EU Clinical Trials Register

Clinical trial results:
A multicenter, open-label, multiple-dose, dose escalation study to investigate the pharmacokinetics, efficacy, and safety of rVIIa-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, clinicaltrials@cslbehring.com
Scientific contact	Trial Registration Coordinator, CSL Behring GmbH, clinicaltrials@cslbehring.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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:

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)	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
Arm title	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

Arm title	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

Arm title	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

Arm title	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

Number of subjects in period 1	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

Number of subjects in period 1	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 (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 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)[1]

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[2]
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)[3]
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[4]
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 (t1/2) in the PK module (PK)

End point title	Elimination half-life (t1/2) in the PK module (PK)[5]

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[6]
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)[7]

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[8]
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)[9][10]

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[11]	4[12]		
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)[13]

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[14]	4[15]		
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)[16]

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[17]	4[18]		
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)[19]

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[20]	4[21]		
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)[22]

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[23]	4[24]		
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)[25]

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[26]		
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)[27]

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[28]		
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)[29]

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[30]		
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 succesfully treated with 1, 2, or 3 injections of CSL689 in the repeated dose module (EP)

End point title	Percentage of bleeding events succesfully treated with 1, 2, or 3 injections of CSL689 in the repeated dose module (EP)[31]

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[32]		
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)[33]

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[34]		
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)[35]

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[36]		
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)[37]

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[38]	4[39]		
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)[40]

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[41]		
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)[42]

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[43]		
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)[44]

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[45]		
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)[46]

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[47]		
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)[48]
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[49]		
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)[50]
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[51]		
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[52]
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)[53]

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[54]	4[55]		
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)[56]

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[57]		
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)[58]

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[59]		
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)[60]

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[61]	4[62]		
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)[63]
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[64]		
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 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)[65]
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[66]	4[67]		
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)[68]
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[69]		
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[70]
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[71]
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[72]
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[73]
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)
withouit 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

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[74]
Units: hours				
arithmetic mean (standard deviation)				
with baseline correction	3.195 (± 0.35297)	2.927 (± 0.34881)	10.10 (± 1.9013)	12.40 (± 1.8022)
without baseline correction	3.415 (± 0.36828)	3.003 (± 0.40168)	11.17 (± 1.0191)	12.54 (± 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 Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1

Immune system disorders Hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0

Infections and infestations Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2015	• Addition of adequate safety stopping rules • Simplification of treatment response evaluation • Specification of the success criteria for the Repeated Dose Module and provision of the algorithm for selection of the final dose • Change of the success criteria from 15% to 25% and modification of the sample size estimation • Additional evaluation of inhibitor assessment
28 April 2016	• 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 • Clarify that Block B would only open to enroll an additional 12 subjects following a recommendation from the IDMC • Update of inclusion criteria #5 to increase the permitted body weight • Increase the window for screening subjects in Blocks B and C from 14 days to 21 days • Include events of hypersensitivity and catheter related complications (e.g., line infections and clotting) as adverse events of special interest • 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
21 March 2017	• Addition of an age group-specific hemophilia quality of life (QoL) questionnaire at beginning as a baseline and at the end of Block C • Enrollment of more than 12 subjects in Block B to compensate for subjects who discontinued participation • Updates according to the Statistical Analysis Plan amendment

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: