EU Clinical Trials Register

Clinical trial results:
A Prospective, Phase 3, Open-label, International Multicenter Study on Efficacy and Safety of Prophylaxis with rVWF in Severe von Willebrand Disease

Summary

EudraCT number	2016-001478-14
Trial protocol	GB IT CZ NL ES DE FI FR
Global end of trial date	06 July 2020

Results information

Result version number	v1 (current)
This version publication date	21 July 2021
First version publication date	21 July 2021

Trial information

Trial identification

Sponsor protocol code	071301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02973087
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.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 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to prospectively evaluate the annualised bleeding rate (ABR) for spontaneous bleeding episodes while on prophylactic treatment with recombinant von Willebrand factor (rVWF) and to compare it to the subject's historical ABR for spontaneous bleeding episodes.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in compliance with all applicable industry regulations, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 (1996), European Union (EU) Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 2017
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	Canada: 1
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	23
EEA total number of subjects	10

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)	20
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 32 sites in the United States, Canada, France, Germany, Italy, Netherlands, Russia, Spain and Turkey between 16 November 2017 (first subject first visit) and 06 July 2020 (last subject last visit).

Pre-assignment

Screening details:

A total of 29 subjects were screened, out of which 6 subjects were screen failures and 23 subjects were grouped into 2 cohorts: Prior On-demand and Switch (based on the previous von Willebrand disease [VWD] treatment they received prior to the study) and received prophylactic treatment with recombinant von Willebrand factor (rVWF).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Prior On-demand Subjects

Arm description:

Subjects who had taken only on-demand von Willebrand factor (VWF) prior to the current study received rVWF (vonicog alpha) initial prophylactic treatment at a dose range of 50 plus minus (+/-) 10 international unit per kilogram (IU/kg), intravenous infusion, twice per week for a planned period of 12 months. Dose escalation to higher dose (up to 80 IU/kg per infusion) or frequency (up to 3 times a week) was based on medical indication and investigator judgment. During this prophylactic treatment period, any breakthrough bleeding episodes requiring replacement therapy with VWF concentrate was treated with rVWF with or without ADVATE (recombinant Factor VIII [rFVIII]); the dose was determined according to the bleeding type and severity, and was adjusted based on the subject's clinical response.

Arm type	Experimental
Investigational medicinal product name	Recombinant von Willebrand factor (rVWF)
Investigational medicinal product code	
Other name	vonicog alpha
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received an initial prophylactic dose of 50 +/- 10 IU/kg, intravenous, infusion, twice per week for up to 12 months.

Investigational medicinal product name	Recombinant Factor VIII (rFVIII)
Investigational medicinal product code	
Other name	octocog alfa/ADVATE
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received rFVIII (octocog alfa/ADVATE), intravenous, infusion for treatment of bleeding episode, if needed.

Arm title	Switch Subjects

Arm description:

Subjects who had taken prophylactic treatment with plasma derived VWF product (pdVWF) prior to current study and switched to prophylaxis with rVWF (vonicog alpha) during the study for a planned period of 12 months; received rVWF twice weekly at an initial prophylactic dose of +/- 10 percent (%) of VWF in the pdVWF weekly dose received prior to this study. Dosing with rVWF up to 80 IU/kg per infusion or at a frequency up to 3 times a week or once a week were allowed depending on the total

weekly dose and the dosing regimen used in their previous pdVWF prophylaxis regimen and based on medical indication and investigator judgment. During this prophylactic treatment period, any breakthrough bleeding episodes requiring replacement therapy with VWF concentrate was treated with rVWF with or without ADVATE (rFVIII); the dose was determined according to the bleeding type and severity, and was adjusted based on the subject's clinical response.

Arm type	Experimental
Investigational medicinal product name	Recombinant von Willebrand factor (rVWF)
Investigational medicinal product code	
Other name	vonicog alpha
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received rVWF at an initial prophylactic dose of +/- 10% of weekly pdVWF dose received prior to this study, intravenous, infusion, twice per week for up to 12 months.

Investigational medicinal product name	Recombinant Factor VIII (rFVIII)
Investigational medicinal product code	
Other name	octocog alfa/ADVATE
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received rFVIII (octocog alfa/ADVATE), intravenous, infusion for treatment of bleeding episode, if needed.

Number of subjects in period 1	Prior On-demand Subjects	Switch Subjects
Started	13	10
Completed	9	8
Not completed	4	2
Consent withdrawn by subject	2	1
Adverse event, non-fatal	1	-
other	1	1

Baseline characteristics

Reporting groups

Reporting group title	Prior On-demand Subjects

Reporting group description:

Subjects who had taken only on-demand von Willebrand factor (VWF) prior to the current study received rVWF (vonicog alpha) initial prophylactic treatment at a dose range of 50 plus minus (+/-) 10 international unit per kilogram (IU/kg), intravenous infusion, twice per week for a planned period of 12 months. Dose escalation to higher dose (up to 80 IU/kg per infusion) or frequency (up to 3 times a week) was based on medical indication and investigator judgment. During this prophylactic treatment period, any breakthrough bleeding episodes requiring replacement therapy with VWF concentrate was treated with rVWF with or without ADVATE (recombinant Factor VIII [rFVIII]); the dose was determined according to the bleeding type and severity, and was adjusted based on the subject's clinical response.

Reporting group title	Switch Subjects

Reporting group description:

Subjects who had taken prophylactic treatment with plasma derived VWF product (pdVWF) prior to current study and switched to prophylaxis with rVWF (vonicog alpha) during the study for a planned period of 12 months; received rVWF twice weekly at an initial prophylactic dose of +/- 10 percent (%) of VWF in the pdVWF weekly dose received prior to this study. Dosing with rVWF up to 80 IU/kg per infusion or at a frequency up to 3 times a week or once a week were allowed depending on the total weekly dose and the dosing regimen used in their previous pdVWF prophylaxis regimen and based on medical indication and investigator judgment. During this prophylactic treatment period, any breakthrough bleeding episodes requiring replacement therapy with VWF concentrate was treated with rVWF with or without ADVATE (rFVIII); the dose was determined according to the bleeding type and severity, and was adjusted based on the subject's clinical response.

Reporting group values	Prior On-demand Subjects	Switch Subjects	Total
Number of subjects	13	10	23
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	12	8	20
From 65-84 years	1	2	3
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	38.0	43.9	
standard deviation	± 17.6	± 21.8	-
Sex: Female, Male			
Units: subjects			
Female	8	3	11
Male	5	7	12
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	13	9	22
More than one race	0	0	0
Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	2	2
Not Hispanic or Latino	13	7	20
Unknown or Not Reported	0	1	1

End points

End points reporting groups

Reporting group title	Prior On-demand Subjects

Reporting group description:

Subjects who had taken only on-demand von Willebrand factor (VWF) prior to the current study received rVWF (vonicog alpha) initial prophylactic treatment at a dose range of 50 plus minus (+/-) 10 international unit per kilogram (IU/kg), intravenous infusion, twice per week for a planned period of 12 months. Dose escalation to higher dose (up to 80 IU/kg per infusion) or frequency (up to 3 times a week) was based on medical indication and investigator judgment. During this prophylactic treatment period, any breakthrough bleeding episodes requiring replacement therapy with VWF concentrate was treated with rVWF with or without ADVATE (recombinant Factor VIII [rFVIII]); the dose was determined according to the bleeding type and severity, and was adjusted based on the subject's clinical response.

Reporting group title	Switch Subjects

Reporting group description:

Subjects who had taken prophylactic treatment with plasma derived VWF product (pdVWF) prior to current study and switched to prophylaxis with rVWF (vonicog alpha) during the study for a planned period of 12 months; received rVWF twice weekly at an initial prophylactic dose of +/- 10 percent (%) of VWF in the pdVWF weekly dose received prior to this study. Dosing with rVWF up to 80 IU/kg per infusion or at a frequency up to 3 times a week or once a week were allowed depending on the total weekly dose and the dosing regimen used in their previous pdVWF prophylaxis regimen and based on medical indication and investigator judgment. During this prophylactic treatment period, any breakthrough bleeding episodes requiring replacement therapy with VWF concentrate was treated with rVWF with or without ADVATE (rFVIII); the dose was determined according to the bleeding type and severity, and was adjusted based on the subject's clinical response.

Primary: Ratio of Annualized Bleeding Rate (ABR) (On-study ABR / Historical ABR) for Spontaneous Bleeding Episodes (BEs) Assessed by Investigator During Prophylactic Treatment With rVWF Through Month 12

End point title	Ratio of Annualized Bleeding Rate (ABR) (On-study ABR / Historical ABR) for Spontaneous Bleeding Episodes (BEs) Assessed by Investigator During Prophylactic Treatment With rVWF Through Month 12[1]

End point description:

ABR for treated spontaneous BEs while on prophylactic treatment with rVWF through Month 12 treatment period/observation period (in years), where an observation period = (date of completion/termination – date of first dose + 1)/365.2425. BEs occurred at the same anatomical location with the same etiology within 24 hours after onset of first bleed were considered single BE. BEs occurred at multiple locations related to same injury were considered as single BE. Observation period for historical BEs was 365 days prior to first dose of study drug. On-study observation period started from first administration of study drug and continuing through the date of completion/discontinuation from study. The comparison of the two ABRs (on-study and historical) for spontaneous BEs (not related to trauma) during prophylactic treatment with rVWF was reported as a ratio of mean ABRs (on-study ABR/historical ABR). Full analysis set (FAS) composed of all subjects who received prophylactic IP treatment.

End point type	Primary

End point timeframe:

Up to 12 months

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: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: ratio				
arithmetic mean (confidence interval 95%)	0.085 (0.021 to 0.346)	0.550 (0.086 to 3.523)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Prior On-demand Subjects Achieved Spontaneous ABR Percent Reduction Success Through Month 12

End point title	Percentage of Prior On-demand Subjects Achieved Spontaneous ABR Percent Reduction Success Through Month 12[2]

End point description:

For prior on-demand subjects, spontaneous ABR percent reduction success was defined as at least 25% reduction of the ABR for treated spontaneous (not related to trauma) BEs during the first 12 months of rVWF (vonicog alfa) prophylactic relative to the subject's own historical treated spontaneous ABR. Percentage of subjects with ABR percent reduction success for on-demand cohort was reported. FAS composed of all subjects who received prophylactic IP treatment. This end point was analyzed only for prior on-demand subjects treated for spontaneous BEs.

End point type	Secondary

End point timeframe:

Up to 12 months

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percentage of subjects				
number (confidence interval 95%)	92.3 (64.0 to 99.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Switch Subjects With Spontaneous ABR Preservation Success Through Month 12

End point title	Percentage of Switch Subjects With Spontaneous ABR Preservation Success Through Month 12[3]

End point description:

For switch subjects, spontaneous ABR preservation success was defined as achieving an ABR for treated spontaneous BEs during 12 months of rVWF (vonicog alfa) prophylaxis that was no greater than the subject's own historical ABR for treated spontaneous BEs during prophylactic treatment with pdVWF. Percentage of subjects with ABR preservation success in switch cohort was reported. FAS composed of all subjects who received prophylactic IP treatment. This end point was analysed only for switch subjects treated for spontaneous BEs.

End point type	Secondary

End point timeframe:

Up to 12 months

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Switch Subjects			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of subjects				
number (confidence interval 95%)	90.0 (55.5 to 99.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Based on Categorized Spontaneous ABR (sABR) Through Month 12

End point title	Number of Subjects Based on Categorized Spontaneous ABR (sABR) Through Month 12

End point description:

The sABR was the number of spontaneous bleeds divided by the observation period in years, where an observation period = (date of completion/termination−date of first dose+1)/365.2425.sABR was categorized based on number of BEs as 0, greater than (>) 0 through 2,>2 through 5,>5 during the prophylactic treatment with rVWF (vonicog alfa) through 12 months. Bleeding at multiple locations related to the same injury was counted as single bleeding episode. BEs of unknown cause were counted as spontaneous bleeds. Observation period for historical BEs was 365 days prior to first dose of study drug. The baseline sABR for treated BEs was based on historical BE data and on-study sABR was based on treated spontaneous BEs during prophylaxis with rVWF through Month 12. On-study observation period started on the day of first administration of study drug continuing through the date of completion/discontinuation from study. Number of participants based on categorized sABR was calculated and reported.

End point type	Secondary

End point timeframe:

Baseline up to 12 months

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: subjects				
Historical: 0 BEs	0	6		
Historical: >0-2 BEs	0	3		
Historical: >2-5 BEs	10	0		
Historical: >5 BEs	3	1		
On-Study through Month 12: 0 BEs	11	7		
On-Study through Month 12: >0-2 BEs	0	1		
On-Study through Month 12: >2-5 BEs	1	1		
On-Study through Month 12: >5 BEs	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Infusions Administered Per Subject During Prophylactic Treatment With rVWF Through Month 12

End point title	Total Number of Infusions Administered Per Subject During Prophylactic Treatment With rVWF Through Month 12

End point description:

For each subject, the total number of infusions was counted as the total number of unique infusions of rVWF which were administered between the dates of informed consent and termination from the study, inclusive, regardless of the date and time of administration. The total number of infusions administered during the study was entered in electronic case record form (eCRF) and recorded in ERT system. Total number of infusions administered per subject during prophylactic treatment With rVWF through 12 months was calculated. FAS composed of all subjects who received prophylactic IP treatment.

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: infusions				
arithmetic mean (standard deviation)	65.1 (± 38.4)	87.8 (± 30.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average Number of Infusions per Week per Subject During Prophylactic

Treatment With rVWF Through Month 12

End point title	Average Number of Infusions per Week per Subject During Prophylactic Treatment With rVWF Through Month 12
End point description:	
Average number of infusions per week per subject during prophylactic treatment With rVWF through 12 months was calculated. FAS composed of all subjects who received prophylactic IP treatment.	
End point type	Secondary
End point timeframe:	
Up to 12 months	

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: infusions				
arithmetic mean (standard deviation)	1.88 (± 0.7)	1.85 (± 0.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Weight Adjusted Consumption of rVWF per Subject During Prophylactic Treatment Through Month 12

End point title	Total Weight Adjusted Consumption of rVWF per Subject During Prophylactic Treatment Through Month 12
End point description:	
For each subject, the body weight-adjusted dose (IU/kg) was derived as the number of units of rVWF infused (IU) divided by the last available body weight (kilogram [kg]) prior to the infusion. Total weight adjusted consumption of rVWF (vonicog alfa) per subject during prophylactic treatment was reported. FAS composed of all subjects who received prophylactic IP treatment.	
End point type	Secondary
End point timeframe:	
Up to 12 months	

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: IU/kg				
arithmetic mean (standard deviation)	3431.584 (± 2117.6562)	4433.752 (± 1844.8761)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Treated Spontaneous BEs by Location of Bleeding While on Prophylactic Treatment With rVWF Through Month 12

End point title	Percentage of Treated Spontaneous BEs by Location of Bleeding While on Prophylactic Treatment With rVWF Through Month 12

End point description:

Percentage of treated spontaneous BEs by location of bleeding (for example: oral and other mucosa, menorrhagia, hemarthrosis, etc.) while on prophylactic treatment with rVWF was reported. FAS composed of all subjects who received prophylactic IP treatment.

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: number of BEs				
number (not applicable)				
Oral and other mucosa	5	14		
Menorrhagia	3	0		
Hemarthrosis	0	1		
Other	1	0		
Unknown	0	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting one or More Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Number of Subjects Reporting one or More Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs

End point description:

An AE is defined as any untoward medical occurrence in a subject administered IP that does not necessarily have a causal relationship with the treatment. TEAEs were events which occurred on or after the date and time of administration of the first dose of study medication. TEAEs included both serious AEs and non-serious AEs. Number of subjects with TEAEs and serious TEAEs were reported. SAS composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

End point type	Secondary

End point timeframe:

From first dose of study drug up to end of study (approximately 32 months)

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: subjects				
Subjects With TEAEs	10	7		
Subjects with serious TEAEs	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Based on Severity of TEAEs

End point title	Number of Subjects Based on Severity of TEAEs

End point description:

An AE is defined as any untoward medical occurrence in a subject administered IP that does not necessarily have a causal relationship with the treatment. TEAEs were events which occurred on or after the date and time of administration of the first dose of study medication. TEAEs included both serious AEs and non-serious AEs. Severity of TEAEs was determined by following definitions: Mild: No limitation of usual activities; Moderate: Some limitation of usual activities and may required therapeutic intervention; Severe: Inability to carry out usual activities with sequelae, which required therapeutic intervention. Subjects were counted by considering the maximum severity of TEAEs. SAS composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

End point type	Secondary

End point timeframe:

From first dose of study drug up to end of study (approximately 32 months)

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: subjects				
Mild	7	4		
Moderate	1	2		
Severe	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With TEAEs Based Causality

End point title	Number of Subjects With TEAEs Based Causality

End point description:

An AE was defined as any untoward medical occurrence in a subject administered IP that does not necessarily have a causal relationship with the treatment. TEAEs were events which occurred on or after the date and time of administration of the first dose of study medication. TEAEs included both serious AEs and non-serious AEs. For each AE, the investigator assessed the causal relationship between the IP and the AE based on clinical expertise and judgment according to the following circumstances of the AE: Not related, Unlikely related, Possibly related, or Probably related. A related TEAE was defined as any TEAE indicated as 'possibly related' or 'probably related'. Number of subjects with TEAEs based causality was reported. SAS composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

End point type	Secondary

End point timeframe:

From first dose of study drug up to end of study (approximately 32 months)

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: subjects				
TEAEs related to IP	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Thromboembolic Events

End point title	Number of Subjects With Thromboembolic Events

End point description:

Thromboembolism defined as formation in a blood vessel of a clot (thrombus) that breaks loose and carried by the blood stream and could plug another vessel. Number of participants with thromboembolic events as TEAEs of special interest was reported. A broad standard search query approach was used (broad SMQ) to identify all potential thromboembolic events of interest which were then medically assessed. Number of subjects with thromboembolic events as TEAEs of special interest was reported. SAS composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

End point type	Secondary

End point timeframe:

From first dose of study drug up to end of study (approximately 32 months)

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: subjects	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Hypersensitivity Reactions

End point title	Number of Subjects With Hypersensitivity Reactions

End point description:

Hypersensitivity (also called hypersensitivity reaction or intolerance) defined as undesirable reactions produced by the normal immune system, including allergies and autoimmunity. Potential hypersensitivity events were identified by broad search criteria and then medically assessed. Number of subjects with hypersensitivity reactions as TEAEs of special interest was calculated. SAS composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

End point type	Secondary

End point timeframe:

From first dose of study drug up to end of study (approximately 32 months)

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: subjects	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Developed Neutralizing Antibodies to von Willebrand Factor (rVWF) and Factor VIII (FVIII)

End point title	Number of Subjects who Developed Neutralizing Antibodies to von Willebrand Factor (rVWF) and Factor VIII (FVIII)

End point description:

Three functional VWF assays for von Willebrand factor collagen binding (VWF:CB), von Willebrand factor: Ristocetin Cofactor (VWF:RCo) and von Willebrand factor VIII B (VWF:FVIIIB) were used to test the presence of neutralizing anti-VWF antibodies. Neutralizing antibodies to VWF:RCo, VWF:CB and VWF:FVIIIB activities was measured by assays based on the Bethesda assay established for quantitative analysis of FVIII inhibitors (Nijmegen modification of the Bethesda assay). Only confirmed neutralizing anti -VWF antibodies were considered inhibitors. Number of subjects who developed neutralizing antibodies to rVWF and FVIII were assessed. SAS composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

End point type	Secondary

End point timeframe:

Baseline through Month 12

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Developed of Total Binding Antibodies to von Willebrand factor (rVWF) and Factor VIII (FVIII)

End point title	Number of Subjects who Developed of Total Binding Antibodies to von Willebrand factor (rVWF) and Factor VIII (FVIII)

End point description:

The presence of total binding anti-VWF antibodies was determined by an enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human Immunoglobulin (Ig) antibodies (IgG, IgM and IgA). Binding antibodies against FVIII was analyzed using a proprietary enzyme immunoassay. Number of subjects who developed of total binding antibodies to rVWF and FVIII was assessed. SAS composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

End point type	Secondary

End point timeframe:

Baseline through Month 12

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Developed Binding Antibodies to Chinese Hamster Ovary (CHO) proteins, Mouse Immunoglobulin G (IgG) and/or rFurin

End point title	Number of Subjects who Developed Binding Antibodies to Chinese Hamster Ovary (CHO) proteins, Mouse Immunoglobulin G (IgG) and/or rFurin

End point description:

Total Ig antibodies (IgG, IgA, IgM) against CHO protein and human furin was analyzed using ELISA. For detection and quantification of IgG antibodies originating from human plasma that were directed against

mouse-IgG (HAMA: human anti- mouse antibodies) was assessed using ELISA (Medac, Hamburg, Germany). Number of subjects who developed binding antibodies to CHO proteins, Mouse IgG and/or rFurin was assessed. SAS composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

End point type	Secondary

End point timeframe:

Baseline through Month 12

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Change From Baseline in Vital Signs

End point title	Number of Subjects With Clinically Significant Change From Baseline in Vital Signs

End point description:

Vital signs included blood pressure (systolic and diastolic), pulse rate, respiratory rate and body temperature. Number of subjects with clinically significant change from baseline in vital signs was assessed. SAS composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

End point type	Secondary

End point timeframe:

Baseline up to end of study (approximately 32 months)

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Change From Baseline in Clinical Laboratory Parameters

End point title	Number of Subjects With Clinically Significant Change From Baseline in Clinical Laboratory Parameters

End point description:

Clinical laboratory parameters included hematology and clinical chemistry assessments. Number of subjects with clinically significant change from baseline in clinical laboratory parameters was assessed. SAS composed of all subjects who received any amount of IP (rVWF, vonicog alpha).

End point type	Secondary

End point timeframe:

Baseline up to end of study (approximately 32 months)

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Assessment: Incremental Recovery (IR) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point title	Pharmacokinetic (PK) Assessment: Incremental Recovery (IR) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity[4]

End point description:

IR at the maximum plasma concentration of VWF:RCo activity at initial PK assessment was reported. Unit of measure: International Units per deciliter/International Units per kilogram ([IU/dL]/[IU/kg]). PK full analysis set (PKFAS) composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: (IU/dL)/(IU/kg)				
arithmetic mean (standard deviation)	1.463 (± 0.3205)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Incremental Recovery (IR) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity

End point title	Pharmacokinetic Assessment: Incremental Recovery (IR) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity[5]

End point description:

IR based on VWF:Ag activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: (IU/dL)/(IU/kg)				
arithmetic mean (standard deviation)	1.699 (± 0.3488)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Incremental Recovery (IR) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point title	Pharmacokinetic Assessment: Incremental Recovery (IR) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity[6]

End point description:

IR at the maximum plasma concentration of VWF:CB activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: (IU/dL)/(IU/kg)				
arithmetic mean (standard deviation)	2.405 (± 0.5737)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Terminal half-life (T1/2) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point title	Pharmacokinetic Assessment: Terminal half-life (T1/2) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity[7]

End point description:

T1/2 defined as the time in hours required for the concentration of the drug to reach half of its original value. T1/2 based on VWF:Rco activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: hours				
median (full range (min-max))	15.98 (9.01 to 45.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Terminal Half-life (T1/2) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity

End point title	Pharmacokinetic Assessment: Terminal Half-life (T1/2) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity[8]

End point description:

T1/2 defined as the time in hours required for the concentration of the drug to reach half of its original value. T1/2 based on VWF:Ag activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hours				
median (full range (min-max))	21.81 (12.6 to 39.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Terminal Half-life (T1/2) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point title	Pharmacokinetic Assessment: Terminal Half-life (T1/2) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity[9]

End point description:

T1/2 defined as the time in hours required for the concentration of the drug to reach half of its original value. T1/2 based on VWF:CB activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hours				
median (full range (min-max))	18.64 (12.8 to 29.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Mean Residence Time (MRT) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point title	Pharmacokinetic Assessment: Mean Residence Time (MRT) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity[10]

End point description:

MRT was calculated as (AUMC0-∞/AUC0-∞) – T1/2 where T1 represented the time duration of infusion, where AUMC represented the area under the first moment curve. MRT based on VWF:Rco activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: hours				
arithmetic mean (standard deviation)	23.27 (± 11.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Mean Residence Time (MRT) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity

End point title	Pharmacokinetic Assessment: Mean Residence Time (MRT)

	Based on Von Willebrand Factor Antigen (VWF:Ag) Activity[11]

End point description:

MRT was calculated as (AUMC0-∞/AUC0-∞) – T1/2 where T1 represented the time duration of infusion, where AUMC represented the area under the first moment curve. MRT based on VWF:Ag activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hours				
arithmetic mean (standard deviation)	33.55 (± 9.777)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Mean Residence Time (MRT) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point title	Pharmacokinetic Assessment: Mean Residence Time (MRT) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity[12]

End point description:

MRT was calculated as (AUMC0-∞/AUC0-∞) – T1/2 where T1 represented the time duration of infusion, where AUMC represented the area under the first moment curve. MRT based on VWF:CB activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hours				
arithmetic mean (standard deviation)	27.39 (± 6.860)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Area Under the Plasma Concentration Versus Time Curve From Time 0 Extrapolated to Infinity (AUC0-∞) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point title	Pharmacokinetic Assessment: Area Under the Plasma Concentration Versus Time Curve From Time 0 Extrapolated to Infinity (AUC0-∞) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity[13]

End point description:

AUC0-∞ based on VWF:Rco activity at initial PK assessment was reported. Unit of measure: International Units*hour per deciliter (IU*h/dL). PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: IU*h/dL				
arithmetic mean (standard deviation)	1199 (± 467.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Area Under the Plasma Concentration Versus Time Curve From Time 0 Extrapolated to Infinity (AUC0-∞) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity

End point title	Pharmacokinetic Assessment: Area Under the Plasma Concentration Versus Time Curve From Time 0 Extrapolated to Infinity (AUC0-∞) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity[14]

End point description:

AUC0-∞ based on VWF:Ag activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: IU*h/dL				
arithmetic mean (standard deviation)	2578 (± 1067)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Area Under the Plasma Concentration Versus Time Curve From Time 0 Extrapolated to Infinity (AUC0-∞) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point title	Pharmacokinetic Assessment: Area Under the Plasma Concentration Versus Time Curve From Time 0 Extrapolated to Infinity (AUC0-∞) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity[15]

End point description:

AUC0-∞ based on VWF:CB activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: IU*h/dL				
arithmetic mean (standard deviation)	3010 (± 1221)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Area Under the Plasma Concentration Versus Time Curve From Time 0 to the Last Measurable Concentration (AUC0-tlast) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point title	Pharmacokinetic Assessment: Area Under the Plasma Concentration Versus Time Curve From Time 0 to the Last Measurable Concentration (AUC0-tlast) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity[16]

End point description:

AUC0-tlast based on VWF:Rco activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: IU*h/dL				
arithmetic mean (standard deviation)	919.8 (± 378.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Area Under the Plasma Concentration Versus Time Curve From Time 0 to the Last Measurable Concentration (AUC0-tlast) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity

End point title	Pharmacokinetic Assessment: Area Under the Plasma

	Concentration Versus Time Curve From Time 0 to the Last Measurable Concentration (AUC0-tlast) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity[17]

End point description:

AUC0-tlast based on VWF:Ag activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: IU*h/dL				
arithmetic mean (standard deviation)	2357 (± 848.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Area Under the Plasma Concentration Versus Time Curve From Time 0 to the Last Measurable Concentration (AUC0-tlast) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point title	Pharmacokinetic Assessment: Area Under the Plasma Concentration Versus Time Curve From Time 0 to the Last Measurable Concentration (AUC0-tlast) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity[18]

End point description:

AUC0-tlast based on VWF:CB activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: IU*h/dL				
arithmetic mean (standard deviation)	2824 (± 1112)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Maximum Plasma Concentration (Cmax) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point title	Pharmacokinetic Assessment: Maximum Plasma Concentration (Cmax) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity[19]

End point description:

Cmax based on VWF:Rco at initial PK assessment was reported. Unit of measure: International Units per deciliter (IU/dL). PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: IU/dL				
arithmetic mean (standard deviation)	74.62 (± 16.09)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Maximum Plasma Concentration (Cmax) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity

End point title	Pharmacokinetic Assessment: Maximum Plasma Concentration (Cmax) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity[20]

End point description:

Cmax based on VWF:Ag activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: IU/dL				
arithmetic mean (standard deviation)	85.1 (± 19.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Maximum Plasma Concentration (Cmax) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point title	Pharmacokinetic Assessment: Maximum Plasma Concentration (Cmax) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity[21]

End point description:

Cmax based on VWF:CB activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: IU/dL				
arithmetic mean (standard deviation)	120.74 (± 29.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Minimum Time to Reach the Maximum Plasma Concentration (Tmax) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point title	Pharmacokinetic Assessment: Minimum Time to Reach the Maximum Plasma Concentration (Tmax) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity[22]

End point description:

Tmax based on VWF:Rco activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hours				
median (full range (min-max))	0.540 (0.27 to 1.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Minimum Time to Reach the Maximum Concentration (Tmax) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity

End point title	Pharmacokinetic Assessment: Minimum Time to Reach the Maximum Concentration (Tmax) Based on Von Willebrand

Factor Antigen (VWF:Ag) Activity[23]

End point description:

Tmax based on VWF:Ag activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hours				
median (full range (min-max))	1 (0.27 to 3.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Minimum Time to Reach the Maximum Plasma Concentration (Tmax) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point title	Pharmacokinetic Assessment: Minimum Time to Reach the Maximum Plasma Concentration (Tmax) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity[24]

End point description:

Tmax based on VWF:CB activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hours				
median (full range (min-max))	0.500 (0.27 to 1.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Volume of Distribution at Steady State (Vss) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point title	Pharmacokinetic Assessment: Volume of Distribution at Steady State (Vss) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity[25]

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Vss based on VWF:Rco activity at initial assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: deciliter per kilogram (dL/kg)				
arithmetic mean (standard deviation)	1.052 (± 0.4981)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Volume of Distribution at Steady State (Vss) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity

End point title	Pharmacokinetic Assessment: Volume of Distribution at Steady

State (Vss) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity[26]

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Vss based on VWF:Ag activity at initial assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: dL/kg				
arithmetic mean (standard deviation)	0.6860 (± 0.1556)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Volume of Distribution at Steady State (Vss) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point title	Pharmacokinetic Assessment: Volume of Distribution at Steady State (Vss) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity[27]

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Vss based on VWF:CB activity at initial assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: dL/kg				
arithmetic mean (standard deviation)	0.4889 (± 0.1371)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Clearance (CL) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point title	Pharmacokinetic Assessment: Clearance (CL) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity[28]

End point description:

Clearance is defined as a quantitative measure of the rate at which a drug substance is removed from the body. CL based on VWF:Rco activity at initial PK assessment was reported. Unit of measure: deciliter per kilogram per hour (dL/kg/h). PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: dL/kg/h				
arithmetic mean (standard deviation)	0.04765 (± 0.01620)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Clearance (CL) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity

End point title	Pharmacokinetic Assessment: Clearance (CL) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity[29]

End point description:

Clearance is defined as a quantitative measure of the rate at which a drug substance is removed from the body. CL based on VWF:Ag activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analyzed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: dL/kg/h				
arithmetic mean (standard deviation)	0.02185 (± 0.006821)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment: Clearance (CL) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point title	Pharmacokinetic Assessment: Clearance (CL) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity[30]

End point description:

Clearance is defined as a quantitative measure of the rate at which a drug substance is removed from the body. CL based on VWF:CB activity at initial PK assessment was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analyzed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: dL/kg/h				
arithmetic mean (standard deviation)	0.01872 (± 0.005946)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic (PD) Assessment: Maximum Plasma Concentration (Cmax) Based on Factor VIII Clotting (FVIII:C) Activity

End point title	Pharmacodynamic (PD) Assessment: Maximum Plasma Concentration (Cmax) Based on Factor VIII Clotting (FVIII:C) Activity[31]

End point description:

Cmax based on FVIII:C activity at initial PD assessment by the 1-stage clotting assay was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: IU/dL				
arithmetic mean (standard deviation)	90.8 (± 32.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic Assessment: Minimum Time to Reach the Maximum Plasma Concentration (Tmax) Based on Factor VIII Clotting (FVIII:C) Activity

End point title	Pharmacodynamic Assessment: Minimum Time to Reach the Maximum Plasma Concentration (Tmax) Based on Factor VIII Clotting (FVIII:C) Activity[32]

End point description:

Tmax based on FVIII:C activity at initial PD assessment by the 1-stage clotting assay was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hours				
median (full range (min-max))	24.055 (11.98 to 46.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic Assessment: Area Under the Plasma Concentration Versus Time Curve From Time 0 to the Last Measurable Concentration (AUC0-tlast) Based on Factor VIII Clotting (FVIII:C) Activity

End point title	Pharmacodynamic Assessment: Area Under the Plasma Concentration Versus Time Curve From Time 0 to the Last Measurable Concentration (AUC0-tlast) Based on Factor VIII Clotting (FVIII:C) Activity[33]

End point description:

AUC0-tlast based on FVIII:C activity at initial PD assessment by the 1-stage clotting assay was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analyzed" were subjects who were evaluable for this end point. As planned, this end point was assessed only for prior on-demand subjects.

End point type	Secondary

End point timeframe:

At baseline: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Prior On-demand Subjects			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: IU*h/dL				
arithmetic mean (standard deviation)	4949 (± 2436)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment at Steady State: Area Under the Plasma Concentration Versus Time Curve From Time 0 to end of the Partial Dosing Interval (AUC0- tau;ss) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point title	Pharmacokinetic Assessment at Steady State: Area Under the Plasma Concentration Versus Time Curve From Time 0 to end of the Partial Dosing Interval (AUC0- tau;ss) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point description:

AUC0-tau;ss based on VWF:Rco activity at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analyzed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	3		
Units: IU*h/dL				
arithmetic mean (standard deviation)	1561 (± 1298)	1662 (± 675.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment at Steady State: Area Under the Plasma Concentration Versus Time Curve From Time 0 to end of the Partial Dosing Interval (AUC0- tau;ss) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity

End point title	Pharmacokinetic Assessment at Steady State: Area Under the Plasma Concentration Versus Time Curve From Time 0 to end of the Partial Dosing Interval (AUC0- tau;ss) Based on Von

Willebrand Factor Antigen (VWF:Ag) Activity

End point description:

AUC0-tau;ss based on VWF:Ag activity at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analyzed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	3		
Units: IU*h/dL				
arithmetic mean (standard deviation)	2908 (± 1372)	3196 (± 838.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Assessment at Steady State: Area Under the Plasma Concentration Versus Time Curve From Time 0 to end of the Partial Dosing Interval (AUC0- tau;ss) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point title	Pharmacokinetic Assessment at Steady State: Area Under the Plasma Concentration Versus Time Curve From Time 0 to end of the Partial Dosing Interval (AUC0- tau;ss) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point description:

AUC0-tau;ss based on VWF:CB activity at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analyzed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	3		
Units: IU*h/dL				
arithmetic mean (standard deviation)	3445 (± 1914)	4276 (± 1471)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics Assessment at Steady State: Maximum Plasma Concentration During the Partial Dosing Interval at Steady State (Cmax;ss) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point title	Pharmacokinetics Assessment at Steady State: Maximum Plasma Concentration During the Partial Dosing Interval at Steady State (Cmax;ss) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point description:

Cmax;ss based on VWF:Rco activity at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: IU/dL				
arithmetic mean (standard deviation)	92.63 (± 37.05)	102.89 (± 44.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics Assessment at Steady State: Maximum Plasma Concentration During the Partial Dosing Interval at Steady State (Cmax;ss) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity

End point title	Pharmacokinetics Assessment at Steady State: Maximum Plasma Concentration During the Partial Dosing Interval at Steady State (Cmax;ss) Based on Von Willebrand Factor

Antigen (VWF:Ag) Activity

End point description:

Cmax;ss based on VWF:Ag activity at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: IU/dL				
arithmetic mean (standard deviation)	108.1 (± 39.6)	107.1 (± 37.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics Assessment at Steady State: Maximum Plasma Concentration During the Partial Dosing Interval at Steady State (Cmax;ss) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point title	Pharmacokinetics Assessment at Steady State: Maximum Plasma Concentration During the Partial Dosing Interval at Steady State (Cmax;ss) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point description:

Cmax;ss based on VWF:CB activity at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: IU/dL				
arithmetic mean (standard deviation)	137.48 (± 44.97)	162.19 (± 60.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics Assessment at Steady State: Minimum Time to Reach the Maximum Plasma Concentration at Steady State (Tmax;ss) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point title	Pharmacokinetics Assessment at Steady State: Minimum Time to Reach the Maximum Plasma Concentration at Steady State (Tmax;ss) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point description:

Tmax;ss based on VWF:Rco activity at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: hours				
median (full range (min-max))	0.330 (0.25 to 1.25)	0.400 (0.33 to 0.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics Assessment at Steady State: Minimum Time to Reach the Maximum Plasma Concentration at Steady State (Tmax;ss) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity

End point title	Pharmacokinetics Assessment at Steady State: Minimum Time to Reach the Maximum Plasma Concentration at Steady State

(Tmax;ss) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity

End point description:

Tmax;ss based on VWF:Ag activity at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: hours				
median (full range (min-max))	0.580 (0.28 to 1.17)	0.330 (0.23 to 1.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics Assessment at Steady State: Minimum Time to Reach the Maximum Plasma Concentration at Steady State (Tmax;ss) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point title	Pharmacokinetics Assessment at Steady State: Minimum Time to Reach the Maximum Plasma Concentration at Steady State (Tmax;ss) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point description:

Tmax;ss based on VWF:CB activity at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: hours				
median (full range (min-max))	0.420 (0.28 to 3.00)	0.670 (0.33 to 3.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics Assessment at Steady State: Minimum Plasma Concentration During the Partial Dosing Interval at Steady State (Cmin;ss) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point title	Pharmacokinetics Assessment at Steady State: Minimum Plasma Concentration During the Partial Dosing Interval at Steady State (Cmin;ss) Based on Von Willebrand Factor: Ristocetin Cofactor (VWF:Rco) Activity

End point description:

Cmin;ss based on VWF:Rco activity at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point. Here "99999" refers to data not available and added as space-fillers as value was below the limit of quantification.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: IU/dL				
arithmetic mean (standard deviation)	99999 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics Assessment at Steady State: Minimum Plasma Concentration During the Partial Dosing Interval at Steady State (Cmin;ss) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity

End point title	Pharmacokinetics Assessment at Steady State: Minimum

	Plasma Concentration During the Partial Dosing Interval at Steady State (Cmin;ss) Based on Von Willebrand Factor Antigen (VWF:Ag) Activity

End point description:

Cmin;ss based on VWF:Rco activity at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: IU/dL				
arithmetic mean (standard deviation)	6.3 (± 4.8)	11.7 (± 8.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics Assessment at Steady State: Minimum Plasma Concentration During the Partial Dosing Interval at Steady State (Cmin;ss) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point title	Pharmacokinetics Assessment at Steady State: Minimum Plasma Concentration During the Partial Dosing Interval at Steady State (Cmin;ss) Based on Von Willebrand Factor Collagen Binding (VWF:CB) Activity

End point description:

Cmin;ss based on VWF:CB activity at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: IU/dL				
arithmetic mean (standard deviation)	3.82 (± 6.86)	9.94 (± 8.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic Assessment at Steady State: Area Under the Plasma Concentration Versus Time Curve From Time 0 to end of the Partial Dosing Interval (AUC0- tau;ss) Based on Factor VIII Clotting (FVIII:C) Activity

End point title	Pharmacodynamic Assessment at Steady State: Area Under the Plasma Concentration Versus Time Curve From Time 0 to end of the Partial Dosing Interval (AUC0- tau;ss) Based on Factor VIII Clotting (FVIII:C) Activity

End point description:

AUC0-tau;ss based on FVIII:C activity at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analyzed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	3		
Units: IU*h/dL				
arithmetic mean (standard deviation)	5984 (± 2490)	5836 (± 1735)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic Assessment at Steady State: Maximum Plasma Concentration During the Partial Dosing Interval at Steady State (Cmax;ss) Based on Factor VIII Clotting (FVIII:C) Activity

End point title	Pharmacodynamic Assessment at Steady State: Maximum Plasma Concentration During the Partial Dosing Interval at Steady State (Cmax;ss) Based on Factor VIII Clotting (FVIII:C) Activity

End point description:

Cmax;ss based on FVIII:C activity was assessed at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: IU/dL				
arithmetic mean (standard deviation)	104.1 (± 35.1)	75.7 (± 37.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic Assessment at Steady State: Minimum Time to Reach the Maximum Plasma Concentration at Steady State (Tmax;ss) Based on Factor VIII Clotting (FVIII:C) Activity

End point title	Pharmacodynamic Assessment at Steady State: Minimum Time to Reach the Maximum Plasma Concentration at Steady State (Tmax;ss) Based on Factor VIII Clotting (FVIII:C) Activity

End point description:

Tmax;ss based on FVIII:C activity at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: hours				
median (full range (min-max))	24.500 (6.17 to 29.27)	24.070 (1.08 to 30.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic Assessment at Steady State: Minimum Plasma Concentration During the Partial Dosing Interval at Steady State (Cmin;ss) Based on Factor VIII Clotting (FVIII:C) Activity

End point title	Pharmacodynamic Assessment at Steady State: Minimum Plasma Concentration During the Partial Dosing Interval at Steady State (Cmin;ss) Based on Factor VIII Clotting (FVIII:C) Activity

End point description:

Cmin;ss based on FVIII:C activity at steady state during end of study (Month 12) was reported. PKFAS composed of all subjects who received at least one IP infusion and who provided at least one quantifiable pharmacokinetic or pharmacodynamic post dose measurement for pharmacokinetic and/or pharmacodynamics analysis. Here "number of subjects analysed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: IU/dL				
arithmetic mean (standard deviation)	15.8 (± 8.6)	22.9 (± 11.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Factor VIII (FVIII) Clotting Activity

End point title	Factor VIII (FVIII) Clotting Activity

End point description:

FVIII clotting activity (FVIII:C) levels was assessed and reported as per pre-specified PK time points at Month 12. FAS will be composed of all participants who receive prophylactic IP treatment. Here "number of subjects analysed" were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

At Month 12: Within 30 minutes pre-infusion; and post-infusion at 15, 30 minutes and 1, 3, 6, 12, 24, 30, 48, 72, and 96 hours

End point values	Prior On-demand Subjects	Switch Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: IU/dL				
arithmetic mean (standard deviation)				
At pre-dose (n = 9, 7)	22.1 (± 23.5)	28.0 (± 21.2)		
15 minutes post-dose (n = 9, 7)	28.7 (± 22.5)	30.9 (± 18.7)		
30 minutes post-dose (n = 9, 7)	32.1 (± 21.5)	33.4 (± 19.5)		
1 hour post-dose (n = 9, 7)	36.0 (± 24.3)	34.0 (± 18.4)		
3 hours post-dose (n = 9, 5)	51.2 (± 23.4)	48.4 (± 20.6)		
6 hours post-dose (n = 9, 4)	66.4 (± 25.1)	69.3 (± 18.4)		
12 hours post-dose (n = 9, 4)	86.3 (± 25.0)	78.0 (± 18.2)		
24 hours post-dose (n = 9, 5)	100.0 (± 36.5)	93.8 (± 17.7)		
30 hours post-dose (n = 9, 5)	95.4 (± 32.6)	90.6 (± 15.8)		
48 hours post-dose (n = 9, 5)	71.8 (± 29.1)	79.2 (± 17.9)		
72 hours post-dose (n = 9, 5)	40.8 (± 37.8)	44.6 (± 18.0)		
96 hours post-dose (n = 9, 4)	20.0 (± 23.5)	16.0 (± 11.6)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
From first dose of study drug up to end of study (approximately 32 months)	
Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Switch Subjects

Reporting group description:

Subjects who had taken prophylactic treatment with pdVWF prior to current study and switched to rVWF (vonicog alpha); received rVWF at an initial prophylactic dose of +/- 10 % of weekly pdVWF dose received prior to this study. Dose escalation to higher dose (up to 80 IU/kg per infusion) or frequency (up to 3 times a week or once a week depending on the total weekly dose and the dosing regimen used in their previous pdVWF prophylaxis regimen) was based on medical indication and investigator judgment. During this prophylaxis treatment period, any bleeding episodes requiring replacement therapy with VWF concentrate was treated with rVWF with or without rFVIII (ADVATE); the dose was determined according to the bleeding type and severity, and was adjusted based on the subject's clinical response.

Reporting group title	On-Demand Subjects

Reporting group description:

Subjects who had taken only on-demand VWF prior to the current study received rVWF (vonicog alpha) initial prophylactic treatment at a dose range of 50 +/- 10 IU/kg, intravenous infusion, twice per week for up to 12 months. Dose was escalated up to 80 IU/kg infusion, dosing frequency up to 3 times a week based on medical indication and investigator judgement. During this prophylaxis treatment period, any bleeding episodes requiring substitution therapy with VWF concentrate was treated with rVWF with or without rFVIII (ADVATE); the dose was determined according to the bleeding type and severity, and was adjusted based on the subject's clinical response.

Serious adverse events	Switch Subjects	On-Demand Subjects	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)	1 / 13 (7.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Multiple injuries			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			

subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Switch Subjects	On-Demand Subjects	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)	10 / 13 (76.92%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Joint injury			
subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Ventricular extrasystoles			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

Nervous system disorders			
Headache			
subjects affected / exposed	0 / 10 (0.00%)	4 / 13 (30.77%)	
occurrences (all)	0	4	
General disorders and administration site conditions			
Injection site irritation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Rash pruritic			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 10 (20.00%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
Neck pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Seronegative arthritis			

subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	1

Infections and infestations
Ear infection

subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	2

Gastroenteritis

subjects affected / exposed	2 / 10 (20.00%)	0 / 13 (0.00%)
occurrences (all)	2	0

Herpes virus infection

subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	1

Nasopharyngitis

subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	1

Oral herpes

subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	1	0

Pharyngitis

subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	1	0

Upper respiratory tract infection

subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	1	0

Urinary tract infection

subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	1

Metabolism and nutrition disorders
Gout

subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	1

Increased appetite

subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)
occurrences (all)	1	0

Iron deficiency

subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Vitamin B12 deficiency			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2017	Protocol Amendment 3: To define the threshold considered as relevant ABR reduction relative to subjects' historical ABR. Include 15 minutes, 3 hours and 30 hours PK sampling timepoints. To clearly define the ADVATE use.
12 March 2018	Protocol Amendment 6: Updated study design. Provided further clarifications on SAE reporting. Added definition of severe VWD. Defined the new study timeline. Provided further clarifications to the purpose of the study. pdVWF switch subject, a new study cohort added in the study. Updated the eligibility of switch subjects and added study design, dosing guide, sample collection and new outcome measures for the switch cohort.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported