



Clinical trial results:

A Phase III, Open-Label, Multicentre Study to Evaluate Efficacy, Pharmacokinetics, and Safety of Biostate® in Paediatric Subjects with Haemophilia A.

Summary

EudraCT number	2009-015112-18
Trial protocol	BG
Global end of trial date	01 July 2014

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-08-53
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01229007
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 August 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To assess the efficacy of Biostate in paediatric subjects with haemophilia A.
2. To investigate the pharmacokinetics (PK) of Biostate in paediatric subjects with haemophilia A.

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

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ukraine: 4
Country: Number of subjects enrolled	Belarus: 7
Country: Number of subjects enrolled	Guatemala: 2
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Georgia: 12
Country: Number of subjects enrolled	Lebanon: 9
Worldwide total number of subjects	35
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	4
Children (2-11 years)	31
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

Arm title	PK Component
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Arm description:

A single dose of 50 IU FVIII/kg body weight of Biostate on Day 1 by intravenous (IV) infusion.

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:

The PK infusion dose received was based on the actual FVIII concentration of the batch used for this infusion in order to dose accurately for the PK component.

Number of subjects in period 1	PK Component
Started	35
Completed	35

Period 2

Period 2 title	Efficacy Component
Is this the baseline period?	Yes ^[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

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

In the efficacy component, each subject received a dose of Biostate as determined by the investigator based on the subject's clinical condition, previous FVIII concentrate requirements, previous response to therapy, weight, and reason for usage.

Guidelines for prophylaxis therapy were 20-40 IU FVIII/kg body weight per day at intervals of 2 to 3 days. In some cases, especially in younger subjects, shorter dosage intervals or higher doses may have been necessary.

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:

The dose received for non-PK infusions was based on the nominal FVIII vial strength of the batch used for this infusion.

Arm title	On-Demand Therapy Arm
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Arm description:

In the efficacy component, each subject received a dose of Biostate as determined by the investigator based on the subject's clinical condition, previous FVIII concentrate requirements, previous response to therapy, weight, and reason for usage.

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:

The dose received for non-PK infusions was based on the nominal FVIII vial strength of the batch used for this infusion.

Notes:

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

Justification: Efficacy Component was chosen to present baseline characteristics by treatment arm.

Number of subjects in period 2	Prophylaxis Therapy Arm	On-Demand Therapy Arm
Started	18	17
Completed	15	13
Not completed	3	4
Consent withdrawn by subject	-	2
FVIII inhibitor development	-	2
Non-compliance with prophylaxis regimen	1	-
Site closure	2	-

Baseline characteristics

Reporting groups

Reporting group title	Prophylaxis Therapy Arm
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Reporting group description:

In the efficacy component, each subject received a dose of Biostate as determined by the investigator based on the subject's clinical condition, previous FVIII concentrate requirements, previous response to therapy, weight, and reason for usage.

Guidelines for prophylaxis therapy were 20-40 IU FVIII/kg body weight per day at intervals of 2 to 3 days. In some cases, especially in younger subjects, shorter dosage intervals or higher doses may have been necessary.

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

In the efficacy component, each subject received a dose of Biostate as determined by the investigator based on the subject's clinical condition, previous FVIII concentrate requirements, previous response to therapy, weight, and reason for usage.

Reporting group values	Prophylaxis Therapy Arm	On-Demand Therapy Arm	Total
Number of subjects	18	17	35
Age categorical Units: Subjects			
0 to < 2 years	0	4	4
2 to < 6 years	4	8	12
6 to < 12 years	14	5	19
Age continuous Units: years			
arithmetic mean	7.3	4.9	
standard deviation	± 2.68	± 3.43	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	18	17	35

End points

End points reporting groups

Reporting group title	PK Component
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Reporting group description:

A single dose of 50 IU FVIII/kg body weight of Biostate on Day 1 by intravenous (IV) infusion.

Reporting group title	Prophylaxis Therapy Arm
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Reporting group description:

In the efficacy component, each subject received a dose of Biostate as determined by the investigator based on the subject's clinical condition, previous FVIII concentrate requirements, previous response to therapy, weight, and reason for usage.

Guidelines for prophylaxis therapy were 20-40 IU FVIII/kg body weight per day at intervals of 2 to 3 days. In some cases, especially in younger subjects, shorter dosage intervals or higher doses may have been necessary.

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

In the efficacy component, each subject received a dose of Biostate as determined by the investigator based on the subject's clinical condition, previous FVIII concentrate requirements, previous response to therapy, weight, and reason for usage.

Subject analysis set title	PK Population: Overall
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Subject analysis set type	Full analysis
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Subject analysis set description:

The PK population used for the PK evaluation following the infusion of Biostate included 33 subjects in total (17 of the prophylaxis arm and 16 of the on-demand arm). One prophylaxis subject (no PK concentrations available) and 1 on-demand subject (pre-existing FVIII inhibitors) were excluded from the PK population.

Subject analysis set title	PK Population: 0 to < 6 Years
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subjects in the PK population who were < 6 years old.

Subject analysis set title	PK Population: 6 to < 12 Years
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subjects in the PK population who were 6 to < 12 years old.

Subject analysis set title	Efficacy Population: Prophylaxis
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Subject analysis set type	Full analysis
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Subject analysis set description:

All treated subjects in the Prophylaxis Therapy arm who participated in the efficacy component of the study with an available haemostatic efficacy assessment.

Subject analysis set title	Efficacy Population: On-demand
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Subject analysis set type	Full analysis
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Subject analysis set description:

All treated subjects in the On-demand Therapy arm who participated in the efficacy component of the study with an available haemostatic efficacy assessment.

Subject analysis set title	Safety Population: Prophylaxis
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Subject analysis set type	Safety analysis
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Subject analysis set description:

All subjects in the Prophylaxis Therapy arm who received at least 1 dose of Biostate.

Subject analysis set title	Safety Population: On-demand
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Subject analysis set type	Safety analysis
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Subject analysis set description:

All subjects in the On-demand Therapy arm who received at least 1 dose of Biostate.

Primary: FVIII:C PK Parameter: Incremental Recovery (IR)

End point title	FVIII:C PK Parameter: Incremental Recovery (IR) ^[1]
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End point description:

PK parameters were calculated by a non-compartmental infusion model. FVIII:C concentrations were used as measured for the derivation of the PK parameters without baseline adjustment.

End point type	Primary
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End point timeframe:

Pre-infusion (up to 5 hours prior to start of infusion); 30 minutes (+5 minutes), 4 hours (±15 minutes), 8 hours (±30 minutes), 24 hours (±2 hours), and 48 hours (±2 hours) 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 summarised by descriptive statistics.

End point values	PK Population: Overall	PK Population: 0 to < 6 Years	PK Population: 6 to < 12 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	15	18	
Units: (IU/mL)/(IU/kg)				
geometric mean (geometric coefficient of variation)	0.015 (± 27.1)	0.014 (± 19)	0.015 (± 32)	

Statistical analyses

No statistical analyses for this end point

Primary: FVIII:C PK Parameter: Half-life (t_{1/2})

End point title	FVIII:C PK Parameter: Half-life (t _{1/2}) ^[2]
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End point description:

PK parameters were calculated by a non-compartmental infusion model. FVIII:C concentrations were used as measured for the derivation of the PK parameters without baseline adjustment.

End point type	Primary
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End point timeframe:

Pre-infusion (up to 5 hours prior to start of infusion); 30 minutes (+5 minutes), 4 hours (±15 minutes), 8 hours (±30 minutes), 24 hours (±2 hours), and 48 hours (±2 hours) after the end of infusion.

Notes:

[2] - 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 summarised by descriptive statistics.

End point values	PK Population: Overall	PK Population: 0 to < 6 Years	PK Population: 6 to < 12 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32 ^[3]	15	17 ^[4]	
Units: hours				
geometric mean (geometric coefficient of variation)	10.4 (± 24.9)	10 (± 25.6)	10.8 (± 24.7)	

Notes:

[3] - subjects with evaluable data

[4] - subjects with evaluable data

Statistical analyses

No statistical analyses for this end point

Primary: FVIII:C PK Parameter: Maximum Plasma Concentration (C_{max})

End point title	FVIII:C PK Parameter: Maximum Plasma Concentration
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End point description:

PK parameters were calculated by a non-compartmental infusion model. FVIII:C concentrations were used as measured for the derivation of the PK parameters without baseline adjustment.

End point type	Primary
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End point timeframe:

Pre-infusion (up to 5 hours prior to start of infusion); 30 minutes (+5 minutes), 4 hours (±15 minutes), 8 hours (±30 minutes), 24 hours (±2 hours), and 48 hours (±2 hours) 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 summarised by descriptive statistics.

End point values	PK Population: Overall	PK Population: 0 to < 6 Years	PK Population: 6 to < 12 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	15	18	
Units: IU/mL				
geometric mean (geometric coefficient of variation)	0.71 (± 29.5)	0.72 (± 19.1)	0.69 (± 35.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Primary: FVIII:C PK Parameter: Area Under the Plasma Concentration-time Curve From Time Point 0 to Last Quantifiable Time Point (AUC[0-t])

End point title	Primary: FVIII:C PK Parameter: Area Under the Plasma Concentration-time Curve From Time Point 0 to Last Quantifiable Time Point (AUC[0-t]) ^[6]
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End point description:

PK parameters were calculated by a non-compartmental infusion model. FVIII:C concentrations were used as measured for the derivation of the PK parameters without baseline adjustment.

End point type	Primary
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End point timeframe:

Pre-infusion (up to 5 hours prior to start of infusion); 30 minutes (+5 minutes), 4 hours (±15 minutes), 8 hours (±30 minutes), 24 hours (±2 hours), and 48 hours (±2 hours) after the end of infusion.

Notes:

[6] - 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 summarised by descriptive statistics.

End point values	PK Population: Overall	PK Population: 0 to < 6 Years	PK Population: 6 to < 12 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	15	18	
Units: h*IU/mL				
geometric mean (geometric coefficient of variation)	7.86 (± 35.1)	7.79 (± 23.2)	7.92 (± 41.2)	

Statistical analyses

No statistical analyses for this end point

Primary: FVIII:C PK Parameter: Area Under the Plasma Concentration-time Curve From Time 0 to Infinite Time (AUC[0-∞])

End point title	FVIII:C PK Parameter: Area Under the Plasma Concentration-time Curve From Time 0 to Infinite Time (AUC[0-∞]) ^[7]
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End point description:

PK parameters were calculated by a non-compartmental infusion model. FVIII:C concentrations were used as measured for the derivation of the PK parameters without baseline adjustment.

End point type	Primary
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End point timeframe:

Pre-infusion (up to 5 hours prior to start of infusion); 30 minutes (+5 minutes), 4 hours (±15 minutes), 8 hours (±30 minutes), 24 hours (±2 hours), and 48 hours (±2 hours) 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 summarised by descriptive statistics.

End point values	PK Population: Overall	PK Population: 0 to < 6 Years	PK Population: 6 to < 12 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32 ^[8]	15	17 ^[9]	
Units: h*IU/mL				
geometric mean (geometric coefficient of variation)	8.68 (± 31.9)	8.12 (± 23.7)	9.21 (± 34.9)	

Notes:

[8] - subjects with evaluable data

[9] - subjects with evaluable data

Statistical analyses

No statistical analyses for this end point

Primary: FVIII:C PK Parameter: Total Clearance (CL)

End point title	FVIII:C PK Parameter: Total Clearance (CL) ^[10]
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End point description:

PK parameters were calculated by a non-compartmental infusion model. FVIII:C concentrations were used as measured for the derivation of the PK parameters without baseline adjustment.

End point type	Primary
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End point timeframe:

Pre-infusion (up to 5 hours prior to start of infusion); 30 minutes (+5 minutes), 4 hours (± 15 minutes), 8 hours (± 30 minutes), 24 hours (± 2 hours), and 48 hours (± 2 hours) after the end of infusion.

Notes:

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

Justification: PK parameters were summarised by descriptive statistics.

End point values	PK Population: Overall	PK Population: 0 to < 6 Years	PK Population: 6 to < 12 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32 ^[11]	15	17	
Units: mL/h/kg				
geometric mean (geometric coefficient of variation)	5.71 (± 35.6)	6.2 (± 28.3)	5.32 (± 42.3)	

Notes:

[11] - subjects with evaluable data

Statistical analyses

No statistical analyses for this end point

Primary: FVIII:C PK Parameter: Volume of Distribution at Steady State (Vss)

End point title	FVIII:C PK Parameter: Volume of Distribution at Steady State (Vss) ^[12]
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End point description:

PK parameters were calculated by a non-compartmental infusion model. FVIII:C concentrations were used as measured for the derivation of the PK parameters without baseline adjustment.

End point type	Primary
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End point timeframe:

Pre-infusion (up to 5 hours prior to start of infusion); 30 minutes (+5 minutes), 4 hours (± 15 minutes), 8 hours (± 30 minutes), 24 hours (± 2 hours), and 48 hours (± 2 hours) after the end of infusion.

Notes:

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

Justification: PK parameters were summarised by descriptive statistics.

End point values	PK Population: Overall	PK Population: 0 to < 6 Years	PK Population: 6 to < 12 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32 ^[13]	15	17 ^[14]	
Units: mL/kg				
geometric mean (geometric coefficient of variation)	79.9 (± 61.3)	81.5 (± 39.1)	78.5 (± 75.8)	

Notes:

[13] - subjects with evaluable data

[14] - subjects with evaluable data

Statistical analyses

No statistical analyses for this end point

Primary: FVIII:C PK Parameter: Mean Residence Time to Infinite Time (MRTinf)

End point title	FVIII:C PK Parameter: Mean Residence Time to Infinite Time (MRTinf) ^[15]
End point description: PK parameters were calculated by a non-compartmental infusion model. FVIII:C concentrations were used as measured for the derivation of the PK parameters without baseline adjustment.	
End point type	Primary

End point timeframe:

Pre-infusion (up to 5 hours prior to start of infusion); 30 minutes (+5 minutes), 4 hours (±15 minutes), 8 hours (±30 minutes), 24 hours (±2 hours), and 48 hours (±2 hours) 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 summarised by descriptive statistics.

End point values	PK Population: Overall	PK Population: 0 to < 6 Years	PK Population: 6 to < 12 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32 ^[16]	15	17 ^[17]	
Units: hours				
geometric mean (geometric coefficient of variation)	13.9828 (± 21.1)	13.1497 (± 19.5)	14.7617 (± 21.4)	

Notes:

[16] - subjects with evaluable data

[17] - subjects with available data

Statistical analyses

No statistical analyses for this end point

Primary: FVIII:C PK Parameter: Time the Maximum Concentration Occurs (Tmax)

End point title	FVIII:C PK Parameter: Time the Maximum Concentration Occurs (Tmax) ^[18]
End point description: PK parameters were calculated by a non-compartmental infusion model. FVIII:C concentrations were used as measured for the derivation of the PK parameters without baseline adjustment.	
End point type	Primary

End point timeframe:

Pre-infusion (up to 5 hours prior to start of infusion); 30 minutes (+5 minutes), 4 hours (±15 minutes), 8 hours (±30 minutes), 24 hours (±2 hours), and 48 hours (±2 hours) after the end of infusion.

Notes:

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

Justification: PK parameters were summarised by descriptive statistics.

End point values	PK Population: Overall	PK Population: 0 to < 6 Years	PK Population: 6 to < 12 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	15	18	
Units: hours				
geometric mean (geometric coefficient of variation)	0.5876 (± 14.7)	0.5753 (± 3.1)	0.598 (± 19.2)	

Statistical analyses

No statistical analyses for this end point

Primary: FVIII:C PK Parameter: Minimum Plasma Concentration (Cmin)

End point title	FVIII:C PK Parameter: Minimum Plasma Concentration
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End point description:

PK parameters were calculated by a non-compartmental infusion model. FVIII:C concentrations were used as measured for the derivation of the PK parameters without baseline adjustment. Any values below the lower limit of quantification (LLOQ) for FVIII:C (LLOQ < 0.008 IU/mL) were set to zero.

End point type	Primary
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End point timeframe:

Pre-infusion (up to 5 hours prior to start 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 summarised by descriptive statistics.

End point values	PK Population: Overall	PK Population: 0 to < 6 Years	PK Population: 6 to < 12 Years	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	15	18	
Units: IU/mL				
arithmetic mean (standard deviation)	0.0066 (± 0.187)	0.0107 (± 0.269)	0.0032 (± 0.0063)	

Statistical analyses

No statistical analyses for this end point

Primary: Investigator's Monthly Assessment of Haemostatic Efficacy

End point title	Investigator's Monthly Assessment of Haemostatic Efficacy ^[20]
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End point description:

For each month 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 1 through 12

Notes:

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

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

End point values	Efficacy Population: Prophylaxis	Efficacy Population: On-demand		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18 ^[21]	16 ^[22]		
Units: subjects				
Month 1: Excellent; n=7, 15	5	2		
Month 1: Good; n=7, 15	2	13		
Month 1: Moderate; n=7, 15	0	0		
Month 1: None; n=7, 15	0	0		
Month 2: Excellent; n=10, 10	8	0		
Month 2: Good; n=10, 10	2	10		
Month 2: Moderate; n=10, 10	0	0		
Month 2: None; n=10, 10	0	0		
Month 3: Excellent; n=7, 9	7	0		
Month 3: Good; n=7, 9	0	9		
Month 3: Moderate; n=7, 9	0	0		
Month 3: None; n=7, 9	0	0		
Month 4: Excellent; n=8, 11	5	0		
Month 4: Good; n=8, 11	3	11		
Month 4: Moderate; n=8, 11	0	0		
Month 4: None; n=8, 11	0	0		
Month 5: Excellent; n=7, 11	7	2		
Month 5: Good; n=7, 11	0	9		
Month 5: Moderate; n=7, 11	0	0		
Month 5: None; n=7, 11	0	0		
Month 6: Excellent; n=7, 12	5	2		
Month 6: Good; n=7, 12	2	10		
Month 6: Moderate; n=7, 12	0	0		
Month 6: None; n=7, 12	0	0		
Month 7: Excellent; n=7, 11	6	0		
Month 7: Good; n=7, 11	1	11		
Month 7: Moderate; n=7, 11	0	0		
Month 7: None; n=7, 11	0	0		
Month 8: Excellent; n=4, 8	4	0		
Month 8: Good; n=4, 8	0	8		
Month 8: Moderate; n=4, 8	0	0		
Month 8: None; n=4, 8	0	0		
Month 9: Excellent; n=5, 7	5	0		
Month 9: Good; n=5, 7	0	7		
Month 9: Moderate; n=5, 7	0	0		
Month 9: None; n=5, 7	0	0		
Month 10: Excellent; n=5, 8	4	1		
Month 10: Good; n=5, 8	1	7		
Month 10: Moderate; n=5, 8	0	0		
Month 10: None; n=5, 8	0	0		
Month 11: Excellent; n=4, 10	4	1		

Month 11: Good; n=4, 10	0	9		
Month 11: Moderate; n=4, 10	0	0		
Month 11: None; n=4, 10	0	0		
Month 12: Excellent; n=1, 11	1	1		
Month 12: Good; n=1, 11	0	10		
Month 12: Moderate; n=1, 11	0	0		
Month 12: None; n=1, 11	0	0		

Notes:

[21] - n=subjects with an assessment at given time point

[22] - n=subjects with an assessment at given time point

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 ^[23]
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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 12

Notes:

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

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

End point values	Efficacy Population: Prophylaxis	Efficacy Population: On-demand		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18 ^[24]	16 ^[25]		
Units: events				
All NSB Events: Excellent; n=172, 318	148	77		
All NSB Events: Good; n=172, 318	23	241		
All NSB Events: Moderate; n=172, 318	1	0		
All NSB Events: None; n=172, 318	0	0		
Spontaneous Events: Excellent; n=54, 123	42	26		
Spontaneous Events: Good; n=54, 123	11	97		
Spontaneous Events: Moderate; n=54, 123	1	0		
Spontaneous Events: None; n=54, 123	0	0		
Trauma Events: Excellent; n=118, 194	106	51		
Trauma Events: Good; n=118, 194	12	143		

Trauma Events: Moderate; n=118, 194	0	0		
Trauma Events: None; n=118, 194	0	0		
Post-surgery Events: Excellent; n=0, 1	0	0		
Post-surgery Events: Good; n=0, 1	0	1		
Post-surgery Events: Moderate; n=0, 1	0	0		
Post-surgery Events: None; n=0, 1	0	0		
Major Events: Excellent; n=85, 98	70	4		
Major Events: Good; n=85, 98	15	94		
Major Events: Moderate; n=85, 98	0	0		
Major Events: None; n=85, 98	0	0		
Minor Events: Excellent; n=87, 220	78	73		
Minor Events: Good; n=87, 220	8	147		
Minor Events: Moderate; n=87, 220	1	0		
Minor Events: None; n=87, 220	0	0		
Joint Events: Excellent; n=143, 176	122	31		
Joint Events: Good; n=143, 176	20	145		
Joint Events: Moderate; n=143, 176	1	0		
Joint Events: None; n=143, 176	0	0		
Mucosal Events: Excellent; n=13, 73	12	24		
Mucosal Events: Good; n=13, 73	1	49		
Mucosal Events: Moderate; n=13, 73	0	0		
Mucosal Events: None; n=13, 73	0	0		
Muscle Events: Excellent; n=14, 67	12	21		
Muscle Events: Good; n=14, 67	2	46		
Muscle Events: Moderate; n=14, 67	0	0		
Muscle Events: None; n=14, 67	0	0		
Other Events: Excellent; n=2, 2	2	1		
Other Events: Good; n=2, 2	0	1		
Other Events: Moderate; n=2, 2	0	0		
Other Events: None; n=2, 2	0	0		

Notes:

[24] - n=NSB events treated with Biostate and with a haemostatic efficacy assessment.

[25] - 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 Nonsurgical Bleeding Event

End point title	Subject's Assessment of Haemostatic Efficacy per Day of Nonsurgical Bleeding Event ^[26]
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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 12

Notes:

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

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

End point values	Efficacy Population: Prophylaxis	Efficacy Population: On-demand		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18 ^[27]	16 ^[28]		
Units: days				
All Days: Excellent; n=182, 363	132	83		
All Days: Good; n=182, 363	37	209		
All Days: Moderate; n=182, 363	13	71		
All Days: None; n=182, 363	0	0		
Day 1: Excellent; n=162, 225	124	69		
Day 1: Good; n=162, 225	26	110		
Day 1: Moderate; n=162, 225	12	46		
Day 1: None; n=162, 225	0	0		
Day 2: Excellent; n=19, 89	8	13		
Day 2: Good; n=19, 89	10	57		
Day 2: Moderate; n=19, 89	1	19		
Day 2: None; n=19, 89	0	0		
Day 3: Excellent; n=1, 31	0	1		
Day 3: Good; n=1, 31	1	26		
Day 3: Moderate; n=1, 31	0	4		
Day 3: None; n=1, 31	0	0		
Day 4: Excellent; n=0, 10	0	0		
Day 4: Good; n=0, 10	0	9		
Day 4: Moderate; n=0, 10	0	1		
Day 4: None; n=0, 10	0	0		
Day 5: Excellent; n=0, 5	0	0		
Day 5: Good; n=0, 5	0	4		
Day 5: Moderate; n=0, 5	0	1		
Day 5: None; n=0, 5	0	0		
Day 7: Excellent; n=0, 2	0	0		
Day 7: Good; n=0, 2	0	2		
Day 7: Moderate; n=0, 2	0	0		
Day 7: None; n=0, 2	0	0		
Day 10: Excellent; n=0, 1	0	0		
Day 10: Good; n=0, 1	0	1		
Day 10: Moderate; n=0, 1	0	0		
Day 10: None; n=0, 1	0	0		

Notes:

[27] - n=total number of days due to bleeds with available subject's assessment.

[28] - n=total number of days due to bleeds with available subject's assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Investigator's Assessment of Haemostatic Efficacy During Surgeries per

In-house Day

End point title	Investigator's Assessment of Haemostatic Efficacy During Surgeries per In-house Day ^[29]
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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	Primary
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End point timeframe:

up to 12 months

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

End point values	Efficacy Population: Prophylaxis	Efficacy Population: On-demand		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18 ^[30]	16 ^[31]		
Units: in-house days due to surgeries				
All Days: Excellent; n=4, 3	4	0		
All Days: Good; n=4, 3	0	3		
All Days: Moderate; n=4, 3	0	0		
All Days: None; n=4, 3	0	0		
Day 1: Excellent; n=2, 3	2	0		
Day 1: Good; n=2, 3	0	3		
Day 1: Moderate; n=2, 3	0	0		
Day 1: None; n=2, 3	0	0		
Day 2: Excellent; n=1, 0	1	0		
Day 2: Good; n=1, 0	0	0		
Day 2: Moderate; n=1, 0	0	0		
Day 2: None; n=1, 0	0	0		
Day 3: Excellent; n=1, 0	1	0		
Day 3: Good; n=1, 0	0	0		
Day 3: Moderate; n=1, 0	0	0		
Day 3: None; n=1, 0	0	0		

Notes:

[30] - n=in-house days due to surgeries with available investigator's assessment.

[31] - n=in-house days due to surgeries with available investigator's assessment.

Statistical analyses

No statistical analyses for this end point

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

End point title	Investigator's Assessment of Haemostatic Efficacy During Surgeries at Discharge ^[32]
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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	Primary
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End point timeframe:

up to 12 months

Notes:

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

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

End point values	Efficacy Population: Prophylaxis	Efficacy Population: On-demand		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18 ^[33]	16 ^[34]		
Units: surgeries				
All Surgeries: Excellent; n=2, 3	2	0		
All Surgeries: Good; n=2, 3	0	3		
All Surgeries: Moderate; n=2, 3	0	0		
All Surgeries: None; n=2, 3	0	0		
Major Surgeries: Excellent; n=0, 2	0	0		
Major Surgeries: Good; n=0, 2	0	2		
Major Surgeries: Moderate; n=0, 2	0	0		
Major Surgeries: None; n=0, 2	0	0		
Minor Surgeries: Excellent; n=2, 1	2	0		
Minor Surgeries: Good; n=2, 1	0	1		
Minor Surgeries: Moderate; n=2, 1	0	0		
Minor Surgeries: None; n=2, 1	0	0		

Notes:

[33] - n=number of surgeries of given type with available investigator's assessment.

[34] - n=number of surgeries of given type with available investigator's assessment.

Statistical analyses

No statistical analyses for this end point

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

End point title	Subject's Daily Post-Surgery Assessment of Haemostatic Efficacy at Home ^[35]
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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	Primary
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End point timeframe:

up to 12 months

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

End point values	Efficacy Population: Prophylaxis	Efficacy Population: On-demand		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18 ^[36]	16 ^[37]		
Units: post-surgery days				
All Days: Excellent; n=1, 2	1	0		
All Days: Good; n=1, 2	0	2		
All Days: Moderate; n=1, 2	0	0		
All Days: None; n=1, 2	0	0		
Day 1: Excellent; n=1, 2	1	0		
Day 1: Good; n=1, 2	0	2		
Day 1: Moderate; n=1, 2	0	0		
Day 1: None; n=1, 2	0	0		

Notes:

[36] - n=total post-surgery days at home with available subject's assessment.

[37] - n=total post-surgery days at home with available subject's assessment.

Statistical analyses

No statistical analyses for this end point

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

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

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

End point type	Primary
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End point timeframe:

up to Month 12

Notes:

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

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

End point values	Efficacy Population: Prophylaxis	Efficacy Population: On-demand		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18 ^[39]	16 ^[40]		
Units: surgeries				
All Surgeries: Less Than Expected; n=2, 3	1	1		

All Surgeries: Equivalent To Expected; n=2, 3	1	2		
All Surgeries: More Than Expected; n=2, 3	0	0		
Major Surgeries: Less Than Expected; n=0, 2	0	0		
Major Surgeries: Equivalent To Expected; n=0, 2	0	2		
Major Surgeries: More Than Expected; n=0, 2	0	0		
Minor Surgeries: Less Than Expected; n=2, 1	1	1		
Minor Surgeries: Equivalent To Expected; n=2, 1	1	0		
Minor Surgeries: More Than Expected; n=2, 1	0	0		

Notes:

[39] - n=number of surgeries of given type.

[40] - n=number of surgeries of given type.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Requiring Surgery-Related Blood Product Transfusions

End point title	Number of Subjects Requiring Surgery-Related Blood Product Transfusions ^[41]
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End point description:

End point type	Primary
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End point timeframe:
up to 12 months

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	Efficacy Population: Prophylaxis	Efficacy Population: On-demand		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	16		
Units: subjects	0	0		

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. Serious TEAEs category include subjects who had a FVIII inhibitor reported. Discontinuation category refers to "drug interrupted" being ticked on the case report form.

End point type	Secondary
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End point timeframe:

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

End point values	Safety Population: Prophylaxis	Safety Population: On-demand		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	17		
Units: subjects				
At Least 1 TEAE	12	11		
At Least 1 Severe TEAE	3	3		
At Least 1 Serious TEAE	2	3		
At Least 1 TEAE Leading to Discontinuation	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Factor VIII Inhibitors

End point title	Factor VIII Inhibitors
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End point description:

End point type	Secondary
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End point timeframe:

Screening, PK Day 2 (24 hours post-dose), Months 1, 3, 6, 9, 12, Final Visit (up to 12 months ± 7 days)

End point values	Safety Population: Prophylaxis	Safety Population: On-demand		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	17		
Units: subjects				
Screening	0	0		
PK Day 2 (24 hours post-dose)	0	1		
Month 1	1	1		

Month 3	2	0		
Month 6	0	1		
Month 9	0	0		
Month 12	0	0		
Final Visit	1	2		

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.0
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Reporting groups

Reporting group title	Safety Population: Prophylaxis
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Reporting group description:

The safety population included all subjects who received at least 1 dose of Biostate.

Reporting group title	Safety Population: On-demand
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Reporting group description:

The safety population included all subjects who received at least 1 dose of Biostate.

Serious adverse events	Safety Population: Prophylaxis	Safety Population: On-demand	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 18 (11.11%)	3 / 17 (17.65%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Tibia fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Factor VIII inhibition			
subjects affected / exposed	2 / 18 (11.11%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety Population: Prophylaxis	Safety Population: On-demand	
Total subjects affected by non-serious adverse events subjects affected / exposed	11 / 18 (61.11%)	9 / 17 (52.94%)	
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all) Femur fracture subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1 0 / 18 (0.00%) 0	0 / 17 (0.00%) 0 1 / 17 (5.88%) 1	
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 17 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 3	0 / 17 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	2 / 17 (11.76%) 2	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	4 / 18 (22.22%) 7	2 / 17 (11.76%) 2	
Eye disorders Corneal oedema subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2	0 / 17 (0.00%) 0	
Gastrointestinal disorders Toothache subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1 2 / 18 (11.11%) 2	2 / 17 (11.76%) 4 0 / 17 (0.00%) 0	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 18 (16.67%)	5 / 17 (29.41%)	
occurrences (all)	4	6	
Upper airway obstruction			
subjects affected / exposed	3 / 18 (16.67%)	0 / 17 (0.00%)	
occurrences (all)	4	0	
Asthma			
subjects affected / exposed	1 / 18 (5.56%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Bronchospasm			
subjects affected / exposed	1 / 18 (5.56%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	1 / 18 (5.56%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Tonsillar hypertrophy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatosplenomegaly			
subjects affected / exposed	0 / 18 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 18 (22.22%)	0 / 17 (0.00%)	
occurrences (all)	6	0	
Dermatitis allergic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Dermatosis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	1 / 18 (5.56%)	0 / 17 (0.00%)	
occurrences (all)	1	0	

Pruritus			
subjects affected / exposed	1 / 18 (5.56%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Skin hypopigmentation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Haemarthrosis			
subjects affected / exposed	0 / 18 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	4	
Pain in extremity			
subjects affected / exposed	1 / 18 (5.56%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Rhinitis			
subjects affected / exposed	4 / 18 (22.22%)	0 / 17 (0.00%)	
occurrences (all)	10	0	
Influenza			
subjects affected / exposed	2 / 18 (11.11%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Acute tonsillitis			
subjects affected / exposed	2 / 18 (11.11%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Bronchitis			
subjects affected / exposed	0 / 18 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Gastroenteritis			
subjects affected / exposed	2 / 18 (11.11%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 18 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Adenoiditis			

subjects affected / exposed	1 / 18 (5.56%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Bronchitis viral			
subjects affected / exposed	0 / 18 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Helminthic infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Pulpitis dental			
subjects affected / exposed	0 / 18 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 17 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2010	The following main changes were included: <ul style="list-style-type: none">- Data recording by electronic case report form (eCRF).- Modification of inclusion criterion 3 because no hepatitis A virus vaccine was available for children aged <1 year.- Change of central laboratory.- Correction of blood volumes collected for PK and efficacy component.- Clarification of Biostate dosing during the PK component.- Explanation of use of patient card.
24 May 2012	The following main changes were included: <ul style="list-style-type: none">- Extension of treatment added to in total 100 exposure days, but no longer than 12 months.- The allowance of continuation of treatment at the discretion of the principle investigator and Independent Monitoring Committee when a clinically insignificant FVIII inhibitor was determined.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported