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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	CSL627_3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02172950
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring GmbH
Sponsor organisation address	Emil-von-Behring-Str. 76, Marburg, Germany, 35041
Public contact	Clin.Trial Registration Coordinator, CSL Behring GmbH, 34 91708 86 00, clinicaltrials@cslbehring.com
Scientific contact	Clin.Trial Registration Coordinator, CSL Behring GmbH, 34 91708 86 00, clinicaltrials@cslbehring.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	17
Children (2-11 years)	74
Adolescents (12-17 years)	23
Adults (18-64 years)	131
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CSL627: Previously treated patients (PTPs)

Arm description: -

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

Dosage and administration details:

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

Arm title	CSL627: Previously untreated patients (PUPs)

Arm description: -

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

Dosage and administration details:

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

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

Baseline characteristics

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

Reporting group values	CSL627: Previously treated patients (PTPs)	CSL627: Previously untreated patients (PUPs)	Total
Number of subjects	222	24	246
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	17	17
Children (2-11 years)	67	7	74
Adolescents (12-17 years)	23	0	23
Adults (18-64 years)	131	0	131
From 65-84 years	1	0	1
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	22.5	1.4	
standard deviation	± 14.55	± 1.18	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	222	24	246

End points

End points reporting groups

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

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

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

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were used for this endpoint.

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

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

Statistical analyses

No statistical analyses for this end point

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

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

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were used for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only for PUPs.

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

Statistical analyses

No statistical analyses for this end point

Primary: Percent treatment success for major bleeding episodes in PUPs

End point title	Percent treatment success for major bleeding episodes in

End point description:

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

End point type	Primary

End point timeframe:

Up to 5 years

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were used for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only for PUPs.

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

Statistical analyses

No statistical analyses for this end point

Primary: Annualized spontaneous bleeding rate in PUPs

End point title	Annualized spontaneous bleeding rate in PUPs[7][8]

End point description:

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

End point type	Primary

End point timeframe:

Up to 5 years

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were used for this endpoint.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only for PUPs.

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

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment success in PTPs

End point title	Treatment success in PTPs[9]

End point description:

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

End point type	Secondary

End point timeframe:

Up to 5 years

Notes:

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized bleeding rate in PTPs and PUPs

End point title	Annualized bleeding rate in PTPs and PUPs

End point description:

End point type	Secondary

End point timeframe:

Up to 5 years

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of bleeding episodes requiring 1, 2, 3 or > 3 infusions of CSL627 to achieve hemostasis

End point description:

End point type	Secondary

End point timeframe:

Up to 5 years

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Hemostatic efficacy of CSL627 for PTPs and PUPs who undergo surgery

End point description:

The investigator will rate the efficacy of the rVIII-SingleChain treatment during surgery based on a hemostatic efficacy four point rating scale of "excellent, good, moderate or poor/no response".

End point type	Secondary

End point timeframe:

From the start of surgery through the post-operative recovery (generally up to 14 days after surgery)

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

End point type	Secondary

End point timeframe:

Up to 5 years

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of PTPs and PUPs developing antibodies against CSL627

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

End point description:

End point type	Secondary

End point timeframe:

Up to 5 years

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

End point type	Secondary

End point timeframe:

Up to 5 years

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Up to 5 years

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Up to 5 years

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of total inhibitor formation to FVIII in PUPs

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

End point description:

End point type	Secondary

End point timeframe:

Up to 5 years

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Up to 5 years

Notes:

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

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

Notes:

[18] - Number of treated bleeding events = 315

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of on-demand infusions of CSL627

End point title	Mean number of on-demand infusions of CSL627

End point description:

End point type	Secondary

End point timeframe:

Up to 5 years

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

Statistical analyses

No statistical analyses for this end point

Secondary: Mean on-demand dose administered of CSL627

End point title	Mean on-demand dose administered of CSL627

End point description:

End point type	Secondary

End point timeframe:

Up to 5 years

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

Statistical analyses

No statistical analyses for this end point

Secondary: Mean prophylaxis dose administered of CSL627

End point title	Mean prophylaxis dose administered of CSL627

End point description:

End point type	Secondary

End point timeframe:

Up to 5 years

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

Statistical analyses

No statistical analyses for this end point

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

PTPs

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

End point description:

End point type	Secondary

End point timeframe:

Day of surgery up to 336 hours post-surgery

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Up to 6 hours after first infusion

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Up to 5 years

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

End point type	Secondary

End point timeframe:

Day of surgery up to 336 hours post-surgery

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 5 years	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1
Reporting groups	
Reporting group title	CSL627: Previously treated patients (PTPs)
Reporting group description: -	
Reporting group title	CSL627: Previously untreated patients (PUPs)
Reporting group description: -	

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

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

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

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

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

subjects affected / exposed	1 / 222 (0.45%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 222 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acinetobacter infection			
subjects affected / exposed	0 / 222 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 222 (0.45%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CSL627: Previously treated patients (PTPs)	CSL627: Previously untreated patients (PUPs)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	130 / 222 (58.56%)	23 / 24 (95.83%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 222 (0.90%)	2 / 24 (8.33%)	
occurrences (all)	2	3	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	14 / 222 (6.31%)	15 / 24 (62.50%)	
occurrences (all)	18	44	
Malaise			
subjects affected / exposed	0 / 222 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	4	
Immune system disorders			

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 March 2014	-Update of section on previous clinical study experience to reflect the start of pediatric Study 3002. -Removal of the overall caregiver / subject assessment of hemostatic efficacy for subjects ≥ 12 to ≤ 65 years of age to provide consistent means of evaluation for pain and symptom relief for all subjects in the study. -Clarification for symptom and pain relief assessments.
05 June 2015	-Addition of Arm 3 (PTPs who were not currently participating in a rVIII-SingleChain study). -Addition of confirmed inhibitors as SAEs.
27 January 2017	-Addition of final blood sample collection for inhibitor assessment at the EOS Visit for Arm 1 PTPs. -Addition of exploratory objective and 2 associated exploratory endpoints for inhibitor incidence in PTPs. -Extension of the individual subject participation / estimated time to reach the required number of EDs. -Change in number of study sites. -Removal of subject's assessment of bleeding / pain relief.
01 October 2019	-Change in number of expected enrolled subjects into Arm 2 PUPs from 50 to 24. -Removal of "at least 50" with respect to number of enrolled subjects. -Change in the inhibitor treatment period from 18 to 24 months. -Clarification for reporting inhibitor relapse SAE. -Clarification in the definition of inhibitor diagnosis. -Change in maximum duration of individual subject participation in the ITI substudy from 24 to 30 months.
26 May 2020	-Change in the number of EDs from 150 to 75 EDs that PUPs in Arm 2 needed to complete the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported