



Clinical trial results:

An Open-label, Multi-centre Study to Assess the Efficacy and Safety of Biostate® in Patients With von Willebrand's Disease (VWD)

Summary

EudraCT number	2014-005401-20
Trial protocol	Outside EU/EEA
Global end of trial date	18 May 2007

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-03-97
-----------------------	-----------------

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	CSL Limited
Sponsor organisation address	45 Poplar Road, Parkville, Australia, 3052
Public contact	Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@csllbehring.com
Scientific contact	Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@csllbehring.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	05 July 2007
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 May 2007
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were to evaluate the efficacy and safety of Biostate® in the treatment of non-surgery bleeds, in the management of surgery procedures and prophylactic therapy in patients with VWD where 1-deamino-8-D-arginine vasopressin/Desmopressin (DDAVP) treatment was deemed by the Investigator to be ineffective, inadequate, or contraindicated.

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. The study protocol and all amendments were approved by the Independent Ethics Committee(s)/ Institutional Review Board(s) 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 December 2004
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	New Zealand: 2
Worldwide total number of subjects	23
EEA total number of subjects	0

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)	1
Adolescents (12-17 years)	0
Adults (18-64 years)	16
From 65 to 84 years	5
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A Screening Visit occurred within 14 days prior to Day 0 of the study. Subject inclusion/exclusion criteria must have been fulfilled before the subject was permitted to receive Biostate. For subjects being treated for a non-surgery bleed/emergency surgery, the Screening Visit and Day 0 occurred on the same day.

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	Prophylactic

Arm description:

Subjects with a diagnosis of VWD who required prophylactic therapy. Subjects were to receive intravenous bolus doses of Biostate at a dose and frequency determined by the investigator in accordance with each subject's weight and pre-treatment Factor VIII:coagulant (FVIII:C) and/or von Willebrand factor:ristocetin co-factor (VWF:RCo) levels. Each subject was to be followed for a minimum period of 12 months following their first dose of Biostate.

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 to be administered as a bolus intravenous infusion over a period of approximately 5 minutes, or as tolerated by the subject.

Arm title	Minor Surgery
------------------	---------------

Arm description:

Subjects with a diagnosis of VWD who were undergoing minor surgery. Subjects were to receive intravenous bolus doses of Biostate at a dose and frequency determined by the investigator in accordance with each subject's weight and pre-treatment FVIII:C and/or VWF:RCo levels. Each subject was to be followed for a minimum period of 12 months following their first dose of Biostate.

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 to be administered as a bolus intravenous infusion over a period of approximately 5 minutes, or as tolerated by the subject.

Arm title	Major Surgery
------------------	---------------

Arm description:

Subjects with a diagnosis of VWD who were undergoing major surgery. Subjects were to receive intravenous bolus doses of Biostate at a dose and frequency determined by the investigator in accordance with each subject's weight and pre-treatment FVIII:C and/or VWF:RCo levels. Each subject was to be followed for a minimum period of 12 months following their first dose of Biostate.

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 to be administered as a bolus intravenous infusion over a period of approximately 5 minutes, or as tolerated by the subject.

Arm title	Non-surgery Bleed
------------------	-------------------

Arm description:

Subjects with a diagnosis of VWD who had a non-surgery bleed. Subjects were to receive intravenous bolus doses of Biostate at a dose and frequency determined by the investigator in accordance with each subject's weight and pre-treatment FVIII:C and/or VWF:RCo levels. Each subject was to be followed for a minimum period of 12 months following their first dose of Biostate.

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 to be administered as a bolus intravenous infusion over a period of approximately 5 minutes, or as tolerated by the subject.

Number of subjects in period 1	Prophylactic	Minor Surgery	Major Surgery
Started	4	8	9
Completed	3	7	6
Not completed	1	1	3
Transferred to a non trial site for treatment	-	-	-
Study termination by sponsor	1	1	2
Lost to follow-up	-	-	1

Number of subjects in period 1	Non-surgery Bleed
Started	2
Completed	1
Not completed	1
Transferred to a non trial site for treatment	1
Study termination by sponsor	-
Lost to follow-up	-

Baseline characteristics

Reporting groups

Reporting group title	Prophylactic
-----------------------	--------------

Reporting group description:

Subjects with a diagnosis of VWD who required prophylactic therapy. Subjects were to receive intravenous bolus doses of Biostate at a dose and frequency determined by the investigator in accordance with each subject's weight and pre-treatment Factor VIII:coagulant (FVIII:C) and/or von Willebrand factor:ristocetin co-factor (VWF:RCo) levels. Each subject was to be followed for a minimum period of 12 months following their first dose of Biostate.

Reporting group title	Minor Surgery
-----------------------	---------------

Reporting group description:

Subjects with a diagnosis of VWD who were undergoing minor surgery. Subjects were to receive intravenous bolus doses of Biostate at a dose and frequency determined by the investigator in accordance with each subject's weight and pre-treatment FVIII:C and/or VWF:RCo levels. Each subject was to be followed for a minimum period of 12 months following their first dose of Biostate.

Reporting group title	Major Surgery
-----------------------	---------------

Reporting group description:

Subjects with a diagnosis of VWD who were undergoing major surgery. Subjects were to receive intravenous bolus doses of Biostate at a dose and frequency determined by the investigator in accordance with each subject's weight and pre-treatment FVIII:C and/or VWF:RCo levels. Each subject was to be followed for a minimum period of 12 months following their first dose of Biostate.

Reporting group title	Non-surgery Bleed
-----------------------	-------------------

Reporting group description:

Subjects with a diagnosis of VWD who had a non-surgery bleed. Subjects were to receive intravenous bolus doses of Biostate at a dose and frequency determined by the investigator in accordance with each subject's weight and pre-treatment FVIII:C and/or VWF:RCo levels. Each subject was to be followed for a minimum period of 12 months following their first dose of Biostate.

Reporting group values	Prophylactic	Minor Surgery	Major Surgery
Number of subjects	4	8	9
Age categorical Units: Subjects			
≤ 12 years	1	0	0
> 12 to < 18 years	0	0	0
≥ 18 to < 65 years	3	7	5
≥ 65 years	0	1	4
Age continuous Units: years			
arithmetic mean	34	39.4	58.4
standard deviation	± 25.6	± 15.4	± 16.1
Gender categorical Units: Subjects			
Female	2	5	3
Male	2	3	6

Reporting group values	Non-surgery Bleed	Total	
Number of subjects	2	23	
Age categorical Units: Subjects			
≤ 12 years	0	1	
> 12 to < 18 years	0	0	

≥ 18 to < 65 years	1	16	
≥ 65 years	1	6	

Age continuous			
Units: years			
arithmetic mean	54.5		
standard deviation	± 38.9	-	
Gender categorical			
Units: Subjects			
Female	1	11	
Male	1	12	

End points

End points reporting groups

Reporting group title	Prophylactic
-----------------------	--------------

Reporting group description:

Subjects with a diagnosis of VWD who required prophylactic therapy. Subjects were to receive intravenous bolus doses of Biostate at a dose and frequency determined by the investigator in accordance with each subject's weight and pre-treatment Factor VIII:coagulant (FVIII:C) and/or von Willebrand factor:ristocetin co-factor (VWF:RCo) levels. Each subject was to be followed for a minimum period of 12 months following their first dose of Biostate.

Reporting group title	Minor Surgery
-----------------------	---------------

Reporting group description:

Subjects with a diagnosis of VWD who were undergoing minor surgery. Subjects were to receive intravenous bolus doses of Biostate at a dose and frequency determined by the investigator in accordance with each subject's weight and pre-treatment FVIII:C and/or VWF:RCo levels. Each subject was to be followed for a minimum period of 12 months following their first dose of Biostate.

Reporting group title	Major Surgery
-----------------------	---------------

Reporting group description:

Subjects with a diagnosis of VWD who were undergoing major surgery. Subjects were to receive intravenous bolus doses of Biostate at a dose and frequency determined by the investigator in accordance with each subject's weight and pre-treatment FVIII:C and/or VWF:RCo levels. Each subject was to be followed for a minimum period of 12 months following their first dose of Biostate.

Reporting group title	Non-surgery Bleed
-----------------------	-------------------

Reporting group description:

Subjects with a diagnosis of VWD who had a non-surgery bleed. Subjects were to receive intravenous bolus doses of Biostate at a dose and frequency determined by the investigator in accordance with each subject's weight and pre-treatment FVIII:C and/or VWF:RCo levels. Each subject was to be followed for a minimum period of 12 months following their first dose of Biostate.

Subject analysis set title	Minor Surgery - Intent to Treat (ITT) Set
----------------------------	---

Subject analysis set type	Intention-to-treat
---------------------------	--------------------

Subject analysis set description:

The ITT Set was defined by treatment event (not subject). An event was included in the ITT Set if the subject received at least one dose of Biostate (either trial or non-trial product) and had at least one post-dose haemostatic efficacy measurement performed for that event. Fifteen treatment events were included in the Minor Surgery ITT set.

Subject analysis set title	Major Surgery - ITT Set
----------------------------	-------------------------

Subject analysis set type	Intention-to-treat
---------------------------	--------------------

Subject analysis set description:

The ITT Set was defined by treatment event (not subject). An event was included in the ITT Set if the subject received at least one dose of Biostate (either trial or non-trial product) and had at least one post-dose haemostatic efficacy measurement performed for that event. Ten treatment events were included in the Major Surgery set.

Subject analysis set title	Non-surgery Bleed - ITT Set
----------------------------	-----------------------------

Subject analysis set type	Intention-to-treat
---------------------------	--------------------

Subject analysis set description:

The ITT Set was defined by treatment event (not subject). An event was included in the ITT Set if the subject received at least one dose of Biostate (either trial or non-trial product) and had at least one post-dose haemostatic efficacy measurement performed for that event. Six treatment events were included in the Non-surgery Bleed ITT set.

Subject analysis set title	Prophylactic - ITT Set
----------------------------	------------------------

Subject analysis set type	Intention-to-treat
---------------------------	--------------------

Subject analysis set description:

The ITT Set was defined by treatment event (not subject). An event was included in the ITT Set if the subject received at least one dose of Biostate (either trial or non-trial product) and had at least one post-dose haemostatic efficacy measurement performed for that event. Twenty-two treatment events were included in the Prophylactic ITT set.

Subject analysis set title	Minor Surgery - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set is defined as all subjects who received at least one dose of Biostate (either trial or non-trial Biostate). Nineteen treatment events were included in the Minor Surgery Safety Set.	
Subject analysis set title	Major Surgery - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set is defined as all subjects who received at least one dose of Biostate (either trial or non-trial Biostate). Ten treatment events were included in the Minor Surgery Safety Set.	
Subject analysis set title	Non-surgery Bleed - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set is defined as all subjects who received at least one dose of Biostate (either trial or non-trial Biostate). Nineteen treatment events were included in the Non-surgery Bleed Safety Set.	
Subject analysis set title	Prophylactic - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set is defined as all subjects who received at least one dose of Biostate (either trial or non-trial Biostate). The 4 prophylactic subjects were included as 4 separate "treatment events" for the safety analysis.	
Subject analysis set title	All Subjects - Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set is defined as all subjects who received at least one dose of Biostate (either trial or non-trial Biostate).	

Primary: Investigator's Assessment of Haemostatic Efficacy for the First 6 Days and Post-treatment Visit, Non-surgery Bleed and Surgery Treatment Groups

End point title	Investigator's Assessment of Haemostatic Efficacy for the First 6 Days and Post-treatment Visit, Non-surgery Bleed and Surgery Treatment Groups ^[1]
-----------------	--

End point description:

The efficacy grading scale was as follows: Excellent = cessation of bleeding; Good = slight oozing/partial but adequate control of bleeding/no additional product required; Moderate = moderate bleeding/moderate control of bleeding/additional product required; None = severe uncontrolled bleeding. Subjects (including those on prophylactic therapy) could be assessed in the study for more than one non-surgery bleed or surgery event with the possibility of the treatment phase for an additional event overlapping the follow-up phase of a previous event. Any haemostatic efficacy assessments for events requiring treatment at Day 0 only were performed at the Post-treatment Visit. If a subject did not receive Biostate on his/her last "Day X Visit" and did not have Post-treatment Visit data either, the haemostatic efficacy result for that last day was recorded but not included in this analysis.

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

End point timeframe:

Days 1, 2, 3, 4, 5, 6, Post-treatment Visit (24 hrs after final dose, applicable for all surgery procedures during the 12-month period)

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 per protocol for this endpoint.

End point values	Minor Surgery - Intent to Treat (ITT) Set	Major Surgery - ITT Set	Non-surgery Bleed - ITT Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	8 ^[2]	9 ^[3]	2 ^[4]	
Units: events				
Day 1: None; n=11, 10, 4	0	0	1	
Day 1: Moderate; n=11, 10, 4	0	0	0	
Day 1: Good; n=11, 10, 4	1	2	2	
Day 1: Excellent; n=11, 10, 4	10	8	1	
Day 2: None; n=3, 9, 2	0	0	1	
Day 2: Moderate; n=3, 9, 2	0	0	0	
Day 2: Good; n=3, 9, 2	0	3	0	
Day 2: Excellent; n=3, 9, 2	3	6	1	
Day 3: None; n=2, 10, 3	0	0	1	
Day 3: Moderate; n=2, 10, 3	0	0	0	
Day 3: Good; n=2, 10, 3	0	3	1	
Day 3: Excellent; n=2, 10, 3	2	7	1	
Day 4: None; n=2, 9, 3	0	0	0	
Day 4: Moderate; n=2, 9, 3	0	0	0	
Day 4: Good; n=2, 9, 3	0	2	2	
Day 4: Excellent; n=2, 9, 3	2	7	1	
Day 5: None; n=1, 7, 3	0	0	0	
Day 5: Moderate; n=1, 7, 3	0	0	1	
Day 5: Good; n=1, 7, 3	0	1	1	
Day 5: Excellent; n=1, 7, 3	1	6	1	
Day 6: None; n=1, 6, 2	0	0	0	
Day 6: Moderate; n=1, 6, 2	0	0	0	
Day 6: Good; n=1, 6, 2	0	1	1	
Day 6: Excellent; n=1, 6, 2	1	5	1	
Post-treatment: None; n=15, 9, 3	0	0	0	
Post-treatment: Moderate; n=15, 9, 3	0	0	0	
Post-treatment: Good; n=15, 9, 3	1	0	0	
Post-treatment: Excellent; n=15, 9, 3	14	9	3	

Notes:

[2] - n=number of events with a corresponding result (out of a total of 15 events for this ITT set).

[3] - n=number of events with a corresponding result (out of a total of 10 events for this ITT set).

[4] - n=number of events with a corresponding result (out of a total of 6 events for this ITT set).

Statistical analyses

No statistical analyses for this end point

Primary: Investigator's Assessment of Haemostatic Efficacy, Prophylactic Treatment Group

End point title	Investigator's Assessment of Haemostatic Efficacy, Prophylactic Treatment Group ^[5]
-----------------	--

End point description:

The efficacy grading scale was as follows: Excellent = cessation of bleeding; Good = slight oozing/partial but adequate control of bleeding/no additional product required; Moderate = moderate bleeding/moderate control of bleeding/additional product required; None = severe uncontrolled bleeding. Subjects (including those on prophylactic therapy) could be assessed in the study for more than one non-surgery bleed or surgery event with the possibility of the treatment phase for an additional event overlapping the follow-up phase of a previous event. Any haemostatic efficacy

assessments for events requiring treatment at Day 0 only were performed at the Post-treatment Visit. If a subject did not receive Biostate on his/her last "Day X Visit" and did not have Post-treatment Visit data either, the haemostatic efficacy result for that last day was recorded but not included in this analysis.

End point type	Primary
End point timeframe:	
Assessed every 3 months up to 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: Descriptive statistics were used per protocol for this endpoint.

End point values	Prophylactic - ITT Set			
Subject group type	Subject analysis set			
Number of subjects analysed	2 ^[6]			
Units: events				
Haemostatic Efficacy: Excellent	18			
Haemostatic Efficacy: Good to Excellent	3			
Haemostatic Efficacy: Good	1			

Notes:

[6] - Total number of events for this ITT set = 22.

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Levels of FVIII:C and VWF for the First 4 Days and Post-treatment Visit

End point title	Plasma Levels of FVIII:C and VWF for the First 4 Days and Post-treatment Visit ^[7]
-----------------	---

End point description:

Blood samples were to be taken before administration of Biostate each day including Day 0. Levels for factor VIII:coagulant activity (FVIII:C) = Low < 50%; Normal 50%-200%; High > 200%. Von Willebrand factor:antigen (VWF:Ag) = Low < 40%; Normal 40%-200%; High > 200%. Von Willebrand factor:collagen binding capacity (VWF:CB) = Low < 50%; Normal 50%-400%; High > 400%. Von Willebrand factor:ristocetin co-factor activity (VWF:RCO) = Low < 45%; Normal 45%-200%; High > 200%. Any missing results were likely to be due to blood samples not being collected at the site or patients administering Biostate at home.

End point type	Primary
End point timeframe:	
Days 0, 1, 2, 3, Post-treatment Visit (24 hrs after final dose, applicable for all surgery procedures during the 12-month 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: Descriptive statistics were used per protocol for this endpoint.

End point values	Minor Surgery - Intent to Treat (ITT) Set	Major Surgery - ITT Set	Non-surgery Bleed - ITT Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	8 ^[8]	9 ^[9]	2 ^[10]	
Units: events				
Day 0: FVIII:C Low; n=14, 9, 2	10	7	0	
Day 0: FVIII:C Normal; n=14, 9, 2	4	2	2	
Day 0: FVIII:C High; n=14, 9, 2	0	0	0	
Day 0: VWF:RCo Low; n=14, 9, 2	11	9	1	
Day 0: VWF:RCo Normal; n=14, 9, 2	3	0	1	
Day 0: VWF:RCo High; n=14, 9, 2	0	0	0	
Day 0: VWF:CB Low; n=14, 9, 2	10	9	1	
Day 0: VWF:CB Normal; n=14, 9, 2	4	0	1	
Day 0: VWF:CB High; n=14, 9, 2	0	0	0	
Day 0: VWF:Ag Low; n=14, 9, 2	10	7	1	
Day 0: VWF:Ag Normal; n=14, 9, 2	4	2	1	
Day 0: VWF:Ag High; n=14, 9, 2	0	0	0	
Day 1: FVIII:C Low; n=10, 9, 3	1	0	1	
Day 1: FVIII:C Normal; n=10, 9, 3	9	9	2	
Day 1: FVIII:C High; n=10, 9, 3	0	0	0	
Day 1: VWF:RCo Low; n=10, 9, 3	5	1	2	
Day 1: VWF:RCo Normal; n=10, 9, 3	5	8	1	
Day 1: VWF:RCo High; n=10, 9, 3	0	0	0	
Day 1: VWF:CB Low; n=10, 9, 3	3	2	3	
Day 1: VWF:CB Normal; n=10, 9, 3	7	7	0	
Day 1: VWF:CB High; n=10, 9, 3	0	0	0	
Day 1: VWF:Ag Low; n=10, 9, 3	1	0	0	
Day 1: VWF:Ag Normal; n=10, 9, 3	9	6	2	
Day 1: VWF:Ag High; n=10, 9, 3	0	3	1	
Day 2: FVIII:C Low; n=3, 9, 1	1	0	0	
Day 2: FVIII:C Normal; n=3, 9, 1	2	9	1	
Day 2: FVIII:C High; n=3, 9, 1	0	0	0	
Day 2: VWF:RCo Low; n=3, 9, 1	1	1	0	
Day 2: VWF:RCo Normal; n=3, 9, 1	2	7	1	
Day 2: VWF:RCo High; n=3, 9, 1	0	1	0	
Day 2: VWF:CB Low; n=3, 9, 1	0	1	0	
Day 2: VWF:CB Normal; n=3, 9, 1	3	8	1	
Day 2: VWF:CB High; n=3, 9, 1	0	0	0	
Day 2: VWF:Ag Low; n=3, 9, 1	0	0	0	
Day 2: VWF:Ag Normal; n=3, 9, 1	3	6	1	
Day 2: VWF:Ag High; n=3, 9, 1	0	3	0	
Day 3: FVIII:C Low; n=2, 6, 2	1	0	1	
Day 3: FVIII:C Normal; n=2, 6, 2	1	5	1	
Day 3: FVIII:C High; n=2, 6, 2	0	1	0	
Day 3: VWF:RCo Low; n=2, 6, 2	2	1	1	
Day 3: VWF:RCo Normal; n=2, 6, 2	0	5	1	
Day 3: VWF:RCo High; n=2, 6, 2	0	0	0	
Day 3: VWF:CB Low; n=2, 6, 2	1	2	1	
Day 3: VWF:CB Normal; n=2, 6, 2	1	4	1	
Day 3: VWF:CB High; n=2, 6, 2	0	0	0	
Day 3: VWF:Ag Low; n=2, 6, 2	0	0	1	

Day 3: VWF:Ag Normal; n=2, 6, 2	2	4	1	
Day 3: VWF:Ag High; n=2, 6, 2	0	2	0	
Post-treatment: FVIII:C Low; n=13, 8, 2	1	1	1	
Post-treatment: FVIII:C Normal; n=13, 8, 2	12	6	1	
Post-treatment: FVIII:C High; n=13, 8, 2	0	1	0	
Post-treatment: VWF:RCo Low; n=13, 7, 2	7	4	2	
Post-treatment: VWF:RCo Normal; n=13, 7, 2	6	3	0	
Post-treatment: VWF:RCo High; n=13, 7, 2	0	0	0	
Post-treatment: VWF:CB Low; n=13, 7, 2	4	2	2	
Post-treatment: VWF:CB Normal; n=13, 7, 2	9	5	0	
Post-treatment: VWF:CB High; n=13, 7, 2	0	0	0	
Post-treatment: VWF:Ag Low; n=13, 7, 2	0	0	2	
Post-treatment: VWF:Ag Normal; n=13, 7, 2	12	6	0	
Post-treatment: VWF:Ag High; n=13, 7, 2	1	1	0	

Notes:

[8] - n=events with a corresponding result (out of a total of 15 events in this set).

[9] - n=events with a corresponding result (out of a total of 10 events in this set).

[10] - n=events with a corresponding result (out of a total of 6 events in this set).

Statistical analyses

No statistical analyses for this end point

Primary: Blood Loss Assessment on Day 0 - Subjects Undergoing Surgery

End point title	Blood Loss Assessment on Day 0 - Subjects Undergoing Surgery ^[11]
-----------------	--

End point description:

Surgical team's assessment of blood loss during surgery is comparing the blood loss to the expected blood loss in a subject without a bleeding disorder undergoing the same procedure (less, equivalent, or more than expected). 'Missing' = assessment of blood loss not provided by surgical team.

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

End point timeframe:

Day 0 (day of surgery)

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: Descriptive statistics were used per protocol for this endpoint.

End point values	Minor Surgery - Intent to Treat (ITT) Set	Major Surgery - ITT Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8 ^[12]	9 ^[13]		
Units: events				
Less than expected; n=15, 10	4	1		
Equivalent to expected; n=15, 10	6	6		

More than expected; n=15, 10	2	1		
Missing; n=15, 10	3	2		

Notes:

[12] - n=number of treatment events in the ITT set.

[13] - n=number of treatment events in the ITT set.

Statistical analyses

No statistical analyses for this end point

Primary: Blood Transfusion Requirements

End point title	Blood Transfusion Requirements ^[14]
-----------------	--

End point description:

The number of units and type of blood transfusions are presented overall (including platelets, packed red blood cells or fresh frozen plasma) and by packed red blood cells.

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

End point timeframe:

Through Month 12

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: Descriptive statistics were used per protocol for this endpoint.

End point values	Minor Surgery - Intent to Treat (ITT) Set	Major Surgery - ITT Set	Non-surgery Bleed - ITT Set	Prophylactic - ITT Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8 ^[15]	9 ^[16]	2 ^[17]	2 ^[18]
Units: units/packs				
median (full range (min-max))				
Units/Packs Required; n=15, 10, 6, 4	0 (0 to 0)	0 (0 to 12)	0 (0 to 9)	0 (0 to 0)
Units/Packs Packed Cells Required; n=15, 10, 6, 4	0 (0 to 0)	0 (0 to 7)	0 (0 to 9)	0 (0 to 0)

Notes:

[15] - n=number of events with a non-missing result (out of a total of 15 events for this ITT set).

[16] - n=number of events with a non-missing result (out of a total of 10 events for this ITT set)

[17] - n=number of events with a non-missing result (out of a total of 6 events for this ITT set)

[18] - n=number of events with a non-missing result (out of a total of 4 events for this ITT set)

Statistical analyses

No statistical analyses for this end point

Primary: Mean Daily Dose per Treatment Event, Minor and Major Surgery and Non-surgery Bleed Treatment Groups

End point title	Mean Daily Dose per Treatment Event, Minor and Major Surgery and Non-surgery Bleed Treatment Groups ^[19]
-----------------	---

End point description:

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

End point timeframe:

through Month 12

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: Descriptive statistics were used per protocol for this endpoint.

End point values	Minor Surgery - Safety Set	Major Surgery - Safety Set	Non-surgery Bleed - Safety Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	8 ^[20]	10 ^[21]	2 ^[22]	
Units: IU FVIII:C/kg/day				
arithmetic mean (standard deviation)	33.48 (± 12.28)	41.35 (± 21.19)	27.36 (± 11.06)	

Notes:

[20] - Number of treatment events = 19

[21] - Number of treatment events = 10

[22] - Number of treatment events = 9

Statistical analyses

No statistical analyses for this end point

Primary: Number of Infusions Per Treatment Event

End point title	Number of Infusions Per Treatment Event ^[23]
End point description:	The number of infusions required until resolution of the event.
End point type	Primary
End point timeframe:	Through Month 12

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: Descriptive statistics were used per protocol for this endpoint.

End point values	Minor Surgery - Safety Set	Major Surgery - Safety Set	Non-surgery Bleed - Safety Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	8 ^[24]	9 ^[25]	2 ^[26]	
Units: infusions				
arithmetic mean (standard deviation)	2.8 (± 3.3)	13.5 (± 10.9)	4.6 (± 4.3)	

Notes:

[24] - number of treatment events with a non-missing result = 19

[25] - number of treatment events with a non-missing result = 10

[26] - number of treatment events with a non-missing result = 9

Statistical analyses

No statistical analyses for this end point

Primary: Average FVIII:C Dose per Prophylactic Subject

End point title	Average FVIII:C Dose per Prophylactic Subject ^[27]
End point description:	

End point type	Primary
End point timeframe:	
Through Month 12	
Notes:	
[27] - 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 per protocol for this endpoint.	

End point values	Prophylactic - Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: IU/kg				
Prophylactic Subject 1	1017			
Prophylactic Subject 2	1465			
Prophylactic Subject 3	1964			
Prophylactic Subject 4	500			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Spontaneous Bleeding Episodes, Prophylactic Group

End point title	Number of Spontaneous Bleeding Episodes, Prophylactic
End point description:	
End point type	Primary
End point timeframe:	
Through Month 12	
Notes:	
[28] - 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 per protocol for this endpoint.	

End point values	Prophylactic - Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: episodes	22			

Statistical analyses

No statistical analyses for this end point

Primary: Summary of Treatment-emergent Adverse Events (TEAEs)

End point title	Summary of Treatment-emergent Adverse Events (TEAEs) ^[29]
-----------------	--

End point description:

A TEAE was defined as an adverse event that began or increased in intensity after the first dose of Biostate. A related TEAE was defined as an event considered by the investigator to be possibly, probably or definitely related Biostate. In addition to adverse events (AEs) collected during the stated time frame, AEs for all subjects undergoing surgery were collected from the first administration of Biostate used to treat/manage any additional nonsurgery bleeds/surgery procedures, up to 30 days after the last administration of Biostate used to treat/manage the event.

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

End point timeframe:

Prophylactic subjects: from Day 0 through Month 12. Elective surgery subjects: Screening Visit through Month 12 + 30 days follow-up. Non-surgery bleeds/emergency surgery subjects: Day 0 through Month 12 + 30 days follow-up.

Notes:

[29] - 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 per protocol for this endpoint.

End point values	All Subjects - Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: subjects				
Subjects with a serious adverse event	2			
Subjects with a TEAE	22			
Subjects with a severe TEAE	6			
Subjects with a related TEAE	2			
Subjects with TEAE leading to discontinuation	0			

Statistical analyses

No statistical analyses for this end point

Primary: FVIII Inhibitors - Subjects Treated for Non-Surgery Bleed or Undergoing Surgery

End point title	FVIII Inhibitors - Subjects Treated for Non-Surgery Bleed or Undergoing Surgery ^[30]
-----------------	---

End point description:

A subject is considered to have a newly detected FVIII inhibitor if the result was 'not detected' at screening and 'detected' at any time post-screening. Subjects are presented based on their initial treatment event.

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

End point timeframe:

Screening through 30-day Follow-up

Notes:

[30] - 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 per protocol for this endpoint.

End point values	Minor Surgery - Safety Set	Major Surgery - Safety Set	Non-surgery Bleed - Safety Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	9	2	
Units: subjects				
FVIII inhibitors not detected at Screening	8	9	2	
FVIII inhibitors detected at Screening	0	0	0	
FVIII inhibitors newly detected at 30- day Followup	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: FVIII Inhibitors - Subjects Receiving Prophylactic Therapy

End point title	FVIII Inhibitors - Subjects Receiving Prophylactic Therapy ^[31]
-----------------	--

End point description:

A subject is considered to have a newly detected FVIII inhibitor if the result was 'not detected' at screening and 'detected' at any time post-screening. Subjects are presented based on their initial treatment event.

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

End point timeframe:

Screening, Months 3, 6, 9, and 12 (or Completion Visit)

Notes:

[31] - 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 per protocol for this endpoint.

End point values	Prophylactic - Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: subjects				
FVIII inhibitors not detected at Screening	4			
FVIII inhibitors detected at Screening	0			
FVIII inhibitors newly detected at Month 3	0			
FVIII inhibitors newly detected at Month 6	0			
FVIII inhibitors newly detected at Month 9	0			
FVIII inhibitors newly detected at Completion	0			
FVIII inhibitors newly detected at any point	0			

Statistical analyses

No statistical analyses for this end point

Primary: Subjects Using Concomitant Medications

End point title	Subjects Using Concomitant Medications ^[32]
-----------------	--

End point description:

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

End point timeframe:

Through Month 12

Notes:

[32] - 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 per protocol for this endpoint.

End point values	All Subjects - Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: subjects				
Used concomitant medications	23			
Used a FVIII/VWF containing-product (not Biostate)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Prophylactic subjects: from Day 0 through Month 12. Elective surgery subjects: Screening Visit through Month 12 + 30 days follow-up. Non-surgery bleeds/emergency surgery subjects: Day 0 through Month 12 + 30 days follow-up.

Adverse event reporting additional description:

Treatment-emergent AEs only. In addition to AEs collected during the stated time frame, AEs for all subjects undergoing surgery were collected from the first administration of Biostate used to treat/manage any additional nonsurgery bleeds/surgery procedures, up to 30 days after the last administration of Biostate used to treat/manage the event.

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

Reporting group title	All Subjects - Safety Set
-----------------------	---------------------------

Reporting group description:

The Safety Set is defined as all subjects who received at least one dose of Biostate (either trial or non-trial Biostate).

Serious adverse events	All Subjects - Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 23 (8.70%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 23 (4.35%)		
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	All Subjects - Safety Set		
Total subjects affected by non-serious adverse events subjects affected / exposed	21 / 23 (91.30%)		
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	7 / 23 (30.43%) 7		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 3		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	6 / 23 (26.09%) 6		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 3 2 / 23 (8.70%) 2		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Oral pain subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain	6 / 23 (26.09%) 6 3 / 23 (13.04%) 3 3 / 23 (13.04%) 3 3 / 23 (13.04%) 3		

subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2 2 / 23 (8.70%) 2		
Infections and infestations Infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2 2 / 23 (8.70%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2004	Amendment 1, dated 4 November 2004, was before the enrollment of the first subject and was considered to be the initial trial protocol.
10 November 2005	<ul style="list-style-type: none">• To include paediatric patients over 3 years old into the study, enrollment was extended to allow patients between the ages of 3 and 12 years old, who were already receiving Biostate, to be enrolled into the study at the discretion of the investigator. For the non-surgery bleed and surgery procedures, the investigator was to take into consideration the blood profile of the patient and the required blood draw volume, bearing in mind that 17 mL of blood was to be drawn prior to each administration of Biostate and that in accordance with the National Institute of Health Clinical Centre Guidelines, a paediatric blood draw should not exceed 3 mL/kg, or 7 mL/kg in a 6-week period.• To incorporate a change in the presentation of Biostate to include the Mix2Vial™ filter set.• To include the details of the New Zealand sites for submission of the protocol to New Zealand Ethics Committees

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported