



## Clinical trial results:

**A multicenter, open-label, multiple-dose, dose escalation study to investigate the pharmacokinetics, efficacy, and safety of rVlla-FP (CSL689) in subjects with hemophilia (A or B) and inhibitors.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-001309-26 |
| Trial protocol           | DE GB ES IT    |
| Global end of trial date | 28 March 2018  |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 04 October 2018 |
| First version publication date | 04 October 2018 |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | CSL689_2001 |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02484638 |
| 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               | Trial Registration Coordinator, CSL Behring GmbH,<br>clinicaltrials@cslbehring.com |
| Scientific contact           | 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-001886-PIP15-01 |
| 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                       | 15 May 2018   |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 28 March 2018 |
| Was the trial ended prematurely?                     | Yes           |

Notes:

## General information about the trial

Main objective of the trial:

Part 1 [Pharmacokinetic (PK) part]: To evaluate the single-dose PK of CSL689 (low dose, high dose) in subjects with hemophilia A or B and inhibitors and to compare with the single-dose PK of Eptacog alfa (low dose or high dose).

Part 2 (Dose-evaluation part): To determine the best dose ("population-based best dose") of the 2 CSL689 dose levels evaluated.

Part 3 (Repeated-dose part): To evaluate the clinical efficacy of the population-based best dose of CSL689 for on-demand therapy of bleeding events in subjects with hemophilia A or B and inhibitors.

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                          | 23 July 2015 |
| 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 | Georgia: 2            |
| Country: Number of subjects enrolled | Italy: 2              |
| Country: Number of subjects enrolled | Japan: 1              |
| Country: Number of subjects enrolled | Malaysia: 2           |
| Country: Number of subjects enrolled | Russian Federation: 2 |
| Country: Number of subjects enrolled | South Africa: 3       |
| Country: Number of subjects enrolled | Serbia: 1             |
| Country: Number of subjects enrolled | Thailand: 4           |
| Country: Number of subjects enrolled | Ukraine: 5            |
| Country: Number of subjects enrolled | Spain: 1              |
| Country: Number of subjects enrolled | United Kingdom: 1     |
| Country: Number of subjects enrolled | France: 1             |
| Worldwide total number of subjects   | 25                    |
| EEA total number of subjects         | 5                     |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 3  |
| Adults (18-64 years)                      | 22 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Performed as a multicenter study in 12 countries (France, Georgia, Great Britain, Italy, Japan, Malaysia, Russia, Serbia, South Africa, Spain, Thailand, and Ukraine). Study conducted at clinics and home of subjects.

### Period 1

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

### Arms

|                              |                      |
|------------------------------|----------------------|
| Are arms mutually exclusive? | No                   |
| <b>Arm title</b>             | NovoSeven (low dose) |

Arm description:

Single injection of 0.09 mg/kg NovoSeven rFVIIa in Part 1 (PK module)

|  |   |
|--|---|
| Arm type                               | Active comparator                             |
| Investigational medicinal product name | Eptacog alfa                                  |
| Investigational medicinal product code |   |
| Other name                             | NovoSeven                                     |
| Pharmaceutical forms                   | Powder and solvent for solution for injection |
| Routes of administration               | Intravenous use                               |

Dosage and administration details:

Delivered by intravenous injection of 0.09 mg/kg

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | NovoSeven (high dose) |
|------------------|-----------------------|

Arm description:

Single injection of 0.27 mg/kg NovoSeven rFVIIa in Part 1 (PK module)

|  |   |
|--|---|
| Arm type                               | Active comparator                             |
| Investigational medicinal product name | Eptacog alfa                                  |
| Investigational medicinal product code |   |
| Other name                             | NovoSeven                                     |
| Pharmaceutical forms                   | Powder and solvent for solution for injection |
| Routes of administration               | Intravenous use                               |

Dosage and administration details:

Delivered by intravenous injection of 0.27 mg/kg

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | CSL689 (low dose) |
|------------------|-------------------|

Arm description:

- Part 1 (PK module): single injection of low-dose CSL689 (0.75 mg/kg) for PK evaluation
  - Part 2 (Dose evaluation module): up to 2 injections of low-dose CSL689 per bleeding event (bleeding events 1 to 3\*)
  - Part 3 (Repeated dose module): up to 3 injections of low-dose CSL689 per bleeding event
- \* Note: All subjects in the low-dose arm will be treated with high-dose CSL689 (1.5 mg/kg) for bleeding events 4-6 in Part 2

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |  |
|--|--|
| Investigational medicinal product name           | Recombinant fusion protein, linking activated coagulation factor VII with albumin (rVIIa-FP) |
| Investigational medicinal product code           |  |
| Other name                                       |  |
| Pharmaceutical forms                             | Powder and solvent for suspension for injection  |
| Routes of administration                         | Intravenous use  |
| Dosage and administration details:               |  |
| Delivered by intravenous injection at 0.75 mg/kg |  |
| <b>Arm title</b>                                 | CSL689 (high dose)   |

Arm description:

- Part 1 (PK module): single injection of high-dose CSL689 (1.5 mg/kg) for PK evaluation
  - Part 2 (Dose evaluation module): up to 2 injections of high-dose CSL689 per bleeding event (bleeding events 4 to 6\*)
  - Part 3 (Repeated dose module): up to 3 injections of high-dose CSL689 per bleeding event
- \* Note: All subjects in the high-dose arm will be treated with low-dose CSL689 (0.75 mg/kg) for bleeding events 1-3 in Part 2

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Recombinant fusion protein, linking activated coagulation factor VII with albumin (rVIIa-FP) |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder and solvent for suspension for injection  |
| Routes of administration               | Intravenous use  |

Dosage and administration details:

Delivered by intravenous injection at 1.5 mg/kg

| <b>Number of subjects in period 1</b> | NovoSeven (low dose) | NovoSeven (high dose) | CSL689 (low dose) |
|---------------------------------------|----------------------|-----------------------|-------------------|
| Started                               | 6                    | 7                     | 8                 |
| Completed                             | 6                    | 4                     | 3                 |
| Not completed                         | 0                    | 3                     | 5                 |
| Consent withdrawn by subject          | -                    | 3                     | 2                 |
| Terminated by sponsor                 | -                    | -                     | 1                 |
| Other reason                          | -                    | -                     | 1                 |
| Lack of efficacy                      | -                    | -                     | 1                 |

| <b>Number of subjects in period 1</b> | CSL689 (high dose) |
|---------------------------------------|--------------------|
| Started                               | 4                  |
| Completed                             | 4                  |
| Not completed                         | 0                  |
| Consent withdrawn by subject          | -                  |
| Terminated by sponsor                 | -                  |
| Other reason                          | -                  |
| Lack of efficacy                      | -                  |



## Baseline characteristics

### Reporting groups

Reporting group title

Overall Trial

Reporting group description: -

| Reporting group values                                | Overall Trial | Total |  |
|---|---------------|-------|--|
| Number of subjects                                    | 25            | 25    |  |
| Age categorical                                       |               |       |  |
| Units: Subjects                                       |               |       |  |
| In utero  | 0             | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                                  | 0             | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0             | 0     |  |
| Children (2-11 years)                                 | 0             | 0     |  |
| Adolescents (12-17 years)                             | 3             | 3     |  |
| Adults (18-64 years)                                  | 22            | 22    |  |
| From 65-84 years                                      | 0             | 0     |  |
| 85 years and over                                     | 0             | 0     |  |
| Age continuous  |               |       |  |
| Units: years  |               |       |  |
| arithmetic mean                                       | 32.5          |       |  |
| standard deviation                                    | ± 13.59       | -     |  |
| Gender categorical                                    |               |       |  |
| Units: Subjects                                       |               |       |  |
| Female  | 0             | 0     |  |
| Male  | 25            | 25    |  |

## End points

### End points reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | NovoSeven (low dose) |
|-----------------------|----------------------|

Reporting group description:

Single injection of 0.09 mg/kg NovoSeven rFVIIa in Part 1 (PK module)

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | NovoSeven (high dose) |
|-----------------------|-----------------------|

Reporting group description:

Single injection of 0.27 mg/kg NovoSeven rFVIIa in Part 1 (PK module)

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | CSL689 (low dose) |
|-----------------------|-------------------|

Reporting group description:

- Part 1 (PK module): single injection of low-dose CSL689 (0.75 mg/kg) for PK evaluation
- Part 2 (Dose evaluation module): up to 2 injections of low-dose CSL689 per bleeding event (bleeding events 1 to 3\*)
- Part 3 (Repeated dose module): up to 3 injections of low-dose CSL689 per bleeding event

\* Note: All subjects in the low-dose arm will be treated with high-dose CSL689 (1.5 mg/kg) for bleeding events 4-6 in Part 2

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | CSL689 (high dose) |
|-----------------------|--------------------|

Reporting group description:

- Part 1 (PK module): single injection of high-dose CSL689 (1.5 mg/kg) for PK evaluation
- Part 2 (Dose evaluation module): up to 2 injections of high-dose CSL689 per bleeding event (bleeding events 4 to 6\*)
- Part 3 (Repeated dose module): up to 3 injections of high-dose CSL689 per bleeding event

\* Note: All subjects in the high-dose arm will be treated with low-dose CSL689 (0.75 mg/kg) for bleeding events 1-3 in Part 2

|                            |                        |
|----------------------------|------------------------|
| Subject analysis set title | Safety Population (SP) |
|----------------------------|------------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

The Safety Population included all subjects who received any quantity of investigational product (CSL689 or NovoSeven® rFVIIa)

|                            |                                 |
|----------------------------|---------------------------------|
| Subject analysis set title | Pharmacokinetic Population (PK) |
|----------------------------|---------------------------------|

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

Subject analysis set description:

The PK Population included all subjects from the Safety Population with at least 1 analyzable PK sample.

|                            |                          |
|----------------------------|--------------------------|
| Subject analysis set title | Efficacy Population (EP) |
|----------------------------|--------------------------|

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

Subject analysis set description:

The Efficacy Population included all subjects who received at least one dose of CSL689 as on-demand treatment during Dose Evaluation and Repeated Dose Module.

### Primary: Area under the FVIIa activity versus time curve from time zero to the last sample with quantifiable FVIIa activity (AUC0-last) in the PK module (PK)

|                 |   |
|-----------------|---|
| End point title | Area under the FVIIa activity versus time curve from time zero to the last sample with quantifiable FVIIa activity (AUC0-last) in the PK module (PK) <sup>[1]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 24 hours for NovoSeven and up to 120 hours for CSL689 post injection



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: Only descriptive statistics were used

| End point values                     | NovoSeven (low dose) | NovoSeven (high dose) | CSL689 (low dose) | CSL689 (high dose) |
|--------------------------------------|----------------------|-----------------------|-------------------|--------------------|
| Subject group type                   | Reporting group      | Reporting group       | Reporting group   | Reporting group    |
| Number of subjects analysed          | 6                    | 6                     | 8                 | 4 <sup>[2]</sup>   |
| Units: h*IU/mL                       |                      |                       |                   |                    |
| arithmetic mean (standard deviation) |                      |                       |                   |                    |
| with baseline correction             | 111.8 (± 20.395)     | 325.0 (± 55.064)      | 443.8 (± 145.22)  | 891.3 (± 265.50)   |
| without baseline correction          | 113.6 (± 21.371)     | 327.0 (± 55.717)      | 464.1 (± 132.37)  | 895.1 (± 266.77)   |

Notes:

[2] - Subjects from the NovoSeven arms also received high dose of CSL689, N=15

## Statistical analyses

No statistical analyses for this end point

### Primary: Incremental Recovery in the PK module (PK)

|                 |   |
|-----------------|---|
| End point title | Incremental Recovery in the PK module (PK) <sup>[3]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 24 hours for NovoSeven and up to 120 hours for CSL689 post injection

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: Only descriptive statistics were used

| End point values                     | NovoSeven (low dose) | NovoSeven (high dose) | CSL689 (low dose) | CSL689 (high dose) |
|--------------------------------------|----------------------|-----------------------|-------------------|--------------------|
| Subject group type                   | Reporting group      | Reporting group       | Reporting group   | Reporting group    |
| Number of subjects analysed          | 6                    | 6                     | 8                 | 4 <sup>[4]</sup>   |
| Units: (IU/dL)/(IU/kg)               |                      |                       |                   |                    |
| arithmetic mean (standard deviation) |                      |                       |                   |                    |
| with baseline correction             | 0.9805 (± 0.11697)   | 0.9670 (± 0.19661)    | 1.557 (± 0.46535) | 1.391 (± 0.35815)  |
| without baseline correction          | 0.9823 (± 0.11961)   | 0.9672 (± 0.19648)    | 1.571 (± 0.45955) | 1.394 (± 0.35785)  |

Notes:

[4] - Subjects from the NovoSeven arms also received high dose of CSL689, N=15

## Statistical analyses

No statistical analyses for this end point

### Primary: Elimination half-life (t<sub>1/2</sub>) in the PK module (PK)

|                 |  |
|-----------------|--|
| End point title | Elimination half-life (t <sub>1/2</sub> ) in the PK module (PK) <sup>[5]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 24 hours for NovoSeven and up to 120 hours for CSL689 post injection

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: Only descriptive statistics were used

| End point values                     | NovoSeven (low dose) | NovoSeven (high dose) | CSL689 (low dose) | CSL689 (high dose) |
|--------------------------------------|----------------------|-----------------------|-------------------|--------------------|
| Subject group type                   | Reporting group      | Reporting group       | Reporting group   | Reporting group    |
| Number of subjects analysed          | 6                    | 6                     | 8                 | 4 <sup>[6]</sup>   |
| Units: hours                         |                      |                       |                   |                    |
| arithmetic mean (standard deviation) |                      |                       |                   |                    |
| with baseline correction             | 2.980 (± 0.48613)    | 2.600 (± 0.26488)     | 9.141 (± 3.0035)  | 8.713 (± 1.1558)   |
| without baseline correction          | 3.473 (± 0.52812)    | 2.795 (± 0.37623)     | 14.21 (± 3.8290)  | 9.402 (± 1.8629)   |

Notes:

[6] - Subjects from the NovoSeven arms also received high dose of CSL689, N=15

## Statistical analyses

No statistical analyses for this end point

## Primary: Total clearance in the PK module (PK)

|                 |  |
|-----------------|--|
| End point title | Total clearance in the PK module (PK) <sup>[7]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 24 hours for NovoSeven and up to 120 hours for CSL689 post injection

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: Only descriptive statistics were used

| End point values                     | NovoSeven (low dose) | NovoSeven (high dose) | CSL689 (low dose) | CSL689 (high dose) |
|--------------------------------------|----------------------|-----------------------|-------------------|--------------------|
| Subject group type                   | Reporting group      | Reporting group       | Reporting group   | Reporting group    |
| Number of subjects analysed          | 6                    | 6                     | 8                 | 4 <sup>[8]</sup>   |
| Units: mL/h/kg                       |                      |                       |                   |                    |
| arithmetic mean (standard deviation) |                      |                       |                   |                    |
| with baseline correction             | 41.07 (± 6.4273)     | 42.58 (± 7.6064)      | 7.280 (± 2.6120)  | 7.149 (± 2.9154)   |
| without baseline correction          | 40.33 (± 6.5292)     | 42.28 (± 7.7021)      | 6.825 (± 2.3415)  | 7.112 (± 2.8984)   |

Notes:

[8] - Subjects from the NovoSeven arms also received high dose of CSL689, N=15

## Statistical analyses

No statistical analyses for this end point

---

**Primary: Percentage of bleeding events successfully treated with 1 injection of CSL689 in the dose evaluation module (EP)**

---

|                 |   |
|-----------------|---|
| End point title | Percentage of bleeding events successfully treated with 1 injection of CSL689 in the dose evaluation module (EP) <sup>[9][10]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 8 hours after first CSL689 injection for each bleeding event

---

Notes:

[9] - 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: Only descriptive statistics were used

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

Justification: Only CSL689 was used in this module

| End point values                  | CSL689 (low dose)     | CSL689 (high dose)    |  |  |
|-----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed       | 8 <sup>[11]</sup>     | 4 <sup>[12]</sup>     |  |  |
| Units: Percent of bleeding events |                       |                       |  |  |
| number (confidence interval 95%)  | 63.6 (51.59 to 74.12) | 55.0 (40.91 to 68.33) |  |  |

Notes:

[11] - Subjects from all groups received both doses of CSL689, N=23

[12] - Subjects from all groups received both doses of CSL689, N=20

---

**Statistical analyses**

---

No statistical analyses for this end point

---

**Secondary: Percentage of bleeding events successfully treated with 1 or 2 injections of CSL689 in the dose evaluation module (EP)**

---

|                 |  |
|-----------------|--|
| End point title | Percentage of bleeding events successfully treated with 1 or 2 injections of CSL689 in the dose evaluation module (EP) <sup>[13]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 8 hours after first CSL689 injection for each bleeding event

---

Notes:

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

Justification: Only CSL689 was used in this module

| End point values                  | CSL689 (low dose)     | CSL689 (high dose)    |  |  |
|-----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed       | 8 <sup>[14]</sup>     | 4 <sup>[15]</sup>     |  |  |
| Units: Percent of bleeding events |                       |                       |  |  |
| number (confidence interval 95%)  | 93.9 (85.33 to 97.54) | 95.0 (81.42 to 98.80) |  |  |

Notes:

[14] - Subjects from all groups received both doses of CSL689, N=23

[15] - Subjects from all groups received both doses of CSL689, N=20

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number and percentage of bleeding events requiring >1 injection of CSL689 in the dose evaluation module (EP)

|                 |  |
|-----------------|--|
| End point title | Number and percentage of bleeding events requiring >1 injection of CSL689 in the dose evaluation module (EP) <sup>[16]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 8 hours after first CSL689 injection for each bleeding event

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: Only CSL689 was used in this module

| End point values            | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------|-------------------|--------------------|--|--|
| Subject group type          | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed | 8 <sup>[17]</sup> | 4 <sup>[18]</sup>  |  |  |
| Units: bleeding events      |                   |                    |  |  |
| number (not applicable)     |                   |                    |  |  |
| Number                      | 24                | 27                 |  |  |
| Percent                     | 36.4              | 45.0               |  |  |

Notes:

[17] - Subjects from all groups received both doses of CSL689, N=23

[18] - Subjects from all groups received both doses of CSL689, N=20

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of CSL689 injections per bleeding episode in the dose evaluation module (EP)

|                 |   |
|-----------------|---|
| End point title | Number of CSL689 injections per bleeding episode in the dose evaluation module (EP) <sup>[19]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 16 hours after first CSL689 injection for each bleeding event

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: Only CSL689 was used in this module

| End point values                     | CSL689 (low dose) | CSL689 (high dose) |  |  |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed          | 8 <sup>[20]</sup> | 4 <sup>[21]</sup>  |  |  |
| Units: Injections per bleed          |                   |                    |  |  |
| arithmetic mean (standard deviation) | 1.4 (± 0.49)      | 1.4 (± 0.57)       |  |  |

Notes:

[20] - Subjects from all groups received both doses of CSL689, N=23

[21] - Subjects from all groups received both doses of CSL689, N=20

### Statistical analyses

No statistical analyses for this end point

### Secondary: Total dose of CSL689 required per bleeding episode in the dose evaluation module (SP)

|                 |   |
|-----------------|---|
| End point title | Total dose of CSL689 required per bleeding episode in the dose evaluation module (SP) <sup>[22]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 16 hours after first CSL689 injection for each bleeding event

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: Only CSL689 was used in this module

| End point values                     | CSL689 (low dose) | CSL689 (high dose) |  |  |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed          | 8 <sup>[23]</sup> | 4 <sup>[24]</sup>  |  |  |
| Units: mg                            |                   |                    |  |  |
| arithmetic mean (standard deviation) | 226.7 (± 105.71)  | 518.5 (± 149.05)   |  |  |

Notes:

[23] - Subjects from all groups received both doses of CSL689, N=23

[24] - Subjects from all groups received both doses of CSL689, N=20

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of bleeding events successfully treated with 1 injection in the repeated dose module (EP)

|                 |  |
|-----------------|--|
| End point title | Percentage of bleeding events successfully treated with 1 injection in the repeated dose module (EP) <sup>[25]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 8 hours after first CSL689 injection

Notes:

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

Justification: Only CSL689 was used in this module

| End point values                  | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------------|-------------------|--------------------|--|--|
| Subject group type                | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed       | 6                 | 4 <sup>[26]</sup>  |  |  |
| Units: Percent of bleeding events |                   |                    |  |  |
| number (not applicable)           | 25.0              | 47.7               |  |  |

Notes:

[26] - Subjects are counted more than once due to dose assignments in modules, N=13

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of bleeding events successfully treated with 1 injection of CSL689 analyzing the first bleeding event of each subject only in the repeated dose module (EP)

|                 |  |
|-----------------|--|
| End point title | Percentage of bleeding events successfully treated with 1 injection of CSL689 analyzing the first bleeding event of each subject only in the repeated dose module (EP) <sup>[27]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 8 hours after first CSL689 injection for first bleeding event

Notes:

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

Justification: Only CSL689 was used in this module

| End point values                  | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------------|-------------------|--------------------|--|--|
| Subject group type                | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed       | 6                 | 4 <sup>[28]</sup>  |  |  |
| Units: Percent of bleeding events |                   |                    |  |  |
| number (not applicable)           | 16.7              | 46.2               |  |  |

Notes:

[28] - Subjects are counted more than once due to dose assignments in modules, N=13

## Statistical analyses

No statistical analyses for this end point

---

**Secondary: Percentage of bleeding events successfully treated with 1 or 2 injections of CSL689 in the repeated dose module (EP)**

---

|                 |  |
|-----------------|--|
| End point title | Percentage of bleeding events successfully treated with 1 or 2 injections of CSL689 in the repeated dose module (EP) <sup>[29]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 24 hours after first CSL689 injection for each bleeding event

Notes:

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

Justification: Only CSL689 was used in this module

| End point values                  | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------------|-------------------|--------------------|--|--|
| Subject group type                | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed       | 6                 | 4 <sup>[30]</sup>  |  |  |
| Units: Percent of bleeding events |                   |                    |  |  |
| number (not applicable)           | 88.9              | 80.7               |  |  |

Notes:

[30] - Subjects are counted more than once due to dose assignments in modules, N=13

---

**Statistical analyses**

---

No statistical analyses for this end point

---

**Secondary: Percentage of bleeding events successfully treated with 1, 2, or 3 injections of CSL689 in the repeated dose module (EP)**

---

|                 |  |
|-----------------|--|
| End point title | Percentage of bleeding events successfully treated with 1, 2, or 3 injections of CSL689 in the repeated dose module (EP) <sup>[31]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 24 hours after first CSL689 injection for each bleeding event

Notes:

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

Justification: Only CSL689 was used in this module

| End point values                  | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------------|-------------------|--------------------|--|--|
| Subject group type                | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed       | 6                 | 4 <sup>[32]</sup>  |  |  |
| Units: Percent of bleeding events |                   |                    |  |  |
| number (not applicable)           | 97.2              | 95.5               |  |  |

Notes:

[32] - Subjects are counted more than once due to dose assignments in modules, N=13

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of bleeding events with only "definite" or "abrupt" subject-reported assessment of pain relief with CSL689 in the repeated dose module (EP)

|                 |  |
|-----------------|--|
| End point title | Percentage of bleeding events with only "definite" or "abrupt" subject-reported assessment of pain relief with CSL689 in the repeated dose module (EP) <sup>[33]</sup> |
|-----------------|--|

End point description:

"Definite" is defined as significant or recognized pain relief; "Abrupt" is defined as rapid, quick, or immediate pain relief. Only joint and muscle bleeds, which have the assessments of pain relief conducted, are summarized.

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

End point timeframe:

Up to 24 hours after CSL689 injection for each bleeding event

Notes:

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

Justification: Only CSL689 was used in this module

| End point values                  | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------------|-------------------|--------------------|--|--|
| Subject group type                | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed       | 6                 | 4 <sup>[34]</sup>  |  |  |
| Units: Percent of bleeding events |                   |                    |  |  |
| number (not applicable)           | 75.8              | 91.6               |  |  |

Notes:

[34] - Subjects are counted more than once due to dose assignments in modules, N=13

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of bleeding events with "Good" or "Excellent" investigator-reported assessment of treatment response with CSL689 in the repeated dose module (EP)

|                 |  |
|-----------------|--|
| End point title | Percentage of bleeding events with "Good" or "Excellent" investigator-reported assessment of treatment response with CSL689 in the repeated dose module (EP) <sup>[35]</sup> |
|-----------------|--|

End point description:

"Good" is defined as improvement in signs of bleeding after 1 injection with CSL689 and achieved hemostasis after 2 injections with CSL689; "Excellent" is defined as pain relief after 1 injection with CSL689 and no additional injections are required to achieve hemostasis.

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

End point timeframe:

Up to 9 months



Notes:

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

Justification: Only CSL689 was used in this module

| End point values                  | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------------|-------------------|--------------------|--|--|
| Subject group type                | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed       | 6                 | 4 <sup>[36]</sup>  |  |  |
| Units: Percent of bleeding events |                   |                    |  |  |
| number (not applicable)           | 88.9              | 79.5               |  |  |

Notes:

[36] - Subjects are counted more than once due to dose assignments in modules, N=13

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number and percentage of bleeding events requiring >1 injection of CSL689 in the repeated dose module (EP)

|                 |  |
|-----------------|--|
| End point title | Number and percentage of bleeding events requiring >1 injection of CSL689 in the repeated dose module (EP) <sup>[37]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 8 hours after first CSL689 injection for each bleeding event

Notes:

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

Justification: Only CSL689 was used in this module

| End point values            | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------|-------------------|--------------------|--|--|
| Subject group type          | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed | 8 <sup>[38]</sup> | 4 <sup>[39]</sup>  |  |  |
| Units: Bleeding events      |                   |                    |  |  |
| number (not applicable)     |                   |                    |  |  |
| Number                      | 27                | 46                 |  |  |
| Percent                     | 75.0              | 52.3               |  |  |

Notes:

[38] - Subjects are counted more than once due to dose assignments in modules, N=19

[39] - Subjects are counted more than once due to dose assignments in modules, N=19

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of bleeding events successfully treated with 1 injection of CSL689 using a bootstrap bias corrected and accelerated 95% confidence interval in

## the repeated dose module (EP)

|                 |   |
|-----------------|---|
| End point title | Percentage of bleeding events successfully treated with 1 injection of CSL689 using a bootstrap bias corrected and accelerated 95% confidence interval in the repeated dose module (EP) <sup>[40]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 9 months

Notes:

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

Justification: Only CSL689 was used in this module

| End point values                  | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------------|-------------------|--------------------|--|--|
| Subject group type                | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed       | 6                 | 4 <sup>[41]</sup>  |  |  |
| Units: Percent of bleeding events |                   |                    |  |  |
| number (confidence interval 95%)  | 2.2 (1.2 to 5.4)  | 1.2 (0.8 to 1.9)   |  |  |

Notes:

[41] - Subjects are counted more than once due to dose assignments in modules, N=13

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of recurrences in the repeated dose module (EP)

|                 |  |
|-----------------|--|
| End point title | Percentage of recurrences in the repeated dose module (EP) <sup>[42]</sup> |
|-----------------|--|

End point description:

Recurrences is defined as a bleeding in the same joint/anatomical location within 24 hours after an initial "good" or "excellent" response assessed by investigator.

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

End point timeframe:

Up to 9 months

Notes:

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

Justification: Only CSL689 was used in this module

| End point values              | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-------------------------------|-------------------|--------------------|--|--|
| Subject group type            | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed   | 6                 | 4 <sup>[43]</sup>  |  |  |
| Units: Percent of recurrences |                   |                    |  |  |
| number (not applicable)       | 0                 | 0                  |  |  |

Notes:

[43] - Subjects are counted more than once due to dose assignments in modules, N=13

## Statistical analyses

No statistical analyses for this end point

---

**Secondary: Percentage of Bleeding Events with ultrarapid progression in the repeated dose module (EP)**

---

|                 |  |
|-----------------|--|
| End point title | Percentage of Bleeding Events with ultrarapid progression in the repeated dose module (EP) <sup>[44]</sup> |
|-----------------|--|

End point description:

Bleeding events with ultrarapid progression is defined as overt, uncontrolled hemorrhage and/or progressive increase in pain and/or rapid progression in hematoma size.

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

End point timeframe:

Up to 9 months

Notes:

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

Justification: Only CSL689 was used in this module

| End point values                  | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------------|-------------------|--------------------|--|--|
| Subject group type                | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed       | 6                 | 4 <sup>[45]</sup>  |  |  |
| Units: Percent of bleeding events |                   |                    |  |  |
| number (not applicable)           | 0                 | 0                  |  |  |

Notes:

[45] - Subjects are counted more than once due to dose assignments in modules, N=13

---

**Statistical analyses**

---

No statistical analyses for this end point

---

**Secondary: Percentage of bleeding events requiring maintenance dosing in the repeated dose module (EP)**

---

|                 |   |
|-----------------|---|
| End point title | Percentage of bleeding events requiring maintenance dosing in the repeated dose module (EP) <sup>[46]</sup> |
|-----------------|---|

End point description:

Maintenance dosing is defined as post-hemostatic injections of CSL689 to maintain hemostasis, prevention of rebleeding or delayed bleeding and improve hematoma resorption after successful initial control of a bleeding event.

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

End point timeframe:

Up to 9 months

Notes:

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

Justification: Only CSL689 was used in this module

| End point values                  | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------------|-------------------|--------------------|--|--|
| Subject group type                | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed       | 6                 | 4 <sup>[47]</sup>  |  |  |
| Units: Percent of bleeding events |                   |                    |  |  |
| number (not applicable)           | 0                 | 0                  |  |  |

Notes:

[47] - Subjects are counted more than once due to dose assignments in modules, N=13

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of CSL689 injections per bleeding episode in the repeated dose module (EP)

|                 |   |
|-----------------|---|
| End point title | Number of CSL689 injections per bleeding episode in the repeated dose module (EP) <sup>[48]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 24 hours after first CSL689 injection for each bleeding event

Notes:

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

Justification: Only CSL689 was used in this module

| End point values                     | CSL689 (low dose) | CSL689 (high dose) |  |  |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed          | 6                 | 4 <sup>[49]</sup>  |  |  |
| Units: Injections per bleed          |                   |                    |  |  |
| arithmetic mean (standard deviation) | 1.9 (± 0.59)      | 1.7 (± 0.76)       |  |  |

Notes:

[49] - Subjects are counted more than once due to dose assignments in modules, N=13

## Statistical analyses

No statistical analyses for this end point

### Secondary: Total dose of CSL689 required per bleeding episode in the repeated dose module (EP)

|                 |   |
|-----------------|---|
| End point title | Total dose of CSL689 required per bleeding episode in the repeated dose module (EP) <sup>[50]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 24 hours after first CSL689 injection for each bleeding event

Notes:

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

Justification: Only CSL689 was used in this module

| End point values                     | CSL689 (low dose) | CSL689 (high dose) |  |  |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed          | 6                 | 4 <sup>[51]</sup>  |  |  |
| Units: mg                            |                   |                    |  |  |
| arithmetic mean (standard deviation) | 579.2 (± 469.62)  | 1124.0 (± 650.06)  |  |  |

Notes:

[51] - Subjects are counted more than once due to dose assignments in modules, N=13

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number and percentage of subjects with treatment emergent adverse events (TEAEs) in the PK module (SP)

|                 |  |
|-----------------|--|
| End point title | Number and percentage of subjects with treatment emergent adverse events (TEAEs) in the PK module (SP) |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 28 days

| End point values            | NovoSeven (low dose) | NovoSeven (high dose) | CSL689 (low dose) | CSL689 (high dose) |
|-----------------------------|----------------------|-----------------------|-------------------|--------------------|
| Subject group type          | Reporting group      | Reporting group       | Reporting group   | Reporting group    |
| Number of subjects analysed | 6                    | 7                     | 8                 | 4 <sup>[52]</sup>  |
| Units: Subjects with TEAEs  |                      |                       |                   |                    |
| number (not applicable)     |                      |                       |                   |                    |
| Number                      | 0                    | 0                     | 1                 | 4                  |
| Percent                     | 0                    | 0                     | 12.5              | 25.0               |

Notes:

[52] - Subjects from the NovoSeven arms also received high dose of CSL689, N=16

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number and percentage of subjects with TEAEs in the dose evaluation module (SP)

|                 |   |
|-----------------|---|
| End point title | Number and percentage of subjects with TEAEs in the dose evaluation module (SP) <sup>[53]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 9 months

Notes:

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

Justification: Only CSL689 was used in this module

| End point values            | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------|-------------------|--------------------|--|--|
| Subject group type          | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed | 8 <sup>[54]</sup> | 4 <sup>[55]</sup>  |  |  |
| Units: Subjects with TEAEs  |                   |                    |  |  |
| number (not applicable)     |                   |                    |  |  |
| Number                      | 8                 | 8                  |  |  |
| Percent                     | 34.8              | 40.0               |  |  |

Notes:

[54] - Subjects from all groups received both doses of CSL689, N=23

[55] - Subjects from all groups received both doses of CSL689, N=20

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number and percentage of subjects with TEAEs in the repeated dose module (SP)

|                 |   |
|-----------------|---|
| End point title | Number and percentage of subjects with TEAEs in the repeated dose module (SP) <sup>[56]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 6 months

Notes:

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

Justification: Only CSL689 was used in this module

| End point values            | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------|-------------------|--------------------|--|--|
| Subject group type          | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed | 6                 | 4 <sup>[57]</sup>  |  |  |
| Units: Subjects with TEAEs  |                   |                    |  |  |
| number (not applicable)     |                   |                    |  |  |
| Number                      | 3                 | 4                  |  |  |
| Percent                     | 50.0              | 30.8               |  |  |

Notes:

[57] - Subjects are counted more than once due to dose assignments in modules, N=13

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number and percentage of subjects with TEAEs related to CSL689 in the PK module (SP)

|                 |  |
|-----------------|--|
| End point title | Number and percentage of subjects with TEAEs related to CSL689 in the PK module (SP) <sup>[58]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 28 days

Notes:

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

Justification: Only CSL689 was used in this module

| End point values            | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------|-------------------|--------------------|--|--|
| Subject group type          | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed | 8                 | 4 <sup>[59]</sup>  |  |  |
| Units: Subjects             |                   |                    |  |  |
| number (not applicable)     |                   |                    |  |  |
| Number                      | 0                 | 0                  |  |  |
| Percent                     | 0                 | 0                  |  |  |

Notes:

[59] - Subjects from the NovoSeven arms also received high dose of CSL689, N=16

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number and percentage of subjects with TEAEs related to CSL689 in the dose evaluation module (SP)

|                 |   |
|-----------------|---|
| End point title | Number and percentage of subjects with TEAEs related to CSL689 in the dose evaluation module (SP) <sup>[60]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 9 months

Notes:

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

Justification: Only CSL689 was used in this module

| End point values            | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------|-------------------|--------------------|--|--|
| Subject group type          | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed | 8 <sup>[61]</sup> | 4 <sup>[62]</sup>  |  |  |
| Units: Subjects             |                   |                    |  |  |
| number (not applicable)     |                   |                    |  |  |
| Number                      | 1                 | 0                  |  |  |
| Percent                     | 4.3               | 0                  |  |  |

Notes:

[61] - Subjects from all groups received both doses of CSL689, N=23

[62] - Subjects from all groups received both doses of CSL689, N=20

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number and percentage of subjects with TEAEs related to CSL689 in the repeated dose module (SP)

|                 |   |
|-----------------|---|
| End point title | Number and percentage of subjects with TEAEs related to CSL689 in the repeated dose module (SP) <sup>[63]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 6 months

Notes:

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

Justification: Only CSL689 was used in this module

| End point values            | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------|-------------------|--------------------|--|--|
| Subject group type          | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed | 6                 | 4 <sup>[64]</sup>  |  |  |
| Units: Subjects             |                   |                    |  |  |
| number (not applicable)     |                   |                    |  |  |
| Number                      | 0                 | 0                  |  |  |
| Percent                     | 0                 | 0                  |  |  |

Notes:

[64] - Subjects are counted more than once due to dose assignments in modules, N=13

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number and percentage of subjects with inhibitors against Factor VII (FVII) in the PK module (SP)

|                 |   |
|-----------------|---|
| End point title | Number and percentage of subjects with inhibitors against Factor VII (FVII) in the PK module (SP) |
|-----------------|---|

End point description:

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



End point timeframe:

Up to 28 days

| End point values            | NovoSeven (low dose) | NovoSeven (high dose) | CSL689 (low dose) | CSL689 (high dose) |
|-----------------------------|----------------------|-----------------------|-------------------|--------------------|
| Subject group type          | Reporting group      | Reporting group       | Reporting group   | Reporting group    |
| Number of subjects analysed | 6                    | 7                     | 8                 | 4                  |
| Units: Subjects             |                      |                       |                   |                    |
| number (not applicable)     |                      |                       |                   |                    |
| Number                      | 0                    | 0                     | 0                 | 0                  |
| Percent                     | 0                    | 0                     | 0                 | 0                  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number and percentage of subjects with inhibitors against FVII in the dose evaluation module (SP)

|                 |   |
|-----------------|---|
| End point title | Number and percentage of subjects with inhibitors against FVII in the dose evaluation module (SP) <sup>[65]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 9 months

Notes:

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

Justification: Only CSL689 was used in this module

| End point values            | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------|-------------------|--------------------|--|--|
| Subject group type          | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed | 8 <sup>[66]</sup> | 4 <sup>[67]</sup>  |  |  |
| Units: Subjects             |                   |                    |  |  |
| number (not applicable)     |                   |                    |  |  |
| Number                      | 0                 | 0                  |  |  |
| Percent                     | 0                 | 0                  |  |  |

Notes:

[66] - Subjects from all groups received both doses of CSL689, N=23

[67] - Subjects from all groups received both doses of CSL689, N=20

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number and percentage of subjects with inhibitors against FVII in the

**repeated dose module (SP)**

|                 |   |
|-----------------|---|
| End point title | Number and percentage of subjects with inhibitors against FVII in the repeated dose module (SP) <sup>[68]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 6 months

Notes:

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

Justification: Only CSL689 was used in this module

| End point values            | CSL689 (low dose) | CSL689 (high dose) |  |  |
|-----------------------------|-------------------|--------------------|--|--|
| Subject group type          | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed | 6                 | 4 <sup>[69]</sup>  |  |  |
| Units: Subjects             |                   |                    |  |  |
| number (not applicable)     |                   |                    |  |  |
| Number                      | 0                 | 0                  |  |  |
| Percent                     | 0                 | 0                  |  |  |

Notes:

[69] - Subjects are counted more than once due to dose assignments in modules, N=13

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Area under the FVIIa activity versus time curve from time zero extrapolated to infinity (AUC0-infinity) in the PK module (PK)**

|                 |   |
|-----------------|---|
| End point title | Area under the FVIIa activity versus time curve from time zero extrapolated to infinity (AUC0-infinity) in the PK module (PK) |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 24 hours for NovoSeven and up to 120 hours for CSL689 post injection

| End point values                     | NovoSeven (low dose) | NovoSeven (high dose) | CSL689 (low dose) | CSL689 (high dose) |
|--------------------------------------|----------------------|-----------------------|-------------------|--------------------|
| Subject group type                   | Reporting group      | Reporting group       | Reporting group   | Reporting group    |
| Number of subjects analysed          | 6                    | 6                     | 8                 | 4 <sup>[70]</sup>  |
| Units: h*IU/mL                       |                      |                       |                   |                    |
| arithmetic mean (standard deviation) |                      |                       |                   |                    |
| with baseline correction             | 112.2 (± 20.293)     | 325.3 (± 55.273)      | 444.1 (± 145.06)  | 905.8 (± 271.85)   |
| without baseline correction          | 114.2 (± 21.170)     | 327.7 (± 55.766)      | 464.9 (± 132.59)  | 910.3 (± 273.30)   |

Notes:

[70] - Subjects from the NovoSeven arms also received high dose of CSL689, N=15

## Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum observed plasma FVIIa concentration (Cmax) in the PK module (PK)

|                 |  |
|-----------------|--|
| End point title | Maximum observed plasma FVIIa concentration (Cmax) in the PK module (PK) |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 24 hours for NovoSeven and up to 120 hours for CSL689 post injection

| End point values                     | NovoSeven (low dose) | NovoSeven (high dose) | CSL689 (low dose) | CSL689 (high dose) |
|--------------------------------------|----------------------|-----------------------|-------------------|--------------------|
| Subject group type                   | Reporting group      | Reporting group       | Reporting group   | Reporting group    |
| Number of subjects analysed          | 6                    | 6                     | 8                 | 4 <sup>[71]</sup>  |
| Units: IU/mL                         |                      |                       |                   |                    |
| arithmetic mean (standard deviation) |                      |                       |                   |                    |
| with baseline correction             | 44.10 (± 5.8237)     | 130.5 (± 26.883)      | 45.38 (± 13.888)  | 77.12 (± 18.683)   |
| without baseline correction          | 44.17 (± 5.8312)     | 130.5 (± 26.883)      | 45.81 (± 13.684)  | 77.15 (± 18.679)   |

Notes:

[71] - Subjects from the NovoSeven arms also received high dose of CSL689, N=13

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time corresponding to occurrence of Cmax (Tmax) in the PK module (PK)

|                 |   |
|-----------------|---|
| End point title | Time corresponding to occurrence of Cmax (Tmax) in the PK module (PK) |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 24 hours for NovoSeven and up to 120 hours for CSL689 post injection

| End point values              | NovoSeven (low dose)    | NovoSeven (high dose)   | CSL689 (low dose)       | CSL689 (high dose)      |
|-------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type            | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed   | 6                       | 6                       | 8                       | 4 <sup>[72]</sup>       |
| Units: hours                  |                         |                         |                         |                         |
| median (full range (min-max)) |                         |                         |                         |                         |
| with baseline correction      | 0.5000 (0.500 to 0.583) | 0.5750 (0.500 to 0.650) | 0.2500 (0.250 to 0.500) | 0.5000 (0.250 to 0.583) |
| without baseline correction   | 0.5000 (0.500 to 0.583) | 0.5750 (0.500 to 0.650) | 0.2500 (0.250 to 0.500) | 0.5000 (0.250 to 0.583) |

Notes:

[72] - Subjects from the NovoSeven arms also received high dose of CSL689, N=13

## Statistical analyses

No statistical analyses for this end point

### Secondary: Volume of distribution at steady state (Vss) in the PK module (PK)

|                 |  |
|-----------------|--|
| End point title | Volume of distribution at steady state (Vss) in the PK module (PK) |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 24 hours for NovoSeven and up to 120 hours for CSL689 post injection

| End point values                     | NovoSeven (low dose) | NovoSeven (high dose) | CSL689 (low dose) | CSL689 (high dose) |
|--------------------------------------|----------------------|-----------------------|-------------------|--------------------|
| Subject group type                   | Reporting group      | Reporting group       | Reporting group   | Reporting group    |
| Number of subjects analysed          | 6                    | 6                     | 8                 | 4 <sup>[73]</sup>  |
| Units: mL/kg                         |                      |                       |                   |                    |
| arithmetic mean (standard deviation) |                      |                       |                   |                    |
| with baseline correction             | 130.5 (± 19.685)     | 123.4 (± 19.045)      | 72.19 (± 28.984)  | 87.41 (± 37.460)   |
| without baseline correction          | 136.7 (± 19.253)     | 125.8 (± 19.716)      | 76.66 (± 30.415)  | 87.93 (± 37.357)   |

Notes:

[73] - Subjects from the NovoSeven arms also received high dose of CSL689, N=15

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean residence time (MRT) in the PK module (PK)

|                 |   |
|-----------------|---|
| End point title | Mean residence time (MRT) in the PK module (PK) |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 24 hours for NovoSeven and up to 120 hours for CSL689 post injection

| <b>End point values</b>              | NovoSeven<br>(low dose) | NovoSeven<br>(high dose) | CSL689 (low<br>dose) | CSL689 (high<br>dose) |
|--------------------------------------|-------------------------|--------------------------|----------------------|-----------------------|
| Subject group type                   | Reporting group         | Reporting group          | Reporting group      | Reporting group       |
| Number of subjects analysed          | 6                       | 6                        | 8                    | 4 <sup>[74]</sup>     |
| Units: hours                         |                         |                          |                      |                       |
| arithmetic mean (standard deviation) |                         |                          |                      |                       |
| with baseline correction             | 3.195 (±<br>0.35297)    | 2.927 (±<br>0.34881)     | 10.10 (±<br>1.9013)  | 12.40 (±<br>1.8022)   |
| without baseline correction          | 3.415 (±<br>0.36828)    | 3.003 (±<br>0.40168)     | 11.17 (±<br>1.0191)  | 12.54 (±<br>1.8812)   |

Notes:

[74] - Subjects from the NovoSeven arms also received high dose of CSL689, N=15

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

23 July 2015- 28 March 2018

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20.1   |

### Reporting groups

|                                |                       |
|--------------------------------|-----------------------|
| Reporting group title          | NovoSeven (low dose)  |
| Reporting group description: - |                       |
| Reporting group title          | NovoSeven (high dose) |
| Reporting group description: - |                       |
| Reporting group title          | CSL689 (low dose)     |
| Reporting group description: - |                       |
| Reporting group title          | CSL689 (high dose)    |
| Reporting group description: - |                       |

| Serious adverse events                            | NovoSeven (low dose) | NovoSeven (high dose) | CSL689 (low dose) |
|---|----------------------|-----------------------|-------------------|
| Total subjects affected by serious adverse events |                      |                       |                   |
| subjects affected / exposed                       | 0 / 6 (0.00%)        | 0 / 7 (0.00%)         | 0 / 24 (0.00%)    |
| number of deaths (all causes)                     | 0                    | 0                     | 0                 |
| number of deaths resulting from adverse events    | 0                    | 0                     | 0                 |

| Serious adverse events                            | CSL689 (high dose) |  |  |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events |                    |  |  |
| subjects affected / exposed                       | 0 / 22 (0.00%)     |  |  |
| number of deaths (all causes)                     | 0                  |  |  |
| number of deaths resulting from adverse events    | 0                  |  |  |

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

| Non-serious adverse events                            | NovoSeven (low dose) | NovoSeven (high dose) | CSL689 (low dose) |
|---|----------------------|-----------------------|-------------------|
| Total subjects affected by non-serious adverse events |                      |                       |                   |
| subjects affected / exposed                           | 0 / 6 (0.00%)        | 0 / 7 (0.00%)         | 1 / 24 (4.17%)    |

|   |                    |                    |                     |
|---|--------------------|--------------------|---------------------|
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0 | 1 / 24 (4.17%)<br>1 |
| Immune system disorders<br>Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)     | 0 / 6 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0 | 0 / 24 (0.00%)<br>0 |
| Infections and infestations<br>Rhinitis<br>subjects affected / exposed<br>occurrences (all)         | 0 / 6 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0 | 0 / 24 (0.00%)<br>0 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)               | 0 / 6 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0 | 0 / 24 (0.00%)<br>0 |

|   |                     |  |  |
|---|---------------------|--|--|
| <b>Non-serious adverse events</b>   | CSL689 (high dose)  |  |  |
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                | 7 / 22 (31.82%)     |  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 2 / 22 (9.09%)<br>2 |  |  |
| Immune system disorders<br>Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)     | 2 / 22 (9.09%)<br>2 |  |  |
| Infections and infestations<br>Rhinitis<br>subjects affected / exposed<br>occurrences (all)         | 2 / 22 (9.09%)<br>3 |  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)               | 2 / 22 (9.09%)<br>2 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 04 February 2015 | <ul style="list-style-type: none"><li>• Addition of adequate safety stopping rules</li><li>• Simplification of treatment response evaluation</li><li>• Specification of the success criteria for the Repeated Dose Module and provision of the algorithm for selection of the final dose</li><li>• Change of the success criteria from 15% to 25% and modification of the sample size estimation</li><li>• Additional evaluation of inhibitor assessment</li></ul>   |
| 28 April 2016    | <ul style="list-style-type: none"><li>• Introduce 4 new PK time-points to Block B (i.e., 15 min, 0,5, 2, 4, 6, 10, 24, 48, 72, 96, and 120 hours after the start of injection) and extend the observation/sample collection period from 48 to 120 hours</li><li>• Clarify that Block B would only open to enroll an additional 12 subjects following a recommendation from the IDMC</li><li>• Update of inclusion criteria #5 to increase the permitted body weight</li><li>• Increase the window for screening subjects in Blocks B and C from 14 days to 21 days</li><li>• Include events of hypersensitivity and catheter related complications (e.g., line infections and clotting) as adverse events of special interest</li><li>• The new PK time-points were added to Block B after the PK analysis of 6 subjects from Block A1 showed that additional PK time-points were required to support full characterization of the CSL689 PK profile</li></ul> |
| 21 March 2017    | <ul style="list-style-type: none"><li>• Addition of an age group-specific hemophilia quality of life (QoL) questionnaire at beginning as a baseline and at the end of Block C</li><li>• Enrollment of more than 12 subjects in Block B to compensate for subjects who discontinued participation</li><li>• Updates according to the Statistical Analysis Plan amendment</li></ul>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Although two subjects had confirmed antibodies directed against the rFVIIa part of CSL689, these antibodies were already pre-existing at screening and were not the result of CSL689 administration during the study. No clinical symptoms were reported.

Notes: