



Clinical trial results:

A Phase 3, Prospective, Multicenter Study to Evaluate Efficacy and Safety of Recombinant von Willebrand Factor (rVWF) with or without ADVATE in Elective Surgical Procedures in Subjects With Severe von Willebrand Disease

Summary

EudraCT number	2014-003575-38
Trial protocol	AT IT CZ GB NL ES DE
Global end of trial date	06 July 2016

Results information

Result version number	v1 (current)
This version publication date	19 July 2017
First version publication date	19 July 2017

Trial information

Trial identification

Sponsor protocol code	071101
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02283268
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Baxalta Innovations GmbH
Sponsor organisation address	Industriestrasse 67, Vienna, Austria, 1221
Public contact	Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com
Scientific contact	Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com
Sponsor organisation name	Baxalta US Inc.
Sponsor organisation address	One Baxter Way, Westlake Village, United States, CA 91362
Public contact	Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.com
Scientific contact	Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 July 2016
Global end of trial reached?	Yes
Global end of trial date	06 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the hemostatic efficacy and safety of rVWF with or without ADVATE in subjects (≥ 18 years) diagnosed with hereditary severe VWD undergoing major or minor elective surgical procedures.

Protection of trial subjects:

The study was conducted in accordance with the study protocol, the International Conference on Harmonization Guideline for Good Clinical Practice E6 (ICH GCP April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2015
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	United States: 2
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Ukraine: 3
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Turkey: 1
Worldwide total number of subjects	24
EEA total number of subjects	8

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	21
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment was conducted at 14 study sites in 10 countries (USA, Australia, Taiwan, Germany, Russia, Spain, Ukraine, United Kingdom, Italy, Turkey).

Pre-assignment

Screening details:

A total of 24 subjects were enrolled (signed informed consent) and screened. Of these, 15 participants were treated with investigational product.

Pre-assignment period milestones

Number of subjects started	24
Number of subjects completed	15

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Screen Failure: 8

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Recombinant von Willebrand Factor (rVWF)
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Arm description:

Surgery participants treated with Recombinant von Willebrand Factor (rVWF)

Arm type	Experimental
Investigational medicinal product name	rVWF (Recombinant von Willebrand Factor)
Investigational medicinal product code	BAX111
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

The dose will be tailored to raise Von Willebrand factor: Ristocetin cofactor activity (VWF:RCO) concentration to 100% of normal for major surgeries and to 50-60% of normal for minor and oral surgeries. PK infusion (major surgeries) with 50 ± 5 IU rVWF:RCO/kg will be given within 42 days prior surgery to guide the preoperative priming dose. Priming dose with rVWF will be administered (12-24 hours prior surgery). If FVIII levels prior to loading dose administration are not at least 30 IU/dL ADVATE will be administered in addition to rVWF in order to raise FVIII:C levels to recommended levels. A rVWF loading dose with or without ADVATE within 1 hour prior to surgery will be administered. The peri- and postoperative substitution regimen will be individualized according to the PK results, intensity and duration of the hemostatic challenge, and the institution's standard of care.

Number of subjects in period 1^[1]	Recombinant von Willebrand Factor (rVWF)
Started	15
Completed	14
Not completed	1
Consent withdrawn by subject	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 24 subjects were enrolled (signed informed consent) and screened. Of these, 15 subjects were treated with investigational product, 8 subjects were screen failures and 1 subject withdrew consent prior to treatment.

Baseline characteristics

Reporting groups

Reporting group title	Recombinant von Willebrand Factor (rVWF)
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Reporting group description:

Surgery participants treated with Recombinant von Willebrand Factor (rVWF)

Reporting group values	Recombinant von Willebrand Factor (rVWF)	Total	
Number of subjects	15	15	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
median	40		
full range (min-max)	20 to 70	-	
Gender categorical			
Units: Subjects			
Female	8	8	
Male	7	7	

End points

End points reporting groups

Reporting group title	Recombinant von Willebrand Factor (rVWF)
Reporting group description:	
Surgery participants treated with Recombinant von Willebrand Factor (rVWF)	
Subject analysis set title	All Subjects Enrolled Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who signed informed consent.	
Subject analysis set title	Full Ananalysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects included in the Safety Analysis Set with at least one hemostatic assessment.	
Subject analysis set title	Per Protocol Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects with available overall assessment of hemostatic efficacy assessed by the investigator 24 hours after last infusion of study drug or at completion visit who met all study entry criteria and who had no major protocol violations that might impact hemostatic efficacy.	
Subject analysis set title	Pharmacokinetic Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects who underwent a PK assessment and have at least one post dose concentration without protocol deviations or events with potential to affect PK.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects included in the All Subjects Enrolled Set that received any amount of investigational product.	
Subject analysis set title	Minor surgery
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who underwent minor surgery.	
Subject analysis set title	Major surgery
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who underwent major surgery.	
Subject analysis set title	Oral surgery
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who underwent oral surgery.	
Subject analysis set title	Von Willebrand Disease Type 1
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects with von Willebrand Disease Type 1.	
Subject analysis set title	Von Willebrand Disease Type 2A
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects with von Willebrand Disease Type 2A.	
Subject analysis set title	Von Willebrand Disease Type 2B
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects with von Willebrand Disease Type 2B.

Subject analysis set title	Von Willebrand Disease Type 2M
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects with von Willebrand Disease Type 2M.

Subject analysis set title	Von Willebrand Disease Type 3
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects with von Willebrand Disease Type 3.

Primary: Overall hemostatic efficacy as assessed by the investigator (hemophilia physician)

End point title	Overall hemostatic efficacy as assessed by the investigator (hemophilia physician) ^[1]
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End point description:

Hemostatic efficacy will be rated on a scale of excellent - good - moderate - none.

Excellent: Intra-, and postoperative hemostasis achieved with rVWF with or without ADVATE was as good or better than that expected for the type of surgical procedure performed in a hemostatically normal subject.

Good: Intra-, and postoperative hemostasis achieved with rVWF with or without ADVATE was probably as good as that expected for the type of surgical procedure performed in a hemostatically normal subject.

Moderate: Intra-, and postoperative hemostasis with rVWF with or without ADVATE was clearly less than optimal for the type of procedure performed but was maintained without the need to change the rVWF concentrate.

None: Participant experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of rVWF concentrate.

End point type	Primary
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End point timeframe:

24 hours after last peri-operative infusion or at completion of Day 14 visit, whichever occurs earlier

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: Per protocol, only descriptive statistics were collected for this endpoint.

End point values	Recombinant von Willebrand Factor (rVWF)	Minor surgery	Major surgery	Oral surgery
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	4	10	1
Units: Subjects				
Excellent	11	4	7	0
Good	4	0	3	1
Moderate	0	0	0	0
None	0	0	0	0

End point values	Von Willebrand Disease Type 1	Von Willebrand Disease Type 2A	Von Willebrand Disease Type 2B	Von Willebrand Disease Type 2M
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	2	1	1
Units: Subjects				
Excellent	2	1	1	0

Good	1	1	0	1
Moderate	0	0	0	0
None	0	0	0	0

End point values	Von Willebrand Disease Type 3			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: Subjects				
Excellent	7			
Good	1			
Moderate	0			
None	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Intraoperative actual versus predicted blood loss as assessed by the operating surgeon

End point title	Intraoperative actual versus predicted blood loss as assessed by the operating surgeon
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End point description:

The predicted blood loss will be estimated preoperatively by the operating surgeon based on a hemostatically normal individual of the same sex, age, stature and co-morbidities as the participant. The actual blood loss will be assessed consisting of the estimated blood loss, including into swabs, towels and suction during the procedure, per the anesthesiologist's record.

End point type	Secondary
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End point timeframe:

Day 0 (at completion of surgery)

End point values	Recombinant von Willebrand Factor (rVWF)	Minor surgery	Major surgery	Oral surgery
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15 ^[2]	4	10 ^[3]	1 ^[4]
Units: mL				
arithmetic mean (standard deviation)				
Actual blood loss	94.3 (± 177.88)	0 (± 0)	127 (± 209.27)	145 (± 9999)
Predicted blood loss	106.1 (± 161.82)	2.5 (± 5)	152.8 (± 186.33)	100 (± 9999)

Notes:

[2] - predicted blood loss: 14

[3] - predicted blood loss: 9

[4] - no dispersion possible as n=1, 9999 entered

End point values	Von Willebrand Disease Type 1	Von Willebrand Disease Type 2A	Von Willebrand Disease Type 2B	Von Willebrand Disease Type 2M
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	2 ^[5]	1 ^[6]	1 ^[7]
Units: mL				
arithmetic mean (standard deviation)				
Actual blood loss	115 (± 103.32)	42.5 (± 53.03)	50 (± 9999)	50 (± 9999)
Predicted blood loss	100 (± 100)	10 (± 9999)	50 (± 9999)	50 (± 9999)

Notes:

[5] - predicted blood loss=1; no dispersion possible as n=1, 9999 entered

[6] - no dispersion possible as n=1, 9999 entered

[7] - no dispersion possible as n=1, 9999 entered

End point values	Von Willebrand Disease Type 3			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: mL				
arithmetic mean (standard deviation)				
Actual blood loss	110.6 (± 240.87)			
Predicted blood loss	134.4 (± 206.46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intraoperative actual blood loss relative to predicted blood loss

End point title	Intraoperative actual blood loss relative to predicted blood loss
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End point description:

Actual blood loss relative to predicted blood loss will be calculated as [Actual Blood loss (mL)] divided by [Predicted Blood Loss (mL)] multiplied by 100.

End point type	Secondary
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End point timeframe:

Day 0 (at completion of surgery)

End point values	Recombinant von Willebrand Factor (rVWF)	Minor surgery	Major surgery	Oral surgery
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	1 ^[8]	9	1 ^[9]
Units: Percent				
arithmetic mean (standard deviation)	69.6 (± 44.77)	0 (± 9999)	68.9 (± 34.48)	145 (± 9999)

Notes:

[8] - No standard deviation possible as only one participant was analyzed. 9999 was entered.

[9] - No standard deviation possible as only one participant was analyzed.

9999 was entered.

End point values	Von Willebrand Disease Type 1	Von Willebrand Disease Type 2A	Von Willebrand Disease Type 2B	Von Willebrand Disease Type 2M
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	1 ^[10]	1 ^[11]	1 ^[12]
Units: Percent				
arithmetic mean (standard deviation)	122.5 (± 31.82)	50 (± 9999)	100 (± 9999)	100 (± 9999)

Notes:

[10] - No standard deviation possible as only one participant was analyzed.
9999 was entered.

[11] - No standard deviation possible as only one participant was analyzed.
9999 was entered.

[12] - No standard deviation possible as only one participant was analyzed.
9999 was entered.

End point values	Von Willebrand Disease Type 3			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Percent				
arithmetic mean (standard deviation)	45 (± 38.92)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intraoperative actual versus predicted blood loss score as assessed by the operating surgeon

End point title	Intraoperative actual versus predicted blood loss score as assessed by the operating surgeon
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End point description:

Hemostatic efficacy will be rated on a scale of excellent - good - moderate - none.

Excellent: Intraoperative blood loss was less than or equal to the maximum blood loss expected for the type of procedure performed in a hemostatically normal subject ($\leq 100\%$).

Good: Intraoperative blood loss was up to 50% more than the maximum expected blood loss for the type of procedure performed in a hemostatically normal subject (101-150%)

Moderate: Intraoperative blood loss was more than 50% of the maximum expected blood loss for the type of procedure performed in a hemostatically normal subject ($>150\%$).

None: Uncontrolled hemorrhage that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of clotting factor replacement regimen.

End point type	Secondary
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End point timeframe:

Day 0 (at completion of surgery)

End point values	Recombinant von Willebrand Factor (rVWF)	Minor surgery	Major surgery	Oral surgery
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	4	10	1
Units: Subjects				
Excellent	13	4	8	1
Good	2	0	2	0
Moderate	0	0	0	0
None	0	0	0	0

End point values	Von Willebrand Disease Type 1	Von Willebrand Disease Type 2A	Von Willebrand Disease Type 2B	Von Willebrand Disease Type 2M
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	2	1	1
Units: Subjects				
Excellent	3	1	1	1
Good	0	1	0	0
Moderate	0	0	0	0
None	0	0	0	0

End point values	Von Willebrand Disease Type 3			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: Subjects				
Excellent	7			
Good	1			
Moderate	0			
None	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Intraoperative hemostatic efficacy score as assessed by the operating surgeon

End point title	Intraoperative hemostatic efficacy score as assessed by the operating surgeon
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End point description:

Hemostatic efficacy will be rated on a scale of excellent - good - moderate - none.

Excellent: Intraoperative hemostasis achieved with rVWF with or without ADVATE was as good or better than that expected for the type of surgical procedure performed in a hemostatically normal subject.

Good: Intraoperative hemostasis achieved with rVWF with or without ADVATE was probably as good as that expected for the type of surgical procedure performed in a hemostatically normal subject.

Moderate: Intraoperative hemostasis with rVWF with or without ADVATE was clearly less than optimal

for the type of procedure performed but was maintained without the need to change the rVWF concentrate.

None: Participant experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of rVWF concentrate.

End point type	Secondary
End point timeframe:	
Day 0 (at completion of surgery)	

End point values	Recombinant von Willebrand Factor (rVWF)	Minor surgery	Major surgery	Oral surgery
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	4	10	1
Units: Subjects				
Excellent	13	4	8	1
Good	2	0	2	0
Moderate	0	0	0	0
None	0	0	0	0

End point values	Von Willebrand Disease Type 1	Von Willebrand Disease Type 2A	Von Willebrand Disease Type 2B	Von Willebrand Disease Type 2M
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	2	1	1
Units: Subjects				
Excellent	3	1	1	1
Good	0	1	0	0
Moderate	0	0	0	0
None	0	0	0	0

End point values	Von Willebrand Disease Type 3			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: Subjects				
Excellent	7			
Good	1			
Moderate	0			
None	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Daily intra- and postoperative weight-adjusted dose of rVWF with or without ADVATE

End point title	Daily intra- and postoperative weight-adjusted dose of rVWF with or without ADVATE
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End point description:

End point type	Secondary
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End point timeframe:

Daily, from day of surgery through postoperative Day 14

End point values	Recombinant von Willebrand Factor (rVWF)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: IU/kg				
median (inter-quartile range (Q1-Q3))				
intraoperative (n=1)	18.1 (18.1 to 18.1)			
postoperative day 1 (n=3)	23.5 (16.9 to 47.2)			
postoperative day 2 (n=11)	42.3 (23.2 to 50.6)			
postoperative day 3 (n=12)	28.6 (20.6 to 48.9)			
postoperative day 4 (n=9)	33.9 (23.2 to 44.3)			
postoperative day 5 (n=7)	31.5 (18.8 to 47.2)			
postoperative day 6 (n=5)	23.2 (18.8 to 23.6)			
postoperative day 7 (n=5)	23.8 (23.6 to 50.8)			
postoperative day 8 (n=7)	33.9 (23.6 to 53.6)			
postoperative day 9 (n=3)	23.6 (16.3 to 53.6)			
postoperative day 10 (n=3)	23.6 (16.3 to 34.8)			
postoperative day 11 (n=3)	23.6 (16.3 to 53.6)			
postoperative day 12 (n=4)	29.3 (20.1 to 44.2)			
postoperative day 13 (n=1)	16.3 (16.3 to 16.3)			
postoperative day 14 (n=2)	25.5 (16.3 to 34.8)			
postoperative day 15 (n=1)	16.3 (16.3 to 16.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of adverse events

End point title	Occurrence of adverse events
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End point description:

Treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs) will be evaluated.

The safety analysis data set, including all subjects who received any amount of investigational product, was used for analysis of this endpoint.

End point type	Secondary
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End point timeframe:

From first infusion of investigational product through study completion (ie, 14 days post surgery)

End point values	Recombinant von Willebrand Factor (rVWF)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Adverse Events				
Treatment emergent Adverse Events (TEAEs)	12			
Severe TEAEs	1			
TEAEs related to rVWF	0			
TEAEs related to ADVATE	0			
TEAEs related to both rVWF and ADVATE	0			
Treatment emergent Serious Adverse Events (TESAEs)	2			
TESAEs related to rVWF	0			
TESAEs related to ADVATE	0			
TESAEs related to both rVWF and ADVATE	0			
TEAEs leading to discontinuation of rVWF	0			
TEAEs leading to discontinuation of ADVATE	0			
TEAEs leading to discontinuation of study	0			
TEAEs leading to death	0			
TEAEs related to study procedure	0			
TESAEs related to study procedure	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of thrombotic events

End point title	Occurrence of thrombotic events
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End point description:

Treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs) will be evaluated.

The safety analysis data set, including all subjects who received any amount of investigational product, was used for analysis of this endpoint.

End point type	Secondary
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End point timeframe:

From first infusion of investigational product through study completion (ie, 14 days post surgery)

End point values	Recombinant von Willebrand Factor (rVWF)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Adverse Events				
Thrombotic TEAEs	2			
Thrombotic TESAEs	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of severe allergic reactions (eg, anaphylaxis)

End point title	Occurrence of severe allergic reactions (eg, anaphylaxis)
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End point description:

Treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs) will be evaluated.

The safety analysis data set, including all subjects who received any amount of investigational product, was used for analysis of this endpoint.

End point type	Secondary
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End point timeframe:

From first infusion of investigational product through study completion (ie, 14 days post surgery)

End point values	Recombinant von Willebrand Factor (rVWF)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Adverse Events				
Severe allergic reaction TEAEs	0			
Severe allergic reaction TESAEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who developed inhibitory and total binding antibodies to von Willebrand Factor (VWF) and inhibitory antibodies to Factor VIII (FVIII)

End point title	Number of subjects who developed inhibitory and total binding antibodies to von Willebrand Factor (VWF) and inhibitory antibodies to Factor VIII (FVIII)
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End point description:

Participants were treated with recombinant von Willebrand Factor (rVWF) with or without ADVATE. The safety analysis data set, including all subjects who received any amount of investigational product, was used for analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Testing occurred throughout the study at screening, prior PK infusion, pre-surgery, post surgery in case of excessive bleeding or unexplained bleeding, at postoperative day 7 and at study completion visit (ie. 14 days post surgery).

End point values	Recombinant von Willebrand Factor (rVWF)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Subjects				
Development of inhibitory antibodies to VWF	0			
Development of total binding antibodies to VWF	1			
Development of inhibitory antibodies to FVIII	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Development of antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) or recombinant Furin (rFurin)

End point title	Development of antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) or recombinant Furin (rFurin)
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End point description:

Participants were treated with recombinant von Willebrand Factor (rVWF) with or without ADVATE. The safety analysis data set, including all subjects who received any amount of investigational product, was used for analysis of this endpoint.

End point type	Secondary
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End point timeframe:

Testing occurred throughout the study at screening, prior PK infusion, pre-surgery, post surgery in case of excessive bleeding or unexplained bleeding, at postoperative day 7 and at study completion visit (ie. 14 days post surgery).

End point values	Recombinant von Willebrand Factor (rVWF)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Area under the plasma concentration versus time curve from 0 to 72 hours post-infusion (AUC 0-72 h/dose)

End point title	Pharmacokinetics: Area under the plasma concentration versus time curve from 0 to 72 hours post-infusion (AUC 0-72 h/dose)
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End point description:

This assessment is only required for subjects undergoing major surgery. Subjects will receive a PK infusion at a dose of 50 ± 5 IU/kg rVWF:RCo within 42 days prior to surgery. The area under the plasma concentration/time curve from 0 to 72 hours post-infusion will be computed using the linear trapezoidal rule. For the calculation of AUC(0-72h) the levels at 72 hours will be linearly interpolated/extrapolated from the 2 nearest sampling time points. PK analysis was performed for the following analytes: VWF Ristocetin Cofactor Activity (VWF:RCo), VWF Antigen Activity (VWF:Ag), VWF Collagen Binding Activity (VWF:CB), VWF Activity Measured INNOVANCE VWF Ac Assay (VWF:Ac), FVIII Coagulation Activity (FVIII:C)

End point type	Secondary
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End point timeframe:

PK measurements were done within 30 minutes pre-infusion, and post infusion at 30 (± 5) minutes, 60 (± 5) minutes, 6 (± 1) hours, 12 (± 1) hours, 24 (± 2) hours, 48 (± 2) hours and 72 (± 2) hours.

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	11 ^[13]			
Units: hours*IU/dL				
geometric mean (geometric coefficient of variation)				
VWF:RCo	31.91 (± 37.5)			
VWF:Ag	57.08 (± 25.6)			
VWF:CB	63.91 (± 29.4)			
VWF:Ac	54.61 (± 28.1)			
FVIII:C	67.49 (± 31.1)			

Notes:

[13] - For FVIII:C n=5

Statistical analyses

Secondary: Pharmacokinetics: Area under the plasma concentration versus time curve from time 0 to infinity (AUC 0-∞ /dose)

End point title	Pharmacokinetics: Area under the plasma concentration versus time curve from time 0 to infinity (AUC 0-∞ /dose)
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End point description:

This assessment is only required for subjects undergoing major surgery. Subjects will receive a PK infusion at a dose of 50±5 IU/kg rVWF:RCo within 42 days prior to surgery. The area under the plasma concentration/time curve from time 0 to infinity and the area under the first moment curve from time 0 to infinity will be calculated as the sum of AUC or AUMC from time 0 to the time of last quantifiable concentration plus a tail area correction calculated as C_t/λ_z and $C_t/\lambda_z(t+1/\lambda_z)$, respectively, where C_t is the last quantifiable concentration, t is the time of last quantifiable concentration and λ_z is the terminal or disposition rate constant. PK analysis was performed for the following analytes: VWF Ristocetin Cofactor Activity (VWF:RCo), VWF Antigen Activity (VWF:Ag), VWF Collagen Binding Activity (VWF:CB), VWF Activity Measured INNOVANCE VWF Ac Assay (VWF:Ac), FVIII Coagulation Activity (FVIII:C)

End point type	Secondary
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End point timeframe:

PK measurements were done within 30 minutes pre-infusion, and post infusion at 30 (± 5) minutes, 60 (± 5) minutes, 6 (± 1) hours, 12 (± 1) hours, 24 (± 2) hours, 48 (± 2) hours and 72 (± 2) hours.

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	11 ^[14]			
Units: hours*IU/dL				
geometric mean (geometric coefficient of variation)				
VWF:RCo	34.43 (± 43.3)			
VWF:Ag	68.87 (± 31.5)			
VWF:CB	71.82 (± 34.1)			
VWF:Ac	61.9 (± 32.2)			
FVIII:C	75 (± 30.9)			

Notes:

[14] - For FVIII:C n=3

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Mean residence time (MRT)

End point title	Pharmacokinetics: Mean residence time (MRT)
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End point description:

This assessment is only required for subjects undergoing major surgery. Subjects will receive a PK infusion at a dose of 50±5 IU/kg rVWF:RCo within 42 days prior to surgery. Mean residence time will be calculated as area under the first moment curve from time 0 to infinity divided by the area under the curve time 0 to infinity minus $T/2$ where T is the duration of the infusion. PK analysis was performed for the following analytes: VWF Ristocetin Cofactor Activity (VWF:RCo), VWF Antigen Activity (VWF:Ag), VWF Collagen Binding Activity (VWF:CB), VWF Activity Measured INNOVANCE VWF Ac Assay (VWF:Ac)

End point type	Secondary
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End point timeframe:

PK measurements were done within 30 minutes pre-infusion, and post infusion at 30 (± 5) minutes, 60 (± 5) minutes, 6 (± 1) hours, 12 (± 1) hours, 24 (± 2) hours, 48 (± 2) hours and 72 (± 2) hours.

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: hours				
geometric mean (geometric coefficient of variation)				
VWF:RCo	22.69 (± 41.3)			
VWF:Ag	37.92 (± 28.4)			
VWF:CB	29.35 (± 31.1)			
VWF:Ac	29.75 (± 28.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Clearance (CL)

End point title	Pharmacokinetics: Clearance (CL)
End point description:	
This assessment is only required for subjects undergoing major surgery. Subjects will receive a PK infusion at a dose of 50±5 IU/kg rVWF:RCo within 42 days prior to surgery. Clearance will be calculated as dose (IU/kg) divided by the area under the curve time 0 to infinity. PK analysis was performed for the following analytes: VWF Ristocetin Cofactor Activity (VWF:RCo), VWF Antigen Activity (VWF:Ag), VWF Collagen Binding Activity (VWF:CB), VWF Activity Measured INNOVANCE VWF Ac Assay (VWF:Ac)	
End point type	Secondary
End point timeframe:	
PK measurements were done within 30 minutes pre-infusion, and post infusion at 30 (± 5) minutes, 60 (± 5) minutes, 6 (± 1) hours, 12 (± 1) hours, 24 (± 2) hours, 48 (± 2) hours and 72 (± 2) hours.	

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: dL/hour/kg				
geometric mean (geometric coefficient of variation)				
VWF:RCo	0.02904 (± 43.3)			
VWF:Ag	0.01452 (± 31.5)			
VWF:CB	0.01392 (± 34.1)			
VWF:Ac	0.01616 (± 32.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Incremental recovery (IR)

End point title	Pharmacokinetics: Incremental recovery (IR)
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End point description:

This assessment is only required for subjects undergoing major surgery. Subjects will receive a PK infusion at a dose of 50 ± 5 IU/kg rVWF:RCo within 42 days prior to surgery. Incremental recovery will be calculated as $(C_{\max} \text{ minus } C_{\text{preinfusion}})$ divided by the dose (IU/kg) where kg refers to the body weight at the time of dosing and C_{\max} is the observed maximum concentration before correction for pre-infusion values. PK analysis was performed for the following analytes: VWF Ristocetin Cofactor Activity (VWF:RCo), VWF Antigen Activity (VWF:Ag), VWF Collagen Binding Activity (VWF:CB), VWF Activity Measured INNOVANCE VWF Ac Assay (VWF:Ac)

End point type	Secondary
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End point timeframe:

PK measurements were done within 30 minutes pre-infusion, and post infusion at 30 (± 5) minutes, 60 (± 5) minutes, 6 (± 1) hours, 12 (± 1) hours, 24 (± 2) hours, 48 (± 2) hours and 72 (± 2) hours.

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: IU/dL				
arithmetic mean (standard deviation)				
VWF:RCo	1.961 (\pm 0.45445)			
VWF:Ag	1.991 (\pm 0.38395)			
VWF:CB	2.78 (\pm 0.5664)			
VWF:Ac	2.635 (\pm 0.3805)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Elimination phase half-life (T_{1/2})

End point title	Pharmacokinetics: Elimination phase half-life (T _{1/2})
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End point description:

This assessment is only required for subjects undergoing major surgery. Subjects will receive a PK infusion at a dose of 50 ± 5 IU/kg rVWF:RCo within 42 days prior to surgery. Terminal or disposition half-life (T_{1/2}) will be calculated as $\ln 2 / \lambda_z$ where λ_z is the terminal elimination rate constant as calculated in

WinNonlin NCA using at least three quantifiable concentrations. PK analysis was performed for the following analytes: VWF Ristocetin Cofactor Activity (VWF:RCo), VWF Antigen Activity (VWF:Ag), VWF Collagen Binding Activity (VWF:CB), VWF Activity Measured INNOVANCE VWF Ac Assay (VWF:Ac)

End point type	Secondary
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End point timeframe:

PK measurements were done within 30 minutes pre-infusion, and post infusion at 30 (\pm 5) minutes, 60 (\pm 5) minutes, 6 (\pm 1) hours, 12 (\pm 1) hours, 24 (\pm 2) hours, 48 (\pm 2) hours and 72 (\pm 2) hours.

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: hours				
geometric mean (geometric coefficient of variation)				
VWF:RCo	16.52 (\pm 42.7)			
VWF:Ag	26.88 (\pm 26.5)			
VWF:CB	21.07 (\pm 33.2)			
VWF:Ac	22.19 (\pm 28.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Volume of distribution at steady state (Vss)

End point title	Pharmacokinetics: Volume of distribution at steady state (Vss)
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End point description:

This assessment is only required for subjects undergoing major surgery. Subjects will receive a PK infusion at a dose of 50 \pm 5 IU/kg rVWF:RCo within 42 days prior to surgery. Vss will be calculated as the clearance multiplied with the mean residence time. PK analysis was performed for the following analytes: VWF Ristocetin Cofactor Activity (VWF:RCo), VWF Antigen Activity (VWF:Ag), VWF Collagen Binding Activity (VWF:CB), VWF Activity Measured INNOVANCE VWF Ac Assay (VWF:Ac)

End point type	Secondary
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End point timeframe:

PK measurements were done within 30 minutes pre-infusion, and post infusion at 30 (\pm 5) minutes, 60 (\pm 5) minutes, 6 (\pm 1) hours, 12 (\pm 1) hours, 24 (\pm 2) hours, 48 (\pm 2) hours and 72 (\pm 2) hours.

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: dL/kg				
geometric mean (geometric coefficient of variation)				
VWF:RCo	0.6591 (\pm 28.8)			
VWF:Ag	0.5506 (\pm 18.4)			

VWF:CB	0.4086 (\pm 24)			
VWF:Ac	0.4806 (\pm 21.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study period (from the first exposure to investigational product until study completion or discontinuation date). Total study duration: 1 year and 3 months. Per participant: up to 58 days.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Recombinant von Willebrand Factor (rVWF)
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Reporting group description:

Surgery participants treated with Recombinant von Willebrand Factor (rVWF)

Serious adverse events	Recombinant von Willebrand Factor (rVWF)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Recombinant von Willebrand Factor (rVWF)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 15 (40.00%)		

Vascular disorders Deep vein thrombosis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
General disorders and administration site conditions Peripheral swelling subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Reproductive system and breast disorders Pelvic pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Musculoskeletal and connective tissue disorders Joint swelling subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Infections and infestations Nasopharyngitis			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 August 2012	<p>The various types of severe VWD that are eligible for the study were clarified to include VWD with a history of requiring substitution therapy containing VWF to control bleeding; Type 1 (VWF:RCoF < 20 IU/dL); Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2N (FVIII:C<10% and historically documented genetics), and Type 2M; or Type 3 (VWF:Ag ≤ 3 IU/dL).</p> <p>The option to give a priming dose of rVWF 12-24 hours before surgery was deleted to reduce the number of different dose regimens investigated.</p> <p>The primary efficacy endpoint was updated to include intra- and post-operative actual versus predicted blood loss; and overall assessment of clinical (hemostatic) efficacy at 24 hours after last infusion of IP. Furthermore, it was made mandatory that the surgeon documents predicted values with a source data document to strengthen the quality of the predicted average and maximum blood loss.</p> <p>Two options for administration of the combination of rVWF and rFVIII were added to ease reconstitution and mixing of study drugs. Option 1: Infusion of premixed drug, Option 2: Sequential infusion</p> <p>Treatment success was defined as a mean primary efficacy rating score of <2 for a subject's IP-covered surgery, dental, or invasive procedure (Excellent = 1, Good = 2, Moderate = 3, None = 4).</p>
27 November 2013	<p>Throughout the protocol, wording on analysis of primary and secondary outcome measures was adjusted to reflect revised primary and secondary objectives.</p> <p>Primary hemostatic efficacy assessment rating scale was revised to reflect the authority's feedback (inclusion of objective measure of cessation of bleeding).</p> <p>Completion visit was changed from 30 days (± 3 days) after the last IP infusion to 14 days (± 2 days) after surgery to standardize treatment duration and evaluation of primary efficacy endpoint.</p> <p>The priming dose VWF infusion 12-24 hours prior surgery included in the original protocol and deleted in Global Amendment 1 was reintroduced to improve the IP treatment scheme.</p>
19 March 2015	The sponsor name/entity was changed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported