



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.

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|----------------------------|------------------------|
| 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

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|-----------------|--|
| 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