Clinical trial results:
A Phase II, Multicentre, Double-blinded, Randomised, Cross-over study to Evaluate Efficacy, Safety and Pharmacokinetics of Biostate® in Subjects With Haemophilia A

Summary

EudraCT number	2008-001104-23
Trial protocol	BG
Global end of trial date	15 October 2010

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	16 August 2015

Trial information

Trial identification

Sponsor protocol code	CSLCT-BIO-07-47

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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	Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.com
Scientific contact	Clinical Trial Disclosure Manager, CSL Behring, 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-000312-PIP01-08
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	10 December 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 October 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To assess the efficacy of Biostate® study product (SP) in subjects with haemophilia A
2. To assess the comparability of the pharmacokinetics of Biostate® reference product (RP)* and Biostate® SP in subjects with haemophilia A

*Biostate reference product (RP), was the initial product, used in clinical studies until May 2003, and Biostate study product (SP) was the product with an additional filter (a filtration step to enhance prion clearance), used as the IMP since March 2009 (start of the clinical development of the IMP in Europe).

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, and standard operating procedures for clinical research and development at CSL Behring (CSLB). The study protocol and all amendments were approved by the Independent Ethics Committee(s) (IECs) / Institutional Review Board(s) (IRBs) of the participating centers. Before undergoing screening procedures for possible enrollment into the study, subjects were informed, in an understandable form, about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's written informed consent to participate in the study.

The investigator may cease study treatment and withdraw the subject, or the subject may withdraw himself from participation in the study at any time. If a subject is withdrawn from the study or further participation is declined, the subject will continue to have access to medical care and will be treated according to routine medical practice, but will no longer receive the investigational medicinal product (IMP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 March 2009
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	Poland: 20
Country: Number of subjects enrolled	Bulgaria: 34
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 4
Country: Number of subjects enrolled	Russian Federation: 23
Worldwide total number of subjects	81
EEA total number of subjects	54

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)	77
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included a Screening period of up to 14 days.

Period 1

Period 1 title	Part 1: PK Component
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Subjects participating in this component (PK subjects) were randomly assigned (1:1, stratified by study site) to either of these sequences. The 2 different Biostate treatments (Biostate SP and RP) were only administered during Part 1 of the study (first part of the PK component). Therefore, blinding was only applicable for Part 1 of the study and not for Parts 2 (efficacy component), or Part 3 (Repeat PK component).

Arms

Are arms mutually exclusive?	No
Arm title	Biostate SP (Day 1 or 8)

Arm description:

A single intravenous (i.v.) dose of 50 IU/kg of Biostate SP on Day 1 or Day 8.

Arm type	Experimental
Investigational medicinal product name	Human coagulation Factor VIII / von Willebrand Factor
Investigational medicinal product code	
Other name	Biostate®, Voncento®
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Biostate SP was administrated as a bolus i.v. dose at a maximum of 6 mL/min as tolerated by the subject.

Arm title	Biostate RP (Day 1 or 8)

Arm description:

A single i.v. dose of 50 IU/kg of Biostate RP on Day 1 or Day 8.

Arm type	Experimental
Investigational medicinal product name	Human coagulation Factor VIII / von Willebrand Factor
Investigational medicinal product code	
Other name	Biostate®, Voncento®
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Biostate RP was administrated as a bolus i.v. dose at a maximum of 6 mL/min as tolerated by the subject.

Number of subjects in period 1	Biostate SP (Day 1 or 8)	Biostate RP (Day 1 or 8)
Started	17	17
Completed	17	17

Period 2

Period 2 title	Part 2: Efficacy Component
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Biostate SP

Arm description:

The frequency and dose (loading and maintenance) of Biostate SP during the efficacy component was determined by the Investigator based on the subject's clinical condition, previous FVIII concentrate requirements, response to therapy, body weight, and reason for usage during the 6-month efficacy period (for a minimum of 50 exposure days).

Arm type	Experimental
Investigational medicinal product name	Human coagulation Factor VIII / von Willebrand Factor
Investigational medicinal product code	
Other name	Biostate®, Voncento®
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Biostate SP was administrated as a bolus i.v. dose at a maximum of 6 mL/min as tolerated by the subject.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The first period was a PK period and did not include all enrolled subjects.

Number of subjects in period 2	Biostate SP
Started	17
Completed	77
Not completed	4
Consent withdrawn by subject	3
Development of FVIII Inhibitors	1
Joined	64
Enrolled for Part 2 Efficacy Component Only	64

Period 3

Period 3 title	Part 3: Repeat PK Component
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Biostate SP (Day 180)

Arm description:

A single i.v. dose of 50 IU/kg of Biostate SP on Day 180.

Arm type	Experimental
Investigational medicinal product name	Human coagulation Factor VIII / von Willebrand Factor
Investigational medicinal product code	
Other name	Biostate®, Voncento®
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Biostate SP was administrated as a bolus i.v. dose at a maximum of 6 mL/min as tolerated by the subject.

Number of subjects in period 3[2]	Biostate SP (Day 180)
Started	15
Completed	15

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The third period was a repeat PK period, and was only open to a subgroup of the first PK period (Period 1).

Baseline characteristics

Reporting groups	
Reporting group title	Part 2: Efficacy Component
Reporting group description:	
Each subject in the efficacy component (Part 2) of the study received a dose of Biostate SP as determined by the Investigator based on the subject's clinical condition, previous FVIII concentrate requirements, response to therapy, body weight, and reason for usage during the 6-month efficacy period (for a minimum of 50 exposure days). The frequency and dose (loading and maintenance) of Biostate SP during the efficacy component was determined by the Investigator.	

Reporting group values	Part 2: Efficacy Component	Total	
Number of subjects	81	81	
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)	77	77	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	33.1		
standard deviation	± 12.8	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	81	81	

End points

End points reporting groups

Reporting group title	Biostate SP (Day 1 or 8)
Reporting group description:	
A single intravenous (i.v.) dose of 50 IU/kg of Biostate SP on Day 1 or Day 8.	
Reporting group title	Biostate RP (Day 1 or 8)
Reporting group description:	
A single i.v. dose of 50 IU/kg of Biostate RP on Day 1 or Day 8.	
Reporting group title	Biostate SP
Reporting group description:	
The frequency and dose (loading and maintenance) of Biostate SP during the efficacy component was determined by the Investigator based on the subject's clinical condition, previous FVIII concentrate requirements, response to therapy, body weight, and reason for usage during the 6-month efficacy period (for a minimum of 50 exposure days).	
Reporting group title	Biostate SP (Day 180)
Reporting group description:	
A single i.v. dose of 50 IU/kg of Biostate SP on Day 180.	

Primary: Investigator's Monthly Assessment of Haemostatic Efficacy

End point title	Investigator's Monthly Assessment of Haemostatic Efficacy[1]
End point description:	
Assessment of haemostatic efficacy by the Investigator was evaluated per subject on a retrospective monthly basis. The efficacy grading scale was as follows: excellent=haemostasis achieved/cessation of bleeding; good=slight oozing/partial but adequate control of bleeding, does not require additional product for unplanned treatment; moderate=moderate bleeding/moderate control of bleeding, required additional product for unplanned treatment; none=severe uncontrolled bleeding.	
End point type	Primary
End point timeframe:	
Up to Month 10	

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: Planned descriptive data for this endpoint are presented in data table.

End point values	Biostate SP			
Subject group type	Reporting group			
Number of subjects analysed	81[2]			
Units: subjects				
Month 1: Excellent; n=81	58			
Month 1: Good; n=81	21			
Month 1: Moderate; n=81	2			
Month 1: None; n=81	0			
Month 2: Excellent; n=81	64			
Month 2: Good; n=81	17			
Month 2: Moderate; n=81	0			
Month 2: None; n=81	0			
Month 3: Excellent; n=80	63			
Month 3: Good; n=80	16			

Month 3: Moderate; n=80	1			
Month 3: None; n=80	0			
Month 4: Excellent; n=80	64			
Month 4: Good; n=80	16			
Month 4: Moderate; n=80	0			
Month 4: None; n=80	0			
Month 5: Excellent; n=79	68			
Month 5: Good; n=79	11			
Month 5: Moderate; n=79	0			
Month 5: None; n=79	0			
Month 6: Excellent; n=78	66			
Month 6: Good; n=78	12			
Month 6: Moderate; n=78	0			
Month 6: None; n=78	0			
Month 7: Excellent; n=20	16			
Month 7: Good; n=20	4			
Month 7: Moderate; n=20	0			
Month 7: None; n=20	0			
Month 8: Excellent; n=15	13			
Month 8: Good; n=15	2			
Month 8: Moderate; n=15	0			
Month 8: None; n=15	0			
Month 9: Excellent; n=9	8			
Month 9: Good; n=9	1			
Month 9: Moderate; n=9	0			
Month 9: None; n=9	0			
Month 10: Excellent; n=7	5			
Month 10: Good; n=7	2			
Month 10: Moderate; n=7	0			
Month 10: None; n=7	0			

Notes:

[2] - All subjects who received study drug; n=subjects with an assessment at given time point.

Statistical analyses

No statistical analyses for this end point

Primary: Blood Product Transfusions: Total Amount Received

End point title	Blood Product Transfusions: Total Amount Received[3]

End point description:

The total amount of blood product(s) required by a subject during the study period was recorded. Blood products included any infusions of whole blood, packed red blood cells, and platelets either from the subject's own blood (auto red blood cells, auto plasma) or from donor blood.

End point type	Primary

End point timeframe:

Screening through the Final Visit (Day 187 or within 7 days after last infusion)

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: Planned descriptive data for this endpoint are presented in data table.

End point values	Biostate SP			
Subject group type	Reporting group			
Number of subjects analysed	5[4]			
Units: mL				
median (full range (min-max))				
Any Blood Product; n=5	910 (250 to 1530)			
Auto Red Blood Cells; n=5	460 (250 to 540)			
Autoplasma; n =4	600 (300 to 600)			
Packed cells; n=1	470 (470 to 470)			

Notes:

[4] - Subjects who required transfusion; n=subjects receiving the respective blood product at least once.

Statistical analyses

No statistical analyses for this end point

Primary: Usage of Biostate SP: Number of Infusions Overall and By Month

End point title	Usage of Biostate SP: Number of Infusions Overall and By Month[5]

End point description:

End point type	Primary

End point timeframe:

Month 1 through Month 12

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: Planned descriptive data for this endpoint are presented in data table.

End point values	Biostate SP			
Subject group type	Reporting group			
Number of subjects analysed	81[6]			
Units: infusions				
median (full range (min-max))				
Overall Efficacy Period; n=81	59 (2 to 2)			
Month 1; n=81	9 (31 to 118)			
Month 2; n=81	9 (2 to 41)			
Month 3; n=81	9 (2 to 35)			
Month 4; n=80	10 (3 to 20)			
Month 5; n=80	9 (3 to 31)			
Month 6; n=79	9 (3 to 29)			
Month 7; n=58	4 (1 to 30)			
Month 8; n=23	5 (1 to 12)			
Month 9; n=15	4 (2 to 23)			
Month 10; n=9	4 (1 to 7)			
Month 11; n=6	3 (2 to 10)			
Month 12; n=1	2 (1 to 4)			

Notes:

[6] - All subjects who received study drug; n=subjects with evaluable data at given time point.

Statistical analyses

No statistical analyses for this end point

Primary: Usage of Biostate SP: Average Dose Overall and By Month

End point title	Usage of Biostate SP: Average Dose Overall and By Month[7]

End point description:

End point type	Primary

End point timeframe:

Months 1 through 12 of efficacy period

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: Planned descriptive data for this endpoint are presented in data table.

End point values	Biostate SP			
Subject group type	Reporting group			
Number of subjects analysed	81[8]			
Units: IU/kg				
median (full range (min-max))				
Overall Efficacy Period; n=81	26.6 (14 to 40)			
Month 1; n=81	25 (12 to 55)			
Month 2; n=81	25.3 (13 to 41)			
Month 3; n=81	25 (15 to 40)			
Month 4; n=80	27.5 (15 to 40)			
Month 5; n=80	26.2 (12 to 47)			
Month 6; n=79	27 (11 to 42)			
Month 7; n=58	26.9 (15 to 44)			
Month 8; n=23	26 (12 to 43)			
Month 9; n=15	25.8 (19 to 35)			
Month 10; n=9	25.7 (18 to 33)			
Month 11; n=6	27.1 (20 to 50)			
Month 12; n=1	35 (35 to 35)			

Notes:

[8] - All subjects who received study drug; n=subjects with evaluable data at given time point.

Statistical analyses

No statistical analyses for this end point

Primary: Investigator's Assessment of Blood Loss Per Surgical Event

End point title	Investigator's Assessment of Blood Loss Per Surgical Event[9]

End point description:

In the case of any surgical procedures, the surgical team provided an assessment at the time of the procedure of the extent of blood loss for each specific surgical procedure performed on a subject. The blood loss was compared to the expected blood loss from a subject without a bleeding disorder undergoing the same procedure. The following grading scale was used: less than expected loss, equivalent to expected loss, more than expected loss. Major surgery included surgery involving a risk to the life of the subject; minor surgery included surgery involving little risk to the life of the subject.

End point type	Primary

End point timeframe:

Efficacy Period (up to Month 12)

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: Planned descriptive data for this endpoint are presented in data table.

End point values	Biostate SP			
Subject group type	Reporting group			
Number of subjects analysed	81[10]			
Units: Surgical Events				
All Surgeries: Less Than Expected; n=37	15			
All Surgeries: Equivalent to Expected; n=37	21			
All Surgeries: More Than Expected; n=37	1			
Major Surgeries: Less Than Expected; n=12	6			
Major Surgeries: Equivalent to Expected; n=12	5			
Major Surgeries: More Than Expected; n=12	1			
Minor Surgeries: Less Than Expected; n=25	9			
Minor Surgeries: Equivalent to Expected; n=25	16			
Minor Surgeries: More Than Expected; n=25	0			

Notes:

[10] - Efficacy population; n=number of surgeries of given type.

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter, Part 1: Incremental Recovery (IR)

End point title	PK Parameter, Part 1: Incremental Recovery (IR)[11]

End point description:

End point type	Primary

End point timeframe:

Days 1 and 8: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2 and 9: 24 h (±2 h), 28 h (±2 h); Days 3 and 10: 48 h (±2 h) after the end of infusion.

Notes:

[11] - 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: Planned analyses for this endpoint are presented in data table.

End point values	Biostate SP (Day 1 or 8)	Biostate RP (Day 1 or 8)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: kg/mL				
arithmetic mean (standard deviation)	0.021 (± 0.006)	0.023 (± 0.005)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter, Part 1: Half-life (t1/2)

End point title	PK Parameter, Part 1: Half-life (t1/2)[12]

End point description:

End point type	Primary

End point timeframe:

Days 1 and 8: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2 and 9: 24 h (±2 h), 28 h (±2 h); Days 3 and 10: 48 h (±2 h) after the end of infusion.

Notes:

[12] - 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: Planned analyses for this endpoint are presented in data table.

End point values	Biostate SP (Day 1 or 8)	Biostate RP (Day 1 or 8)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: hours				
arithmetic mean (standard deviation)	13.4 (± 2.53)	13.07 (± 1.82)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter, Part 1: Area Under the Plasma Concentration-Time Curve From Time 0 to 48 Hours (AUC[0-48])

End point title	PK Parameter, Part 1: Area Under the Plasma Concentration-Time Curve From Time 0 to 48 Hours (AUC[0-48])

End point description:

End point type	Primary

End point timeframe:

Days 1 and 8: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2 and 9: 24 h (±2 h), 28 h (±2 h); Days 3 and 10: 48 h (±2 h) after the end of infusion.

End point values	Biostate SP (Day 1 or 8)	Biostate RP (Day 1 or 8)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: h*IU/mL				
arithmetic mean (standard deviation)	13.79 (± 3.79)	14.34 (± 3.63)		

Statistical analyses

Statistical analysis title	Bioequivalence of Biostate SP versus Biostate RP

Statistical analysis description:

From a mixed effects analysis of variance with treatment (Biostate SP, Biostate RP), period (Infusion 1, Infusion 2), and sequence (Sequence 1, Sequence 2) as fixed effects, and subject nested in sequence as random effect.

Comparison groups	Biostate RP (Day 1 or 8) v Biostate SP (Day 1 or 8)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence[13]
P-value	= 0.374
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.14
upper limit	0.05

Notes:

[13] - For establishing bioequivalence, the 90% CI should lie within the acceptance interval of 0.80 - 1.25 [Chow SC and Liu JP, 1992]. It is however noted that the conclusion that products are bioequivalent is based on the overall scientific assessment of the PK studies, not only on meeting the acceptance range.

Primary: PK Parameter, Part 1: Mean Residence Time (MRT)

End point title	PK Parameter, Part 1: Mean Residence Time (MRT)[14]

End point description:

End point type	Primary

End point timeframe:

Days 1 and 8: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2 and 9: 24 h (±2 h), 28 h (±2 h); Days 3 and 10: 48 h (±2 h) after the end of infusion.

Notes:

[14] - 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: Planned analyses for this endpoint are presented in data table.

End point values	Biostate SP (Day 1 or 8)	Biostate RP (Day 1 or 8)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: hours				
arithmetic mean (standard deviation)	16.96 (± 3.68)	16.96 (± 2.55)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter, Part 1: Maximum Plasma Concentration (Cmax)

End point title	PK Parameter, Part 1: Maximum Plasma Concentration (Cmax)

End point description:

End point type	Primary

End point timeframe:

Days 1 and 8: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2 and 9: 24 h (±2 h), 28 h (±2 h); Days 3 and 10: 48 h (±2 h) after the end of infusion.

End point values	Biostate SP (Day 1 or 8)	Biostate RP (Day 1 or 8)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: IU/mL				
arithmetic mean (standard deviation)	1.07 (± 0.28)	1.13 (± 0.27)		

Statistical analyses

Statistical analysis title	Bioequivalence of Biostate SP versus Biostate RP

Statistical analysis description:

From a mixed effects analysis of variance with treatment (Biostate SP, Biostate RP), period (Infusion 1, Infusion 2), and sequence (Sequence 1, Sequence 2) as fixed effects, and subject nested in sequence as random effect.

Comparison groups	Biostate SP (Day 1 or 8) v Biostate RP (Day 1 or 8)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence[15]
P-value	= 0.384
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.07

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.22
upper limit	0.07

Notes:

[15] - For establishing bioequivalence, the 90% CI should lie within the acceptance interval of 0.80 - 1.25 [Chow SC and Liu JP, 1992]. It is however noted that the conclusion that products are bioequivalent is based on the overall scientific assessment of the PK studies, not only on meeting the acceptance range.

Primary: PK Parameter, Part 1: Time of Maximum Concentration (tmax)

End point title	PK Parameter, Part 1: Time of Maximum Concentration

End point description:

End point type	Primary

End point timeframe:

Days 1 and 8: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2 and 9: 24 h (±2 h), 28 h (±2 h); Days 3 and 10: 48 h (±2 h) after the end of infusion.

Notes:

[16] - 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: Planned analyses for this endpoint are presented in data table.

End point values	Biostate SP (Day 1 or 8)	Biostate RP (Day 1 or 8)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: hours				
median (full range (min-max))	0.5 (0.42 to 4.03)	0.5 (0.48 to 0.5)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter, Part 1: Minimum Plasma Concentration (Cmin)

End point title	PK Parameter, Part 1: Minimum Plasma Concentration

End point description:

End point type	Primary

End point timeframe:

Days 1 and 8: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2 and 9: 24 h (±2 h), 28 h (±2 h); Days 3 and 10: 48 h (±2 h) after the end of infusion.

Notes:

[17] - 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: Planned analyses for this endpoint are presented in data table.

End point values	Biostate SP (Day 1 or 8)	Biostate RP (Day 1 or 8)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: IU/mL				
arithmetic mean (standard deviation)	0.06 (± 0.028)	0.061 (± 0.024)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter, Part 1: Total Clearance (CL)

End point title	PK Parameter, Part 1: Total Clearance (CL)[18]

End point description:

End point type	Primary

End point timeframe:

Days 1 and 8: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2 and 9: 24 h (±2 h), 28 h (±2 h); Days 3 and 10: 48 h (±2 h) after the end of infusion.

Notes:

[18] - 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: Planned analyses for this endpoint are presented in data table.

End point values	Biostate SP (Day 1 or 8)	Biostate RP (Day 1 or 8)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: mL/(h*kg)				
arithmetic mean (standard deviation)	3.92 (± 1.22)	3.78 (± 1.33)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter, Part 1: Volume at Steady State (Vss)

End point title	PK Parameter, Part 1: Volume at Steady State (Vss)[19]

End point description:

End point type	Primary

End point timeframe:

Days 1 and 8: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2 and 9: 24 h (±2 h), 28 h (±2 h); Days 3 and 10: 48 h (±2 h) after the end of infusion.

Notes:

[19] - 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: Planned analyses for this endpoint are presented in data table.

End point values	Biostate SP (Day 1 or 8)	Biostate RP (Day 1 or 8)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: mL/kg				
arithmetic mean (standard deviation)	65.33 (± 20.65)	62.57 (± 23.12)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter, Part 1 Versus Part 3: Incremental Recovery (IR)

End point title	PK Parameter, Part 1 Versus Part 3: Incremental Recovery

End point description:

End point type	Primary

End point timeframe:

Days 1, 8, and Day 180: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2, 9, and 181: 24 h (±2 h), 28 h (±2 h); Days 3, 10, and 182: 48 h (±2 h) after the end of infusion.

Notes:

[20] - 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: Planned analyses for this endpoint are presented in data table.

End point values	Biostate SP (Day 1 or 8)	Biostate SP (Day 180)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: kg/mL				
arithmetic mean (standard deviation)	0.021 (± 0.005)	0.022 (± 0.004)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter, Part 1 Versus Part 3: Half-life (t1/2)

End point title	PK Parameter, Part 1 Versus Part 3: Half-life (t1/2)[21]

End point description:

End point type	Primary

End point timeframe:

Days 1, 8, and Day 180: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2, 9, and 181: 24 h (±2 h), 28 h (±2 h); Days 3, 10, and 182: 48 h (±2 h) after the end of infusion.

Notes:

[21] - 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: Planned analyses for this endpoint are presented in data table.

End point values	Biostate SP (Day 1 or 8)	Biostate SP (Day 180)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: hours				
arithmetic mean (standard deviation)	13.49 (± 2.59)	13.16 (± 2.01)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter, Part 1 Versus Part 3: Area Under the Plasma Concentration-Time Curve From Time 0 to 48 Hours (AUC[0-48])

End point title	PK Parameter, Part 1 Versus Part 3: Area Under the Plasma Concentration-Time Curve From Time 0 to 48 Hours (AUC[0-48])

End point description:

End point type	Primary

End point timeframe:

Days 1, 8, and Day 180: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2, 9, and 181: 24 h (±2 h), 28 h (±2 h); Days 3, 10, and 182: 48 h (±2 h) after the end of infusion.

End point values	Biostate SP (Day 1 or 8)	Biostate SP (Day 180)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: h*IU/mL				
arithmetic mean (standard deviation)	13.26 (± 3.24)	14.46 (± 3.66)		

Statistical analyses

Statistical analysis title	Part 1 versus Part 3 AUC0-48

Statistical analysis description:

From a mixed effects analysis of variance with period (Part 1, Part 3) as fixed effect and subject as random effect.

Comparison groups	Biostate SP (Day 1 or 8) v Biostate SP (Day 180)

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.099
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	0.18

Primary: PK Parameter, Part 1 Versus Part 3: Mean Residence Time (MRT)

End point title	PK Parameter, Part 1 Versus Part 3: Mean Residence Time (MRT)[22]

End point description:

End point type	Primary

End point timeframe:

Days 1, 8, and Day 180: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2, 9, and 181: 24 h (±2 h), 28 h (±2 h); Days 3, 10, and 182: 48 h (±2 h) after the end of infusion.

Notes:

[22] - 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: Planned analyses for this endpoint are presented in data table.

End point values	Biostate SP (Day 1 or 8)	Biostate SP (Day 180)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: hours				
arithmetic mean (standard deviation)	17.07 (± 3.78)	16.68 (± 3.11)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter, Part 1 Versus Part 3: Maximum Plasma Concentration (Cmax)

End point title	PK Parameter, Part 1 Versus Part 3: Maximum Plasma Concentration (Cmax)

End point description:

End point type	Primary

End point timeframe:

Days 1, 8, and Day 180: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2, 9, and 181: 24 h (±2 h), 28 h (±2 h); Days 3, 10, and 182: 48 h (±2 h) after the

end of infusion.

End point values	Biostate SP (Day 1 or 8)	Biostate SP (Day 180)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: IU/mL				
arithmetic mean (standard deviation)	1.03 (± 0.26)	1.08 (± 0.21)		

Statistical analyses

Statistical analysis title	Part 1 versus Part 3 AUC0-48Cmax
Comparison groups	Biostate SP (Day 1 or 8) v Biostate SP (Day 180)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.471
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.09
upper limit	0.21

Primary: PK Parameter, Part 1 Versus Part 3: Time of Maximum Concentration (tmax)

End point title	PK Parameter, Part 1 Versus Part 3: Time of Maximum Concentration (tmax)[23]

End point description:

End point type	Primary

End point timeframe:

Days 1, 8, and Day 180: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2, 9, and 181: 24 h (±2 h), 28 h (±2 h); Days 3, 10, and 182: 48 h (±2 h) after the end of infusion.

Notes:

[23] - 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: Planned analyses for this endpoint are presented in data table.

End point values	Biostate SP (Day 1 or 8)	Biostate SP (Day 180)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: hours				
median (full range (min-max))	0.5 (0.42 to 4.03)	0.5 (0.42 to 2)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter, Part 1 Versus Part 3: Minimum Plasma Concentration (Cmin)

End point title	PK Parameter, Part 1 Versus Part 3: Minimum Plasma Concentration (Cmin)[24]

End point description:

End point type	Primary

End point timeframe:

Blood samples were collected prior to dosing, at 30 min, 2, 4, 8, 12, 24, 28, and 48 hours after the end of infusion on Days 1 and 8 (Part 1) or Day 180 (Part 3)

Notes:

[24] - 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: Planned analyses for this endpoint are presented in data table.

End point values	Biostate SP (Day 1 or 8)	Biostate SP (Day 180)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: IU/mL				
arithmetic mean (standard deviation)	0.059 (± 0.029)	0.06 (± 0.026)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter, Part 1 Versus Part 3: Total Clearance (CL)

End point title	PK Parameter, Part 1 Versus Part 3: Total Clearance (CL)[25]

End point description:

End point type	Primary

End point timeframe:

Days 1, 8, and Day 180: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2, 9, and 181: 24 h (±2 h), 28 h (±2 h); Days 3, 10, and 182: 48 h (±2 h) after the end of infusion.

Notes:

[25] - 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: Planned analyses for this endpoint are presented in data table.

End point values	Biostate SP (Day 1 or 8)	Biostate SP (Day 180)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: mL/(h*kg)				
arithmetic mean (standard deviation)	4.03 (± 1.18)	3.64 (± 0.81)		

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameter, Part 1 Versus Part 3: Volume at Steady State (Vss)

End point title	PK Parameter, Part 1 Versus Part 3: Volume at Steady State (Vss)[26]

End point description:

End point type	Primary

End point timeframe:

Days 1, 8, and Day 180: preinfusion; 30 (±5) min, 2 h (±5 min), 4 h (±15 min), 8 h (±30 min), 12 h (±30 min); Days 2, 9, and 181: 24 h (±2 h), 28 h (±2 h); Days 3, 10, and 182: 48 h (±2 h) after the end of infusion.

Notes:

[26] - 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: Planned analyses for this endpoint are presented in data table.

End point values	Biostate SP (Day 1 or 8)	Biostate SP (Day 180)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: mL/kg				
arithmetic mean (standard deviation)	67.35 (± 19.68)	60.07 (± 16.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overview of Adverse Events During the Entire Study

End point title	Overview of Adverse Events During the Entire Study

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have a causal relationship to the study product. A serious AE was defined as any untoward medical occurrence that at any dose: results in death; is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in

persistent or significant disability/incapacity; is a congenital anomaly/birth defect; is another medically important condition. The intensity/severity of AEs was categorized as mild, moderate, or severe.

End point type	Secondary

End point timeframe:

Day 1 through the Final Study Visit (Day 187 or within 7 days after last infusion)

End point values	Biostate SP			
Subject group type	Reporting group			
Number of subjects analysed	81[27]			
Units: subjects				
At Least 1 Adverse Event (AE)	39			
At Least 1 Severe AE	3			
At Least 1 Serious AE	4			
At Least 1 AE Leading to Discontinuation	1			
At Least 1 AE Leading to Death	0			

Notes:

[27] - Safety population: all subjects who received at least 1 dose of of Biostate SP or Biostate RP.

Statistical analyses

No statistical analyses for this end point

Secondary: Development of FVIII Inhibitors

End point title	Development of FVIII Inhibitors

End point description:

Testing at Screening and Day 1 was prior to treatment. No subject developed inhibitors during the study; 1 subject had a positive test result, which was also reported as SAE that led to study discontinuation, however, after the event, delayed analysis of the subject’s blood sample from Day 1 revealed that an increased inhibitor titre was already present at baseline prior to the first dose of Biostate.

End point type	Secondary

End point timeframe:

Screening, Day 1, Month 1, Month 3, and Final Visit (Day 187 or within 7 days after last infusion)

End point values	Biostate SP			
Subject group type	Reporting group			
Number of subjects analysed	81[28]			
Units: subjects				
Screening: FVIII Inhibitor Test Negative; n=81	81			
Screening: FVIII Inhibitor Test Positive; n=81	0			
Day 1: FVIII Inhibitor Test Negative; n=18	17			
Day 1: FVIII Inhibitor Test Positive; n=18	1			
Month 1: FVIII Inhibitor Test Negative; n=81	81			

Month 1: FVIII Inhibitor Test Positive; n=81	0			
Month 3: FVIII Inhibitor Test Negative; n=80	80			
Month 3: FVIII Inhibitor Test Positive; n=80	0			
Final Visit: FVIII Inhibitor Test Negative; n=79	78			
Final Visit: FVIII Inhibitor Test Positive; n=79	1			

Notes:

[28] - In 1 subject an inhibitor was found at final visit that was already present before the 1st dose (D1)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 through Final Visit (Day 187 or within 7 days after last infusion)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Safety Population

Reporting group description:

All subjects who received at least 1 dose of Biostate SP or Biostate RP were monitored throughout their participation in the study and included in the safety population analysis.

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 81 (4.94%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Factor VIII inhibition			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Epstein-Barr virus infection			

subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic echinococciasis			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 81 (19.75%)		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	34		
Infections and infestations			
Viral infection			
subjects affected / exposed	8 / 81 (9.88%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2009	- The duration of the screening period was increased from up to 7 days to up to 14 days to allow sufficient processing time for the screening assessment. - Reduced blood volumes for children were inserted. - Introduction of the Independent Data Monitoring Committee (IDMC). - Definition of major bleeding events was revised. - FVIII level, haematology, and biochemistry determinations prior to major bleeding events or surgical procedures, respectively, were deleted.
29 April 2009	- Change of the exclusion criteria to allow the admission of subjects with a positive hepatitis C viral load but to exclude subjects with an active hepatitis C. - Bicarbonate testing was deleted from biochemistry determinations as the testing procedure is contraindicated for bleeding disorders. - Inconsistencies with regard to the start of the reporting period of AEs were resolved.
04 November 2009	- Change of laboratory parameters at screening to perform HIV viral load testing only if subjects were HIV antibody positive. - Increase of the number of enrolled subjects from approximately 62 to approximately 80. This change in sample size was made in order to collect more efficacy data; the PK component and thus the sample size estimation as given in Section 9.7.2 was not affected by this change. - Increase of the number of evaluable subjects from at least 50 subjects to at least 65 subjects. - Specification of "prevention of bleedings" within the on-demand treatment regimen. As described in Section 9.4.5, it was found that in some centres subjects did not take Biostate in a prophylaxis regimen with regular administrations at intervals of 2-3 days (see Table 1) but as "prophlylactic treatment" only when they expected to have an increased bleeding risk, eg, prior to physical exercise. This mainly occurred with subjects who undertook muscle or joint exercises as part of their rehabilitation after a surgical event or after a bleeding event in joints. A dose of 25-30 IU/kg FVIII was administered prior to such exercises. An algorithm to differentiate between prophylaxis and prevention treatment, and to assign subjects to corresponding subgroups was defined in the SAP prior to final database lock.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported