before enrollment and/or the subject's bleeding phenotype. The dose for on-demand treatment of a bleeding episode was based on the recommendations of the World Federation of Hemophilia (WFH), with a minimum dose of 15 IU/kg. All subjects were to be treated for a minimum of 50 EDs. For the PK evaluation, the subjects received a single IV dose of 50 IU/kg of rVIII-SingleChain on Day 1 at the start of the PK evaluation period.

| <b>Number of subjects in period 1</b>          | rVIII-SingleChain |
|--|-------------------|
| Started  | 84                |
| Completed                                      | 65                |
| Not completed                                  | 19                |
| Physician decision                             | 1                 |
| Adverse event, non-fatal                       | 1                 |
| Planned age group closure once numbers reached | 17                |

## Baseline characteristics

### Reporting groups

|                                |               |
|--------------------------------|---------------|
| Reporting group title          | Overall trial |
| Reporting group description: - |               |

| Reporting group values   | Overall trial | Total |  |
|--|---------------|-------|--|
| Number of subjects   | 84            | 84    |  |
| Age categorical  |               |       |  |
| Units: Subjects  |               |       |  |
| In utero   | 0             | 0     |  |
| Preterm newborn infants (gestational age < 37 wks)   | 0             | 0     |  |
| Newborns (0-27 days)   | 0             | 0     |  |
| Infants and toddlers (28 days-23 months)   | 2             | 2     |  |
| Children (2-11 years)  | 82            | 82    |  |
| Adolescents (12-17 years)  | 0             | 0     |  |
| Adults (18-64 years)   | 0             | 0     |  |
| From 65-84 years   | 0             | 0     |  |
| 85 years and over  | 0             | 0     |  |
| Age continuous   |               |       |  |
| Units: years   |               |       |  |
| arithmetic mean  | 6.6           |       |  |
| standard deviation   | ± 3.11        | -     |  |
| Gender categorical   |               |       |  |
| Units: Subjects  |               |       |  |
| Female   | 0             | 0     |  |
| Male   | 84            | 84    |  |
| Type of FVIII product used before enrollment   |               |       |  |
| Type of FVIII product used by the subjects within the 12 months before enrollment into the study. This could have been a plasma FVIII product or a recombinant FVIII product.                        |               |       |  |
| Units: Subjects  |               |       |  |
| Plasma product   | 33            | 33    |  |
| Recombinant Product  | 49            | 49    |  |
| Unknown  | 2             | 2     |  |
| Treatment modality of FVIII therapy before enrollment  |               |       |  |
| Treatment modality of FVIII therapy within the 12 months before enrollment, ie, routine prophylaxis or on-demand treatment. If a subject used both modalities, only the most recent one was counted. |               |       |  |
| Units: Subjects  |               |       |  |
| Prophylaxis  | 60            | 60    |  |
| On-Demand  | 24            | 24    |  |

## End points

### End points reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | rVIII-SingleChain |
|-----------------------|-------------------|

Reporting group description:

Subjects were assigned to either an on-demand or prophylaxis regimen and received rVIII-SingleChain as an intravenous (IV) infusion. Subjects assigned to a prophylaxis regimen were treated with 15 to 50 IU/kg of rVIII-SingleChain every second day or 2 to 3 times per week, or at the investigator's discretion, based on available PK data, the FVIII treatment regimen used before enrollment and/or the subject's bleeding phenotype. The dose for on-demand treatment of a bleeding episode was based on the recommendations of the World Federation of Hemophilia (WFH), with a minimum dose of 15 IU/kg. All subjects were to be treated for a minimum of 50 EDs. For the PK evaluation, the subjects received a single IV dose of 50 IU/kg of rVIII-SingleChain on Day 1 at the start of the PK evaluation period. A total of 5313 CSL627 infusions were administered to 84 subjects during the study. As planned, groups were closed and subjects discontinued when 25 subjects reached 50 EDs per group.

|                            |           |
|----------------------------|-----------|
| Subject analysis set title | On-demand |
|----------------------------|-----------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

The Efficacy Population consisted of all subjects who received at least 1 dose of rVIII-SingleChain as part of either a routine prophylaxis or on-demand regimen during the study. One subject was excluded from the efficacy population because of a pre-existing inhibitor to FVIII (confirmed by reexamination of a screening sample initially reported as negative due to laboratory error).

Subjects assigned to the on-demand treatment regimen treated themselves, or were treated by a caregiver/guardian, as needed for any bleeding episode and did not receive routine assigned infusions. Preventative and additional doses of rVIII-SingleChain were allowed; data from such doses are included in the analysis of 'Consumption of rVIII-SingleChain' end points. "Preventative dose" was defined as a dose taken before an activity or a minor procedure to prevent or minimize a bleeding episode, and "additional dose" was defined as a dose taken beyond the need to control hemostasis.

|                            |             |
|----------------------------|-------------|
| Subject analysis set title | Prophylaxis |
|----------------------------|-------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

The Efficacy Population consisted of all subjects who received at least 1 dose of rVIII-SingleChain as part of either a routine prophylaxis or on-demand regimen during the study (1 subject was excluded from the efficacy population as described previously). Subjects receiving routine prophylaxis treatment were initially treated with 15-50 IU/kg of rVIII-SingleChain every 2nd day or 2 to 3 times per week, or at the investigator's discretion, based upon available PK data, the FVIII treatment regimen used before enrollment and/or the subject's bleeding phenotype. The dose or dosing frequency may have been adjusted if necessary.

Preventative and additional doses of rVIII-SingleChain were allowed; data from such doses are included in the analysis of 'Consumption of rVIII-SingleChain' end points. "Preventative dose" was a dose taken before an activity or a minor procedure to prevent or minimize a bleeding episode and "additional dose" was a dose taken beyond the need to control hemostasis.

|                            |                     |
|----------------------------|---------------------|
| Subject analysis set title | Efficacy Population |
|----------------------------|---------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

The Efficacy Population consisted of all subjects who received at least 1 dose of rVIII-SingleChain as part of either a routine prophylaxis or on-demand regimen during the study. One subject was excluded from the efficacy population because of a pre-existing inhibitor to FVIII (confirmed by reexamination of a screening sample initially reported as negative due to laboratory error).

|                            |                            |
|----------------------------|----------------------------|
| Subject analysis set title | Pharmacokinetic Population |
|----------------------------|----------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

The PK Population comprised those subjects who participated in the PK assessment and received at least 1 dose of rVIII-SingleChain and for whom a sufficient number of analyzable PK samples were obtained to permit the evaluation of the PK profile of rVIII-SingleChain.

## Primary: Treatment success

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Treatment success <sup>[1]</sup> |
|-----------------|----------------------------------|

End point description:

Rate of treatment success where treatment success of a bleeding episode is defined as a rating of "excellent" or "good" based on the investigator's overall clinical assessment of hemostatic efficacy (using a 4-point scale of excellent, good, moderate or poor/no response) on the on-demand and prophylaxis regimens combined. The rate of success was based on the number of treated bleeding events; there were 347 treated bleeding events in the Efficacy Population.

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

End point timeframe:

Up to 1 year

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: Primary endpoint data were analysed descriptively and no statistical analyses were planned or conducted.

| End point values                             | Efficacy Population  |  |  |  |
|--|----------------------|--|--|--|
| Subject group type                           | Subject analysis set |  |  |  |
| Number of subjects analysed                  | 83                   |  |  |  |
| Units: Percentage of treated bleeding events |                      |  |  |  |
| number (confidence interval 95%)             | 96.3 (91.3 to 98.4)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Annualized bleeding rate

|                 |                          |
|-----------------|--------------------------|
| End point title | Annualized bleeding rate |
|-----------------|--------------------------|

End point description:

The annualized bleeding rate was defined as the number of bleeding episodes requiring treatment divided by the efficacy evaluation period in days, x 365.25, and is presented separately for the on-demand regimen and the prophylaxis regimens.

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

End point timeframe:

Up to 1 year

| End point values                          | On-demand              | Prophylaxis          |  |  |
|---|------------------------|----------------------|--|--|
| Subject group type                        | Subject analysis set   | Subject analysis set |  |  |
| Number of subjects analysed               | 3                      | 80                   |  |  |
| Units: Treated bleeding episodes per year |                        |                      |  |  |
| median (inter-quartile range (Q1-Q3))     | 78.56 (35.12 to 86.62) | 3.69 (0 to 7.2)      |  |  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of bleeding episodes requiring 1, 2, 3 or > 3 infusions of rVIII-SingleChain to achieve hemostasis

|                 |   |
|-----------------|---|
| End point title | Percentage of bleeding episodes requiring 1, 2, 3 or > 3 infusions of rVIII-SingleChain to achieve hemostasis |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 1 year

| End point values                           | Efficacy Population  |  |  |  |
|--|----------------------|--|--|--|
| Subject group type                         | Subject analysis set |  |  |  |
| Number of subjects analysed                | 83 <sup>[2]</sup>    |  |  |  |
| Units: Percentage (%) of bleeding episodes |                      |  |  |  |
| number (not applicable)                    |                      |  |  |  |
| Requiring 1 infusion                       | 85.9                 |  |  |  |
| Requiring 2 infusions                      | 9.8                  |  |  |  |
| Requiring 3 infusions                      | 2.3                  |  |  |  |
| Requiring > 3 infusions                    | 2                    |  |  |  |

Notes:

[2] - Number of treated bleeds = 347

## Statistical analyses

No statistical analyses for this end point

### Secondary: Consumption of rVIII-SingleChain - IU/kg per subject per month

|                 |  |
|-----------------|--|
| End point title | Consumption of rVIII-SingleChain - IU/kg per subject per month |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 1 year

| End point values                   | On-demand            | Prophylaxis          |  |  |
|------------------------------------|----------------------|----------------------|--|--|
| Subject group type                 | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed        | 3                    | 80                   |  |  |
| Units: IU/kg per subject per month |                      |                      |  |  |
| median (full range (min-max))      | 202 (126 to 231)     | 378 (153 to 1394)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Consumption of rVIII-SingleChain - IU/kg per subject per year

|                 |   |
|-----------------|---|
| End point title | Consumption of rVIII-SingleChain - IU/kg per subject per year |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 1 year

| End point values                  | On-demand            | Prophylaxis          |  |  |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type                | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed       | 3                    | 80                   |  |  |
| Units: IU/kg per subject per year |                      |                      |  |  |
| median (full range (min-max))     | 2429 (1508 to 2771)  | 4541 (1839 to 16727) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Consumption of rVIII-SingleChain - IU/kg per bleeding event

|                 |   |
|-----------------|---|
| End point title | Consumption of rVIII-SingleChain - IU/kg per bleeding event |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 1 year

| End point values              | On-demand            | Prophylaxis          |  |  |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type            | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed   | 3                    | 80                   |  |  |
| Units: IU/kg per event        |                      |                      |  |  |
| median (full range (min-max)) | 25.9 (21 to 78)      | 37 (16 to 282)       |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Consumption of rVIII-SingleChain (on-demand regimen) - number of infusions per subject per month

|                        |  |
|------------------------|--|
| End point title        | Consumption of rVIII-SingleChain (on-demand regimen) - number of infusions per subject per month |
| End point description: |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Up to 1 year           |  |

| End point values                                | On-demand            |  |  |  |
|---|----------------------|--|--|--|
| Subject group type                              | Subject analysis set |  |  |  |
| Number of subjects analysed                     | 3                    |  |  |  |
| Units: number of infusion per subject per month |                      |  |  |  |
| median (full range (min-max))                   | 7.58 (5.1 to 7.7)    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Consumption of rVIII-SingleChain (on-demand regimen) - number of infusions per subject per year

|                        |   |
|------------------------|---|
| End point title        | Consumption of rVIII-SingleChain (on-demand regimen) - number of infusions per subject per year |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Up to 1 year           |   |

|   |                      |  |  |  |
|---|----------------------|--|--|--|
| <b>End point values</b>                         | On-demand            |  |  |  |
| Subject group type                              | Subject analysis set |  |  |  |
| Number of subjects analysed                     | 3 <sup>[3]</sup>     |  |  |  |
| Units: number of infusions per subject per year |                      |  |  |  |
| median (full range (min-max))                   | 90.95 (60.9 to 92.3) |  |  |  |

Notes:

[3] - Subjects assigned to the on-demand treatment regimen.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Incremental recovery

|   |                      |
|---|----------------------|
| End point title   | Incremental recovery |
| End point description:<br>Incremental recovery expressed as (IU/dL)/(IU/kg) corrected for subject's predose plasma FVIII activity measured using the chromogenic substrate assay. |                      |
| End point type  | Secondary            |
| End point timeframe:<br>At 1 hour after the start of infusion   |                      |

|                                      |                            |  |  |  |
|--------------------------------------|----------------------------|--|--|--|
| <b>End point values</b>              | Pharmacokinetic Population |  |  |  |
| Subject group type                   | Subject analysis set       |  |  |  |
| Number of subjects analysed          | 39                         |  |  |  |
| Units: (IU/dL)/(IU/kg)               |                            |  |  |  |
| arithmetic mean (standard deviation) | 1.63 (± 0.329)             |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Half-life (t<sub>1/2</sub>) of rVIII-SingleChain

|   |  |
|---|--|
| End point title   | Half-life (t <sub>1/2</sub> ) of rVIII-SingleChain |
| End point description:<br>Half-life (t <sub>1/2</sub> ) of rVIII-SingleChain, baseline uncorrected; plasma FVIII activity measured using the chromogenic substrate assay. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Immediately before dosing, and at approximately 1, 5, 10, 24, and 48 hours after dosing.  |  |

| End point values                     | Pharmacokinetic Population |  |  |  |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type                   | Subject analysis set       |  |  |  |
| Number of subjects analysed          | 39                         |  |  |  |
| Units: hour                          |                            |  |  |  |
| arithmetic mean (standard deviation) | 10.3 ( $\pm$ 2.51)         |  |  |  |

### Statistical analyses

No statistical analyses for this end point

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

|  |  |
|--|--|
| End point title  | Area under the concentration curve (AUC) |
| End point description:<br>AUC to the last sample with quantifiable drug concentration (AUC <sub>0-t</sub> ), baseline uncorrected; plasma FVIII activity measured using the chromogenic substrate assay. |  |
| End point type   | Secondary                                |
| End point timeframe:<br>Immediately before dosing, and at approximately 1, 5, 10, 24, and 48 hours after dosing.   |  |

| End point values                     | Pharmacokinetic Population |  |  |  |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type                   | Subject analysis set       |  |  |  |
| Number of subjects analysed          | 39                         |  |  |  |
| Units: IU*h/dL                       |                            |  |  |  |
| arithmetic mean (standard deviation) | 1050 ( $\pm$ 286)          |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clearance (Cl) of rVIII-SingleChain

|  |                                     |
|--|-------------------------------------|
| End point title  | Clearance (Cl) of rVIII-SingleChain |
| End point description:<br>Clearance (Cl) of rVIII-SingleChain, baseline uncorrected; plasma FVIII activity measured using the chromogenic substrate assay. |                                     |
| End point type   | Secondary                           |
| End point timeframe:<br>Immediately before dosing, and at approximately 1, 5, 10, 24, and 48 hours after dosing.   |                                     |

| End point values                     | Pharmacokinetic Population |  |  |  |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type                   | Subject analysis set       |  |  |  |
| Number of subjects analysed          | 39                         |  |  |  |
| Units: mL/h/kg                       |                            |  |  |  |
| arithmetic mean (standard deviation) | 4.86 ( $\pm$ 1.43)         |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with inhibitor formation to rVIII-SingleChain

|  |  |
|--|--|
| End point title  | Number of subjects with inhibitor formation to rVIII-SingleChain |
| End point description:<br>The number of subjects who develop inhibitors to rVIII-SingleChain, defined as a rVIII-SingleChain antibody titer of at least 0.6 Bethesda Units (BU) per mL after receiving study drug. |  |
| End point type   | Secondary  |
| End point timeframe:<br>At screening, then after dosing at approximately monthly intervals for 6 months, then every 3 months until reaching 50 EDs, and at the end of study visit (up to approximately 12 months). |  |

| End point values            | rVIII-SingleChain |  |  |  |
|-----------------------------|-------------------|--|--|--|
| Subject group type          | Reporting group   |  |  |  |
| Number of subjects analysed | 84                |  |  |  |
| Units: subjects             | 0                 |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

For the duration of the study, approximately 1 year, 5 months.

Adverse event reporting additional description:

The Safety Population comprised all subjects treated with rVIII-SingleChain. A total of 5313 CSL627 infusions were administered to 84 subjects during the study.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | rVIII-SingleChain |
|-----------------------|-------------------|

Reporting group description: -

| Serious adverse events                            | rVIII-SingleChain  |  |  |
|---|--|--|--|
| Total subjects affected by serious adverse events |  |  |  |
| subjects affected / exposed                       | 9 / 84 (10.71%)  |  |  |
| number of deaths (all causes)                     | 0  |  |  |
| number of deaths resulting from adverse events    | 0  |  |  |
| Investigations                                    |  |  |  |
| Inhibiting antibodies positive                    | Additional description: Subject identified with pre-existing inhibitor to FVIII confirmed by reexamination of screening sample initially reported as negative due to laboratory error. Therefore, event is not a de-novo inhibitor developed during exposure to rVIII-SingleChain. |  |  |
| subjects affected / exposed                       | 1 / 84 (1.19%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1  |  |  |
| deaths causally related to treatment / all        | 0 / 0  |  |  |
| Injury, poisoning and procedural complications    |  |  |  |
| Hand fracture                                     |  |  |  |
| subjects affected / exposed                       | 1 / 84 (1.19%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1  |  |  |
| deaths causally related to treatment / all        | 0 / 0  |  |  |
| Laceration  |  |  |  |
| subjects affected / exposed                       | 1 / 84 (1.19%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1  |  |  |
| deaths causally related to treatment / all        | 0 / 0  |  |  |
| Splenic rupture                                   |  |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 1 / 84 (1.19%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Device occlusion                                     |                |  |  |
| subjects affected / exposed                          | 1 / 84 (1.19%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Systemic inflammatory response syndrome              |                |  |  |
| subjects affected / exposed                          | 1 / 84 (1.19%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Blood and lymphatic system disorders                 |                |  |  |
| Anaemia  |                |  |  |
| subjects affected / exposed                          | 1 / 84 (1.19%) |  |  |
| occurrences causally related to treatment / all      | 0 / 3          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Gastrointestinal disorders                           |                |  |  |
| Dyspepsia  |                |  |  |
| subjects affected / exposed                          | 1 / 84 (1.19%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Infections and infestations                          |                |  |  |
| Bacteraemia  |                |  |  |
| subjects affected / exposed                          | 1 / 84 (1.19%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Pneumonia  |                |  |  |
| subjects affected / exposed                          | 1 / 84 (1.19%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |



|   |                   |  |  |
|---|-------------------|--|--|
| <b>Non-serious adverse events</b>                     | rVIII-SingleChain |  |  |
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 31 / 84 (36.90%)  |  |  |
| Injury, poisoning and procedural complications        |                   |  |  |
| Head injury   |                   |  |  |
| subjects affected / exposed                           | 5 / 84 (5.95%)    |  |  |
| occurrences (all)                                     | 6                 |  |  |
| Nervous system disorders                              |                   |  |  |
| Headache  |                   |  |  |
| subjects affected / exposed                           | 7 / 84 (8.33%)    |  |  |
| occurrences (all)                                     | 9                 |  |  |
| General disorders and administration site conditions  |                   |  |  |
| Pyrexia   |                   |  |  |
| subjects affected / exposed                           | 5 / 84 (5.95%)    |  |  |
| occurrences (all)                                     | 5                 |  |  |
| Respiratory, thoracic and mediastinal disorders       |                   |  |  |
| Cough   |                   |  |  |
| subjects affected / exposed                           | 7 / 84 (8.33%)    |  |  |
| occurrences (all)                                     | 10                |  |  |
| Musculoskeletal and connective tissue disorders       |                   |  |  |
| Arthralgia  |                   |  |  |
| subjects affected / exposed                           | 8 / 84 (9.52%)    |  |  |
| occurrences (all)                                     | 8                 |  |  |
| Infections and infestations                           |                   |  |  |
| Nasopharyngitis                                       |                   |  |  |
| subjects affected / exposed                           | 14 / 84 (16.67%)  |  |  |
| occurrences (all)                                     | 15                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment  |
|---------------|--|
| 21 May 2013   | <ul style="list-style-type: none"><li>- Extended duration of study participation to allow at least 50 EDs</li><li>- Increased cohort size of subjects screened for participation</li><li>- Added assessment for Chinese hamster ovary (CHO) antibodies</li><li>- Defined preventative dosing and additional dosing</li><li>- Added collection of additional subject information including blood group and hemophilia A gene defect</li><li>- Updated Independent Data and Safety Monitoring Committee responsibilities</li></ul> |
| 28 March 2014 | <ul style="list-style-type: none"><li>- Identified change in Coordinating Investigator</li><li>- Incorporated a change in PK collection time points as recommended by Food and Drug Administration (FDA)</li><li>- Updated Independent Data and Safety Monitoring Committee data review information</li></ul>  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported