



## Clinical trial results:

### An Open-label, Multi-centre Study to Assess the Pharmacokinetics, Efficacy and Safety of Biostate® in Subjects with Von Willebrand Disease

#### Summary

EudraCT number	2008-004922-18
Trial protocol	BG
Global end of trial date	16 February 2012

#### 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-08-54
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##### Additional study identifiers

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

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	03 August 2012
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 February 2012
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

1. To investigate the initial and repeat pharmacokinetic profile of Biostate in subjects with von Willebrand disease (VWD).
2. To assess the haemostatic efficacy of Biostate in subjects with VWD who require a von Willebrand Factor product to control a non-surgical bleeding (NSB) event.
3. To assess the effectiveness of a prophylaxis regimen as compared to on-demand therapy with Biostate in preventing NSB events.

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	30 June 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Ukraine: 3
Worldwide total number of subjects	22
EEA total number of subjects	13

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)	18
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 28 days.

### Period 1

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

### Arms

<b>Arm title</b>	PK Component
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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:

A single bolus i.v.infusion of 80 IU/kg Biostate on Day 1 (for the initial PK assessment) and on Day 180 (repeat PK for Type 3 VWD PK subjects only).

<b>Number of subjects in period 1</b>	PK Component
Started	15
Repeat PK (Type 3 VWD PK Subjects Only)	8 <sup>[1]</sup>
Completed	15

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: 8 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 <sup>[2]</sup>
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	No
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<b>Arm title</b>	Arm 1: Prophylaxis Therapy
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### Arm description:

Subjects who were being treated on a set prophylaxis regimen with a VWF product at the time of study entry, or who were not on a set prophylaxis regimen but in whom prophylaxis treatment was justifiable in the opinion of the investigator, were enrolled into Arm 1 and received Biostate as part of a prophylaxis regimen as determined by the severity of their disease for a period of 12 months. Arm 1 subjects completed the study with a Final Visit at Month 12.

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:

Frequency and dose was determined by the Investigator based on the subject's clinical condition, previous VWF concentrate requirements, response to therapy, body weight and reason for usage.

<b>Arm title</b>	Arm 2: On-Demand Therapy
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### Arm description:

Subjects who were not 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 (spontaneous or trauma-induced), were enrolled into Arm 2 and commenced using Biostate as on-demand therapy for the treatment of NSB events. At the Month 12 visit and based on the extent and location of any bleeding events, Arm 2 subjects were assessed for eligibility to be switched to a set prophylaxis regimen with Biostate for an additional 12 months (Arm 3). The total treatment duration for subjects in Arm 2 only was up to 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:

Frequency and dose was determined by the Investigator based on the subject's clinical condition, previous VWF concentrate requirements, response to therapy, body weight and reason for usage.

<b>Arm title</b>	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)
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### Arm description:

Subjects who completed treatment (on-demand therapy with Biostate) in Arm 2 and who at the Month 12 visit qualified to be switched to a set prophylactic regimen according to the criteria prespecified in the study protocol, entered Arm 3 and started Biostate treatment as prophylaxis therapy for an additional 12 months. The prophylaxis regimen was determined by the extent and location of NSB events during the preceding 12-month on-demand therapy period. The total treatment duration for subjects in Arm 3 was up to 24 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:

Frequency and dose was determined by the Investigator based on the subject's clinical condition, previous VWF concentrate requirements, response to therapy, body weight and reason for usage.

Notes:

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

Justification: The PK component (period 1), which took place prior to the Efficacy component (used as for Baseline values), does not include all subjects enrolled in this study.

Number of subjects in period 2	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)
Started	1	21	8
Completed	1	21	7
Not completed	0	0	1
Consent withdrawn by subject	-	-	1

## Baseline characteristics

### Reporting groups

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

Subjects who were being treated on a set prophylaxis regimen with a VWF product at the time of study entry, or who were not on a set prophylaxis regimen but in whom prophylaxis treatment was justifiable in the opinion of the investigator, were enrolled into Arm 1 and received Biostate as part of a prophylaxis regimen as determined by the severity of their disease for a period of 12 months. Arm 1 subjects completed the study with a Final Visit at Month 12.

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

Subjects who were not 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 (spontaneous or trauma-induced), were enrolled into Arm 2 and commenced using Biostate as on-demand therapy for the treatment of NSB events. At the Month 12 visit and based on the extent and location of any bleeding events, Arm 2 subjects were assessed for eligibility to be switched to a set prophylaxis regimen with Biostate for an additional 12 months (Arm 3). The total treatment duration for subjects in Arm 2 only was up to 12 months.

Reporting group title	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)
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#### Reporting group description:

Subjects who completed treatment (on-demand therapy with Biostate) in Arm 2 and who at the Month 12 visit qualified to be switched to a set prophylactic regimen according to the criteria prespecified in the study protocol, entered Arm 3 and started Biostate treatment as prophylaxis therapy for an additional 12 months. The prophylaxis regimen was determined by the extent and location of NSB events during the preceding 12-month on-demand therapy period. The total treatment duration for subjects in Arm 3 was up to 24 months.

Reporting group values	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)
Number of subjects	1	21	8
Age categorical Units: Subjects			
<18 years	0	3	0
≥18 years	1	18	8
Age continuous Units: years			
arithmetic mean	46	33	43
standard deviation	± 0	± 15.3	± 15.9
Gender categorical Units: Subjects			
Female	1	11	2
Male	0	10	6

Reporting group values	Total		
Number of subjects	22		
Age categorical Units: Subjects			
<18 years	3		
≥18 years	19		

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	12		
Male	10		



## End points

### End points reporting groups

Reporting group title	PK Component
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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
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Reporting group description:

Subjects who were being treated on a set prophylaxis regimen with a VWF product at the time of study entry, or who were not on a set prophylaxis regimen but in whom prophylaxis treatment was justifiable in the opinion of the investigator, were enrolled into Arm 1 and received Biostate as part of a prophylaxis regimen as determined by the severity of their disease for a period of 12 months. Arm 1 subjects completed the study with a Final Visit at Month 12.

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

Subjects who were not 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 (spontaneous or trauma-induced), were enrolled into Arm 2 and commenced using Biostate as on-demand therapy for the treatment of NSB events. At the Month 12 visit and based on the extent and location of any bleeding events, Arm 2 subjects were assessed for eligibility to be switched to a set prophylaxis regimen with Biostate for an additional 12 months (Arm 3). The total treatment duration for subjects in Arm 2 only was up to 12 months.

Reporting group title	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)
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Reporting group description:

Subjects who completed treatment (on-demand therapy with Biostate) in Arm 2 and who at the Month 12 visit qualified to be switched to a set prophylactic regimen according to the criteria prespecified in the study protocol, entered Arm 3 and started Biostate treatment as prophylaxis therapy for an additional 12 months. The prophylaxis regimen was determined by the extent and location of NSB events during the preceding 12-month on-demand therapy period. The total treatment duration for subjects in Arm 3 was up to 24 months.

### Primary: Initial PK Assessment: Incremental Recovery (IR)

End point title	Initial PK Assessment: Incremental Recovery (IR) <sup>[1]</sup>
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End point description:

Baseline-adjusted IR of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor:collagen binding (VWF:CB) from the initial PK assessment. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.

End point type	Primary
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End point timeframe:

Day 1: preinfusion; Days 1-4: 15 (±5) min, 1 h (±5 min), 3 h (±5 min), 6 h (±15 min), 8 h (±30 min), 12 h (±30 min), 24 h (±2 h), 30 h (±2 h), 48 h (±2 h), 72 h (±2 h) after the end of infusion.

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: 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	14 <sup>[2]</sup>			
Units: kg/mL				
arithmetic mean (standard deviation)				
VWF:RCo	0.016 (± 0.003)			
VWF:Ag	0.018 (± 0.003)			
VWF:CB	0.02 (± 0.004)			

Notes:

[2] - PK population (subjects who participated in the PK component) with evaluable data.

## Statistical analyses

No statistical analyses for this end point

## Primary: Initial PK Assessment: Half-life (t<sub>1/2</sub>)

End point title	Initial PK Assessment: Half-life (t <sub>1/2</sub> ) <sup>[3]</sup>
End point description: Baseline-adjusted t <sub>1/2</sub> of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor: collagen binding (VWF:CB) from the initial PK assessment. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.	
End point type	Primary
End point timeframe: Day 1: preinfusion; Days 1-4: 15 (±5 min), 1 h (±5 min), 3 h (±5 min), 6 h (±15 min), 8 h (±30 min), 12 h (±30 min), 24 h (±2 h), 30 h (±2 h), 48 h (±2 h), 72 h (±2 h) after the end of 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: 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	15 <sup>[4]</sup>			
Units: hours				
arithmetic mean (standard deviation)				
VWF:RCo; n=9	12.6 (± 9.2)			
VWF:Ag; n=13	18.3 (± 3.8)			
VWF:CB; n=13	15.8 (± 4.5)			

Notes:

[4] - PK population (subjects who participated in the PK component); n=subjects w/evaluable data specified

## Statistical analyses

No statistical analyses for this end point

### Primary: Initial PK Assessment: Area Under the Plasma Concentration-time Curve From Time 0 to 72 hours (AUC[0-72])

End point title	Initial PK Assessment: Area Under the Plasma Concentration-time Curve From Time 0 to 72 hours (AUC[0-72])[ <sup>5</sup> ]
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End point description:

Baseline-adjusted AUC(0-72) of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor: antigen (VWF:Ag), and von Willebrand factor: collagen binding (VWF:CB) from the initial PK assessment. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.

End point type	Primary
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End point timeframe:

Day 1: preinfusion; Days 1-4: 15 ( $\pm 5$ ) min, 1 h ( $\pm 5$  min), 3 h ( $\pm 5$  min), 6 h ( $\pm 15$  min), 8 h ( $\pm 30$  min), 12 h ( $\pm 30$  min), 24 h ( $\pm 2$  h), 30 h ( $\pm 2$  h), 48 h ( $\pm 2$  h), 72 h ( $\pm 2$  h) after the end of infusion.

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: 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	15 <sup>[6]</sup>			
Units: h*IU/mL				
arithmetic mean (standard deviation)				
VWF:RCo; n=14	17.2 ( $\pm 9$ )			
VWF:Ag; n=14	35.9 ( $\pm 13.4$ )			
VWF:CB; n=13	24.5 ( $\pm 8.5$ )			

Notes:

[6] - PK population (subjects who participated in the PK component); n=subjects w/evaluable data specified

## 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) <sup>[7]</sup>
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End point description:

Baseline-adjusted MRT of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor: collagen binding (VWF:CB) from the initial PK assessment. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.

End point type	Primary
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End point timeframe:

Day 1: preinfusion; Days 1-4: 15 ( $\pm 5$ ) min, 1 h ( $\pm 5$  min), 3 h ( $\pm 5$  min), 6 h ( $\pm 15$  min), 8 h ( $\pm 30$  min), 12 h ( $\pm 30$  min), 24 h ( $\pm 2$  h), 30 h ( $\pm 2$  h), 48 h ( $\pm 2$  h), 72 h ( $\pm 2$  h) after the end of infusion.

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: 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	15 <sup>[8]</sup>			
Units: hours				
arithmetic mean (standard deviation)				
VWF:RCo; n=9	13.2 ( $\pm 5.3$ )			
VWF:Ag; n=13	23.4 ( $\pm 4.9$ )			
VWF:CB; n=13	19.8 ( $\pm 4.3$ )			

Notes:

[8] - PK population (subjects who participated in the PK component); n=subjects w/evaluable data specified

## Statistical analyses

No statistical analyses for this end point

## Primary: Initial PK Assessment: Maximum Plasma Concentration (Cmax)

End point title	Initial PK Assessment: Maximum Plasma Concentration
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End point description:

Baseline-adjusted Cmax of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor: collagen binding (VWF:CB) from the initial PK assessment. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.

End point type	Primary
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End point timeframe:

Day 1: preinfusion; Days 1-4: 15 ( $\pm 5$ ) min, 1 h ( $\pm 5$  min), 3 h ( $\pm 5$  min), 6 h ( $\pm 15$  min), 8 h ( $\pm 30$  min), 12 h ( $\pm 30$  min), 24 h ( $\pm 2$  h), 30 h ( $\pm 2$  h), 48 h ( $\pm 2$  h), 72 h ( $\pm 2$  h) after the end of infusion.

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: 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	14 <sup>[10]</sup>			
Units: IU/mL				
arithmetic mean (standard deviation)				
VWF:RCo	1.6 ( $\pm 0.6$ )			
VWF:Ag	2.28 ( $\pm 0.63$ )			
VWF:CB	1.65 ( $\pm 0.52$ )			

Notes:

[10] - PK population (subjects who participated in the PK component) with evaluable data.

## Statistical analyses

No statistical analyses for this end point

### Primary: Initial PK Assessment: Time the Maximum Concentration Occurs (Tmax)

End point title	Initial PK Assessment: Time the Maximum Concentration Occurs (Tmax) <sup>[11]</sup>
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End point description:

Baseline-adjusted Tmax of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor: collagen binding (VWF:CB) from the initial PK assessment. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.

End point type	Primary
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End point timeframe:

Day 1: preinfusion; Days 1-4: 15 (±5) min, 1 h (±5 min), 3 h (±5 min), 6 h (±15 min), 8 h (±30 min), 12 h (±30 min), 24 h (±2 h), 30 h (±2 h), 48 h (±2 h), 72 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: 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	14 <sup>[12]</sup>			
Units: hours				
median (full range (min-max))				
VWF:RCo	0.25 (0.25 to 1.03)			
VWF:Ag	0.25 (0.25 to 1)			
VWF:CB	0.25 (0.25 to 1)			

Notes:

[12] - PK population (subjects who participated in the PK component) with evaluable data.

## Statistical analyses

No statistical analyses for this end point

### Primary: Initial PK Assessment: Minimum Plasma Concentration (Cmin)

End point title	Initial PK Assessment: Minimum Plasma Concentration
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End point description:

Baseline-adjusted Cmin of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor: collagen binding (VWF:CB) from the initial PK assessment. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted

concentrations and actual sampling times.

End point type	Primary
End point timeframe:	
Day 1: preinfusion; Days 1-4: 15 (±5) min, 1 h (±5 min), 3 h (±5 min), 6 h (±15 min), 8 h (±30 min), 12 h (±30 min), 24 h (±2 h), 30 h (±2 h), 48 h (±2 h), 72 h (±2 h) after the end of infusion.	
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: 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	14 <sup>[14]</sup>			
Units: IU/mL				
arithmetic mean (standard deviation)				
VWF:RCo	0.02 (± 0.03)			
VWF:Ag	0.09 (± 0.05)			
VWF:CB	0.05 (± 0.02)			

Notes:

[14] - PK population (subjects who participated in the PK component) with evaluable data.

## Statistical analyses

No statistical analyses for this end point

## Primary: Initial PK Assessment: Total Clearance (CL)

End point title	Initial PK Assessment: Total Clearance (CL) <sup>[15]</sup>
End point description:	
Baseline-adjusted total clearance of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor: collagen binding (VWF:CB) from the initial PK assessment. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.	
End point type	Primary
End point timeframe:	
Day 1: preinfusion; Days 1-4: 15 (±5) min, 1 h (±5 min), 3 h (±5 min), 6 h (±15 min), 8 h (±30 min), 12 h (±30 min), 24 h (±2 h), 30 h (±2 h), 48 h (±2 h), 72 h (±2 h) after the end of infusion.	
Notes:	
[15] - 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	15 <sup>[16]</sup>			
Units: mL/(h*kg)				
arithmetic mean (standard deviation)				
VWF:RCo; n=14	6.18 (± 1.69)			
VWF:Ag; n=14	3.82 (± 0.93)			
VWF:CB; n=13	3.59 (± 0.88)			

Notes:

[16] - PK population (subjects who participated in the PK component); n=subjects w/evaluable data specified

## 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) <sup>[17]</sup>
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End point description:

Baseline-adjusted Vss of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor: collagen binding (VWF:CB) from the initial PK assessment. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.

End point type	Primary
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End point timeframe:

Day 1: preinfusion; Days 1-4: 15 (±5) min, 1 h (±5 min), 3 h (±5 min), 6 h (±15 min), 8 h (±30 min), 12 h (±30 min), 24 h (±2 h), 30 h (±2 h), 48 h (±2 h), 72 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: 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	15 <sup>[18]</sup>			
Units: mL/kg				
arithmetic mean (standard deviation)				
VWF:RCo; n=9	73.1 (± 33.5)			
VWF:Ag; n=13	83.6 (± 18.1)			
VWF:CB; n=13	69.1 (± 15.1)			

Notes:

[18] - PK population (subjects who participated in the PK component); n=subjects w/evaluable data specified

## Statistical analyses

No statistical analyses for this end point

### Primary: Initial and Repeat PK Assessment: Incremental Recovery (IR)

End point title	Initial and Repeat PK Assessment: Incremental Recovery
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End point description:

Baseline-adjusted IR of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor: collagen binding (VWF:CB) from the initial and repeat PK assessments. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.

End point type	Primary
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End point timeframe:

Day 1 and Day 180: preinfusion; Days 1-4 and Days 180-183: 15 (±5) min, 1 h (±5 min), 3 h (±5 min), 6 h (±15 min), 8 h (±30 min), 12 h (±30 min), 24 h (±2 h), 30 h (±2 h), 48 h (±2 h), 72 h (±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: 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	7 <sup>[20]</sup>			
Units: kg/mL				
arithmetic mean (standard deviation)				
Initial VWF:RCo	0.017 (± 0.003)			
Repeat VWF:RCo	0.017 (± 0.005)			
Initial VWF:Ag	0.019 (± 0.001)			
Repeat VWF:Ag	0.022 (± 0.004)			
Initial VWF:CB	0.023 (± 0.001)			
Repeat VWF:CB	0.021 (± 0.003)			

Notes:

[20] - Repeat PK population (Type 3 VWD subjects who participated in the PK component) with evaluable data.

## Statistical analyses

No statistical analyses for this end point

## Primary: Initial and Repeat PK Assessment: Half-life (t<sub>1/2</sub>)

End point title	Initial and Repeat PK Assessment: Half-life (t <sub>1/2</sub> ) <sup>[21]</sup>
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End point description:

Baseline-adjusted t<sub>1/2</sub> of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor:collagen binding (VWF:CB) from the initial and repeat PK assessments. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.

End point type	Primary
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End point timeframe:

Day 1 and Day 180: preinfusion; 15 (±5) min, 1 h (±5 min), 3 h (±5 min), 6 h (±15 min), 8 h (±30 min), 12 h (±30 min), 24 h (±2 h), 30 h (±2 h), 48 h (±2 h), 72 h (±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: 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	7 <sup>[22]</sup>			
Units: hours				
arithmetic mean (standard deviation)				
Initial VWF:RCo; n=5	10.5 (± 4.2)			
Repeat VWF:RCo; n=3	14.3 (± 6.3)			
Initial VWF:Ag; n=7	18.5 (± 5.1)			
Repeat VWF:Ag; n=7	15.5 (± 2.4)			
Initial VWF:CB; n=7	14.8 (± 5.07)			
Repeat VWF:CB; n=6	11.3 (± 2.7)			

Notes:

[22] - Repeat PK population (Type 3 VWD subjects in the PK component); n=subjects w/evaluable data specified

## Statistical analyses

No statistical analyses for this end point

## Primary: Initial and Repeat PK Assessment: Area Under the Plasma Concentration-time Curve From Time 0 to 72 hours (AUC[0-72])

End point title	Initial and Repeat PK Assessment: Area Under the Plasma Concentration-time Curve From Time 0 to 72 hours (AUC[0-72]) <sup>[23]</sup>
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End point description:

Baseline-adjusted AUC(0-72) of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor: antigen (VWF:Ag), and von Willebrand factor: collagen binding (VWF:CB) from the initial and repeat PK assessments. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.

End point type	Primary
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End point timeframe:

Day 1 and Day 180: preinfusion; Days 1-4 and Days 180-183: 15 (±5) min, 1 h (±5 min), 3 h (±5 min), 6 h (±15 min), 8 h (±30 min), 12 h (±30 min), 24 h (±2 h), 30 h (±2 h), 48 h (±2 h), 72 h (±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: 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	8 <sup>[24]</sup>			
Units: h*IU/mL				
arithmetic mean (standard deviation)				
Initial VWF:RCo; n=7	17.7 (± 8.8)			
Repeat VWF:RCo; n=6	14.3 (± 4.3)			
Initial VWF:Ag; n=7	38.3 (± 12.5)			
Repeat VWF:Ag; n=7	41.1 (± 10.3)			
Initial VWF:CB; n=7	26 (± 9)			
Repeat VWF:CB; n=7	20.2 (± 6.5)			

Notes:

[24] - Repeat PK population (Type 3 VWD subjects in the PK component); n=subjects w/evaluable data specified

## Statistical analyses

No statistical analyses for this end point

### Primary: Initial and Repeat PK Assessment: Mean Residence Time (MRT)

End point title	Initial and Repeat PK Assessment: Mean Residence Time
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End point description:

Baseline-adjusted MRT of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor: collagen binding (VWF:CB) from the initial and repeat PK assessments. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.

End point type	Primary
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End point timeframe:

Day 1 and Day 180: preinfusion; Days 1-4 and Days 180-183: 15 (±5) min, 1 h (±5 min), 3 h (±5 min), 6 h (±15 min), 8 h (±30 min), 12 h (±30 min), 24 h (±2 h), 30 h (±2 h), 48 h (±2 h), 72 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: 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	8 <sup>[26]</sup>			
Units: hours				
arithmetic mean (standard deviation)				
Initial VWF:RCo; n=5	11.9 (± 3)			
Repeat VWF:RCo; n=3	12.7 (± 2.5)			
Initial VWF:Ag; n=7	23.1 (± 6.5)			
Repeat VWF:Ag; n=7	20.3 (± 3.6)			
Initial VWF:CB; n=7	18.5 (± 4.3)			
Repeat VWF:CB; n=6	14.3 (± 3.4)			

Notes:

[26] - Repeat PK population (Type 3 VWD subjects in the PK component); n=subjects w/evaluable data specified

## Statistical analyses

No statistical analyses for this end point

### Primary: Initial and Repeat PK Assessment: Maximum Plasma Concentration (Cmax)

End point title	Initial and Repeat PK Assessment: Maximum Plasma Concentration (Cmax) <sup>[27]</sup>
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End point description:

Baseline-adjusted Cmax of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor:collagen binding (VWF:CB) from the initial and repeat PK assessments. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.

End point type	Primary
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End point timeframe:

Day 1 and Day 180: preinfusion; Days 1-4 and Days 180-183: 15 (±5) min, 1 h (±5 min), 3 h (±5 min), 6 h (±15 min), 8 h (±30 min), 12 h (±30 min), 24 h (±2 h), 30 h (±2 h), 48 h (±2 h), 72 h (±2 h) after the end of infusion.

Notes:

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

Justification: 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	7 <sup>[28]</sup>			
Units: IU/mL				
arithmetic mean (standard deviation)				
Initial VWF:RCo	1.63 (± 0.33)			
Repeat VWF:RCo	1.56 (± 0.4)			
Initial VWF:Ag	2.44 (± 0.46)			
Repeat VWF:Ag	2.68 (± 0.42)			
Initial VWF:CB	1.87 (± 0.31)			
Repeat VWF:CB	1.58 (± 0.21)			

Notes:

[28] - Repeat PK population (Type 3 VWD subjects who participated in the PK component) with evaluable data.

## Statistical analyses

No statistical analyses for this end point

## Primary: Initial and Repeat PK Assessment: Time the Maximum Concentration Occurs (Tmax)

End point title	Initial and Repeat PK Assessment: Time the Maximum Concentration Occurs (Tmax) <sup>[29]</sup>
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End point description:

Baseline-adjusted Tmax of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor:collagen binding (VWF:CB) from the initial and repeat PK assessment. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.

End point type	Primary
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End point timeframe:

Day 1 and Day 180: preinfusion; Days 1-4 and Days 180-183: 15 (±5) min, 1 h (±5 min), 3 h (±5 min), 6 h (±15 min), 8 h (±30 min), 12 h (±30 min), 24 h (±2 h), 30 h (±2 h), 48 h (±2 h), 72 h (±2 h) after the end of infusion.

Notes:

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

Justification: 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	7 <sup>[30]</sup>			
Units: hours				
median (full range (min-max))				
Initial VWF:RCo	0.25 (0.25 to 1.03)			
Repeat VWF:RCo	0.25 (0.2 to 1)			
Initial VWF:Ag	0.25 (0.25 to 1)			
Repeat VWF:Ag	0.25 (0.2 to 0.25)			
Initial VWF:CB	0.25 (0.25 to 1)			
Repeat VWF:CB	0.25 (0.2 to 0.25)			

Notes:

[30] - Repeat PK population (Type 3 VWD subjects who participated in the PK component) with evaluable data.

## Statistical analyses

No statistical analyses for this end point

## Primary: Initial and Repeat PK Assessment: Minimum Plasma Concentration (Cmin)

End point title	Initial and Repeat PK Assessment: Minimum Plasma Concentration (Cmin) <sup>[31]</sup>
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End point description:

Baseline-adjusted Cmin of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor:collagen binding (VWF:CB) from the initial and repeat PK assessments. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.

End point type	Primary
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End point timeframe:

Day 1 and Day 180: preinfusion; Days 1-4 and Days 180-183: 15 (±5) min, 1 h (±5 min), 3 h (±5 min), 6 h (±15 min), 8 h (±30 min), 12 h (±30 min), 24 h (±2 h), 30 h (±2 h), 48 h (±2 h), 72 h (±2 h) after the end of infusion.

Notes:

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

Justification: 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	7 <sup>[32]</sup>			
Units: IU/mL				
arithmetic mean (standard deviation)				
Initial VWF:RCo	0.01 (± 0.01)			
Repeat VWF:RCo	0.02 (± 0.02)			
Initial VWF:Ag	0.1 (± 0.06)			
Repeat VWF:Ag	0.1 (± 0.07)			
Initial VWF:CB	0.05 (± 0.03)			
Repeat VWF:CB	0.04 (± 0.05)			

Notes:

[32] - Repeat PK population (Type 3 VWD subjects who participated in the PK component) with evaluable data.

## Statistical analyses

No statistical analyses for this end point

### Primary: Initial and Repeat PK Assessment: Total Clearance (CL)

End point title	Initial and Repeat PK Assessment: Total Clearance (CL) <sup>[33]</sup>
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End point description:

Baseline-adjusted total clearance of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor:collagen binding (VWF:CB) from the initial and repeat PK assessments. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.

End point type	Primary
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End point timeframe:

Day 1 and Day 180: preinfusion; Days 1-4 and Days 180-183: 15 (±5) min, 1 h (±5 min), 3 h (±5 min), 6 h (±15 min), 8 h (±30 min), 12 h (±30 min), 24 h (±2 h), 30 h (±2 h), 48 h (±2 h), 72 h (±2 h) after the end of infusion.

Notes:

[33] - 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	8 <sup>[34]</sup>			
Units: mL/(h*kg)				
arithmetic mean (standard deviation)				
Initial VWF:RCo; n=7	6.13 (± 1.91)			
Repeat VWF:RCo; n=6	6.94 (± 2.31)			
Initial VWF:Ag; n=7	3.62 (± 0.93)			
Repeat VWF:Ag; n=7	3.1 (± 0.7)			
Initial VWF:CB; n=7	3.42 (± 0.9)			
Repeat VWF:CB; n=7	4.07 (± 0.93)			

Notes:

[34] - Repeat PK population (Type 3 VWD subjects in the PK component);n=subjects w/evaluable data specified

## Statistical analyses

No statistical analyses for this end point

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

End point title	Initial and Repeat PK Assessment: Volume of Distribution at Steady State (Vss) <sup>[35]</sup>
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**End point description:**

Baseline-adjusted Vss of von Willebrand factor:ristocetin cofactor (VWF:RCo), von Willebrand factor:antigen (VWF:Ag), and von Willebrand factor:collagen binding (VWF:CB) from the initial and repeat PK assessments. PK parameters were calculated by non-compartmental analysis based on baseline-adjusted concentrations and actual sampling times.

End point type	Primary
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**End point timeframe:**

Day 1 and Day 180: preinfusion; Days 1-4 and Days 180-183: 15 ( $\pm 5$ ) min, 1 h ( $\pm 5$  min), 3 h ( $\pm 5$  min), 6 h ( $\pm 15$  min), 8 h ( $\pm 30$  min), 12 h ( $\pm 30$  min), 24 h ( $\pm 2$  h), 30 h ( $\pm 2$  h), 48 h ( $\pm 2$  h), 72 h ( $\pm 2$  h) after the end of infusion.

**Notes:**

[35] - 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	8 <sup>[36]</sup>			
Units: mL/kg				
arithmetic mean (standard deviation)				
Initial VWF:RCo; n=5	62 ( $\pm 10.5$ )			
Repeat VWF:RCo; n=3	85.6 ( $\pm 22$ )			
Initial VWF:Ag; n=7	80.9 ( $\pm 23.1$ )			
Repeat VWF:Ag; n=7	60.9 ( $\pm 7.1$ )			
Initial VWF:CB; n=7	60.7 ( $\pm 11.5$ )			
Repeat VWF:CB; n=6	59.7 ( $\pm 8.7$ )			

**Notes:**

[36] - Repeat PK population (Type 3 VWD subjects in the PK component);n=subjects w/evaluable data specified

**Statistical analyses**

No statistical analyses for this end point

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

End point title	Investigator's 3-monthly Assessment of Haemostatic
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**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
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**End point timeframe:**

Months 3, 6, 9, 12, 15, 18, 21, 24

**Notes:**

[37] - 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.

<b>End point values</b>	<b>Arm 1: Prophylaxis Therapy</b>	<b>Arm 2: On- Demand Therapy</b>	<b>Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)</b>	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[38]</sup>	20 <sup>[39]</sup>	8 <sup>[40]</sup>	
Units: subjects				
Month 3: Excellent; n=0, 17, 0	0	15	0	
Month 3: Good; n=0, 17, 0	0	2	0	
Month 3: Moderate; n=0, 17, 0	0	0	0	
Month 3: None; n=0, 17, 0	0	0	0	
Month 6: Excellent; n=1, 19, 0	0	13	0	
Month 6: Good; n=1, 19, 0	0	6	0	
Month 6: Moderate; n=1, 19, 0	1	0	0	
Month 6: None; n=1, 19, 0	0	0	0	
Month 9: Excellent; n=1, 16, 0	1	13	0	
Month 9: Good; n=1, 16, 0	0	3	0	
Month 9: Moderate; n=1, 16, 0	0	0	0	
Month 9: None; n=1, 16, 0	0	0	0	
Month 12: Excellent; n=1, 18, 8	0	15	8	
Month 12: Good; n=1, 18, 8	0	3	0	
Month 12: Moderate; n=1, 18, 8	1	0	0	
Month 12: None; n=1, 18, 8	0	0	0	
Month 15: Excellent; n=0, 0, 6	0	0	6	
Month 15: Good; n=0, 0, 6	0	0	0	
Month 15: Moderate; n=0, 0, 6	0	0	0	
Month 15: None; n=0, 0, 6	0	0	0	
Month 18: Excellent; n=0, 0, 6	0	0	6	
Month 18: Good; n=0, 0, 6	0	0	0	
Month 18: Moderate; n=0, 0, 6	0	0	0	
Month 18: None; n=0, 0, 6	0	0	0	
Month 21: Excellent; n=0, 0, 3	0	0	3	
Month 21: Good; n=0, 0, 3	0	0	0	
Month 21: Moderate; n=0, 0, 3	0	0	0	
Month 21: None; n=0, 0, 3	0	0	0	
Month 24: Excellent; n=0, 0, 3	0	0	3	
Month 24: Good; n=0, 0, 3	0	0	0	
Month 24: Moderate; n=0, 0, 3	0	0	0	
Month 24: None; n=0, 0, 3	0	0	0	

Notes:

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

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

[40] - 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 <sup>[41]</sup>
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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
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End point timeframe:

Up to Month 24

Notes:

[41] - 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	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[42]</sup>	20 <sup>[43]</sup>	8 <sup>[44]</sup>	
Units: events				
All NSB Events: Excellent; n=1, 407, 10	0	375	10	
All NSB Events: Good; n=1, 407, 10	1	25	0	
All NSB Events: Moderate; n=1, 407, 10	0	7	0	
All NSB Events: None; n=1, 407, 10	0	0	0	
Spontaneous Events: Excellent; n=1, 403, 10	0	371	10	
Spontaneous Events: Good; n=1, 403, 10	1	25	0	
Spontaneous Events: Moderate; n=1, 403, 10	0	7	0	
Spontaneous Events: None; n=1, 403, 10	0	0	0	
Trauma Events: Excellent; n=0, 3, 0	0	3	0	
Trauma Events: Good; n=0, 3, 0	0	0	0	
Trauma Events: Moderate; n=0, 3, 0	0	0	0	
Trauma Events: None; n=0, 3, 0	0	0	0	
Post-surgery Events: Excellent; n=0, 1, 0	0	1	0	
Post-surgery Events: Good; n=0, 1, 0	0	0	0	
Post-surgery Events: Moderate; n=0, 1, 0	0	0	0	
Post-surgery Events: None; n=0, 1, 0	0	0	0	
Major Events: Excellent; n=1, 125, 3	0	117	3	
Major Events: Good; n=1, 125, 3	1	2	0	
Major Events: Moderate; n=1, 125, 3	0	6	0	
Major Events: None; n=1, 125, 3	0	0	0	



Minor Events: Excellent; n=0, 282, 7	0	285	7	
Minor Events: Good; n=0, 282, 7	0	23	0	
Minor Events: Moderate; n=0, 282, 7	0	1	0	
Minor Events: None; n=0, 282, 7	0	0	0	
Joint Events: Excellent; n=0, 101, 2	0	99	2	
Joint Events: Good; n=0, 101, 2	0	2	0	
Joint Events: Moderate; n=0, 101, 2	0	0	0	
Joint Events: None; n=0, 101, 2	0	0	0	
Mucosal Events: Excellent; n=1, 291, 8	0	261	8	
Mucosal Events: Good; n=1, 291, 8	1	23	0	
Mucosal Events: Moderate; n=1, 291, 8	0	7	0	
Mucosal Events: None; n=1, 291, 8	0	0	0	
Muscle Events: Excellent; n=0, 17, 0	0	17	0	
Muscle Events: Good; n=0, 17, 0	0	0	0	
Muscle Events: Moderate; n=0, 17, 0	0	0	0	
Muscle Events: None; n=0, 17, 0	0	0	0	

Notes:

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

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

[44] - 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 <sup>[45]</sup>
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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
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End point timeframe:

Up to Month 24

Notes:

[45] - 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	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[46]</sup>	20 <sup>[47]</sup>	8 <sup>[48]</sup>	
Units: days				

All Days: Excellent; n=2, 606, 13	0	480	13	
All Days: Good; n=2, 606, 13	2	104	0	
All Days: Moderate; n=2, 606, 13	0	21	0	
All Days: None; n=2, 606, 13	0	1	0	
Day 1: Excellent; n=1, 394, 10	0	336	10	
Day 1: Good; n=1, 394, 10	1	44	0	
Day 1: Moderate; n=1, 394, 10	0	14	0	
Day 1: None; n=1, 394, 10	0	0	0	
Day 2: Excellent; n=1, 78, 1	0	48	1	
Day 2: Good; n=1, 78, 1	1	25	0	
Day 2: Moderate; n=1, 78, 1	0	4	0	
Day 2: None; n=1, 78, 1	0	1	0	
Day 3: Excellent; n=0, 63, 1	0	46	1	
Day 3: Good; n=0, 63, 1	0	16	0	
Day 3: Moderate; n=0, 63, 1	0	1	0	
Day 3: None; n=0, 63, 1	0	0	0	
Day 4: Excellent; n=0, 52, 1	0	41	1	
Day 4: Good; n=0, 52, 1	0	10	0	
Day 4: Moderate; n=0, 52, 1	0	1	0	
Day 4: None; n=0, 52, 1	0	0	0	
Day 5: Excellent; n=0, 19, 0	0	9	0	
Day 5: Good; n=0, 19, 0	0	9	0	
Day 5: Moderate; n=0, 19, 0	0	1	0	
Day 5: None; n=0, 19, 0	0	0	0	

Notes:

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

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

[48] - 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: Number of Subjects Requiring Blood Product Transfusions

End point title	Number of Subjects Requiring Blood Product Transfusions <sup>[49]</sup>
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End point description:

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

End point type	Primary
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End point timeframe:

Up to 24 Months

Notes:

[49] - 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	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[50]</sup>	20 <sup>[51]</sup>	8 <sup>[52]</sup>	
Units: subjects				

Any Blood Product Transfusion	0	1	0	
Packed Red Blood Cells	0	1	0	

Notes:

[50] - Efficacy population

[51] - Efficacy population

[52] - Efficacy population

## 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>[53]</sup>
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End point description:

The type of blood product, and the number of units required by a subject during the study period was recorded. This includes any infusions of whole blood, packed red blood cells, and platelets.

End point type	Primary
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End point timeframe:

Up to Month 24

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	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[54]</sup>	20 <sup>[55]</sup>	8 <sup>[56]</sup>	
Units: mL				
median (full range (min-max))				
Total Amount of Any Product; n=0, 1, 0	0 (0 to 0)	600 (600 to 600)	0 (0 to 0)	
Total Amount of Packed Cells; n=0, 1, 0	0 (0 to 0)	600 (600 to 600)	0 (0 to 0)	

Notes:

[54] - Efficacy population; n=subjects receiving the respective blood product at least once.

[55] - Efficacy population; n=subjects receiving the respective blood product at least once.

[56] - Efficacy population; n=subjects receiving the respective blood product at least once.

## Statistical analyses

No statistical analyses for this end point

### Primary: Usage of Biostate: Average Dose by Study Month

End point title	Usage of Biostate: Average Dose by Study Month <sup>[57]</sup>
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End point description:

End point type	Primary
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End point timeframe:

Month 1 through Month 24

Notes:

[57] - 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	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[58]</sup>	20 <sup>[59]</sup>	8 <sup>[60]</sup>	
Units: IU/kg				
median (full range (min-max))				
Overall Study Period; n=1, 20, 8	38 (38 to 38)	36.1 (29 to 64)	28.8 (25 to 35)	
Month 1; n=1, 15, 0	40 (40 to 40)	34.2 (29 to 53)	0 (0 to 0)	
Month 2; n=1, 12, 0	40 (40 to 40)	34.3 (27 to 58)	0 (0 to 0)	
Month 3; n=1, 13, 0	40 (40 to 40)	33.3 (10 to 49)	0 (0 to 0)	
Month 4; n=1, 16, 0	38 (38 to 38)	34 (28 to 75)	0 (0 to 0)	
Month 5; n=1, 13, 0	38 (38 to 38)	35.3 (24 to 52)	0 (0 to 0)	
Month 6; n=1, 18, 0	38 (38 to 38)	34.9 (26 to 75)	0 (0 to 0)	
Month 7; n=1, 13, 0	38 (38 to 38)	40.8 (29 to 73)	0 (0 to 0)	
Month 8; n=1, 13, 0	38 (38 to 38)	40.8 (17 to 53)	0 (0 to 0)	
Month 9; n=1, 15, 0	38 (38 to 38)	34.4 (27 to 54)	0 (0 to 0)	
Month 10; n=1, 13, 0	43 (43 to 43)	35.3 (28 to 76)	0 (0 to 0)	
Month 11; n=1, 15, 0	38 (38 to 38)	34.5 (27 to 63)	0 (0 to 0)	
Month 12; n=1, 17, 0	36 (36 to 36)	33.3 (23 to 72)	0 (0 to 0)	
Month 13; n=1, 0, 8	31 (31 to 31)	0 (0 to 0)	31.1 (14 to 46)	
Month 14; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	34.2 (14 to 44)	
Month 15; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	26 (14 to 46)	
Month 16; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	30.2 (22 to 55)	
Month 17; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	29.7 (25 to 44)	
Month 18; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	29.7 (25 to 50)	
Month 19; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	28.8 (23 to 42)	
Month 20; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	25 (20 to 33)	
Month 21; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	25.7 (20 to 33)	
Month 22; n=0, 0, 7	0 (0 to 0)	0 (0 to 0)	25.3 (20 to 34)	
Month 23; n=0, 0, 6	0 (0 to 0)	0 (0 to 0)	26.9 (20 to 40)	
Month 24; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	28.9 (20 to 36)	

Notes:

[58] - Efficacy population; n=subjects with an infusion during given time period.

[59] - Efficacy population; n=subjects with an infusion during given time period.

[60] - Efficacy population; n=subjects with an infusion during given time period.

## 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
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End point description:

In the case of any surgical procedures, the surgical team was to provide 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.

End point type	Primary
End point timeframe:	
Up to Month 24	

Notes:

[61] - 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	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[62]</sup>	20 <sup>[63]</sup>	8 <sup>[64]</sup>	
Units: surgeries				
All Surgeries: Less Than Expected; n=0, 4, 2	0	1	1	
All Surgeries: Equivalent To Expected; n=0, 4, 2	0	3	1	
All Surgeries: More Than Expected; n=0, 4, 2	0	0	0	
Major Surgery: Less Than Expected; n=0, 0, 0	0	0	0	
Major Surgery: Equivalent To Expected; n=0, 0, 0	0	0	0	
Major Surgery: More Than Expected; n=0, 0, 0	0	0	0	
Minor Surgery: Less Than Expected; n=0, 4, 2	0	1	1	
Minor Surgery: Equivalent To Expected; n=0, 4, 2	0	3	1	
Minor Surgery: More Than Expected; n=0, 4, 2	0	0	0	

Notes:

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

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

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

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Non-Surgical Bleeding (NSB) Events Per Subject

End point title	Number of Non-Surgical Bleeding (NSB) Events Per Subject <sup>[65]</sup>
End point description:	
End point type	Primary
End point timeframe:	
Up to Month 24	

Notes:

[65] - 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	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[66]</sup>	20 <sup>[67]</sup>	8 <sup>[68]</sup>	
Units: bleeding events				
median (full range (min-max))				
All NSB Events; N=1, 20, 5 / n=10, 533, 10	10 (10 to 10)	19.5 (2 to 82)	1 (1 to 6)	
Spontaneous Events; N=1, 20, 5 / n=10, 529, 10	10 (10 to 10)	19.5 (2 to 82)	1 (1 to 6)	
Trauma Events; N=0, 3, 0 / n=0, 3, 0	0 (0 to 0)	1 (1 to 1)	0 (0 to 0)	
Post-surgery Events; N=0, 1, 0 / n=0, 1, 0	0 (0 to 0)	1 (1 to 1)	0 (0 to 0)	
Major Events; N=1, 8, 2 / n=8, 125, 3	8 (8 to 8)	3 (2 to 59)	1.5 (1 to 2)	
Minor Events; N=1, 20, 4 / n=2, 408, 7	2 (2 to 2)	16 (2 to 69)	1 (1 to 4)	
Joint Events; N=0, 4, 1 / n=0, 101, 2	0 (0 to 0)	20.5 (2 to 58)	2 (2 to 2)	
Mucosal Events; N=1, 20, 5 / n=10, 417, 8	10 (10 to 10)	16 (2 to 69)	1 (1 to 4)	
Muscle Events; N=0, 4, 0 / n=0, 17, 0	0 (0 to 0)	2 (1 to 12)	0 (0 to 0)	
Treated at Home; N=1, 16, 5 / n=1, 381, 10	1 (1 to 1)	18.5 (3 to 81)	1 (1 to 6)	
Treated at Hospital; N=0, 16, 0 / n=0, 26, 0	0 (0 to 0)	1 (1 to 4)	0 (0 to 0)	
Biostate Not Needed; N=1, 6, 0 / n=9, 126, 0	9 (9 to 9)	7 (1 to 65)	0 (0 to 0)	

Notes:

[66] - Efficacy population; N=subjects with respective events / n=total number of bleeding events.

[67] - Efficacy population; N=subjects with respective events / n=total number of bleeding events.

[68] - Efficacy population; N=subjects with respective events / n=total number of bleeding events.

## Statistical analyses

No statistical analyses for this end point

## Primary: Usage of Biostate: Number of Infusions by Study Month

End point title	Usage of Biostate: Number of Infusions by Study Month <sup>[69]</sup>
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End point description:

End point type	Primary
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End point timeframe:

Month 1 through Month 24

Notes:

[69] - 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	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[70]</sup>	20 <sup>[71]</sup>	8 <sup>[72]</sup>	
Units: infusions				
median (inter-quartile range (Q1-Q3))				
Overall Study Period; n=1, 20, 8	197 (197 to 197)	20 (11.5 to 30.5)	72.5 (57 to 113.5)	
Month 1; n=1, 15, 0	13 (13 to 13)	2 (1 to 4)	0 (0 to 0)	
Month 2; n=1, 12, 0	13 (13 to 13)	1.5 (1 to 4)	0 (0 to 0)	
Month 3; n=1, 13, 0	13 (13 to 13)	2 (1 to 4)	0 (0 to 0)	
Month 4; n=1, 16, 0	13 (13 to 13)	1.5 (1 to 3)	0 (0 to 0)	
Month 5; n=1, 13, 0	14 (14 to 14)	2 (1 to 3)	0 (0 to 0)	
Month 6; n=1, 18, 0	12 (12 to 12)	2 (1 to 3)	0 (0 to 0)	
Month 7; n=1, 13, 0	13 (13 to 13)	2 (1 to 3)	0 (0 to 0)	
Month 8; n=1, 13, 0	20 (20 to 20)	2 (1 to 4)	0 (0 to 0)	
Month 9; n=1, 15, 0	4 (4 to 4)	2 (1 to 4)	0 (0 to 0)	
Month 10; n=1, 13, 0	18 (18 to 18)	2 (1 to 3)	0 (0 to 0)	
Month 11; n=1, 15, 0	9 (9 to 9)	2 (1 to 4)	0 (0 to 0)	
Month 12; n=1, 17, 0	46 (46 to 46)	3 (1 to 3)	0 (0 to 0)	
Month 13; n=1, 0, 8	9 (9 to 9)	0 (0 to 0)	7 (4.5 to 10.5)	
Month 14; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	6.5 (4 to 8.5)	
Month 15; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	6 (4.5 to 10)	
Month 16; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	5.5 (5 to 7)	
Month 17; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	5 (4.5 to 8)	
Month 18; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	5.5 (4 to 9.5)	
Month 19; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	6 (4 to 12)	
Month 20; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	4 (4 to 7)	
Month 21; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	5.5 (4 to 8)	
Month 22; n=0, 0, 7	0 (0 to 0)	0 (0 to 0)	6 (4 to 8)	
Month 23; n=0, 0, 6	0 (0 to 0)	0 (0 to 0)	6 (5 to 7)	
Month 24; n=0, 0, 8	0 (0 to 0)	0 (0 to 0)	6.5 (3 to 13)	

Notes:

[70] - Efficacy population; n=subjects receiving an infusion at given time point. 0=not applicable.

[71] - Efficacy population; n=subjects receiving an infusion at given time point. 0=not applicable.

[72] - Efficacy population; n=subjects receiving an infusion at given time point. 0=not applicable.

## Statistical analyses

No statistical analyses for this end point

## Primary: Subject's Monthly Self-rating of Biostate Efficacy: Arms 1 and 3

End point title	Subject's Monthly Self-rating of Biostate Efficacy: Arms 1 and 3
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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.

End point type	Primary
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End point timeframe:

Month 1 through Month 24

Notes:

[73] - 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.

[74] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis was planned for Arms 1 and 3, per protocol.

End point values	Arm 1: Prophylaxis Therapy	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 <sup>[75]</sup>	8 <sup>[76]</sup>		
Units: subjects				
Month 1: Excellent; n=1, 0	1	0		
Month 1: Good; n=1, 0	0	0		
Month 1: Moderate; n=1, 0	0	0		
Month 1: None; n=1, 0	0	0		
Month 2: Excellent; n=1, 0	0	0		
Month 2: Good; n=1, 0	0	0		
Month 2: Moderate; n=1, 0	1	0		
Month 2: None; n=1, 0	0	0		
Month 3: Excellent; n=1, 0	0	0		
Month 3: Good; n=1, 0	0	0		
Month 3: Moderate; n=1, 0	1	0		
Month 3: None; n=1, 0	0	0		
Month 4: Excellent; n=1, 0	1	0		
Month 4: Good; n=1, 0	0	0		
Month 4: Moderate; n=1, 0	0	0		
Month 4: None; n=1, 0	0	0		
Month 5: Excellent; n=1, 0	0	0		
Month 5: Good; n=1, 0	1	0		
Month 5: Moderate; n=1, 0	0	0		
Month 5: None; n=1, 0	0	0		
Month 6: Excellent; n=1, 0	0	0		
Month 6: Good; n=1, 0	0	0		
Month 6: Moderate; n=1, 0	1	0		
Month 6: None; n=1, 0	0	0		
Month 7: Excellent; n=1, 0	1	0		
Month 7: Good; n=1, 0	0	0		
Month 7: Moderate; n=1, 0	0	0		
Month 7: None; n=1, 0	0	0		
Month 8: Excellent; n=1, 0	1	0		
Month 8: Good; n=1, 0	0	0		
Month 8: Moderate; n=1, 0	0	0		
Month 8: None; n=1, 0	0	0		
Month 9: Excellent; n=1, 0	1	0		
Month 9: Good; n=1, 0	0	0		



Month 9: Moderate; n=1, 0	0	0		
Month 9: None; n=1, 0	0	0		
Month 10: Excellent; n=1, 0	1	0		
Month 10: Good; n=1, 0	0	0		
Month 10: Moderate; n=1, 0	0	0		
Month 10: None; n=1, 0	0	0		
Month 11: Excellent; n=1, 0	1	0		
Month 11: Good; n=1, 0	0	0		
Month 11: Moderate; n=1, 0	0	0		
Month 11: None; n=1, 0	0	0		
Month 12: Excellent; n=1, 1	1	1		
Month 12: Good; n=1, 1	0	0		
Month 12: Moderate; n=1, 1	0	0		
Month 12: None; n=1, 1	0	0		
Month 13: Excellent; n=0, 3	0	3		
Month 13: Good; n=0, 3	0	0		
Month 13: Moderate; n=0, 3	0	0		
Month 13: None; n=0, 3	0	0		
Month 14: Excellent; n=0, 3	0	3		
Month 14: Good; n=0, 3	0	0		
Month 14: Moderate; n=0, 3	0	0		
Month 14: None; n=0, 3	0	0		
Month 15: Excellent; n=0, 4	0	4		
Month 15: Good; n=0, 4	0	0		
Month 15: Moderate; n=0, 4	0	0		
Month 15: None; n=0, 4	0	0		
Month 16: Excellent; n=0, 3	0	3		
Month 16: Good; n=0, 3	0	0		
Month 16: Moderate; n=0, 3	0	0		
Month 16: None; n=0, 3	0	0		
Month 17: Excellent; n=0, 3	0	3		
Month 17: Good; n=0, 3	0	0		
Month 17: Moderate; n=0, 3	0	0		
Month 17: None; n=0, 3	0	0		
Month 18: Excellent; n=0, 3	0	3		
Month 18: Good; n=0, 3	0	0		
Month 18: Moderate; n=0, 3	0	0		
Month 18: None; n=0, 3	0	0		
Month 19: Excellent; n=0, 3	0	3		
Month 19: Good; n=0, 3	0	0		
Month 19: Moderate; n=0, 3	0	0		
Month 19: None; n=0, 3	0	0		
Month 20: Excellent; n=0, 3	0	3		
Month 20: Good; n=0, 3	0	0		
Month 20: Moderate; n=0, 3	0	0		
Month 20: None; n=0, 3	0	0		
Month 21: Excellent; n=0, 3	0	3		
Month 21: Good; n=0, 3	0	0		
Month 21: Moderate; n=0, 3	0	0		
Month 21: None; n=0, 3	0	0		
Month 22: Excellent; n=0, 3	0	3		
Month 22: Good; n=0, 3	0	0		

Month 22: Moderate; n=0, 3	0	0		
Month 22: None; n=0, 3	0	0		
Month 23: Excellent; n=0, 2	0	2		
Month 23: Good; n=0, 2	0	0		
Month 23: Moderate; n=0, 2	0	0		
Month 23: None; n=0, 2	0	0		
Month 24: Excellent; n=0, 3	0	3		
Month 24: Good; n=0, 3	0	0		
Month 24: Moderate; n=0, 3	0	0		
Month 24: None; n=0, 3	0	0		

Notes:

[75] - Efficacy population

[76] - Efficacy population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overview of Treatment Emergent Adverse Events (TEAEs)

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

An adverse event (AE) is any untoward medical occurrence that does not necessarily have a causal relationship to the study product. A serious AE (SAE) was defined as any untoward medical occurrence that at any dose: results in death; is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; is another medically important condition. The intensity/severity of AEs was categorized as mild, moderate, or severe. The relationship of the AE to the study product was categorized as not related, unlikely, possibly, probably or definitely. AEs occurring after the first dose of study medication were considered treatment-emergent.

End point type	Secondary
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End point timeframe:

From 1st study drug dose on Day 1 (PK component), or after 1st study drug dose (Efficacy only component), until Final Visit or 7 days after last dose of study drug, whichever occurs last. AEs related to a study procedure recorded from informed consent.

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On- Demand Therapy	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[77]</sup>	21 <sup>[78]</sup>	8 <sup>[79]</sup>	
Units: subjects				
At Least 1 TEAE	1	13	3	
At Least 1 Severe TEAE	1	3	0	
At Least 1 Serious TEAE	0	1	1	
At Least 1 TEAE Leading to Discontinuation	0	0	0	
At Least 1 TEAE Leading to Death	0	0	0	

Notes:

[77] - Safety population

[78] - 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
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End point description:

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

End point type	Secondary
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End point timeframe:

Screening, Months 3, 6, 9, 12, 15, 18, 21, 24

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On- Demand Therapy	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[80]</sup>	21 <sup>[81]</sup>	8 <sup>[82]</sup>	
Units: subjects				
VWF Inhibitor: Screening; n=0, 13, 0	0	0	0	
VWF Inhibitor: Month 3; n=1, 18, 0	0	0	0	
VWF Inhibitor: Month 6; n=1, 17, 0	0	0	0	
VWF Inhibitor: Month 9; n=1, 17, 0	0	0	0	
VWF Inhibitor: Month 12; n=1, 18, 5	0	0	0	
VWF Inhibitor: Month 15; n=0, 0, 7	0	0	0	
VWF Inhibitor: Month 18; n=0, 0, 8	0	0	0	
VWF Inhibitor: Month 21; n=0, 0, 8	0	0	0	
VWF Inhibitor: Month 24; n=0, 0, 8	0	0	0	
FVIII Inhibitor: Screening; n=1, 21, 0	0	0	0	
FVIII Inhibitor: Month 3; n=1, 21, 0	0	0	0	
FVIII Inhibitor: Month 6; n=1, 20, 0	0	0	0	
FVIII Inhibitor: Month 9; n=1, 21, 0	0	0	0	
FVIII Inhibitor: Month 12; n=1, 21, 8	0	0	0	
FVIII Inhibitor: Month 15; n=0, 0, 1	0	0	0	
FVIII Inhibitor: Month 18; n=0, 0, 5	0	0	0	
FVIII Inhibitor: Month 21; n=0, 0, 6	0	0	0	
FVIII Inhibitor: Month 24; n=0, 0, 5	0	0	0	

Notes:

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

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

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

## Statistical analyses

No statistical analyses for this end point

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

End point title	Investigator's Assessment of Haemostatic Efficacy During Surgeries at Discharge
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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	Secondary
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End point timeframe:

Up to Month 24

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On- Demand Therapy	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[83]</sup>	20 <sup>[84]</sup>	8 <sup>[85]</sup>	
Units: surgeries				
All Surgeries: Excellent; n=0, 3, 2	0	2	2	
All Surgeries: Good; n=0, 3, 2	0	1	0	
All Surgeries: Moderate; n=0, 3, 2	0	0	0	
All Surgeries: None; n=0, 3, 2	0	0	0	
Major Surgeries: Excellent; n=0, 0, 0	0	0	0	
Major Surgeries: Good; n=0, 0, 0	0	0	0	
Major Surgeries: Moderate; n=0, 0, 0	0	0	0	
Major Surgeries: None; n=0, 0, 0	0	0	0	
Minor Surgeries: Excellent; n=0, 3, 2	0	2	2	
Minor Surgeries: Good; n=0, 3, 2	0	1	0	
Minor Surgeries: Moderate; n=0, 3, 2	0	0	0	
Minor Surgeries: None; n=0, 3, 2	0	0	0	

Notes:

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

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

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

## Statistical analyses

No statistical analyses for this end point

### Secondary: Investigator's Assessment of Haemostatic Efficacy During Surgeries per

## In-house Day

End point title	Investigator's Assessment of Haemostatic Efficacy During Surgeries per In-house Day
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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	Secondary
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End point timeframe:

Up to Month 24

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On- Demand Therapy	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[86]</sup>	20 <sup>[87]</sup>	8 <sup>[88]</sup>	
Units: in-house days due to surgeries				
All Days: Excellent; n=0, 5, 3	0	2	3	
All Days: Good; n=0, 5, 3	0	3	0	
All Days: Moderate; n=0, 5, 3	0	0	0	
All Days: None; n=0, 5, 3	0	0	0	
Day 1: Excellent; n=0, 3, 2	0	2	2	
Day 1: Good; n=0, 3, 2	0	1	0	
Day 1: Moderate; n=0, 3, 2	0	0	0	
Day 1: None; n=0, 3, 2	0	0	0	
Day 2: Excellent; n=0, 1, 1	0	0	1	
Day 2: Good; n=0, 1, 1	0	1	0	
Day 2: Moderate; n=0, 1, 1	0	0	0	
Day 2: None; n=0, 1, 1	0	0	0	
Day 3: Excellent; n=0, 1, 0	0	0	0	
Day 3: Good; n=0, 1, 0	0	1	0	
Day 3: Moderate; n=0, 1, 0	0	0	0	
Day 3: None; n=0, 1, 0	0	0	0	

Notes:

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

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

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Investigator's Post-Surgery Assessment of Haemostatic Efficacy at Home

End point title	Investigator's Post-Surgery Assessment of Haemostatic Efficacy at Home
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End point description:

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	Secondary
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End point timeframe:

Up to Month 24

End point values	Arm 1: Prophylaxis Therapy	Arm 2: On- Demand Therapy	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[89]</sup>	20 <sup>[90]</sup>	8 <sup>[91]</sup>	
Units: surgeries				
All Surgeries: Excellent; n=0, 2, 2	0	2	4	
All Surgeries: Good; n=0, 2, 2	0	0	0	
All Surgeries: Moderate; n=0, 2, 2	0	0	0	
All Surgeries: None; n=0, 2, 2	0	0	0	
Major Surgeries: Excellent; n=0, 0, 0	0	0	0	
Major Surgeries: Good; n=0, 0, 0	0	0	0	
Major Surgeries: Moderate; n=0, 0, 0	0	0	0	
Major Surgeries: None; n=0, 0, 0	0	0	0	
Minor Surgeries: Excellent; n=0, 2, 2	0	2	4	
Minor Surgeries: Good; n=0, 2, 2	0	0	0	
Minor Surgeries: Moderate; n=0, 2, 2	0	0	0	
Minor Surgeries: None; n=0, 2, 2	0	0	0	

Notes:

[89] - Efficacy population; n=surgeries of the given type with available post-surgery assessment.

[90] - Efficacy population; n=surgeries of the given type with available post-surgery assessment.

[91] - Efficacy population; n=surgeries of the given type with available post-surgery assessment.

## Statistical analyses

No statistical analyses for this end point

## Secondary: 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
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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	Secondary
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End point timeframe:

Up to Month 24

<b>End point values</b>	Arm 1: Prophylaxis Therapy	Arm 2: On- Demand Therapy	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[92]</sup>	20 <sup>[93]</sup>	8 <sup>[94]</sup>	
Units: post-surgery days				
All Days: Excellent; n=0, 5, 4	0	5	4	
All Days: Good; n=0, 5, 4	0	0	0	
All Days: Moderate; n=0, 5, 4	0	0	0	
All Days: None; n=0, 5, 4	0	0	0	
Day 1: Excellent; n=0, 2, 2	0	2	2	
Day 1: Good; n=0, 2, 2	0	0	0	
Day 1: Moderate; n=0, 2, 2	0	0	0	
Day 1: None; n=0, 2, 2	0	0	0	
Day 2: Excellent; n=0, 1, 2	0	1	2	
Day 2: Good; n=0, 1, 2	0	0	0	
Day 2: Moderate; n=0, 1, 2	0	0	0	
Day 2: None; n=0, 1, 2	0	0	0	
Day 3: Excellent; n=0, 1, 0	0	1	0	
Day 3: Good; n=0, 1, 0	0	0	0	
Day 3: Moderate; n=0, 1, 0	0	0	0	
Day 3: None; n=0, 1, 0	0	0	0	
Day 4: Excellent; n=0, 1, 0	0	1	0	
Day 4: Good; n=0, 1, 0	0	0	0	
Day 4: Moderate; n=0, 1, 0	0	0	0	
Day 4: None; n=0, 1, 0	0	0	0	

Notes:

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

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

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects Requiring Surgery-Related Blood Product Transfusions

End point title	Number of Subjects Requiring Surgery-Related Blood Product Transfusions
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End point description:

End point type	Secondary
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End point timeframe:

Up to Month 24

<b>End point values</b>	Arm 1: Prophylaxis Therapy	Arm 2: On- Demand Therapy	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1 <sup>[95]</sup>	20 <sup>[96]</sup>	8 <sup>[97]</sup>	
Units: subjects	0	0	0	

Notes:

[95] - Efficacy population

[96] - Efficacy population

[97] - Efficacy population

### **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 24 months). Events considered related to a study procedure were recorded from the point of informed consent.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.1
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### Reporting groups

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

Subjects who were being treated on a set prophylaxis regimen with a VWF product at the time of study entry, or who were not on a set prophylaxis regimen but in whom prophylaxis treatment was justifiable in the opinion of the investigator, were enrolled into Arm 1 and received Biostate as part of a prophylaxis regimen as determined by the severity of their disease for a period of 12 months. Arm 1 subjects completed the study with a Final Visit at Month 12.

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

Subjects who were not 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 (spontaneous or trauma-induced), were enrolled into Arm 2 and commenced using Biostate as on-demand therapy for the treatment of NSB events. At the Month 12 visit and based on the extent and location of any bleeding events, Arm 2 subjects were assessed for eligibility to be switched to a set prophylaxis regimen with Biostate for an additional 12 months (Arm 3). The total treatment duration for subjects in Arm 2 only was up to 12 months.

Reporting group title	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)
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Reporting group description:

Subjects who completed treatment (on-demand therapy with Biostate) in Arm 2 and who at the Month 12 visit qualified to be switched to a set prophylactic regimen according to the criteria prespecified in the study protocol, entered Arm 3 and started Biostate treatment as prophylaxis therapy for an additional 12 months. The prophylaxis regimen was determined by the extent and location of NSB events during the preceding 12-month on-demand therapy period. The total treatment duration for subjects in Arm 3 was up to 24 months.

Serious adverse events	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	1 / 21 (4.76%)	1 / 8 (12.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Prostatic specific antigen increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 21 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Cataract			
subjects affected / exposed	0 / 1 (0.00%)	0 / 21 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 1 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	Arm 1: Prophylaxis Therapy	Arm 2: On-Demand Therapy	Arm 3: Prophylaxis Therapy (Post On-Demand Therapy)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	13 / 21 (61.90%)	3 / 8 (37.50%)
Investigations			
Prostatic specific antigen increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 21 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 21 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 1 (0.00%)	1 / 21 (4.76%)	1 / 8 (12.50%)
occurrences (all)	0	3	1
Hypertensive crisis			
subjects affected / exposed	0 / 1 (0.00%)	2 / 21 (9.52%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 1 (0.00%)	0 / 21 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Nervous system disorders			

Ageusia subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 21 (0.00%) 0	0 / 8 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 3	3 / 21 (14.29%) 7	0 / 8 (0.00%) 0
Somnolence subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 21 (0.00%) 0	0 / 8 (0.00%) 0
General disorders and administration site conditions			
Infusion site pruritus subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 21 (0.00%) 0	0 / 8 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 21 (0.00%) 0	0 / 8 (0.00%) 0
Eye disorders			
Cataract subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	2 / 21 (9.52%) 3	0 / 8 (0.00%) 0
Gastrointestinal disorders			
Toothache subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	2 / 21 (9.52%) 5	0 / 8 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 2	0 / 21 (0.00%) 0	0 / 8 (0.00%) 0
Flatulence subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 21 (0.00%) 0	0 / 8 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	1 / 21 (4.76%) 1	0 / 8 (0.00%) 0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	1 / 1 (100.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 1 (100.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	3	1	0
Bronchopneumonia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2008	<ul style="list-style-type: none"><li>• All subjects had their VWD phenotype confirmed at the screening visit. This was performed by a central laboratory to ensure consistency in the phenotyping method used across sites and to ensure reliability of the phenotype result.</li><li>• The duration of the screening period was increased from up to 14 days to up to 21 days to allow sufficient processing time for the phenotype assessment.</li><li>• Reduced blood volumes for adolescents were inserted.</li><li>• Introduction of a Data Safety Monitoring Board.</li><li>• Text inserted to emphasize that, whilst the initial PK component could be performed in Types 1, 2a, and 3 VWD subjects, only the Type 3 PK subjects were to participate in the repeat PK assessment.</li></ul>
23 April 2009	<ul style="list-style-type: none"><li>• A reduction in the volume of blood taken for both adults and adolescents (the same volumes required for adults and adolescents).</li><li>• Amendment to exclusion criterion number 9.</li><li>• Removal of Human Immunodeficiency Virus testing at screening.</li><li>• Modification of the requirements for Hepatitis C testing at screening.</li><li>• The duration of the screening period was increased from up to 21 days to up to 28 days to allow sufficient processing time for the phenotype assessment.</li><li>• Confirmation that a urine pregnancy test rather than a serum pregnancy test was to be performed in females of childbearing potential at screening.</li><li>• Bicarbonate testing was deleted from Biochemistry determinations as the testing procedure is contraindicated in bleeding disorders.</li><li>• Clarification regarding Hepatitis A and Hepatitis B eligibility testing at screening and pre-dose vaccination requirements.</li></ul>
15 December 2009	<ul style="list-style-type: none"><li>• Adjustment of inclusion criterion number 3 to allow for the enrolment of subjects in Bulgaria where DDAVP is not available.</li><li>• Wash-out period prior to the screening visit.</li><li>• Adjustment of safety assessments with regard to suspected inhibitor formation.</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported