



## Clinical trial results:

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

#### Summary

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

#### Results information

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

#### Trial information

##### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | CSLCT-BIO-07-47 |
|-----------------------|-----------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |                                                                               |
|------------------------------|-------------------------------------------------------------------------------|
| Sponsor organisation name    | CSL Behring GmbH                                                              |
| Sponsor organisation address | Emil-von-Behring-Str. 76, Marburg, Germany, 35041                             |
| Public contact               | Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.com |
| Scientific contact           | Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.com |

Notes:

#### Paediatric regulatory details

|                                                                      |                     |
|----------------------------------------------------------------------|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000312-PIP01-08 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No                  |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes                 |

Notes:

## Results analysis stage

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 10 December 2010 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 15 October 2010  |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

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

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

Protection of trial subjects:

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

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

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 31 March 2009 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                                               |
|--------------------------------------|-----------------------------------------------|
| Country: Number of subjects enrolled | Poland: 20                                    |
| Country: Number of subjects enrolled | Bulgaria: 34                                  |
| Country: Number of subjects enrolled | Macedonia, the former Yugoslav Republic of: 4 |
| Country: Number of subjects enrolled | Russian Federation: 23                        |
| Worldwide total number of subjects   | 81                                            |
| EEA total number of subjects         | 54                                            |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 3  |
| Adults (18-64 years)                      | 77 |
| From 65 to 84 years                       | 1  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

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

### Period 1

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

Blinding implementation details:

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

### Arms

|                              |                          |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | No                       |
| <b>Arm title</b>             | Biostate SP (Day 1 or 8) |

Arm description:

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

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

Dosage and administration details:

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

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | Biostate RP (Day 1 or 8) |
|------------------|--------------------------|

Arm description:

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

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

Dosage and administration details:

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

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

## Period 2

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

## Arms

|           |             |
|-----------|-------------|
| Arm title | Biostate SP |
|-----------|-------------|

### Arm description:

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

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

### Dosage and administration details:

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

### Notes:

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

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

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

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**Period 3**

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

**Arms**

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | Biostate SP (Day 180) |
|------------------|-----------------------|

Arm description:

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

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

Dosage and administration details:

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

|                                                     |                       |
|-----------------------------------------------------|-----------------------|
| <b>Number of subjects in period 3<sup>[2]</sup></b> | Biostate SP (Day 180) |
| Started                                             | 15                    |
| Completed                                           | 15                    |

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Notes:

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

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

## Baseline characteristics

### Reporting groups

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Part 2: Efficacy Component |
|-----------------------|----------------------------|

Reporting group description:

Each subject in the efficacy component (Part 2) of the study received a dose of Biostate SP as determined by the Investigator based on the subject's clinical condition, previous FVIII concentrate requirements, response to therapy, body weight, and reason for usage during the 6-month efficacy period (for a minimum of 50 exposure days).

The frequency and dose (loading and maintenance) of Biostate SP during the efficacy component was determined by the Investigator.

| Reporting group values                             | Part 2: Efficacy Component | Total |  |
|----------------------------------------------------|----------------------------|-------|--|
| Number of subjects                                 | 81                         | 81    |  |
| Age categorical                                    |                            |       |  |
| Units: Subjects                                    |                            |       |  |
| In utero                                           | 0                          | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0                          | 0     |  |
| Newborns (0-27 days)                               | 0                          | 0     |  |
| Infants and toddlers (28 days-23 months)           | 0                          | 0     |  |
| Children (2-11 years)                              | 0                          | 0     |  |
| Adolescents (12-17 years)                          | 3                          | 3     |  |
| Adults (18-64 years)                               | 77                         | 77    |  |
| From 65-84 years                                   | 1                          | 1     |  |
| 85 years and over                                  | 0                          | 0     |  |
| Age continuous                                     |                            |       |  |
| Units: years                                       |                            |       |  |
| arithmetic mean                                    | 33.1                       |       |  |
| standard deviation                                 | ± 12.8                     | -     |  |
| Gender categorical                                 |                            |       |  |
| Units: Subjects                                    |                            |       |  |
| Female                                             | 0                          | 0     |  |
| Male                                               | 81                         | 81    |  |

## End points

### End points reporting groups

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

### Primary: Investigator's Monthly Assessment of Haemostatic Efficacy

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

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



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

Notes:

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

## Statistical analyses

No statistical analyses for this end point

### Primary: Blood Product Transfusions: Total Amount Received

|                 |                                                                  |
|-----------------|------------------------------------------------------------------|
| End point title | Blood Product Transfusions: Total Amount Received <sup>[3]</sup> |
|-----------------|------------------------------------------------------------------|

End point description:

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

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

End point timeframe:

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

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

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

Notes:

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

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                               |
|-----------------|-------------------------------------------------------------------------------|
| End point title | Usage of Biostate SP: Number of Infusions Overall and By Month <sup>[5]</sup> |
|-----------------|-------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

Month 1 through Month 12

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

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

Notes:

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

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                        |
|-----------------|------------------------------------------------------------------------|
| End point title | Usage of Biostate SP: Average Dose Overall and By Month <sup>[7]</sup> |
|-----------------|------------------------------------------------------------------------|

End point description:

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

End point timeframe:

Months 1 through 12 of efficacy period

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

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

Notes:

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

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                           |
|-----------------|---------------------------------------------------------------------------|
| End point title | Investigator's Assessment of Blood Loss Per Surgical Event <sup>[9]</sup> |
|-----------------|---------------------------------------------------------------------------|

**End point description:**

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

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

End point timeframe:

Efficacy Period (up to Month 12)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

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

Notes:

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

**Statistical analyses**

No statistical analyses for this end point

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

|                 |                                                                 |
|-----------------|-----------------------------------------------------------------|
| End point title | PK Parameter, Part 1: Incremental Recovery (IR) <sup>[11]</sup> |
|-----------------|-----------------------------------------------------------------|

End point description:

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

End point timeframe:

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

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Planned analyses for this endpoint are presented in data table.

| End point values                     | Biostate SP<br>(Day 1 or 8) | Biostate RP<br>(Day 1 or 8) |  |  |
|--------------------------------------|-----------------------------|-----------------------------|--|--|
| Subject group type                   | Reporting group             | Reporting group             |  |  |
| Number of subjects analysed          | 16                          | 16                          |  |  |
| Units: kg/mL                         |                             |                             |  |  |
| arithmetic mean (standard deviation) | 0.021 ( $\pm$ 0.006)        | 0.023 ( $\pm$ 0.005)        |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: PK Parameter, Part 1: Half-life (t<sub>1/2</sub>)

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | PK Parameter, Part 1: Half-life (t <sub>1/2</sub> ) <sup>[12]</sup> |
|-----------------|---------------------------------------------------------------------|

End point description:

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

End point timeframe:

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

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Planned analyses for this endpoint are presented in data table.

| End point values                     | Biostate SP<br>(Day 1 or 8) | Biostate RP<br>(Day 1 or 8) |  |  |
|--------------------------------------|-----------------------------|-----------------------------|--|--|
| Subject group type                   | Reporting group             | Reporting group             |  |  |
| Number of subjects analysed          | 16                          | 16                          |  |  |
| Units: hours                         |                             |                             |  |  |
| arithmetic mean (standard deviation) | 13.4 ( $\pm$ 2.53)          | 13.07 ( $\pm$ 1.82)         |  |  |

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point timeframe:

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

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

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                                                                          | Bioequivalence of Biostate SP versus Biostate RP    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| Statistical analysis description:<br>From a mixed effects analysis of variance with treatment (Biostate SP, Biostate RP), period (Infusion 1, Infusion 2), and sequence (Sequence 1, Sequence 2) as fixed effects, and subject nested in sequence as random effect. |                                                     |
| Comparison groups                                                                                                                                                                                                                                                   | Biostate RP (Day 1 or 8) v Biostate SP (Day 1 or 8) |
| Number of subjects included in analysis                                                                                                                                                                                                                             | 32                                                  |
| Analysis specification                                                                                                                                                                                                                                              | Pre-specified                                       |
| Analysis type                                                                                                                                                                                                                                                       | equivalence <sup>[13]</sup>                         |
| P-value                                                                                                                                                                                                                                                             | = 0.374                                             |
| Method                                                                                                                                                                                                                                                              | ANOVA                                               |
| Parameter estimate                                                                                                                                                                                                                                                  | Mean difference (final values)                      |
| Point estimate                                                                                                                                                                                                                                                      | -0.05                                               |
| Confidence interval                                                                                                                                                                                                                                                 |                                                     |
| level                                                                                                                                                                                                                                                               | 90 %                                                |
| sides                                                                                                                                                                                                                                                               | 2-sided                                             |
| lower limit                                                                                                                                                                                                                                                         | -0.14                                               |
| upper limit                                                                                                                                                                                                                                                         | 0.05                                                |

Notes:

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

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

| End point title        | PK Parameter, Part 1: Mean Residence Time (MRT) <sup>[14]</sup> |
|------------------------|-----------------------------------------------------------------|
| End point description: |                                                                 |
| End point type         | Primary                                                         |

End point timeframe:

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

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Planned analyses for this endpoint are presented in data table.

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point timeframe:

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

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

## Statistical analyses

|                            |                                                  |
|----------------------------|--------------------------------------------------|
| Statistical analysis title | Bioequivalence of Biostate SP versus Biostate RP |
|----------------------------|--------------------------------------------------|

Statistical analysis description:

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

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

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

Notes:

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

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

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

End point description:

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

End point timeframe:

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

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Planned analyses for this endpoint are presented in data table.

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point timeframe:

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

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Planned analyses for this endpoint are presented in data table.



| End point values                     | Biostate SP<br>(Day 1 or 8) | Biostate RP<br>(Day 1 or 8) |  |  |
|--------------------------------------|-----------------------------|-----------------------------|--|--|
| Subject group type                   | Reporting group             | Reporting group             |  |  |
| Number of subjects analysed          | 16                          | 16                          |  |  |
| Units: IU/mL                         |                             |                             |  |  |
| arithmetic mean (standard deviation) | 0.06 ( $\pm$ 0.028)         | 0.061 ( $\pm$ 0.024)        |  |  |

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                            |
|-----------------|------------------------------------------------------------|
| End point title | PK Parameter, Part 1: Total Clearance (CL) <sup>[18]</sup> |
|-----------------|------------------------------------------------------------|

End point description:

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

End point timeframe:

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

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Planned analyses for this endpoint are presented in data table.

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

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                    |
|-----------------|--------------------------------------------------------------------|
| End point title | PK Parameter, Part 1: Volume at Steady State (Vss) <sup>[19]</sup> |
|-----------------|--------------------------------------------------------------------|

End point description:

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

End point timeframe:

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

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Planned analyses for this endpoint are presented in data table.

| End point values                     | Biostate SP<br>(Day 1 or 8) | Biostate RP<br>(Day 1 or 8) |  |  |
|--------------------------------------|-----------------------------|-----------------------------|--|--|
| Subject group type                   | Reporting group             | Reporting group             |  |  |
| Number of subjects analysed          | 16                          | 16                          |  |  |
| Units: mL/kg                         |                             |                             |  |  |
| arithmetic mean (standard deviation) | 65.33 ( $\pm$ 20.65)        | 62.57 ( $\pm$ 23.12)        |  |  |

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point timeframe:

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

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Planned analyses for this endpoint are presented in data table.

| End point values                     | Biostate SP<br>(Day 1 or 8) | Biostate SP<br>(Day 180) |  |  |
|--------------------------------------|-----------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group             | Reporting group          |  |  |
| Number of subjects analysed          | 15                          | 15                       |  |  |
| Units: kg/mL                         |                             |                          |  |  |
| arithmetic mean (standard deviation) | 0.021 ( $\pm$ 0.005)        | 0.022 ( $\pm$ 0.004)     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: PK Parameter, Part 1 Versus Part 3: Half-life (t<sub>1/2</sub>)

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | PK Parameter, Part 1 Versus Part 3: Half-life (t <sub>1/2</sub> ) <sup>[21]</sup> |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

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

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Planned analyses for this endpoint are presented in data table.

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point timeframe:

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

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

## Statistical analyses

|                            |                              |
|----------------------------|------------------------------|
| Statistical analysis title | Part 1 versus Part 3 AUC0-48 |
|----------------------------|------------------------------|

Statistical analysis description:

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

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

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

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

|                 |                                                                               |
|-----------------|-------------------------------------------------------------------------------|
| End point title | PK Parameter, Part 1 Versus Part 3: Mean Residence Time (MRT) <sup>[22]</sup> |
|-----------------|-------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

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

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Planned analyses for this endpoint are presented in data table.

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point timeframe:

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

| <b>End point values</b>              | Biostate SP<br>(Day 1 or 8) | Biostate SP<br>(Day 180) |  |  |
|--------------------------------------|-----------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group             | Reporting group          |  |  |
| Number of subjects analysed          | 15                          | 15                       |  |  |
| Units: IU/mL                         |                             |                          |  |  |
| arithmetic mean (standard deviation) | 1.03 ( $\pm$ 0.26)          | 1.08 ( $\pm$ 0.21)       |  |  |

### Statistical analyses

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

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

|                 |                                                                                          |
|-----------------|------------------------------------------------------------------------------------------|
| End point title | PK Parameter, Part 1 Versus Part 3: Time of Maximum Concentration (tmax) <sup>[23]</sup> |
|-----------------|------------------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

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

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Planned analyses for this endpoint are presented in data table.

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

### Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------|
| End point title | PK Parameter, Part 1 Versus Part 3: Minimum Plasma Concentration (Cmin) <sup>[24]</sup> |
|-----------------|-----------------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

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

Notes:

[24] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Planned analyses for this endpoint are presented in data table.

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

### Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                          |
|-----------------|--------------------------------------------------------------------------|
| End point title | PK Parameter, Part 1 Versus Part 3: Total Clearance (CL) <sup>[25]</sup> |
|-----------------|--------------------------------------------------------------------------|

End point description:

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

End point timeframe:

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

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Planned analyses for this endpoint are presented in data table.

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

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                                  |
|-----------------|----------------------------------------------------------------------------------|
| End point title | PK Parameter, Part 1 Versus Part 3: Volume at Steady State (Vss) <sup>[26]</sup> |
|-----------------|----------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

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

Notes:

[26] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Planned analyses for this endpoint are presented in data table.

| End point values                     | Biostate SP<br>(Day 1 or 8) | Biostate SP<br>(Day 180) |  |  |
|--------------------------------------|-----------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group             | Reporting group          |  |  |
| Number of subjects analysed          | 15                          | 15                       |  |  |
| Units: mL/kg                         |                             |                          |  |  |
| arithmetic mean (standard deviation) | 67.35 ( $\pm$ 19.68)        | 60.07 ( $\pm$ 16.15)     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overview of Adverse Events During the Entire Study

|                 |                                                    |
|-----------------|----------------------------------------------------|
| End point title | Overview of Adverse Events During the Entire Study |
|-----------------|----------------------------------------------------|

End point description:

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

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

|                                                                                    |           |
|------------------------------------------------------------------------------------|-----------|
| End point type                                                                     | Secondary |
| End point timeframe:                                                               |           |
| Day 1 through the Final Study Visit (Day 187 or within 7 days after last infusion) |           |

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

Notes:

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Development of FVIII Inhibitors

|                                                                                                                                                                                                                                                                                                                                                                                                                      |                                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                      | Development of FVIII Inhibitors |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                               |                                 |
| Testing at Screening and Day 1 was prior to treatment. No subject developed inhibitors during the study; 1 subject had a positive test result, which was also reported as SAE that led to study discontinuation, however, after the event, delayed analysis of the subject's blood sample from Day 1 revealed that an increased inhibitor titre was already present at baseline prior to the first dose of Biostate. |                                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                       | Secondary                       |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                 |                                 |
| Screening, Day 1, Month 1, Month 3, and Final Visit (Day 187 or within 7 days after last infusion)                                                                                                                                                                                                                                                                                                                   |                                 |

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



|                                                     |    |  |  |  |
|-----------------------------------------------------|----|--|--|--|
| Month 1: FVIII Inhibitor Test Positive;<br>n=81     | 0  |  |  |  |
| Month 3: FVIII Inhibitor Test Negative;<br>n=80     | 80 |  |  |  |
| Month 3: FVIII Inhibitor Test Positive;<br>n=80     | 0  |  |  |  |
| Final Visit: FVIII Inhibitor Test Negative;<br>n=79 | 78 |  |  |  |
| Final Visit: FVIII Inhibitor Test Positive;<br>n=79 | 1  |  |  |  |

Notes:

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

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 11.1 |
|--------------------|------|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Safety Population |
|-----------------------|-------------------|

Reporting group description:

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

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 21 January 2009  | <ul style="list-style-type: none"><li>- The duration of the screening period was increased from up to 7 days to up to 14 days to allow sufficient processing time for the screening assessment.</li><li>- Reduced blood volumes for children were inserted.</li><li>- Introduction of the Independent Data Monitoring Committee (IDMC).</li><li>- Definition of major bleeding events was revised.</li><li>- FVIII level, haematology, and biochemistry determinations prior to major bleeding events or surgical procedures, respectively, were deleted.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 29 April 2009    | <ul style="list-style-type: none"><li>- Change of the exclusion criteria to allow the admission of subjects with a positive hepatitis C viral load but to exclude subjects with an active hepatitis C.</li><li>- Bicarbonate testing was deleted from biochemistry determinations as the testing procedure is contraindicated for bleeding disorders.</li><li>- Inconsistencies with regard to the start of the reporting period of AEs were resolved.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 04 November 2009 | <ul style="list-style-type: none"><li>- Change of laboratory parameters at screening to perform HIV viral load testing only if subjects were HIV antibody positive.</li><li>- Increase of the number of enrolled subjects from approximately 62 to approximately 80. This change in sample size was made in order to collect more efficacy data; the PK component and thus the sample size estimation as given in Section 9.7.2 was not affected by this change.</li><li>- Increase of the number of evaluable subjects from at least 50 subjects to at least 65 subjects.</li><li>- Specification of "prevention of bleedings" within the on-demand treatment regimen. As described in Section 9.4.5, it was found that in some centres subjects did not take Biostat in a prophylaxis regimen with regular administrations at intervals of 2-3 days (see Table 1) but as "prophylactic treatment" only when they expected to have an increased bleeding risk, eg, prior to physical exercise. This mainly occurred with subjects who undertook muscle or joint exercises as part of their rehabilitation after a surgical event or after a bleeding event in joints. A dose of 25-30 IU/kg FVIII was administered prior to such exercises. An algorithm to differentiate between prophylaxis and prevention treatment, and to assign subjects to corresponding subgroups was defined in the SAP prior to final database lock.</li></ul> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported