



Clinical trial results:

An Open-Label, Multi-Centre Extension Study to Assess the Efficacy and Safety of Biostate® in Paediatric, Adolescent, and Adult Subjects with Von Willebrand Disease who Completed Clinical Studies CSLCT-BIO-08-52 or CSLCTBIO-08-54

Summary

EudraCT number	2009-017301-11
Trial protocol	BG PL DE
Global end of trial date	28 March 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	CSLCT-BIO-09-64
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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)	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	29 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives were:

- To assess the effectiveness of a prophylaxis regimen as compared to on-demand therapy with Biostate in preventing non-surgical bleeding (NSB) events.
- To assess the haemostatic efficacy of Biostate in subjects with Von Willebrand disease (VWD) who require a Von Willebrand factor (VWF) product to control an NSB event.

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	08 October 2010
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	Bulgaria: 6
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Ukraine: 3
Worldwide total number of subjects	20
EEA total number of subjects	13

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)	3
Adolescents (12-17 years)	2
Adults (18-64 years)	14
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Three subjects were enrolled in this extension study from study 2009-017753-34 (CSLCT-BIO-08-52) and 17 subjects from study 2008-004922-18 (CSLCT-BIO-08-54).

Pre-assignment

Screening details:

After eligibility of the subject was confirmed by prior participation and completion of study 2009-017753-34 (CSLCT-BIO-08-52) and 17 subjects from study 2008-004922-18 (CSLCT-BIO-08-54), the subject was admitted to this study. Visit 1 (Day 1) of this study should have coincided with the Final Visit of the subject's respective previous study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Prophylaxis Arm

Arm description:

Single bolus doses were administered intravenously as required to manage the subject's VWD. Subjects received Biostate on a regular basis 1-3 times per week as part of a prophylactic therapy regimen. Individual doses and regimen were determined by the investigator based on the subject's clinical condition, previous Factor VIII (FVIII) / VWF concentrate requirements, response to therapy, body weight, and reason for usage.

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 was administrated intravenously as a bolus dose at a maximum infusion rate of 6 mL/min as tolerated by the subject.

Arm title	On-demand Arm
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Arm description:

Single bolus doses were administered intravenously as required to manage the subject's VWD. Subjects received Biostate to treat a spontaneous or traumatic bleeding event, to provide haemostatic control during a surgical procedure. If subjects used Biostate for irregular prevention of bleedings this was recorded as "on-demand" treatment. Individual doses and regimen were determined by the investigator based on the subject's clinical condition, previous FVIII / VWF concentrate requirements, response to therapy, body weight, and reason for usage.

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 was administrated intravenously as a bolus dose at a maximum infusion rate of 6 mL/min as tolerated by the subject.

Arm title	Prophylaxis and On-demand Arm
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Arm description:

Single bolus doses were administered intravenously as required to manage their VWD. Subjects received Biostate to treat a spontaneous or traumatic bleeding event, to provide haemostatic control during a surgical procedure, or on a regular basis 1-3 times per week as part of a prophylactic therapy regimen. If subjects used Biostate for irregular prevention of bleedings this was recorded as "on-demand" treatment. Individual doses were determined by the investigator based on the subject's clinical condition, previous FVIII / VWF concentrate requirements, response to therapy, body weight, and reason for usage.

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 was administrated intravenously as a bolus dose at a maximum infusion rate of 6 mL/min as tolerated by the subject.

Number of subjects in period 1	Prophylaxis Arm	On-demand Arm	Prophylaxis and On-demand Arm
Started	10	8	2
Received at least 1 dose of Biostate	10	7	2
Completed	9	7	2
Not completed	1	1	0
Investigator's decision	1	-	-
Death	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Prophylaxis Arm
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Reporting group description:

Single bolus doses were administered intravenously as required to manage the subject's VWD. Subjects received Biostate on a regular basis 1-3 times per week as part of a prophylactic therapy regimen. Individual doses and regimen were determined by the investigator based on the subject's clinical condition, previous Factor VIII (FVIII) / VWF concentrate requirements, response to therapy, body weight, and reason for usage.

Reporting group title	On-demand Arm
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Reporting group description:

Single bolus doses were administered intravenously as required to manage the subject's VWD. Subjects received Biostate to treat a spontaneous or traumatic bleeding event, to provide haemostatic control during a surgical procedure. If subjects used Biostate for irregular prevention of bleedings this was recorded as "on-demand" treatment. Individual doses and regimen were determined by the investigator based on the subject's clinical condition, previous FVIII / VWF concentrate requirements, response to therapy, body weight, and reason for usage.

Reporting group title	Prophylaxis and On-demand Arm
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Reporting group description:

Single bolus doses were administered intravenously as required to manage their VWD. Subjects received Biostate to treat a spontaneous or traumatic bleeding event, to provide haemostatic control during a surgical procedure, or on a regular basis 1-3 times per week as part of a prophylactic therapy regimen. If subjects used Biostate for irregular prevention of bleedings this was recorded as "on-demand" treatment. Individual doses were determined by the investigator based on the subject's clinical condition, previous FVIII / VWF concentrate requirements, response to therapy, body weight, and reason for usage.

Reporting group values	Prophylaxis Arm	On-demand Arm	Prophylaxis and On-demand Arm
Number of subjects	10	8	2
Age categorical Units: Subjects			
6 to < 12 years	3	0	0
12 to < 18 years	0	1	1
>= 18 years	7	7	1
Age continuous Units: years			
arithmetic mean	35.8	28.4	28
standard deviation	± 23.02	± 11.94	± 16.97
Gender categorical Units: Subjects			
Female	2	6	0
Male	8	2	2

Reporting group values	Total		
Number of subjects	20		
Age categorical Units: Subjects			
6 to < 12 years	3		
12 to < 18 years	2		
>= 18 years	15		

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	8		
Male	12		

Subject analysis sets

Subject analysis set title	Prophylaxis - Safety/Efficacy/Per-protocol Set
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects in the Prophylaxis Arm were included in the Safety/Efficacy/Per-protocol sets.

Subject analysis set title	On-demand - Safety/Efficacy/Per-protocol Set
Subject analysis set type	Full analysis

Subject analysis set description:

One subject in the on-demand arm did not receive any Biostate during this extension study and was therefore excluded from the analysis populations used for efficacy and safety analyses.

Subject analysis set title	Prophylaxis and On-demand - Safety/Efficacy/Per-protocol Set
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects in the Prophylaxis and On-demand Arm were included in the Safety/Efficacy/Per-protocol sets.

Reporting group values	Prophylaxis - Safety/Efficacy/Per- protocol Set	On-demand - Safety/Efficacy/Per- protocol Set	Prophylaxis and On- demand - Safety/Efficacy/Per- protocol Set
Number of subjects	10	7	2
Age categorical Units: Subjects			
6 to < 12 years	3	0	0
12 to < 18 years	0	1	1
>= 18 years	7	6	1
Age continuous Units: years arithmetic mean standard deviation	35.8 ± 23.02	29.7 ± 12.23	28 ± 16.97
Gender categorical Units: Subjects			
Female	2	5	0
Male	8	2	2

End points

End points reporting groups

Reporting group title	Prophylaxis Arm
Reporting group description: Single bolus doses were administered intravenously as required to manage the subject's VWD. Subjects received Biostate on a regular basis 1-3 times per week as part of a prophylactic therapy regimen. Individual doses and regimen were determined by the investigator based on the subject's clinical condition, previous Factor VIII (FVIII) / VWF concentrate requirements, response to therapy, body weight, and reason for usage.	
Reporting group title	On-demand Arm
Reporting group description: Single bolus doses were administered intravenously as required to manage the subject's VWD. Subjects received Biostate to treat a spontaneous or traumatic bleeding event, to provide haemostatic control during a surgical procedure. If subjects used Biostate for irregular prevention of bleedings this was recorded as "on-demand" treatment. Individual doses and regimen were determined by the investigator based on the subject's clinical condition, previous FVIII / VWF concentrate requirements, response to therapy, body weight, and reason for usage.	
Reporting group title	Prophylaxis and On-demand Arm
Reporting group description: Single bolus doses were administered intravenously as required to manage their VWD. Subjects received Biostate to treat a spontaneous or traumatic bleeding event, to provide haemostatic control during a surgical procedure, or on a regular basis 1-3 times per week as part of a prophylactic therapy regimen. If subjects used Biostate for irregular prevention of bleedings this was recorded as "on-demand" treatment. Individual doses were determined by the investigator based on the subject's clinical condition, previous FVIII / VWF concentrate requirements, response to therapy, body weight, and reason for usage.	
Subject analysis set title	Prophylaxis - Safety/Efficacy/Per-protocol Set
Subject analysis set type	Full analysis
Subject analysis set description: All subjects in the Prophylaxis Arm were included in the Safety/Efficacy/Per-protocol sets.	
Subject analysis set title	On-demand - Safety/Efficacy/Per-protocol Set
Subject analysis set type	Full analysis
Subject analysis set description: One subject in the on-demand arm did not receive any Biostate during this extension study and was therefore excluded from the analysis populations used for efficacy and safety analyses.	
Subject analysis set title	Prophylaxis and On-demand - Safety/Efficacy/Per-protocol Set
Subject analysis set type	Full analysis
Subject analysis set description: All subjects in the Prophylaxis and On-demand Arm were included in the Safety/Efficacy/Per-protocol sets.	

Primary: Investigator's 3-monthly Assessment of Haemostatic Efficacy

End point title	Investigator's 3-monthly Assessment of Haemostatic Efficacy ^[1]
End point description: The Investigator's subjective 3-monthly assessment of haemostatic efficacy of Biostate in its usage with a NSB event, surgical procedure, or use in a prophylactic regimen. 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. Subjects who did not have any bleeding events are included in this table. Not Applicable: Subject did not experience any bleeding event which required Biostate in the respective 3-monthly period.	
End point type	Primary
End point timeframe: Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 32, and Final Visit (Final Visit assessment was included in the corresponding 3-monthly period based on the Final Visit date.)	

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 data was collected per protocol and is reported.

End point values	Prophylaxis - Safety/Efficacy /Per-protocol Set	On-demand - Safety/Efficacy /Per-protocol Set	Prophylaxis and On- demand - Safety/Efficacy /Per-protocol Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10 ^[2]	7 ^[3]	2 ^[4]	
Units: subjects				
Month 3: Excellent; n=10, 7, 2	5	1	0	
Month 3: Good; n=10, 7, 2	1	1	0	
Month 3: Moderate; n=10, 7, 2	0	0	0	
Month 3: None; n=10, 7, 2	0	0	0	
Month 3: Not Applicable; n=10, 7, 2	4	5	2	
Month 6: Excellent; n=10, 7, 2	3	3	1	
Month 6: Good; n=10, 7, 2	2	1	1	
Month 6: Moderate; n=10, 7, 2	0	0	0	
Month 6: None; n=10, 7, 2	0	0	0	
Month 6: Not Applicable; n=10, 7, 2	5	3	0	
Month 9: Excellent; n=10, 7, 2	4	4	1	
Month 9: Good; n=10, 7, 2	2	1	1	
Month 9: Moderate; n=10, 7, 2	0	0	0	
Month 9: None; n=10, 7, 2	0	0	0	
Month 9: Not Applicable; n=10, 7, 2	4	2	0	
Month 12: Excellent; n=9, 7, 2	1	2	0	
Month 12: Good; n=9, 7, 2	2	1	2	
Month 12: Moderate; n=9, 7, 2	0	0	0	
Month 12: None; n=9, 7, 2	0	0	0	
Month 12: Not Applicable; n=9, 7, 2	6	4	0	
Month 15: Excellent; n=9, 5, 2	2	1	1	
Month 15: Good; n=9, 5, 2	3	2	1	
Month 15: Moderate; n=9, 5, 2	0	0	0	
Month 15: None; n=9, 5, 2	0	0	0	
Month 15: Not Applicable; n=9, 5, 2	4	2	0	
Month 18: Excellent; n=9, 5, 2	3	0	1	
Month 18: Good; n=9, 5, 2	2	4	1	
Month 18: Moderate; n=9, 5, 2	0	0	0	
Month 18: None; n=9, 5, 2	0	0	0	
Month 18: Not Applicable; n=9, 5, 2	4	1	0	
Month 21: Excellent; n=8, 5, 2	4	2	2	
Month 21: Good; n=8, 5, 2	0	2	0	
Month 21: Moderate; n=8, 5, 2	0	0	0	
Month 21: None; n=8, 5, 2	0	0	0	
Month 21: Not Applicable; n=8, 5, 2	4	1	0	
Month 24: Excellent; n=6, 5, 2	1	3	2	
Month 24: Good; n=6, 5, 2	0	1	0	
Month 24: Moderate; n=6, 5, 2	0	0	0	
Month 24: None; n=6, 5, 2	0	0	0	

Month 24: Not Applicable; n=6, 5, 2	5	1	0
Month 27: Excellent; n=2, 4, 2	0	1	1
Month 27: Good; n=2, 4, 2	1	1	1
Month 27: Moderate; n=2, 4, 2	0	0	0
Month 27: None; n=2, 4, 2	0	0	0
Month 27: Not Applicable; n=2, 4, 2	1	2	0
Month 30: Excellent; n=1, 4, 2	1	0	1
Month 30: Good; n=1, 4, 2	0	2	1
Month 30: Moderate; n=1, 4, 2	0	0	0
Month 30: None; n=1, 4, 2	0	0	0
Month 30: Not Applicable; n=1, 4, 2	0	2	0
Month 32: Excellent; n=0, 4, 2	0	1	2
Month 32: Good; n=0, 4, 2	0	2	0
Month 32: Moderate; n=0, 4, 2	0	0	0
Month 32: None; n=0, 4, 2	0	0	0
Month 32: Not Applicable; n=0, 4, 2	0	1	0
Final Visit: Excellent; n=10, 6, 2	6	1	2
Final Visit: Good; n=10, 6, 2	0	2	0
Final Visit: Moderate; n=10, 6, 2	0	0	0
Final Visit: None; n=10, 6, 2	0	0	0
Final Visit: Not Applicable; n=10, 6, 2	4	3	0

Notes:

[2] - n=subjects with an assessment at respective time point.

[3] - n=subjects with an assessment at respective time point.

[4] - n=subjects with an assessment at respective time point.

Statistical analyses

No statistical analyses for this end point

Primary: Investigator's Assessment of Haemostatic Efficacy per Bleeding Event

End point title	Investigator's Assessment of Haemostatic Efficacy per Bleeding Event ^[5]
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End point description:

Investigator's subjective assessment of haemostatic efficacy of Biostate per non-surgical bleeding (NSB) event. 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. Major bleeding event=one that involves any bleeding into a joint, muscle, or mucosal bleeds of the gastro-intestinal tract (excluding nasal or oral bleeding). All other bleeding events were classified as minor unless the Investigator assessment noted otherwise.

End point type	Primary
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End point timeframe:

Up to Week 32

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 data was collected per protocol and is reported.

End point values	Prophylaxis - Safety/Efficacy /Per-protocol Set	On-demand - Safety/Efficacy /Per-protocol Set	Prophylaxis and On- demand - Safety/Efficacy /Per-protocol Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10 ^[6]	7 ^[7]	2 ^[8]	
Units: Number of events				
All NSB Events: Excellent; n=96, 77, 97	70	35	62	
All NSB Events: Good; n=96, 77, 97	24	41	35	
All NSB Events: Moderate; n=96, 77, 97	2	1	0	
All NSB Events: None; n=96, 77, 97	0	0	0	
Spontaneous NSB: Excellent; n=76, 73, 93	56	33	61	
Spontaneous NSB: Good; n=76, 73, 93	18	39	32	
Spontaneous NSB: Moderate; n=76, 73, 93	2	1	0	
Spontaneous NSB: None; n=76, 73, 93	0	0	0	
Trauma NSB: Excellent; n=19, 1, 4	13	1	1	
Trauma NSB: Good; n=19, 1, 4	6	0	3	
Trauma NSB: Moderate; n=19, 1, 4	0	0	0	
Trauma NSB: None; n=19, 1, 4	0	0	0	
Post-surgery NSB: Excellent; n=1, 3, 0	1	1	0	
Post-surgery NSB: Good; n=1, 3, 0	0	2	0	
Post-surgery NSB: Moderate; n=1, 3, 0	0	0	0	
Post-surgery NSB: None; n=1, 3, 0	0	0	0	
Major NSB: Excellent; n=12, 9, 6	5	6	2	
Major NSB: Good; n=12, 9, 6	7	3	4	
Major NSB: Moderate; n=12, 9, 6	0	0	0	
Major NSB: None; n=12, 9, 6	0	0	0	
Minor NSB: Excellent; n=84, 68, 91	65	29	60	
Minor NSB: Good; n=84, 68, 91	17	38	31	
Minor NSB: Moderate; n=84, 68, 91	2	1	0	
Minor NSB: None; n=84, 68, 91	0	0	0	
Joint NSB: Excellent; n=4, 6, 3	2	5	1	
Joint NSB: Good; n=4, 6, 3	2	1	2	
Joint NSB: Moderate; n=4, 6, 3	0	0	0	
Joint NSB: None; n=4, 6, 3	0	0	0	
Mucosal NSB: Excellent; n=84, 69, 91	64	29	60	
Mucosal NSB: Good; n=84, 69, 91	18	39	31	
Mucosal NSB: Moderate; n=84, 69, 91	2	1	0	
Mucosal NSB: None; n=84, 69, 91	0	0	0	
Muscle NSB: Excellent; n=3, 2, 3	0	1	1	
Muscle NSB: Good; n=3, 2, 3	3	1	2	
Muscle NSB: Moderate; n=3, 2, 3	0	0	0	
Muscle NSB: None; n=3, 2, 3	0	0	0	
Other NSB: Excellent; n=5, 0, 0	4	0	0	
Other NSB: Good; n=5, 0, 0	1	0	0	
Other NSB: Moderate; n=5, 0, 0	0	0	0	
Other NSB: None; n=5, 0, 0	0	0	0	

Notes:

[6] - n=NSB events treated with Biostate and with a haemostatic efficacy assessment.

[7] - n=NSB events treated with Biostate and with a haemostatic efficacy assessment.

[8] - n=NSB events treated with Biostate and with a haemostatic efficacy assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: Overview of Treatment-emergent Adverse Events (TEAEs)

End point title	Overview of Treatment-emergent Adverse Events (TEAEs)
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End point description:

An adverse event (AE) is any untoward medical occurrence that does not necessarily have a causal relationship to the study product. A serious AE (SAE) 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. The relationship of the AE to the study product was categorized as not related, unlikely, possibly, probably or definitely. AEs occurring after the first dose of study medication were considered treatment-emergent.

End point type	Secondary
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End point timeframe:

Day 1 up to a maximum duration of 32 months or until marketing approval of registration of Biostate, whichever occurred earlier, for countries in which Biostate was initially licensed; up to a maximum of 12 months for countries outside the EU.

End point values	Prophylaxis - Safety/Efficacy /Per-protocol Set	On-demand - Safety/Efficacy /Per-protocol Set	Prophylaxis and On- demand - Safety/Efficacy /Per-protocol Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	7	2	
Units: subjects				
At least 1 TEAE	7	7	2	
At least 1 severe AE	1	1	0	
At least 1 serious AE	0	3	0	
At least 1 TEAE leading to IMP discontinuation	0	0	0	
At least 1 TEAE leading to death	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: VWF and Factor VIII Inhibitors

End point title	VWF and Factor VIII Inhibitors
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End point description:

Number of subjects with a positive test result for VWF and FVIII inhibitors at each 3-monthly visit.

End point type	Secondary
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End point timeframe:

Baseline, Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 32 and Final Visit (included in the corresponding 3-monthly period based on Final Visit date).

End point values	Prophylaxis - Safety/Efficacy /Per-protocol Set	On-demand - Safety/Efficacy /Per-protocol Set	Prophylaxis and On- demand - Safety/Efficacy /Per-protocol Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10 ^[9]	7 ^[10]	2 ^[11]	
Units: subjects				
VWF inhibitor: Baseline; n=10, 7, 2	0	0	0	
VWF inhibitor: Month 3; n=10, 7, 2	0	0	0	
VWF inhibitor: Month 6; n=10, 7, 2	0	0	0	
VWF inhibitor: Month 9; n=10, 7, 2	0	0	0	
VWF inhibitor: Month 12; n=9, 7, 2	0	0	0	
VWF inhibitor: Month 15; n=9, 5, 2	0	0	0	
VWF inhibitor: Month 18; n=9, 5, 2	0	0	0	
VWF inhibitor: Month 21; n=7, 5, 2	0	0	0	
VWF inhibitor: Month 24; n=6, 5, 2	0	0	0	
VWF inhibitor: Month 27; n=2, 4, 2	0	0	0	
VWF inhibitor: Month 30; n=1, 4, 2	0	0	0	
VWF inhibitor: Month 32; n=0, 4, 2	0	0	0	
VWF inhibitor: Final Visit; n=10, 6, 2	0	0	0	
FVIII inhibitor: Baseline; n=8, 7, 2	0	0	0	
FVIII inhibitor: Month 3; n=10, 7, 2	0	0	0	
FVIII inhibitor: Month 6; n=10, 7, 2	0	0	0	
FVIII inhibitor: Month 9; n=10, 7, 2	0	0	0	
FVIII inhibitor: Month 12; n=9, 7, 2	0	0	0	
FVIII inhibitor: Month 15; n=9, 5, 2	0	0	0	
FVIII inhibitor: Month 18; n=9, 5, 2	0	0	0	
FVIII inhibitor: Month 21; n=7, 5, 2	0	0	0	
FVIII inhibitor: Month 24; n=6, 5, 2	0	0	0	
FVIII inhibitor: Month 27; n=2, 4, 2	0	0	0	
FVIII inhibitor: Month 30; n=1, 4, 2	0	0	0	
FVIII inhibitor: Month 32; n=0, 4, 2	0	0	0	
FVIII inhibitor: Final Visit; n=10, 6, 2	0	0	0	

Notes:

[9] - n=subjects with an available test result for the respective visit.

[10] - n=subjects with an available test result for the respective visit.

[11] - n=subjects with an available test result for the respective visit.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to a maximum duration of 32 months or until marketing approval of registration of Biostate, whichever occurred earlier, for countries in which Biostate was initially licensed; up to a maximum of 12 months for countries outside the EU.

Adverse event reporting additional description:

Treatment-emergent AEs are presented (those occurring after the first dose of study medication).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.0
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Reporting groups

Reporting group title	Prophylaxis Arm
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Reporting group description:

Single bolus doses were administered intravenously as required to manage the subject's VWD. Subjects received Biostate on a regular basis 1-3 times per week as part of a prophylactic therapy regimen. Individual doses and regimen were determined by the investigator based on the subject's clinical condition, previous FVIII / VWF concentrate requirements, response to therapy, body weight, and reason for usage.

Reporting group title	On-demand Arm
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Reporting group description:

Single bolus doses were administered intravenously as required to manage the subject's VWD. Subjects received Biostate to treat a spontaneous or traumatic bleeding event, to provide haemostatic control during a surgical procedure. If subjects used Biostate for irregular prevention of bleedings this was recorded as "on-demand" treatment. Individual doses and regimen were determined by the investigator based on the subject's clinical condition, previous FVIII / VWF concentrate requirements, response to therapy, body weight, and reason for usage.

Reporting group title	Prophylaxis and On-demand Arm
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Reporting group description:

Single bolus doses were administered intravenously as required to manage their VWD. Subjects received Biostate to treat a spontaneous or traumatic bleeding event, to provide haemostatic control during a surgical procedure, or on a regular basis 1-3 times per week as part of a prophylactic therapy regimen. If subjects used Biostate for irregular prevention of bleedings this was recorded as "on-demand" treatment. Individual doses were determined by the investigator based on the subject's clinical condition, previous FVIII / VWF concentrate requirements, response to therapy, body weight, and reason for usage.

Serious adverse events	Prophylaxis Arm	On-demand Arm	Prophylaxis and On-demand Arm
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	3 / 7 (42.86%)	0 / 2 (0.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma stage 0			

subjects affected / exposed	0 / 10 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	0 / 10 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 10 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Prophylaxis Arm	On-demand Arm	Prophylaxis and On-demand Arm
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)	5 / 7 (71.43%)	2 / 2 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine cancer			
subjects affected / exposed	0 / 10 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	2 / 10 (20.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	7	0	0
Injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	1 / 2 (50.00%)
occurrences (all)	1	0	1
Abdominal injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Head injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Post-traumatic pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Road traffic accident			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Skeletal injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Traumatic haematoma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Essential hypertension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hypertensive crisis			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 7 (14.29%) 1	0 / 2 (0.00%) 0
Nervous system disorders			
Headache			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 7 (28.57%) 2	0 / 2 (0.00%) 0
Post-traumatic headache			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	1 / 7 (14.29%) 3	0 / 2 (0.00%) 0
Iron deficiency anaemia			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0
Influenza like illness			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0
Pyrexia			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	1 / 7 (14.29%) 1	0 / 2 (0.00%) 0
Abdominal pain			

subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Duodenal ulcer			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 10 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 10 (20.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	3	0	0
Epistaxis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 10 (30.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	4	0	0
Bone pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Muscle haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	2 / 10 (20.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 10 (20.00%)	0 / 7 (0.00%)	1 / 2 (50.00%)
occurrences (all)	2	0	1
Bronchitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 7 (14.29%)	1 / 2 (50.00%)
occurrences (all)	0	1	1
Influenza			
subjects affected / exposed	1 / 10 (10.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Rhinitis			
subjects affected / exposed	2 / 10 (20.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Acute tonsillitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Gastroenteritis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 7 (14.29%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Streptococcal infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Tonsillitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 7 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2010	<ul style="list-style-type: none">• Data recording by electronic case report form (eCRF).• Inclusion of height assessment at Day 1 Visit.• Inclusion of an interim analysis.• Addition of thrombogenicity markers for paediatric patients ≤ 12 years of age, who underwent surgery (request from Paul-Ehrlich-Institut for the paediatric study CSLT-BIO-08-52).
12 May 2011	<ul style="list-style-type: none">• Correction of nominal VWF concentration.• Addition of study duration differentiation between Biostate-licensed and unlicensed countries.
26 September 2011	<ul style="list-style-type: none">• Addition of thrombogenicity markers for all subjects who underwent surgery.• Additional exclusion criterion: "Participation in another clinical study was not allowed during the course of the requested clinical trial period with the exception of the studies CSLCT-BIO-08-52 or CSLCT-BIO-08-54".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported