EU Clinical Trials Register

Clinical trial results:
A Phase III Open-label, Multi-centre Study to Assess the Pharmacokinetics, Efficacy, and Safety of Biostate® in Paediatric Subjects With von Willebrand Disease

Summary

EudraCT number	2009-017753-34
Trial protocol	DE BG
Global end of trial date	27 August 2013

Results information

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

Trial information

Trial identification

Sponsor protocol code	CSLCT-BIO-08-52

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To assess the efficacy of Biostate in paediatric subjects with von Willebrand disease (VWD).
2. To investigate the pharmacokinetics (PK) profile of Biostate in paediatric subjects with VWD.

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	29 July 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Ukraine: 3
Country: Number of subjects enrolled	Belarus: 2
Country: Number of subjects enrolled	Guatemala: 1
Country: Number of subjects enrolled	Georgia: 2
Country: Number of subjects enrolled	Lebanon: 6
Worldwide total number of subjects	17
EEA total number of subjects	3

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	2
Children (2-11 years)	15
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included a Screening period of up to 35 days.

Period 1

Period 1 title	Pharmacokinetic (PK) Component
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	PK Component

Arm description:

A single bolus intravenous (i.v.) infusion of 80 IU/kg von Willebrand factor: ristocetin cofactor (VWF RCo) on Day 1 (for the initial PK assessment) and on Day 180 (Month 6) for the repeat PK assessment (in type 3 VWD subjects only).

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

Dosage and administration details:

Biostate was administered at a maximum of 6 mL/min as tolerated by the subject.

Number of subjects in period 1	PK Component
Started	17
Repeat PK (Type 3 VWD PK Subjects Only)	9 [1]
Completed	17

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 9 subjects with VWD Type 3 participated in the repeat PK assessment, which occurred after the treatment period of the study had started. These subjects continued in the treatment period until the end of the study along with the other subjects.

Period 2

Period 2 title	Treatment Period (Efficacy Component)
Is this the baseline period?	Yes[2]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1: Prophylaxis Therapy

Arm description:

Subjects who were treated on a set prophylaxis regimen with a VWF product at the time of study entry were enrolled into the prophylaxis arm to receive Biostate as a pre-defined prophylaxis regimen determined by the Investigator according to the severity of their disease for a period of 12 months.

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

Dosage and administration details:

Biostate was administered at a maximum of 6 mL/min as tolerated by the subject.

Arm title	Arm 2: On-Demand Therapy

Arm description:

Subjects who were not treated on a set prophylaxis regimen with a VWF product at the time of study entry and who required a VWF product for the treatment of non-surgical bleeding (NSB) events (control during surgery, or spontaneous, or trauma induced) were enrolled to start Biostate treatment of NSB events (on-demand therapy). If Biostate was used for irregular prevention of bleedings, this was considered as "on demand" therapy. Subjects who had been on an on-demand therapy previously were allowed to switch to prophylaxis therapy at the beginning of the efficacy component.

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

Dosage and administration details:

Biostate was administered at a maximum of 6 mL/min as tolerated by the subject.

Notes:

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

Justification: The PK component ran concurrently with the Treatment period, which presents data by arm and was therefore chosen to present subject disposition.

Number of subjects in period 2	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy
Started	4	13
Completed	4	13

Baseline characteristics

Reporting groups

Reporting group title	Arm 1: Prophylaxis Therapy
Reporting group description:	

Subjects who were treated on a set prophylaxis regimen with a VWF product at the time of study entry were enrolled into the prophylaxis arm to receive Biostate as a pre-defined prophylaxis regimen determined by the Investigator according to the severity of their disease for a period of 12 months.

Reporting group title	Arm 2: On-Demand Therapy
Reporting group description:	

Subjects who were not treated on a set prophylaxis regimen with a VWF product at the time of study entry and who required a VWF product for the treatment of non-surgical bleeding (NSB) events (control during surgery, or spontaneous, or trauma induced) were enrolled to start Biostate treatment of NSB events (on-demand therapy). If Biostate was used for irregular prevention of bleedings, this was considered as "on demand" therapy. Subjects who had been on an on-demand therapy previously were allowed to switch to prophylaxis therapy at the beginning of the efficacy component.

Reporting group values	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy	Total
Number of subjects	4	13	17
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	2	2
Children (2-11 years)	4	11	15
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	5	5.3	
standard deviation	± 2.5	± 3.7	-
Gender categorical			
Units: Subjects			
Female	0	10	10
Male	4	3	7

End points

End points reporting groups

Reporting group title	PK Component
Reporting group description:	

A single bolus intravenous (i.v.) infusion of 80 IU/kg von Willebrand factor: ristocetin cofactor (VWF RCo) on Day 1 (for the initial PK assessment) and on Day 180 (Month 6) for the repeat PK assessment (in type 3 VWD subjects only).

Reporting group title	Arm 1: Prophylaxis Therapy
Reporting group description:	

Subjects who were treated on a set prophylaxis regimen with a VWF product at the time of study entry were enrolled into the prophylaxis arm to receive Biostate as a pre-defined prophylaxis regimen determined by the Investigator according to the severity of their disease for a period of 12 months.

Reporting group title	Arm 2: On-Demand Therapy
Reporting group description:	

Subjects who were not treated on a set prophylaxis regimen with a VWF product at the time of study entry and who required a VWF product for the treatment of non-surgical bleeding (NSB) events (control during surgery, or spontaneous, or trauma induced) were enrolled to start Biostate treatment of NSB events (on-demand therapy). If Biostate was used for irregular prevention of bleedings, this was considered as "on demand" therapy. Subjects who had been on an on-demand therapy previously were allowed to switch to prophylaxis therapy at the beginning of the efficacy component.

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

End point title	Investigator's 3-Monthly Assessment of Haemostatic Efficacy[1]
End point description:	

For each 3-month interval of the study, haemostatic efficacy was assessed by the Investigator for subjects with a bleeding event. The efficacy grading scale was as follows: excellent=haemostasis achieved/cessation of bleeding; good=slight oozing/partial but adequate control of bleeding, does not require additional product for unplanned treatment; moderate=moderate bleeding/moderate control of bleeding, required additional product for unplanned treatment; none=severe uncontrolled bleeding. Subjects who did not have any bleeding events are included in this table. Bleeding events for which no Biostate treatment was needed are not included in this table.

End point type	Primary
End point timeframe:	

Months 3, 6, 9, 12

Notes:

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

Justification: All efficacy variables were descriptively summarised by treatment arm and overall. No formal statistical tests were performed.

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[2]	12[3]		
Units: subjects				
Month 3: Excellent (n=4, 7)	2	3		
Month 3: Good (n=4, 7)	2	4		
Month 3: Moderate (n=4, 7)	0	0		
Month 3: None (n=4, 7)	0	0		
Month 6: Excellent (n=4, 10)	4	7		
Month 6: Good (n=4, 10)	0	3		

Month 6: Moderate (n=4, 10)	0	0		
Month 6: None (n=4, 10)	0	0		
Month 9: Excellent (n=4, 7)	4	4		
Month 9: Good (n=4, 7)	0	3		
Month 9: Moderate (n=4, 7)	0	0		
Month 9: None (n=4, 7)	0	0		
Month 12: Excellent (n=4, 10)	3	5		
Month 12: Good (n=4, 10)	1	5		
Month 12: Moderate (n=4, 10)	0	0		
Month 12: None (n=4, 10)	0	0		

Notes:

[2] - Efficacy population; n=subjects with available Investigator's assessment in given month interval.

[3] - Efficacy population; n=subjects with available Investigator's assessment in given month interval.

Statistical analyses

No statistical analyses for this end point

Primary: Investigator's Assessment of Haemostatic Efficacy per Non-surgical Bleeding (NSB) Event

End point title	Investigator's Assessment of Haemostatic Efficacy per Non-surgical Bleeding (NSB) Event[4]

End point description:

Clinical assessments of haemostatic efficacy for all non-surgical bleeding events were done by the investigator in conjunction with the subject (or legal guardian) throughout the efficacy component of the study. 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. Bleeding events with missing Investigator's assessment for efficacy, or events for which no Biostate treatment was needed, were not considered for this table. Major bleeding event=one that involves any bleeding into a joint, muscle, or mucosal bleeds of the gastro-intestinal tract (excluding nasal or oral bleeding). All other bleeding events were classified as minor unless the Investigator assessment noted otherwise.

End point type	Primary

End point timeframe:

Up to Month 12

Notes:

[4] - 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: All efficacy variables were descriptively summarised by treatment arm and overall. No formal statistical tests were performed.

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[5]	12[6]		
Units: events				
All NSB Events: Excellent; n=73, 80	59	36		
All NSB Events: Good; n=73, 80	14	44		
All NSB Events: Moderate; n=73, 80	0	0		
All NSB Events: None; n=73, 80	0	0		
Spontaneous Events: Excellent; n=59, 62	49	26		
Spontaneous Events: Good; n=59, 62	10	36		
Spontaneous Events: Moderate; n=59, 62	0	0		

Spontaneous Events: None; n=59, 62	0	0
Trauma Events: Excellent; n=14, 18	10	10
Trauma Events: Good; n=14, 18	4	8
Trauma Events: Moderate; n=14, 18	0	0
Trauma Events: None; n=14, 18	0	0
Post-surgery Events: Excellent; n=0, 0	0	0
Post-surgery Events: Good; n=0, 0	0	0
Post-surgery Events: Moderate; n=0, 0	0	0
Post-surgery Events: None; n=0, 0	0	0
Major Events: Excellent; n=3, 26	1	13
Major Events: Good; n=3, 26	2	13
Major Events: Moderate; n=3, 26	0	0
Major Events: None; n=3, 26	0	0
Minor Events: Excellent; n=70, 54	58	23
Minor Events: Good; n=70, 54	12	31
Minor Events: Moderate; n=70, 54	0	0
Minor Events: None; n=70, 54	0	0
Joint Events: Excellent; n=3, 11	0	2
Joint Events: Good; n=3, 11	3	9
Joint Events: Moderate; n=3, 11	0	0
Joint Events: None; n=3, 11	0	0
Mucosal Events: Excellent; n=62, 65	53	30
Mucosal Events: Good; n=62, 65	9	35
Mucosal Events: Moderate; n=62, 65	0	0
Mucosal Events: None; n=62, 65	0	0
Muscle Events: Excellent; n=0, 1	0	1
Muscle Events: Good; n=0, 1	0	0
Muscle Events: Moderate; n=0, 1	0	0
Muscle Events: None; n=0, 1	0	0
Other Events: Excellent; n=8, 3	6	3
Other Events: Good; n=8, 3	2	0
Other Events: Moderate; n=8, 3	0	0
Other Events: None; n=8, 3	0	0

Notes:

[5] - Efficacy population; n=NSB events treated with Biostate and with a haemostatic efficacy assessment.

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

Statistical analyses

No statistical analyses for this end point

Primary: Subject's Assessment of Haemostatic Efficacy per Day of Non-surgical Bleeding (NSB) Event

End point title	Subject's Assessment of Haemostatic Efficacy per Day of Non-surgical Bleeding (NSB) Event[7]

End point description:

Assessments of haemostatic efficacy were done by the subject (or legal guardian) throughout the efficacy component of the study. 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. Bleeding events with missing subject's assessment for efficacy or events for which no Biostate treatment was needed are not included in this table.

End point type	Primary

End point timeframe:
Up to Month 12

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: All efficacy variables were descriptively summarised by treatment arm and overall. No formal statistical tests were performed.

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[8]	12[9]		
Units: days				
All Days: Excellent; n=76, 55	60	33		
All Days: Good; n=76, 55	16	12		
All Days: Moderate; n=76, 55	0	10		
All Days: None; n=76, 55	0	0		
Day 1: Excellent; n=72, 45	60	29		
Day 1: Good; n=72, 45	12	7		
Day 1: Moderate; n=72, 45	0	9		
Day 1: None; n=72, 45	0	0		
Day 2: Excellent; n=1, 8	0	3		
Day 2: Good; n=1, 8	1	4		
Day 2: Moderate; n=1, 8	0	1		
Day 2: None; n=1, 8	0	0		
Day 3: Excellent; n=1, 1	0	1		
Day 3: Good; n=1, 1	1	0		
Day 3: Moderate; n=1, 1	0	0		
Day 3: None; n=1, 1	0	0		
Day 4: Excellent; n=1, 1	0	0		
Day 4: Good; n=1, 1	1	1		
Day 4: Moderate; n=1, 1	0	0		
Day 4: None; n=1, 1	0	0		
Day 5: Excellent; n=1, 0	0	0		
Day 5: Good; n=1, 0	1	0		
Day 5: Moderate; n=1, 0	0	0		
Day 5: None; n=1, 0	0	0		

Notes:

[8] - Efficacy population; n=total number of days due to bleeds with available subject's assessment.

[9] - Efficacy population; n=total number of days due to bleeds with available subject's assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Investigator's Assessment of Haemostatic Efficacy During Surgeries at Discharge

End point title	Investigator's Assessment of Haemostatic Efficacy During Surgeries at Discharge[10]

End point description:

Clinical assessments of haemostatic efficacy were done by the investigator in conjunction with the subject (or legal guardian) throughout the efficacy component of the study. 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. Surgeries with missing investigator's assessment for efficacy are not included. 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:

Up to Month 12

Notes:

[10] - 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: All efficacy variables were descriptively summarised by treatment arm and overall. No formal statistical tests were performed.

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[11]	12[12]		
Units: surgeries				
All surgeries: Excellent; n=0, 8	0	7		
All surgeries: Good; n=0, 8	0	1		
All surgeries: Moderate; n=0, 8	0	0		
All surgeries: None; n=0, 8	0	0		
Major surgeries: Excellent; n=0, 0	0	0		
Major surgeries: Good; n=0, 0	0	0		
Major surgeries: Moderate; n=0, 0	0	0		
Major surgeries: None; n=0, 0	0	0		
Minor surgeries: Excellent; n=0, 8	0	7		
Minor surgeries: Good; n=0, 8	0	1		
Minor surgeries: Moderate; n=0, 8	0	0		
Minor surgeries: None; n=0, 8	0	0		

Notes:

[11] - Efficacy population; n=number of surgeries of given type with available investigator's assessment.

[12] - Efficacy population; n=number of surgeries of given type with available investigator's assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Investigator's Assessment of Haemostatic Efficacy for Surgeries per In-house Day

End point title	Investigator's Assessment of Haemostatic Efficacy for Surgeries per In-house Day[13]

End point description:

Clinical assessments of haemostatic efficacy were done by the investigator in conjunction with the subject (or legal guardian) throughout the efficacy component of the study. 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. Surgeries with missing investigator's assessment for efficacy are not included.

End point type	Primary

End point timeframe:

Up to Month 12

Notes:

[13] - 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: All efficacy variables were descriptively summarised by treatment arm and overall. No formal statistical tests were performed.

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[14]	12[15]		
Units: in-house days due to surgeries				
All Days: Excellent; n=0, 8	0	7		
All Days: Good; n=0, 8	0	1		
All Days: Moderate; n=0, 8	0	0		
All Days: None; n=0, 8	0	0		
Day 1: Excellent; n=0, 7	0	7		
Day 1: Good; n=0, 7	0	0		
Day 1: Moderate; n=0, 7	0	0		
Day 1: None; n=0, 7	0	0		
Day 7: Excellent; n=0, 1	0	0		
Day 7: Good; n=0, 1	0	1		
Day 7: Moderate; n=0, 1	0	0		
Day 7: None; n=0, 1	0	0		

Notes:

[14] - Efficacy population; n=in-house days due to surgeries with available investigator's assessment.

[15] - Efficacy population; n=in-house days due to surgeries with available investigator's assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Investigator's Post-Surgery Assessment of Haemostatic Efficacy

End point title	Investigator's Post-Surgery Assessment of Haemostatic

End point description:

Clinical assessments of haemostatic efficacy were done by the investigator in conjunction with the subject (or legal guardian) throughout the efficacy component of the study. 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. Surgeries with missing investigator's assessment for efficacy are not included. 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:

Up to Month 12

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: All efficacy variables were descriptively summarised by treatment arm and overall. No formal statistical tests were performed.

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[17]	12[18]		
Units: surgeries				
All Surgeries: Excellent; n=0, 4	0	3		
All Surgeries: Good; n=0, 4	0	1		
All Surgeries: Moderate; n=0, 4	0	0		
All Surgeries: None; n=0, 4	0	0		
Major Surgeries: Excellent; n=0, 0	0	0		
Major Surgeries: Good; n=0, 0	0	0		
Major Surgeries: Moderate; n=0, 0	0	0		
Major Surgeries: None; n=0, 0	0	0		
Minor Surgeries: Excellent; n=0, 4	0	3		
Minor Surgeries: Good; n=0, 4	0	1		
Minor Surgeries: Moderate; n=0, 4	0	0		
Minor Surgeries: None; n=0, 4	0	0		

Notes:

[17] - Efficacy population; n=surgeries with available investigator's post-surgery assessment.

[18] - Efficacy population; n=surgeries with available investigator's post-surgery assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Subject's Daily Post-Surgery Assessment of Haemostatic Efficacy at Home

End point title	Subject's Daily Post-Surgery Assessment of Haemostatic Efficacy at Home[19]

End point description:

Assessments of haemostatic efficacy were done by the subject (or legal guardian) throughout the efficacy component of the study. 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. Surgeries with missing subject's assessment for efficacy are not included.

End point type	Primary

End point timeframe:

Up to Month 12

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All efficacy variables were descriptively summarised by treatment arm and overall. No formal statistical tests were performed.

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[20]	12[21]		
Units: post-surgery days				
All Days: Excellent; n=0, 2	0	0		
All Days: Good; n=0, 2	0	2		
All Days: Moderate; n=0, 2	0	0		
All Days: None; n=0, 2	0	0		
Day 6: Excellent; n=0, 1	0	0		

Day 6: Good; n=0, 1	0	1		
Day 6: Moderate; n=0, 1	0	0		
Day 6: None; n=0, 1	0	0		
Day 7: Excellent; n=0, 1	0	0		
Day 7: Good; n=0, 1	0	1		
Day 7: Moderate; n=0, 1	0	0		
Day 7: None; n=0, 1	0	0		

Notes:

[20] - Efficacy population; n=total post-surgery days at home with available subject's assessment.

[21] - Efficacy population; n=total post-surgery days at home with available subject's assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Initial PK Assessment: Incremental Recovery (IR)

End point title	Initial PK Assessment: Incremental Recovery (IR)[22]

End point description:

Baseline-adjusted IR of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant activity (FVIII:C) from the initial PK assessment.

End point type	Primary

End point timeframe:

Day 1: preinfusion; Days 1-3: 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±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: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	17[23]			
Units: IU/mL / IU/kg				
geometric mean (geometric coefficient of variation)				
VWF:RCo; n=17	0.014 (± 19.1)			
VWF:Ag; n=17	0.014 (± 23.7)			
VWF:CB; n=17	0.013 (± 16.9)			
FVIII:C; n=16	0.018 (± 45.8)			

Notes:

[23] - PK population; n=number of subjects with an evaluable assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Initial PK Assessment: Half-life (t1/2)

End point title	Initial PK Assessment: Half-life (t1/2)[24]

End point description:

Baseline-adjusted t1/2 of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:

antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant activity (FVIII:C) from the initial PK assessment.

End point type	Primary

End point timeframe:

Day 1: preinfusion; Days 1-3: 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±2) h after the end of infusion.

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: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	17[25]			
Units: hours				
geometric mean (geometric coefficient of variation)				
VWF:RCo; n=11	10 (± 49.7)			
VWF:Ag; n=16	11.2 (± 28.3)			
VWF:CB; n=16	10 (± 20.8)			
FVIII:C; n=10	21 (± 52.5)			

Notes:

[25] - PK population; n=number of subjects with an evaluable assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Initial PK Assessment: Maximum Concentration (Cmax)

End point title	Initial PK Assessment: Maximum Concentration (Cmax)[26]

End point description:

Baseline-adjusted Cmax of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant activity (FVIII:C) from the initial PK assessment.

End point type	Primary

End point timeframe:

Day 1: preinfusion; Days 1-3: 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±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: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	17[27]			
Units: IU/mL				
geometric mean (geometric coefficient of variation)				

VWF:RCo; n=17	1.23 (± 44.9)			
VWF:Ag; n=17	1.91 (± 48.1)			
VWF:CB; n=17	1.67 (± 43.5)			
FVIII:C; n=16	0.75 (± 48.4)			

Notes:

[27] - PK population; n=number of subjects with evaluable assessments.

Statistical analyses

No statistical analyses for this end point

Primary: Initial PK Assessment: Area Under the Plasma Concentration-time Curve From Time 0 to the Last Sampling Time (AUC[0-t])

End point title	Initial PK Assessment: Area Under the Plasma Concentration-time Curve From Time 0 to the Last Sampling Time (AUC[0-t])[28]

End point description:

Baseline-adjusted AUC(0-t) of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor: antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant activity (FVIII:C) from the initial PK assessment.

End point type	Primary

End point timeframe:

Day 1: preinfusion; Days 1-3: 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±2) h after the end of infusion.

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	17[29]			
Units: h*IU/mL				
geometric mean (geometric coefficient of variation)				
VWF:RCo; n=17	9.85 (± 62.4)			
VWF:Ag; n=17	23 (± 51.8)			
VWF:CB; n=17	18.5 (± 50.3)			
FVIII:C; n=16	16.8 (± 71.3)			

Notes:

[29] - PK population; n=number of subjects with evaluable assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Initial PK Assessment: Area Under the Plasma Concentration-time Curve From Time 0 to Infinity (AUC[0-inf])

End point title	Initial PK Assessment: Area Under the Plasma Concentration-time Curve From Time 0 to Infinity (AUC[0-inf])[30]

End point description:

Baseline-adjusted AUC(0-inf) of von Willebrand factor: ristocetin cofactor (VWF:RCo), von Willebrand factor: antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant activity (FVIII:C) from the initial PK assessment.

End point type	Primary

End point timeframe:

Day 1: preinfusion; Days 1-3: 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±2) h after the end of infusion.

Notes:

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

Justification: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	17[31]			
Units: h*IU/mL				
geometric mean (geometric coefficient of variation)				
VWF:RCo; n=11	13.3 (± 56.1)			
VWF:Ag; n=16	25.6 (± 51.1)			
VWF:CB; n=16	19.6 (± 50.5)			
FVIII:C; n=10	20.1 (± 96.2)			

Notes:

[31] - PK population; n=number of subjects with an evaluable assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Initial PK Assessment: Clearance (CL)

End point title	Initial PK Assessment: Clearance (CL)[32]

End point description:

Baseline-adjusted clearance of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant activity (FVIII:C) from the initial PK assessment.

End point type	Primary

End point timeframe:

Day 1: preinfusion; Days 1-3: 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±2) h after the end of infusion.

Notes:

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

Justification: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	17[33]			
Units: mL/h/kg				
geometric mean (geometric coefficient of variation)				
VWF:RCo; n=11	7.23 (± 49.2)			
VWF:Ag; n=16	5.4 (± 45.8)			
VWF:CB; n=16	6.51 (± 27.5)			
FVIII:C; n=10	2.26 (± 171)			

Notes:

[33] - PK population;n=number of subjects with evaluable assessments.

Statistical analyses

No statistical analyses for this end point

Primary: Initial PK Assessment: Volume of Distribution at Steady State (Vss)

End point title	Initial PK Assessment: Volume of Distribution at Steady State (Vss)[34]

End point description:

Baseline-adjusted Vss of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant activity (FVIII:C) from the initial PK assessment.

End point type	Primary

End point timeframe:

Day 1: preinfusion; Days 1-3: 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±2) h after the end of infusion.

Notes:

[34] - 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: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	17[35]			
Units: mL/kg				
geometric mean (geometric coefficient of variation)				
VWF:RCo; n=11	87 (± 28.2)			
VWF:Ag; n=16	76.1 (± 27)			
VWF:CB; n=16	80.4 (± 18.5)			
FVIII:C; n=10	62.8 (± 57.9)			

Notes:

[35] - PK population; n=number of subjects with an evaluable assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Repeat PK Assessment: Incremental Recovery (IR)

End point title	Repeat PK Assessment: Incremental Recovery (IR)[36]

End point description:

Baseline-adjusted IR of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant activity

End point type	Primary

End point timeframe:

Day 180: preinfusion, 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±2) h after the end of infusion.

Notes:

[36] - 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: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	9[37]			
Units: (IU/mL)/(IU/kg)				
geometric mean (geometric coefficient of variation)				
VWF:RCo	0.016 (± 18.9)			
VWF:Ag	0.013 (± 16.1)			
VWF:CB	0.013 (± 14.3)			
FVIII:C	0.02 (± 20.3)			

Notes:

[37] - Repeat PK population

Statistical analyses

No statistical analyses for this end point

Primary: Repeat PK Assessment: Half-life (t1/2)

End point title	Repeat PK Assessment: Half-life (t1/2)[38]

End point description:

Baseline-adjusted t1/2 of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant activity

End point type	Primary

End point timeframe:

Day 180: preinfusion, 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±2) h after the end of infusion.

Notes:

[38] - 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: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	9[39]			
Units: hours				
geometric mean (geometric coefficient of variation)				
VWF:RCo; n=9	12.1 (± 36.3)			
VWF:Ag; n=9	12.4 (± 20.7)			
VWF:CB; n=9	11 (± 19.3)			
FVIII:C; n=3	33.9 (± 25.5)			

Notes:

[39] - Repeat PK population; n=number of subjects with an evaluable assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Repeat PK Assessment: Maximum Concentration (Cmax)

End point title	Repeat PK Assessment: Maximum Concentration (Cmax)[40]

End point description:

Baseline-adjusted Cmax of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant activity (FVIII:C) from the initial PK assessment.

End point type	Primary

End point timeframe:

Day 180: preinfusion, 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±2) h after the end of infusion.

Notes:

[40] - 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: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	9[41]			
Units: IU/mL				
geometric mean (geometric coefficient of variation)				
VWF:RCo	1.42 (± 18.2)			
VWF:Ag	1.94 (± 27.6)			
VWF:CB	1.75 (± 19.8)			
FVIII:C	0.85 (± 36.5)			

Notes:

[41] - Repeat PK population

Statistical analyses

No statistical analyses for this end point

Primary: Repeat PK Assessment: Area Under the Plasma Concentration-time Curve

From Time 0 to the Last Sampling Time (AUC[0-t])

End point title	Repeat PK Assessment: Area Under the Plasma Concentration-time Curve From Time 0 to the Last Sampling Time (AUC[0-t])[42]

End point description:

Baseline-adjusted AUC(0-t) of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor: antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant activity (FVIII:C) from the initial PK assessment.

End point type	Primary

End point timeframe:

Day 180: preinfusion, 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±2) h after the end of infusion.

Notes:

[42] - 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: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	9[43]			
Units: h*IU/mL				
geometric mean (geometric coefficient of variation)				
VWF:RCo	13.5 (± 36.8)			
VWF:Ag	27.2 (± 34.3)			
VWF:CB	22.6 (± 33.7)			
FVIII:C	28.1 (± 45.9)			

Notes:

[43] - Repeat PK population

Statistical analyses

No statistical analyses for this end point

Primary: Repeat PK Assessment: Area Under the Plasma Concentration-time Curve From Time 0 to Infinity (AUC[0-inf])

End point title	Repeat PK Assessment: Area Under the Plasma Concentration-time Curve From Time 0 to Infinity (AUC[0-inf])[44]

End point description:

Baseline-adjusted AUC(0-inf) of von Willebrand factor: ristocetin cofactor (VWF:RCo), von Willebrand factor: antigen (VWF:Ag), von Willebrand factor: collagen binding (VWF:CB) and Factor VIII: coagulant activity (FVIII:C) from the initial PK assessment.

End point type	Primary

End point timeframe:

Day 180: preinfusion, 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±2) h after the end of infusion.

Notes:

[44] - 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: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	9[45]			
Units: h*IU/mL				
geometric mean (geometric coefficient of variation)				
VWF:RCo; n=9	15.2 (± 36.4)			
VWF:Ag; n=9	29.2 (± 36.4)			
VWF:CB; n=9	23.8 (± 36.7)			
FVIII:C; n=3	41.3 (± 27.1)			

Notes:

[45] - Repeat PK population; n=number of subjects with an evaluable assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Repeat PK Assessment: Clearance (CL)

End point title	Repeat PK Assessment: Clearance (CL)[46]

End point description:

Baseline-adjusted clearance of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor: antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant activity (FVIII:C) from the initial PK assessment.

End point type	Primary

End point timeframe:

Day 180: preinfusion, 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±2) h after the end of infusion.

Notes:

[46] - 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: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	17[47]			
Units: mL/h/kg				
geometric mean (geometric coefficient of variation)				
VWF:RCo; n=9	5.81 (± 42)			
VWF:Ag; n=9	5.13 (± 19)			
VWF:CB; n=9	5.52 (± 13.9)			
FVIII:C; n=3	0.91 (± 28.1)			

Notes:

[47] - Repeat PK population;n=number of subjects with evaluable assessments.

Statistical analyses

No statistical analyses for this end point

Primary: Repeat PK Assessment: Volume of Distribution at Steady State (Vss)

End point title	Repeat PK Assessment: Volume of Distribution at Steady State (Vss)[48]

End point description:

Baseline-adjusted Vss of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant activity (FVIII:C) from the initial PK assessment.

End point type	Primary

End point timeframe:

Day 180: preinfusion, 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±2) h after the end of infusion.

Notes:

[48] - 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: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	9[49]			
Units: mL/kg				
geometric mean (geometric coefficient of variation)				
VWF:RCo; n=9	87.9 (± 21.6)			
VWF:Ag; n=9	81.8 (± 25.1)			
VWF:CB; n=9	77.3 (± 18)			
FVIII:C; n=3	41.9 (± 7.1)			

Notes:

[49] - Repeat PK population; n=number of subjects with an evaluable assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Assessment of Blood Loss During Surgeries By Type of Surgery

End point title	Assessment of Blood Loss During Surgeries By Type of

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:

Up to Month 12

Notes:

[50] - 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: All efficacy variables were descriptively summarised by treatment arm and overall. No formal statistical tests were performed.

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[51]	12[52]		
Units: surgeries				
All Surgeries: Less Than Expected; n=0, 8	0	0		
All Surgeries: Equivalent To Expected; n=0, 8	0	8		
All Surgeries: More Than Expected; n=0, 8	0	0		
Major Surgeries: Less Than Expected; n=0, 0	0	0		
Major Surgeries: Equivalent To Expected; n=0, 0	0	0		
Major Surgeries: More Than Expected; n=0, 0	0	0		
Minor Surgeries: Less Than Expected; n=0, 8	0	0		
Minor Surgeries: Equivalent To Expected; n=0, 8	0	8		
Minor Surgeries: More Than Expected; n=0, 8	0	0		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Requiring Blood Product Transfusions

End point title	Number of Subjects Requiring Blood Product Transfusions[53]

End point description:

Blood products include any infusions of whole blood, packed red blood cells, and platelets.

End point type	Primary

End point timeframe:

Up to Month 12

Notes:

[53] - 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: All efficacy variables were descriptively summarised by treatment arm and overall. No formal statistical tests were performed.

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[54]	12[55]		
Units: subjects	0	0		

Notes:

[54] - Efficacy population

[55] - Efficacy population

Statistical analyses

No statistical analyses for this end point

Primary: Initial PK Assessment: Mean Residence Time (MRT)

End point title	Initial PK Assessment: Mean Residence Time (MRT)[56]

End point description:

Baseline-adjusted MRT of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant activity (FVIII:C) from the initial PK assessment.

End point type	Primary

End point timeframe:

Day 1: preinfusion; Days 1-3: 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±2) h after the end of infusion.

Notes:

[56] - 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: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	17[57]			
Units: hours				
geometric mean (geometric coefficient of variation)				
VWF:RCo; n=11	12.0269 (± 61.2)			
VWF:Ag; n=16	14.081 (± 33.9)			
VWF:CB; n=16	12.3401 (± 24.2)			
FVIII:C; n=10	27.7228 (± 56.4)			

Notes:

[57] - PK population; n=number of subjects with evaluable assessments.

Statistical analyses

No statistical analyses for this end point

Primary: Repeat PK Assessment: Mean Residence Time (MRT)

End point title	Repeat PK Assessment: Mean Residence Time (MRT)[58]

End point description:

Baseline-adjusted MRT of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant

End point type	Primary

End point timeframe:

Day 180: preinfusion, 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±2) h after the end of infusion.

Notes:

[58] - 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: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by

descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	9[59]			
Units: hours				
geometric mean (geometric coefficient of variation)				
VWF:RCo; n=9	15.1403 (± 38.4)			
VWF:Ag; n=9	15.958 (± 21.2)			
VWF:CB; n=9	14.007 (± 21.4)			
FVIII:C; n=3	45.907 (± 25.5)			

Notes:

[59] - Repeat PK population; n=number of subjects with an evaluable assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Repeat PK Assessment: Minimum Concentration (Cmin)

End point title	Repeat PK Assessment: Minimum Concentration (Cmin)[60]

End point description:

Baseline-adjusted Cmin of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), von Willebrand factor:collagen binding (VWF:CB) and Factor VIII:coagulant activity (FVIII:C) from the repeat PK assessment. For the calculation of Cmin, values below the lower limit of quantification (LLOQ), preceding the first quantifiable measurement in a profile, was set to zero. (The geometric mean was calculated for values >0). LLOQ for this parameter was <0.1 IU/mL.

End point type	Primary

End point timeframe:

Day 180: preinfusion, 0.5 (±15) min, 4 h (±15 min), 8 h (±30 min), 24 (±2) h, 48 (±2) h after the end of infusion.

Notes:

[60] - 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: PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times and were summarised per infusion (initial or repeat) by descriptive statistics.

End point values	PK Component			
Subject group type	Reporting group			
Number of subjects analysed	9[61]			
Units: IU/mL				
arithmetic mean (standard deviation)				
VWF:RCo	0 (± 0)			
VWF:Ag	0 (± 0)			
VWF:CB	0 (± 0)			
FVIII:C	0 (± 0)			

Notes:

[61] - Repeat PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Treatment Emergent Adverse Events

End point title	Percentage of Subjects with Treatment Emergent Adverse Events

End point description:

An adverse event (AE) is any untoward medical occurrence in a subject administered the IMP. An AE does not necessarily have a causal relationship with the IMP. A serious AE (SAE) is defined as any untoward medical occurrence that at any dose: results in death; is life-threatening; requires in-patient hospitalisation or prolongation of existing hospitalization; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; or is medically significant. Treatment emergent AEs (TEAEs) occured after exposure to study drug. Adverse drug reacions (ADRs) are TEAEs that were considered at least possibly related to Biostate.

End point type	Secondary

End point timeframe:

From first administration of the IMP until Final Visit or until 7 days (for AEs) or 30 days (for SAEs) after the last IMP administration (up to 12 months). Events considered related to a study procedure were recorded from the point of informed consent.

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[62]	13[63]		
Units: Percentage of subjects				
number (not applicable)				
At Least 1 TEAE	75	69.2		
At Least 1 Severe TEAE	50	7.7		
At Least 1 ADR	25	7.7		
At Least 1 Serious TEAE	0	0		

Notes:

[62] - Safety population

[63] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: VWF and Factor VIII Inhibitors

End point title	VWF and Factor VIII Inhibitors

End point description:

Number of subjects with VWF and Factor VIII inhibitors at given time points.

End point type	Secondary

End point timeframe:

Screening, Months 3, 6, 9, 12

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[64]	12[65]		
Units: subjects				
number (not applicable)				
VWF Inhibitor: Screening; n=4, 13	0	0		
VWF Inhibitor: Month 3; n=4, 12	0	0		
VWF Inhibitor: Month 6; n=4, 13	0	0		
VWF Inhibitor: Month 9; n=4, 13	0	0		
VWF Inhibitor: Month 12; n=4, 13	0	0		
FVIII Inhibitor: Screening; n=4, 13	0	0		
FVIII Inhibitor: Month 3; n=4, 13	0	0		
FVIII Inhibitor: Month 6; n=4, 13	0	0		
FVIII Inhibitor: Month 9; n=4, 13	0	0		
FVIII Inhibitor: Month 12; n=4, 13	0	0		

Notes:

[64] - Safety population; n=subjects with an available test result for given visit.

[65] - Safety population; n=subjects with an available test result for given visit.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of the IMP until Final Visit or until 7 days (for AEs) or 30 days (for SAEs) after the last IMP administration (up to 12 months). Events considered related to a study procedure were recorded from the point of informed consent.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Prophylaxis Arm

Reporting group description:

Subjects who were treated on a set prophylaxis regimen with a VWF product at the time of study entry were enrolled into the prophylaxis arm to receive Biostate as a pre-defined prophylaxis regimen determined by the severity of their disease for a period of 12 months.

Reporting group title	On-Demand Therapy Arm

Reporting group description:

Subjects who were not treated on a set prophylaxis regimen with a VWF product at the time of study entry and who required a VWF product for the treatment of non-surgical bleeding (NSB) events (control during surgery, or spontaneous, or trauma induced) were enrolled to start Biostate treatment of NSB events (on-demand therapy). If Biostate was used for irregular prevention of bleedings, this was considered as "on demand" therapy. Subjects who had been previously on an on-demand therapy were allowed to switch to prophylaxis therapy at the beginning of the efficacy component.

Serious adverse events	Prophylaxis Arm	On-Demand Therapy Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 13 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Prophylaxis Arm	On-Demand Therapy Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	9 / 13 (69.23%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 4 (50.00%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Joint Injury			

subjects affected / exposed	2 / 4 (50.00%)	0 / 13 (0.00%)
occurrences (all)	2	0
Skin Laceration		
subjects affected / exposed	2 / 4 (50.00%)	0 / 13 (0.00%)
occurrences (all)	2	0
Clavicle Fracture		
subjects affected / exposed	0 / 4 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	1
Eye Injury		
subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)
occurrences (all)	1	0
Injury		
subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)
occurrences (all)	1	0
Injury Corneal		
subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)
occurrences (all)	1	0
Mouth Injury		
subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)
occurrences (all)	1	0
Road Traffic Accident		
subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)
occurrences (all)	1	0
Congenital, familial and genetic disorders		
Heart Disease Congenital		
subjects affected / exposed	0 / 4 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	1
Cardiac disorders		
Cardiomyopathy		
subjects affected / exposed	0 / 4 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	1
Sinus Arrhythmia		
subjects affected / exposed	0 / 4 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	1
Supraventricular Extrasystoles		

subjects affected / exposed	0 / 4 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

Nervous system disorders

Tongue Biting

subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)	
occurrences (all)	3	0	

General disorders and administration site conditions

Pyrexia

subjects affected / exposed	1 / 4 (25.00%)	5 / 13 (38.46%)	
occurrences (all)	1	10	

Infusion Site Erythema

subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

Blood and lymphatic system disorders

Anaemia

subjects affected / exposed	0 / 4 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

Ear and labyrinth disorders

Ear Pain

subjects affected / exposed	1 / 4 (25.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	

Eye disorders

Conjunctivitis

subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

Gastrointestinal disorders

Abdominal Pain Upper

subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)	
occurrences (all)	3	0	

Cheilitis

subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

Diarrhoea

subjects affected / exposed	0 / 4 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

Stomatitis

subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Tooth Loss			
subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	0 / 4 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 4 (50.00%)	2 / 13 (15.38%)	
occurrences (all)	2	2	
Adenoidal Hypertrophy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Tonsillar Hypertrophy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Upper Airway Obstruction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Muscle Spasms			
subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal Pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Rhinitis			
subjects affected / exposed	1 / 4 (25.00%)	3 / 13 (23.08%)	
occurrences (all)	3	6	
Nasopharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	2 / 13 (15.38%)	
occurrences (all)	2	2	
Acute Tonsilitis			

	subjects affected / exposed	1 / 4 (25.00%)	1 / 13 (7.69%)	
	occurrences (all)	1	1	
Bronchitis				
	subjects affected / exposed	0 / 4 (0.00%)	1 / 13 (7.69%)	
	occurrences (all)	0	1	
Chlamydial Infection				
	subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)	
	occurrences (all)	1	0	
Ear Infection				
	subjects affected / exposed	0 / 4 (0.00%)	1 / 13 (7.69%)	
	occurrences (all)	0	1	
Gastroenteritis				
	subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)	
	occurrences (all)	2	0	
Pulpitis Dental				
	subjects affected / exposed	0 / 4 (0.00%)	1 / 13 (7.69%)	
	occurrences (all)	0	1	
Tonsilitis Streptococcal				
	subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)	
	occurrences (all)	1	0	
Tracheitis				
	subjects affected / exposed	0 / 4 (0.00%)	1 / 13 (7.69%)	
	occurrences (all)	0	1	
Upper Respiratory Tract Infection				
	subjects affected / exposed	1 / 4 (25.00%)	0 / 13 (0.00%)	
	occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 November 2010	- Data recording by eCRF: Correction of number of enrolled subjects from 20 to 12. - An additional primary endpoint was added: Assessment of response was to also include haemostasis during surgical procedure, blood loss, and transfusion requirements. - Correction of blood volumes for PK and efficacy component. - Modification of inclusion criterion 5, because no HAV vaccine is available for children aged younger than 1 year. - Modification of inclusion criterion 4 to comply with upper limit of VWF:RCo activity range as outlined in Guideline CPMP/BPWG/220/02. - Inclusion of monitoring of thrombogenicity markers for subjects undergoing surgery (Paul Ehrlich Institute). - Contact details for SAE reporting were changed.
19 April 2011	- Updates to the nominal VWF concentration. - List of personnel was removed, contact details for SAE reporting was changed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported