



Clinical trial results:

A Phase 3 clinical study to determine the pharmacokinetics, safety, and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes in subjects diagnosed with von Willebrand disease

Summary

EudraCT number	2010-024108-84
Trial protocol	GB DE SE AT NL BE BG IT ES
Global end of trial date	15 February 2014

Results information

Result version number	v1
This version publication date	01 March 2016
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	071001
-----------------------	--------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01410227
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

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

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study were:

To compare the pharmacokinetic (PK) parameters of recombinant von Willebrand Factor (rVWF) alone or concomitantly with recombinant Factor VIII (rFVIII) [rVWF:rFVIII] in subjects with type 3 von Willebrand Disease (VWD);

To examine the PK parameters of rVWF in subjects with severe VWD;

To evaluate the hemostatic efficacy, safety, and tolerability of rVWF:rFVIII and rVWF alone in subjects with VWD receiving the investigational product for the treatment of bleeding episodes (BEs);

To evaluate tolerability and safety of rVWF including the development of inhibitory and total binding anti-VWF antibodies and clinically significant changes in laboratory parameters following study product administration;

To assess changes in Health-Related Quality of Life (HRQoL)

Protection of trial subjects:

This study was conducted in accordance with the standards of Good Clinical Practice (GCP) in effect at the time of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 January 2011
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	Australia: 2
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 6

Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	37
EEA total number of subjects	21

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)	37
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled (signed informed consent) from 30 sites in 15 countries.

Pre-assignment

Screening details:

49 subjects provided informed consent and were screened for study, of which 37 were exposed to study product. Reasons for discontinuation are provided in Pre-assignment period.

Pre-assignment period milestones

Number of subjects started	49 ^[1]
Number of subjects completed	37

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 3
Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	Screen failure: 6
Reason: Number of subjects	High doses of rFVIII for oral procedure: 1
Reason: Number of subjects	Arm for which subject eligible was closed: 1

Notes:

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

Justification: The worldwide number of subjects enrolled are for subjects treated with study product (N=37) as per definition in EudraCT and the number of subjects who started pre-assignment are all subjects enrolled i.e. signed informed consent (N=49).

Period 1

Period 1 title	Overall Trial (Part A and B Combined) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Part Randomized: Subjects in Arms 1 and 2 were randomized at ratio of 1:1 to receive either recombinant von Willebrand Factor:recombinant Factor VIII (rVWF:rFVIII) or rVWF:saline (placebo) for pharmacokinetic (PK) analysis. After a washout period, subjects crossed over to receive the alternative treatment to the initial infusion for a further PK analysis.

Subject/investigator were blinded and the study product was reconstituted by an unblinded third party (preferably by the hospital pharmacist)

Arms

Are arms mutually exclusive?	No
Arm title	PK50+Treatment

Arm description:

In Part A, (pharmacokinetic [PK] assessment followed by on-demand treatment for bleeding episodes [BEs] for 6 months) subjects were initially infused either with 50 IU/kg recombinant von Willebrand Factor: von Willebrand Ristocetin cofactor (VWF:RCo rVWF) [rVWF] administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) [rVWF:rFVIII] or 50 IU/kg rVWF administered together with saline. Subjects then crossed over to the alternate infusion after washout (PK).

For on-demand treatment, subjects received study product [VWF:rFVIII or rVWF], where BEs were initially treated with rVWF:rFVIII and subsequently with rVWF with or without rFVIII, based on FVIII levels (dose based on previous FVIII levels or if not available from the individual subject's PK data at discretion of investigator).

In part, B subjects continued to receive on demand treatment for BEs with study product [VWF:rFVIII or

rVWF] for a further 6 months.

Arm type	Experimental
Investigational medicinal product name	rVWF:rFVIII
Investigational medicinal product code	BAX111 with ADVATE
Other name	vonicog alfa with ADVATE
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] co-infused with 38.5 IU/kg recombinant Factor VIII (rFVIII) at a ratio of 1.3:1±0.2 [rVWF:rFVIII] (Arms 1 and 2 -PK50 only). Dose and frequency of study product for on-demand treatment of bleeding episodes for Arms 1, 3 and 4 dependent on severity and location of bleed. The initial bleeding episode was to be treated with rVWF:rFVIII at a ratio of 1.3:1±0.2 with subsequent doses of rVWF alone as long as therapeutic FVIII levels were maintained.

Investigational medicinal product name	rVWF
Investigational medicinal product code	BAX111
Other name	vonicog alfa
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] (Arms 1 and 2 -PK50 only), 80 IU/kg VWF:RCo rVWF [rVWF] rVWF (Arm 3 - PK80 only). Dose and frequency of study product for on-demand treatment of bleeding episodes for Arms 1, 3 and 4 dependent on severity and location of bleed. The initial bleeding episode was to be treated with rVWF:rFVIII at a ratio of 1.3:1±0.2 with subsequent doses of rVWF alone as long as therapeutic FVIII levels were maintained

Arm title	PK50 only
------------------	-----------

Arm description:

In Part A, (pharmacokinetic [PK] assessment followed by on-demand treatment for bleeding episodes [BEs] for 6 months) subjects were initially infused either with 50 IU/kg recombinant von Willebrand Factor: von Willebrand Ristocetin cofactor (VWF:RCo rVWF) [rVWF] administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) [rVWF:rFVIII] or 50 IU/kg rVWF administered together with saline. Subjects then crossed over to the alternate infusion after washout (PK).

For on-demand treatment, subjects received study product [VWF:rFVIII or rVWF], where BEs were initially treated with rVWF:rFVIII and subsequently with rVWF with or without rFVIII, based on FVIII levels (dose based on previous FVIII levels or if not available from the individual subject's PK data at discretion of investigator).

Subjects then exited the study or could opt to sign informed consent to move to Arm 1 receive treatment for bleeding episodes with study product.

Arm type	Experimental
Investigational medicinal product name	rVWF
Investigational medicinal product code	BAX111
Other name	vonicog alfa
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] (Arms 1 and 2 -PK50 only), 80 IU/kg VWF:RCo rVWF [rVWF] rVWF (Arm 3 - PK80 only). Dose and frequency of study product for on-demand treatment of bleeding episodes for Arms 1, 3 and 4 dependent on severity and location of bleed. The initial bleeding episode was to be treated with rVWF:rFVIII at a ratio of 1.3:1±0.2 with subsequent doses of rVWF alone as long as therapeutic FVIII levels were maintained

Investigational medicinal product name	rVWF:rFVIII
Investigational medicinal product code	BAX111 with ADVATE
Other name	vonicog alfa with ADVATE
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] co-infused with 38.5 IU/kg recombinant Factor VIII (rFVIII) at a ratio of 1.3:1±0.2 [rVWF:rFVIII] (Arms 1 and 2 -PK50 only). Dose and frequency of study product for on-demand treatment of bleeding episodes for Arms 1, 3 and 4 dependent on severity and location of bleed. The initial bleeding episode was to be treated with rVWF:rFVIII at a ratio of 1.3:1±0.2 with subsequent doses of rVWF alone as long as therapeutic FVIII levels were maintained.

Arm title	PK80+Treatment
------------------	----------------

Arm description:

In Part A, subjects underwent pharmacokinetic (PK) assessment for 2 infusions of recombinant von Willebrand Factor (rVWF). Subjects initially underwent an initial PK assessment of an infusion of 80 IU/kg recombinant von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF]. After the first PK assessment subjects received on demand treatment for bleeding episodes (BEs) with study product [VWF:rFVIII or rVWF], where BEs were initially treated with rVWF:rFVIII and subsequently with rVWF with or without rFVIII, based on FVIII levels. If FVIII levels not available, the individual subject's PK data was used to determine rFVIII dose at discretion of investigator.

Subjects received on demand treatment for 6 months after the first study product infusion. After 6 months subjects underwent a second PK assessment of an infusion of 80 IU/kg rVWF.

In part B, subjects continued to receive on demand treatment for BEs with study product [VWF:rFVIII or rVWF] for a further 6 months.

Arm type	Experimental
Investigational medicinal product name	rVWF
Investigational medicinal product code	BAX111
Other name	vonicog alfa
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] (Arms 1 and 2 -PK50 only), 80 IU/kg VWF:RCo rVWF [rVWF] rVWF (Arm 3 - PK80 only). Dose and frequency of study product for on-demand treatment of bleeding episodes for Arms 1, 3 and 4 dependent on severity and location of bleed. The initial bleeding episode was to be treated with rVWF:rFVIII at a ratio of 1.3:1±0.2 with subsequent doses of rVWF alone as long as therapeutic FVIII levels were maintained.

Investigational medicinal product name	rVWF:rFVIII
Investigational medicinal product code	BAX111 with ADVATE
Other name	vonicog alfa with ADVATE
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] co-infused with 38.5 IU/kg recombinant Factor VIII (rFVIII) at a ratio of 1.3:1±0.2 [rVWF:rFVIII] (Arms 1 and 2 -PK50 only). Dose and frequency of study product for on-demand treatment of bleeding episodes for Arms 1, 3 and 4 dependent on severity and location of bleed. The initial bleeding episode was to be treated with rVWF:rFVIII at a ratio of 1.3:1±0.2 with subsequent doses of rVWF alone as long as therapeutic FVIII levels were maintained.

Arm title	Treatment
------------------	-----------

Arm description:

In Part A, subjects received on demand treatment for bleeding episodes (BEs) with study product (recombinant von Willebrand Factor [rVWF] administered together with recombinant Factor VIII [rFVIII] (rVWF:rFVIII) or rVWF alone), where BEs were initially treated with rVWF:rFVIII and subsequently with rVWF with or without rFVIII, based on FVIII levels. If not available, the individual subject's PK data was used to determine rFVIII dose at discretion of investigator.

Subjects received on demand treatment for 6 months after the first study product infusion.

In part, B subjects continued to receive on demand treatment for BEs with study product [VWF:rFVIII or rVWF] for a further 6 months.

No pharmacokinetic (PK) assessments were conducted in this arm.

Arm type	Experimental
----------	--------------

Investigational medicinal product name	rVWF:rFVIII
Investigational medicinal product code	BAX111 with ADVATE
Other name	vonicog alfa with ADVATE
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] co-infused with 38.5 IU/kg recombinant Factor VIII (rFVIII) at a ratio of 1.3:1±0.2 [rVWF:rFVIII] (Arms 1 and 2 -PK50 only). Dose and frequency of study product for on-demand treatment of bleeding episodes for Arms 1, 3 and 4 dependent on severity and location of bleed. The initial bleeding episode was to be treated with rVWF:rFVIII at a ratio of 1.3:1±0.2 with subsequent doses of rVWF alone as long as therapeutic FVIII levels were maintained.

Investigational medicinal product name	rVWF
Investigational medicinal product code	BAX111
Other name	vonicog alfa
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] (Arms 1 and 2 -PK50 only), 80 IU/kg VWF:RCo rVWF [rVWF] rVWF (Arm 3 - PK80 only). Dose and frequency of study product for on-demand treatment of bleeding episodes for Arms 1, 3 and 4 dependent on severity and location of bleed. The initial bleeding episode was to be treated with rVWF:rFVIII at a ratio of 1.3:1±0.2 with subsequent doses of rVWF alone as long as therapeutic FVIII levels were maintained

Arm title	Safety Analysis Set
------------------	---------------------

Arm description:

The Safety Analysis Set comprises of subjects who were treated with study product (recombinant von Willebrand Factor [rVWF] with or without recombinant factor VIII [rFVIII]) at least once during the study.

Arm type	Experimental
Investigational medicinal product name	rVWF
Investigational medicinal product code	BAX111
Other name	vonicog alfa
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] (Arms 1 and 2 -PK50 only), 80 IU/kg VWF:RCo rVWF [rVWF] rVWF (Arm 3 - PK80 only). Dose and frequency of study product for on-demand treatment of bleeding episodes for Arms 1, 3 and 4 dependent on severity and location of bleed. The initial bleeding episode was to be treated with rVWF:rFVIII at a ratio of 1.3:1±0.2 with subsequent doses of rVWF alone as long as therapeutic FVIII levels were maintained

Investigational medicinal product name	rVWF:rFVIII
Investigational medicinal product code	BAX111 with ADVATE
Other name	vonicog alfa with ADVATE
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] co-infused with 38.5 IU/kg recombinant Factor VIII (rFVIII) at a ratio of 1.3:1±0.2 [rVWF:rFVIII] (Arms 1 and 2 -PK50 only). Dose and frequency of study product for on-demand treatment of bleeding episodes for Arms 1, 3 and 4 dependent on severity and location of bleed. The initial bleeding episode was to be treated with rVWF:rFVIII at a ratio of 1.3:1±0.2 with subsequent doses of rVWF alone as long as therapeutic FVIII levels were maintained.

Arm title	Full Analysis Set
------------------	-------------------

Arm description:

The Full Analysis Set comprised of subjects treated with study product (recombinant von Willebrand

Factor [rVWF] with or without recombinant factor VIII [rFVIII]) for whom at least one efficacy rating scale was available.

Arm type	Experimental
Investigational medicinal product name	rVWF:rFVIII
Investigational medicinal product code	BAX111 with ADVATE
Other name	vonicog alfa with ADVATE
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] co-infused with 38.5 IU/kg recombinant Factor VIII (rFVIII) at a ratio of 1.3:1±0.2 [rVWF:rFVIII] (Arms 1 and 2 -PK50 only). Dose and frequency of study product for on-demand treatment of bleeding episodes for Arms 1, 3 and 4 dependent on severity and location of bleed. The initial bleeding episode was to be treated with rVWF:rFVIII at a ratio of 1.3:1±0.2 with subsequent doses of rVWF alone as long as therapeutic FVIII levels were maintained.

Investigational medicinal product name	rVWF
Investigational medicinal product code	BAX111
Other name	vonicog alfa
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] (Arms 1 and 2 -PK50 only), 80 IU/kg VWF:RCo rVWF [rVWF] rVWF (Arm 3 - PK80 only). Dose and frequency of study product for on-demand treatment of bleeding episodes for Arms 1, 3 and 4 dependent on severity and location of bleed. The initial bleeding episode was to be treated with rVWF:rFVIII at a ratio of 1.3:1±0.2 with subsequent doses of rVWF alone as long as therapeutic FVIII levels were maintained

Arm title	PK50 Arms
------------------	-----------

Arm description:

The PK50 arm comprised of subjects who underwent PK analysis of study product (50 IU/kg recombinant von Willebrand Factor (rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) [rVWF:rFVIII] or 50 IU/kg rVWF administered together with saline [rVWF]) i.e. a total subjects from Arm 1 [PK50+Treatment] and Arm 2 [PK50 only]. Subjects in this arm have received at least one PK infusion and have provided data suitable for PK analysis. Only PK data included in this arm.

Arm type	Experimental
Investigational medicinal product name	rVWF:rFVIII
Investigational medicinal product code	BAX111 with ADVATE
Other name	vonicog alfa with ADVATE
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] co-infused with 38.5 IU/kg recombinant Factor VIII (rFVIII) at a ratio of 1.3:1±0.2 [rVWF:rFVIII] (Arms 1 and 2 -PK50 only). Dose and frequency of study product for on-demand treatment of bleeding episodes for Arms 1, 3 and 4 dependent on severity and location of bleed. The initial bleeding episode was to be treated with rVWF:rFVIII at a ratio of 1.3:1±0.2 with subsequent doses of rVWF alone as long as therapeutic FVIII levels were maintained.

Investigational medicinal product name	rVWF
Investigational medicinal product code	BAX111
Other name	vonicog alfa
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] (Arms 1 and 2 -PK50 only), 80 IU/kg VWF:RCo rVWF [rVWF] rVWF (Arm 3 - PK80 only). Dose and frequency of study product for on-demand treatment of bleeding episodes for Arms 1, 3 and 4 dependent on severity and location of bleed. The initial bleeding episode was to be treated with rVWF:rFVIII at a ratio of 1.3:1±0.2 with subsequent doses of rVWF alone as long as therapeutic FVIII

were maintained

Arm title	PK80 Arm
Arm description: The PK80 arm comprised of subjects who underwent PK analysis of study product (80 IU/kg recombinant von Willebrand Factor [rVWF]) i.e. subjects from Arm 3 [PK80+Treatment]. Subjects in this arm have received at least one PK infusion and have provided data suitable for PK analysis. Only PK data included in this arm.	
Arm type	Experimental
Investigational medicinal product name	rVWF
Investigational medicinal product code	BAX111
Other name	vonicog alfa
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] (Arms 1 and 2 -PK50 only), 80 IU/kg VWF:RCo rVWF [rVWF] rVWF (Arm 3 - PK80 only). Dose and frequency of study product for on-demand treatment of bleeding episodes for Arms 1, 3 and 4 dependent on severity and location of bleed. The initial bleeding episode was to be treated with rVWF:rFVIII at a ratio of 1.3:1±0.2 with subsequent doses of rVWF alone as long as therapeutic FVIII levels were maintained

Number of subjects in period 1	PK50+Treatment	PK50 only	PK80+Treatment
Started	8	8	15
Completed	4	8	13
Not completed	4	0	2
Consent withdrawn by subject	3	-	1
Adverse event, non-fatal	1	-	-
Pregnancy	-	-	-
met exclusion criteria after starting study	-	-	1

Number of subjects in period 1	Treatment	Safety Analysis Set	Full Analysis Set
Started	6	37	22
Completed	5	30	20
Not completed	1	7	2
Consent withdrawn by subject	-	4	2
Adverse event, non-fatal	-	1	-
Pregnancy	1	1	-
met exclusion criteria after starting study	-	1	-

Number of subjects in period 1	PK50 Arms	PK80 Arm
Started	16	15

Completed	16	13
Not completed	0	2
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	-
Pregnancy	-	-
met exclusion criteria after starting study	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial (Part A and B Combined)
-----------------------	---------------------------------------

Reporting group description:

Overall Trial (Part A and B Combined)

Reporting group values	Overall Trial (Part A and B Combined)	Total	
Number of subjects	37	37	
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	37 18 to 64	-	
Gender categorical Units:			
Female	20	20	
Male	17	17	

End points

End points reporting groups

Reporting group title	PK50+Treatment
-----------------------	----------------

Reporting group description:

In Part A, (pharmacokinetic [PK] assessment followed by on-demand treatment for bleeding episodes [BEs] for 6 months) subjects were initially infused either with 50 IU/kg recombinant von Willebrand Factor: von Willebrand Ristocetin cofactor (VWF:RCo rVWF) [rVWF] administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) [rVWF:rFVIII] or 50 IU/kg rVWF administered together with saline. Subjects then crossed over to the alternate infusion after washout (PK).

For on-demand treatment, subjects received study product [VWF:rFVIII or rVWF], where BEs were initially treated with rVWF:rFVIII and subsequently with rVWF with or without rFVIII, based on FVIII levels (dose based on previous FVIII levels or if not available from the individual subject's PK data at discretion of investigator).

In part, B subjects continued to receive on demand treatment for BEs with study product [VWF:rFVIII or rVWF] for a further 6 months.

Reporting group title	PK50 only
-----------------------	-----------

Reporting group description:

In Part A, (pharmacokinetic [PK] assessment followed by on-demand treatment for bleeding episodes [BEs] for 6 months) subjects were initially infused either with 50 IU/kg recombinant von Willebrand Factor: von Willebrand Ristocetin cofactor (VWF:RCo rVWF) [rVWF] administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) [rVWF:rFVIII] or 50 IU/kg rVWF administered together with saline. Subjects then crossed over to the alternate infusion after washout (PK).

For on-demand treatment, subjects received study product [VWF:rFVIII or rVWF], where BEs were initially treated with rVWF:rFVIII and subsequently with rVWF with or without rFVIII, based on FVIII levels (dose based on previous FVIII levels or if not available from the individual subject's PK data at discretion of investigator).

Subjects then exited the study or could opt to sign informed consent to move to Arm 1 receive treatment for bleeding episodes with study product.

Reporting group title	PK80+Treatment
-----------------------	----------------

Reporting group description:

In Part A, subjects underwent pharmacokinetic (PK) assessment for 2 infusions of recombinant von Willebrand Factor (rVWF). Subjects initially underwent an initial PK assessment of an infusion of 80 IU/kg recombinant von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF]. After the first PK assessment subjects received on demand treatment for bleeding episodes (BEs) with study product [VWF:rFVIII or rVWF], where BEs were initially treated with rVWF:rFVIII and subsequently with rVWF with or without rFVIII, based on FVIII levels. If FVIII levels not available, the individual subject's PK data was used to determine rFVIII dose at discretion of investigator.

Subjects received on demand treatment for 6 months after the first study product infusion. After 6 months subjects underwent a second PK assessment of an infusion of 80 IU/kg rVWF.

In part B, subjects continued to receive on demand treatment for BEs with study product [VWF:rFVIII or rVWF] for a further 6 months.

Reporting group title	Treatment
-----------------------	-----------

Reporting group description:

In Part A, subjects received on demand treatment for bleeding episodes (BEs) with study product (recombinant von Willebrand Factor [rVWF] administered together with recombinant Factor VIII [rFVIII] (rVWF:rFVIII) or rVWF alone), where BEs were initially treated with rVWF:rFVIII and subsequently with rVWF with or without rFVIII, based on FVIII levels. If not available, the individual subject's PK data was used to determine rFVIII dose at discretion of investigator.

Subjects received on demand treatment for 6 months after the first study product infusion.

In part, B subjects continued to receive on demand treatment for BEs with study product [VWF:rFVIII or rVWF] for a further 6 months.

No pharmacokinetic (PK) assessments were conducted in this arm.

Reporting group title	Safety Analysis Set
-----------------------	---------------------

Reporting group description:

The Safety Analysis Set comprises of subjects who were treated with study product (recombinant von Willebrand Factor [rVWF] with or without recombinant factor VIII [rFVIII]) at least once during the study.

Reporting group title	Full Analysis Set
-----------------------	-------------------

Reporting group description:

The Full Analysis Set comprised of subjects treated with study product (recombinant von Willebrand Factor [rVWF] with or without recombinant factor VIII [rFVIII]) for whom at least one efficacy rating

scale was available.

Reporting group title	PK50 Arms
Reporting group description:	
The PK50 arm comprised of subjects who underwent PK analysis of study product (50 IU/kg recombinant von Willebrand Factor (rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) [rVWF:rFVIII] or 50 IU/kg rVWF administered together with saline [rVWF]) i.e. a total subjects from Arm 1 [PK50+Treatment] and Arm 2 [PK50 only]. Subjects in this arm have received at least one PK infusion and have provided data suitable for PK analysis. Only PK data included in this arm.	

Reporting group title	PK80 Arm
Reporting group description:	
The PK80 arm comprised of subjects who underwent PK analysis of study product (80 IU/kg recombinant von Willebrand Factor [rVWF]) i.e. subjects from Arm 3 [PK80+Treatment]. Subjects in this arm have received at least one PK infusion and have provided data suitable for PK analysis. Only PK data included in this arm.	

Primary: Percentage of subjects with treatment success for treated bleeding episodes

End point title	Percentage of subjects with treatment success for treated bleeding episodes ^{[1][2]}
-----------------	---

End point description:

Treatment success was defined as the extent of control of bleeding episodes (BEs) using a mean efficacy rating score of <2.5 for a subject's BEs treated with study product (recombinant von Willebrand Factor [rVWF] with or without recombinant factor VIII [rFVIII]) during the study period.

Scores used:

Excellent = 1 - actual infusions ≤ estimated number of infusions required to treat BE; no additional VWF required (all BEs);

Good = 2 - >1-2 infusions (minor/moderate BEs) or <1.5 infusions (major BEs) greater than estimated required to control BE; no additional VWF required (all BEs);

Moderate = 3 ≥ 3 infusions (minor/moderate BEs) or ≥ 1.5 infusions (major BEs) greater than estimated required to control BE; no additional VWF required (all BEs);

None = 4 - severe uncontrolled bleeding or intensity of bleeding not changed; additional VWF required.

There are 18 subjects with available primary efficacy rating (excluding gastrointestinal bleeds) in the Full Analysis Set.

End point type	Primary
----------------	---------

End point timeframe:

for 12 months after first infusion of rVWF:rFVIII or rVWF

Notes:

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

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

[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: Statistics for the primary endpoint were based on Treatment Success of Bleeding Episodes for all subjects in the Full Analysis Set which was for one comparison group, whereas statistics in EudraCT require two comparison groups, so unable to supply statistical analysis for this endpoint.

End point values	Full Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percent of subjects				
number (confidence interval 90%)	100 (84.7 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of treated bleeding episodes treated with an efficacy rating of "excellent" or "good"

End point title	Percentage of treated bleeding episodes treated with an efficacy rating of "excellent" or "good" ^[3]
-----------------	---

End point description:

Efficacy ratings "excellent" or "good" for the control of bleeding episodes (BEs) with study product (recombinant von Willebrand Factor [rVWF] with or without recombinant factor VIII [rFVIII]) are defined as follows:

Excellent - actual infusions \leq estimated number of infusions required to treat BE; no additional von Willebrand Factor (VWF) required (all BEs);

Good - >1 -2 infusions (minor/moderate BEs) or <1.5 infusions (major BEs) greater than estimated required to control BE; no additional VWF required (all BEs).

Out of 193 BEs treated with study product, the number of infusions required was estimated prospectively for 130 BEs with an available efficacy rating from subjects in the Full Analysis Set.

Note that use of a VWF concentrate other than study product was permissible under certain circumstances, but subjects were excluded from efficacy analysis.

End point type	Secondary
----------------	-----------

End point timeframe:

for 12 months after first infusion of rVWF:rFVIII or rVWF

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

End point values	Full Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percent of bleeding episodes				
number (confidence interval 90%)	100 (97.7 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of treated bleeding episodes with an efficacy rating of "excellent" or "good", excluding gastrointestinal bleeds

End point title	Percentage of treated bleeding episodes with an efficacy rating of "excellent" or "good", excluding gastrointestinal bleeds ^[4]
-----------------	--

End point description:

Efficacy ratings of "excellent" or "good" for the control of bleeding episodes (BEs) with study product (recombinant von Willebrand Factor [rVWF] with or without recombinant factor VIII [rFVIII]) are defined as follows:

Excellent - actual infusions \leq estimated number of infusions required to treat BE; no additional von Willebrand Factor (VWF) required (all BEs);

Good - >1 -2 infusions (minor/moderate BEs) or <1.5 infusions (major BEs) greater than estimated required to control BE; no additional VWF required (all BEs).

Out of 193 BEs treated with study product, 126 BEs (excluding gastrointestinal [GI] bleeds) were prospectively estimated with an available efficacy rating from subjects in the Full Analysis Set.

End point type	Secondary
----------------	-----------

End point timeframe:
for 12 months after first infusion of rVWF:rFVIII or rVWF

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

End point values	Full Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percent of bleeding episodes				
geometric mean (confidence interval 90%)	100 (97.7 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of infusions of rVWF:rFVIII and/or vVWF per bleeding episode

End point title	Number of infusions of rVWF:rFVIII and/or vVWF per bleeding episode ^[5]
-----------------	--

End point description:

The actual number of infusions of recombinant von Willebrand factor:recombinant factor VIII (rVWF:rFVIII) and/or rVWF required to treat a bleeding episode (BE).

BEs were to be initially treated with an infusion of rVWF:rFVIII and subsequently with rVWF with or without rFVIII, based on FVIII levels, if available. In cases, where no FVIII levels were available, the individual subject's PK data was used to determine the rFVIII dose.

Out of 193 BEs treated with study product, 192 BEs had an available efficacy rating from subjects in the Full Analysis Set (one subject had HAEMATE P for the third infusion due to logistical reasons so this BE was excluded from this analysis).

End point type	Secondary
----------------	-----------

End point timeframe:

for 12 months after first infusion of rVWF:rFVIII or rVWF

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

End point values	Full Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Number of infusions				
median (confidence interval 90%)	1 (1 to 1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of units of rVWF:rFVIII and/or vVWF per bleeding episode

End point title	Number of units of rVWF:rFVIII and/or vVWF per bleeding episode ^[6]
-----------------	--

End point description:

The number of units is provided as the actual dose [IU/kg] of recombinant von Willebrand factor:recombinant factor VIII (rVWF:rFVIII) and/or rVWF required to treat a bleeding episode (BE). BEs were to be initially treated with an infusion of rVWF:rFVIII and subsequently with rVWF with or without rFVIII, based on FVIII levels, if available. In cases, where no FVIII levels were available, the individual subject's PK data was used to determine the rFVIII dose.

Out of 193 BEs treated with study product, 192 BEs had an available efficacy rating from subjects in the Full Analysis Set (one subject had HAEMATE P for the third infusion due to logistical reasons so this BE was excluded from this analysis).

End point type	Secondary
----------------	-----------

End point timeframe:

for 12 months after first infusion of rVWF:rFVIII or rVWF

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

End point values	Full Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: IU/kg				
median (confidence interval 90%)	48.2 (43.9 to 50.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who develop inhibitory antibodies to FVIII

End point title	Percentage of subjects who develop inhibitory antibodies to FVIII ^[7]
-----------------	--

End point description:

Development of neutralizing antibodies (inhibitors) to factor VIII (FVIII) was assessed by the Nijmegen modification of the Bethesda assay. Positive FVIII inhibitor tests were defined as ≥ 0.4 Bethesda units/mL (BU/mL) by the Nijmegen-modified Bethesda assay that is confirmed by a second test performed on an independent sample obtained 2-4 weeks following the first test.

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

After signing informed consent until 12 months after first infusion of rVWF:rFVIII or rVWF

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

End point values	Safety Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Percent of subjects				
number (not applicable)				
Before 1st treatment with study product [N=37]	0			
During 1st treatment until study end [N=27]	0			
At final study visit [N=24]	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who develop inhibitory antibodies to VWF

End point title	Percentage of subjects who develop inhibitory antibodies to VWF ^[8]
-----------------	--

End point description:

Neutralizing antibodies (inhibitors) to Von Willebrand Factor Ristocetin cofactor (VWF:RCo), VWF collagen binding (VWF:CB) and VWF Factor VIII binding (VWF:FVIIIb) activities were measured using Nijmegen modification of the Bethesda assay. One Bethesda Unit (BU) is thereby defined as the amount of inhibitor that decreased the measured activity in the assays to 50% of that of the negative control samples. The assays were validated using human plasma samples from two type 3 VWD patients with low (1-2 BU/mL) and high (~10 BU/mL) titer inhibitors and plasma samples from non-human primates immunized with human rVWF (>100 BU/mL).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

After signing informed consent until 12 months after first infusion of rVWF:rFVIII or rVWF

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

End point values	Safety Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Percent of subjects				
number (not applicable)				
Before 1st treatment with study product [N=37]	0			
During 1st treatment until study end [N=27]	0			
At final study visit [N=24]	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who develop binding antibodies to VWF

End point title	Percentage of subjects who develop binding antibodies to
-----------------	--

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). Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

After signing informed consent until 12 months after first infusion of rVWF:rFVIII or rVWF

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

End point values	Safety Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Percent of subjects				
number (not applicable)				
Before 1st treatment with study product [N=37]	0			
During 1st treatment until study end [N=28]	0			
At final study visit [N=24]	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who develop binding antibodies to CHO

End point title	Percentage of subjects who develop binding antibodies to
-----------------	--

End point description:

The presence of total binding anti-CHO antibodies was determined by measuring total immunoglobulin (Ig) antibodies (IgG, IgA, IgM) against Chinese Hamster Ovary (CHO) protein using an enzyme-linked immunosorbent assay (ELISA).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

After signing informed consent until 12 months after first infusion of rVWF:rFVIII or rVWF

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

End point values	Safety Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Percent of subjects				
number (not applicable)				
Before 1st treatment with study product [N=37]	0			
During 1st treatment until study end [N=28]	0			
At final study visit [N=24]	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who develop binding antibodies to rFurin

End point title	Percentage of subjects who develop binding antibodies to rFurin ^[11]
-----------------	---

End point description:

The presence of total binding anti-rFurin antibodies was determined by measuring total immunoglobulin (Ig) antibodies (IgG, IgA, IgM) against rFurin protein using an enzyme-linked immunosorbent assay (ELISA).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

After signing informed consent until 12 months after first infusion of rVWF:rFVIII or rVWF

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

End point values	Safety Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Percent of subjects				
number (not applicable)				
Before 1st treatment with study product [N=37]	0			
During 1st treatment until study end [N=28]	0			
At final study visit [N=24]	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who develop binding antibodies to mouse immunoglobulin

End point title	Percentage of subjects who develop binding antibodies to mouse immunoglobulin ^[12]
End point description: The presence of total binding anti-Murine immunoglobulin (IgG) antibodies was determined using an enzyme-linked immunosorbent assay (ELISA). Category title includes number of subjects [N] who provided data for the category.	
End point type	Secondary

End point timeframe:

After signing informed consent until 12 months after first infusion of rVWF:rFVIII or rVWF

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

End point values	Safety Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Percent of subjects				
number (not applicable)				
Before 1st treatment with study product [N=36]	2.8			
During 1st treatment until study end [N=28]	0			
At final study visit [N=24]	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who had an occurrence of thrombotic events

End point title	Percentage of subjects who had an occurrence of thrombotic events ^[13]
-----------------	---

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

After signing informed consent until 12 months after first infusion of rVWF:rFVIII or rVWF

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

End point values	Safety Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Percent of subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events related to study product including clinically significant changes in laboratory parameters and vital signs

End point title	Number of adverse events related to study product including clinically significant changes in laboratory parameters and vital signs ^[14]
-----------------	---

End point description:

Adverse Events (AEs) related to study product (recombinant von Willebrand Factor [rVWF] with or without recombinant factor VIII [rFVIII]) are described. Only laboratory parameters (hematology and clinical chemistry) and vital signs (physical examination, ECG) with clinically significant findings that are recorded as AEs are included.

Categories presented as Severity-System Organ Class-Preferred Term

Seriousness: serious adverse event (SAE); non serious adverse event (nsAE)

System Organ Class: Cardiac disorders (CARD); General disorders and administration site conditions (GEN); Investigations (INV); Nervous system disorders (NERV); Skin and subcutaneous tissue disorders (SKN); Vascular disorders (VAS)

Category title includes number of AEs [N] for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

for 12 months after first infusion of rVWF:rFVIII or rVWF

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

End point values	Safety Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Number of AEs				
SAE-GEN-Chest discomfort [N=1]	1			
SAE-INV-Heart rate increased [N=1]	1			
nsAE-CARD-Tachycardia [N=1]	1			
nsAE-GEN-Infusion site paraesthesia [N=1]	1			
nsAE-INV-ECG T wave inversion [N=1]	1			
nsAE-NERV-Dysgeusia [N=1]	1			
nsAE-SKN-Pruritus generalized [N=1]	1			
nsAE-VAS-Hot flush [N=1]	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events related to study product including clinically significant changes in laboratory parameters and vital signs

End point title	Number of subjects with adverse events related to study product including clinically significant changes in laboratory parameters and vital signs ^[15]
-----------------	---

End point description:

Number of subjects with Adverse Events (AEs) related to study product (recombinant von Willebrand Factor [rVWF] with or without recombinant factor VIII [rFVIII]) are described. Only laboratory parameters (hematology and clinical chemistry) and vital signs (physical examination, ECG) with clinically significant findings that are recorded as AEs are included.

Categories presented as Severity-System Organ Class-Preferred Term

Seriousness: serious adverse event (SAE); non serious adverse event (nsAE)

System Organ Class: Cardiac disorders (CARD); General disorders and administration site conditions (GEN); Investigations (INV); Nervous system disorders (NERV); Skin and subcutaneous tissue disorders (SKN); Vascular disorders (VAS)

End point type	Secondary
----------------	-----------

End point timeframe:

for 12 months after first infusion of rVWF:rFVIII or rVWF

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

End point values	Safety Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Number of subjects				
SAE-GEN-Chest discomfort	1			
SAE-INV-Heart rate increased	1			
nsAE-CARD-Tachycardia	1			
nsAE-GEN-Infusion site paraesthesia	1			
nsAE-INV-ECG T wave inversion	1			
nsAE-NERV-Dysgeusia	1			
nsAE-SKN-Pruritus generalized	1			
nsAE-VAS-Hot flush	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events by infusion related to study product including clinically significant changes in laboratory parameters and vital signs

End point title	Number of adverse events by infusion related to study product including clinically significant changes in laboratory parameters and vital signs ^[16]
-----------------	---

End point description:

Adverse Events (AEs) by infusion related to study product (recombinant von Willebrand Factor [rVWF] with or without recombinant factor VIII [rFVIII]) are described. Only laboratory parameters (hematology and clinical chemistry) and vital signs (physical examination, ECG) with clinically significant findings that are recorded as AEs are included.

Categories presented as Severity-System Organ Class-Preferred Term

Seriousness: serious adverse event (SAE); non serious adverse event (nsAE)

System Organ Class: Cardiac disorders (CARD); General disorders and administration site conditions (GEN); Investigations (INV); Nervous system disorders (NERV); Skin and subcutaneous tissue disorders (SKN); Vascular disorders (VAS)

A total of 318 infusions were given.

Category title includes number of AEs by infusion [N] for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

for 12 months after first infusion of rVWF:rFVIII or rVWF

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

End point values	Safety Analysis Set			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Number of AEs				
SAE-GEN-Chest discomfort [N=1]	1			
SAE-INV-Heart rate increased [N=1]	1			
nsAE-CARD-Tachycardia [N=1]	1			
nsAE-GEN-Infusion site paraesthesia [N=1]	1			
nsAE-INV-ECG T wave inversion [N=1]	1			
nsAE-NERV-Dysgeusia [N=1]	1			
nsAE-SKN-Pruritus generalized [N=1]	1			
nsAE-VAS-Hot flush [N=1]	1			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Area under the plasma concentration/time curve from time 0 to infinity (AUC_{0-∞}/Dose) of VWF:RCo

End point title	PK50 - Area under the plasma concentration/time curve from time 0 to infinity (AUC _{0-∞} /Dose) of VWF:RCo ^[17]
-----------------	---

End point description:

Area under the plasma concentration curve (AUC) from time 0 to infinity of von Willebrand Factor Ristocetin cofactor (VWF:RCo) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: (hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	32.4 (27.5 to 40.1)			
rVWF [N=14]	32.7 (29 to 47.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of VWF:RCo

End point title	PK50 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of VWF:RCo ^[18]
-----------------	--

End point description:

Area under the plasma concentration curve (AUC) from time 0 to 96 hours of von Willebrand Factor Ristocetin cofactor (VWF:RCo) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: (hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	31.6 (27.3 to 37.3)			
rVWF [N=14]	31.3 (28.4 to 43.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Mean Residence Time of VWF:RCo

End point title	PK50 - Mean Residence Time of VWF:RCo ^[19]
-----------------	---

End point description:

Mean Residence Time (MRT) of von Willebrand Factor Ristocetin cofactor (VWF:RCo) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Hours				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	25.2 (20 to 30.1)			
rVWF [N=14]	26.7 (22.7 to 36)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Clearance of VWF:RCo

End point title	PK50 - Clearance of VWF:RCo ^[20]
-----------------	---

End point description:

Clearance (CL) of von Willebrand Factor Ristocetin cofactor (VWF:RCo) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for

the PK50 arms (Arm 1 and Arm 2)

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: dL/kg/hours				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	0.031 (0.025 to 0.041)			
rVWF [N=14]	0.031 (0.021 to 0.035)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Incremental Recovery of VWF:RCo

End point title	PK50 - Incremental Recovery of VWF:RCo ^[21]
-----------------	--

End point description:

Incremental Recovery (IR) at the maximum plasma concentration of von Willebrand Factor Ristocetin cofactor (VWF:RCo) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1 \pm 0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: (U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	1.8 (1.6 to 2.4)			
rVWF [N=14]	1.8 (1.5 to 2.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Elimination Phase Half-Life of VWF:Co

End point title	PK50 - Elimination Phase Half-Life of VWF:Co ^[22]
-----------------	--

End point description:

Elimination Phase Half-Life (T_{1/2}) of von Willebrand Factor Ristocetin cofactor (VWF:RCo) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant FVIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2)..

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	16.6 (14.7 to 20.4)			
rVWF [N=14]	19.4 (15.5 to 31.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Volume of Distribution at Steady State of VWF:RCo

End point title	PK50 - Volume of Distribution at Steady State of VWF:RCo ^[23]
-----------------	--

End point description:

Volume of Distribution at Steady State (V_{ss}) of von Willebrand Factor Ristocetin cofactor (VWF:RCo) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: dL/kg				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	0.7 (0.66 to 0.93)			
rVWF [N=14]	0.83 (0.7 to 0.97)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Area under the plasma concentration/time curve from time 0 to infinity (AUC_{0-∞}/Dose) of VWF:Ag

End point title	PK50 - Area under the plasma concentration/time curve from time 0 to infinity (AUC _{0-∞} /Dose) of VWF:Ag ^[24]
-----------------	--

End point description:

Area under the plasma concentration curve (AUC) from time 0 to infinity of von Willebrand Factor Antigen (VWF:Ag) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: (hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	67.8 (55.1 to 81.7)			
rVWF [N=14]	67.1 (55.6 to 80.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of VWF:Ag

End point title	PK50 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of VWF:Ag ^[25]
-----------------	---

End point description:

Area under the plasma concentration curve (AUC) from time 0 to 96 hours of von Willebrand Factor Antigen (VWF:Ag) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: (hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	62.1 (52.8 to 74.9)			
rVWF [N=14]	62.2 (54.7 to 74.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Mean Residence Time of VWF:Ag

End point title	PK50 - Mean Residence Time of VWF:Ag ^[26]
-----------------	--

End point description:

Mean Residence Time (MRT) of von Willebrand Factor Antigen (VWF:Ag) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	32.1 (29.8 to 41.1)			
rVWF [N=14]	34.3 (30.4 to 41.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Clearance of VWF:Ag

End point title	PK50 - Clearance of VWF:Ag ^[27]
-----------------	--

End point description:

Clearance (CL) of von Willebrand Factor Antigen (VWF:Ag) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: dL/kg/hours				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	0.015 (0.013 to 0.018)			
rVWF [N=14]	0.015 (0.013 to 0.018)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Incremental Recovery of VWF:Ag

End point title	PK50 - Incremental Recovery of VWF:Ag ^[28]
-----------------	---

End point description:

Incremental Recovery (IR) at the maximum plasma concentration of von Willebrand Factor Antigen (VWF:Ag) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: (U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	2.3 (2 to 2.5)			
rVWF [N=14]	2.2 (1.9 to 2.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Elimination Phase Half-Life of VWF:Ag

End point title	PK50 - Elimination Phase Half-Life of VWF:Ag ^[29]
-----------------	--

End point description:

Elimination Phase Half-Life (T_{1/2}) of von Willebrand Factor Antigen (VWF:Ag) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant FVIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	21.8 (19.5 to 27.2)			
rVWF [N=14]	25.2 (21.9 to 30.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Volume of Distribution at Steady State of VWF:Ag

End point title	PK50 - Volume of Distribution at Steady State of VWF:Ag ^[30]
-----------------	---

End point description:

Volume of Distribution at Steady State (V_{ss}) of von Willebrand Factor Antigen (VWF:Ag) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: dL/kg				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	0.5 (0.45 to 0.56)			
rVWF [N=14]	0.49 (0.45 to 0.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Area under the plasma concentration/time curve from time 0 to infinity (AUC0-∞/Dose) of VWF:CB

End point title	PK50 - Area under the plasma concentration/time curve from time 0 to infinity (AUC0-∞/Dose) of VWF:CB ^[31]
-----------------	---

End point description:

Area under the plasma concentration curve (AUC) from time 0 to infinity of von Willebrand Factor Collagen Binding (VWF:CB) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: (hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	80.1 (68.4 to 95)			
rVWF [N=14]	81.3 (71.2 to 99.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of VWF:CB

End point title	PK50 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of VWF:CB ^[32]
-----------------	---

End point description:

Area under the plasma concentration curve (AUC) from time 0 to 96 hours of von Willebrand Factor Collagen Binding (VWF:CB) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: (hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	78.7 (66.5 to 90.5)			
rVWF [N=14]	75.1 (69.2 to 97)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Mean Residence Time of VWF:CB

End point title	PK50 - Mean Residence Time of VWF:CB ^[33]
-----------------	--

End point description:

Mean Residence Time (MRT) of von Willebrand Factor Collagen Binding (VWF:CB) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF)

administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

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

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	27.5 (22.7 to 32.1)			
rVWF [N=14]	26.1 (25.1 to 33.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Clearance of VWF:CB

End point title	PK50 - Clearance of VWF:CB ^[34]
-----------------	--

End point description:

Clearance (CL) of von Willebrand Factor Collagen Binding (VWF:CB) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[34] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: dL/kg/hours				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	0.012 (0.011 to 0.015)			
rVWF [N=14]	0.012 (0.011 to 0.015)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Incremental Recovery of VWF:CB

End point title	PK50 - Incremental Recovery of VWF:CB ^[35]
-----------------	---

End point description:

Incremental Recovery (IR) at the maximum plasma concentration of von Willebrand Factor Collagen Binding (VWF:CB) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[35] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: (U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	3.4 (3 to 3.7)			
rVWF [N=14]	3.2 (2.8 to 3.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Elimination Phase Half-Life of VWF:CB

End point title	PK50 - Elimination Phase Half-Life of VWF:CB ^[36]
-----------------	--

End point description:

Elimination Phase Half-Life (T_{1/2}) of von Willebrand Factor Collagen Binding (VWF:CB) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant FVIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[36] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	19.3 (14.9 to 23.4)			
rVWF [N=14]	18.3 (17.4 to 24.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Volume of Distribution at Steady State of VWF:CB

End point title	PK50 - Volume of Distribution at Steady State of VWF:CB ^[37]
-----------------	---

End point description:

Volume of Distribution at Steady State (V_{ss}) of von Willebrand Factor Collagen Binding (VWF:CB) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[37] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: dL/kg				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	0.35 (0.31 to 0.4)			
rVWF [N=14]	0.36 (0.28 to 0.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Area under the plasma concentration/time curve from time 0 to infinity (AUC0-∞/Dose) of FVIII:C

End point title	PK50 - Area under the plasma concentration/time curve from time 0 to infinity (AUC0-∞/Dose) of FVIII:C ^[38]
-----------------	--

End point description:

Area under the plasma concentration curve (AUC) from time 0 to infinity of Factor VIII activity (FVIII:C) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[38] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	145.4 (118.8 to 189.5)			
rVWF [N=14]	113 (93 to 167.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of FVIII:C

End point title	PK50 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of FVIII:C ^[39]
-----------------	--

End point description:

Area under the plasma concentration curve (AUC) from time 0 to 96 hours of Factor VIII activity (FVIII:C) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[39] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	127.8 (112.3 to 145.1)			
rVWF [N=14]	101.8 (74.4 to 124.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Mean Residence Time of FVIII:C

End point title	PK50 - Mean Residence Time of FVIII:C ^[40]
-----------------	---

End point description:

Mean Residence Time (MRT) of Factor VIII activity (FVIII:C) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK

evaluation for both infusions and washout.

Notes:

[40] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	44 (38 to 75)			
rVWF [N=0]	0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Clearance of FVIII:C

End point title	PK50 - Clearance of FVIII:C ^[41]
-----------------	---

End point description:

Clearance (CL) of Factor VIII activity (FVIII:C) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2). Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[41] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: dL/kg/hours				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	0.007 (0.006 to 0.009)			
rVWF [N=0]	0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Incremental Recovery of FVIII:C

End point title	PK50 - Incremental Recovery of FVIII:C ^[42]
End point description: Incremental Recovery (IR) at the maximum plasma concentration of Factor VIII activity (FVIII:C) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2). Category title includes number of subjects [N] who provided data for the category.	
End point type	Secondary
End point timeframe: PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion. PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.	
Notes: [42] - 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: Per protocol, descriptive statistics were collected for this endpoint.	

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: (U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	2.3 (1.9 to 2.7)			
rVWF [N=0]	0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Elimination Phase Half-Life of FVIII:C

End point title	PK50 - Elimination Phase Half-Life of FVIII:C ^[43]
End point description: Elimination Phase Half-Life (T _{1/2}) of Factor VIII activity (FVIII:C) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant FVIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).	
Category title includes number of subjects [N] who provided data for the category.	
End point type	Secondary
End point timeframe: PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion. PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.	

Notes:

[43] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	24.8 (20.1 to 50.5)			
rVWF [N=0]	0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK50 - Volume of Distribution at Steady State of FVIII:C

End point title	PK50 - Volume of Distribution at Steady State of FVIII:C ^[44]
-----------------	--

End point description:

Volume of Distribution at Steady State (Vss) of Factor VIII activity (FVIII:C) after infusion of 50 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) administered together with 38.5 IU/kg recombinant Factor VIII (rFVIII) (ratio of 1.3:1±0.2) [rVWF:rFVIII], or 50 IU/kg VWF:RCo rVWF administered together with saline (placebo) [rVWF] for subjects in the PK50 arms (Arm 1 and Arm 2).

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[44] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK50 Arms			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: dL/kg				
median (confidence interval 95%)				
rVWF:rFVIII [N=16]	0.32 (0.29 to 0.44)			
rVWF [N=0]	0 (0 to 0)			

Statistical analyses

Secondary: PK80 - Area under the plasma concentration/time curve from time 0 to infinity (AUC0-∞/Dose) of VWF:RCo

End point title	PK80 - Area under the plasma concentration/time curve from time 0 to infinity (AUC0-∞/Dose) of VWF:RCo ^[45]
-----------------	--

End point description:

Area under the plasma concentration curve (AUC) from time 0 to infinity of von Willebrand Factor Ristocetin cofactor (VWF:RCo) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[45] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: (hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	36.9 (29.2 to 41.7)			
PK2 of rVWF [N=13]	38.9 (28.1 to 43.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of VWF:RCo

End point title	PK80 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of VWF:RCo ^[46]
-----------------	--

End point description:

Area under the plasma concentration curve (AUC) from time 0 to 96 hours of von Willebrand Factor Ristocetin cofactor (VWF:RCo) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
End point timeframe:	
PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.	
PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.	

Notes:

[46] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: (hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	35.6 (28.9 to 41.2)			
PK2 of rVWF [N=13]	37.9 (25.9 to 41.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Mean Residence Time of VWF:RCo

End point title	PK80 - Mean Residence Time of VWF:RCo ^[47]
End point description:	
Mean Residence Time (MRT) of von Willebrand Factor Ristocetin cofactor (VWF:RCo) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).	
PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].	

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
End point timeframe:	
PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.	
PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.	

Notes:

[47] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: hours				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	26.4 (20.9 to 31.1)			
PK2 of rVWF [N=13]	26.4 (23.7 to 32.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Clearance of VWF:RCo

End point title	PK80 - Clearance of VWF:RCo ^[48]
-----------------	---

End point description:

Clearance (CL) of von Willebrand Factor Ristocetin cofactor (VWF:RCo) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[48] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: dL/kg/hours				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	0.027 (0.024 to 0.034)			
PK2 of rVWF [N=13]	0.026 (0.023 to 0.036)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Incremental Recovery of VWF:RCo

End point title	PK80 - Incremental Recovery of VWF:RCo ^[49]
-----------------	--

End point description:

Incremental Recovery (IR) at the maximum plasma concentration Area under the plasma concentration curve (AUC) from time 0 to infinity of von Willebrand Factor Ristocetin cofactor (VWF:RCo) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).
PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[49] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: (U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	1.8 (1.7 to 2.2)			
PK2 of rVWF [N=13]	1.8 (1.6 to 2)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Elimination Phase Half-Life of VWF:Co

End point title	PK80 - Elimination Phase Half-Life of VWF:Co ^[50]
-----------------	--

End point description:

Elimination Phase Half-Life (T_{1/2}) of von Willebrand Factor Ristocetin cofactor (VWF:RCo) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).
PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[50] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: hours				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	18.4 (16.4 to 22.1)			
PK2 of rVWF [N=13]	19.8 (15.2 to 23.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Volume of Distribution at Steady State of VWF:RCo

End point title	PK80 - Volume of Distribution at Steady State of VWF:RCo ^[51]
-----------------	--

End point description:

Volume of Distribution at Steady State (Vss) of von Willebrand Factor Ristocetin cofactor (VWF:RCo) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only). PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study PK evaluations at pre-infusion, then at 15, 30 and 60 minutes, and 3, 6, 12, 24, 48, 72 and 96 hours post-infusion.

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[51] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: dL/kg				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	0.78 (0.58 to 0.86)			

PK2 of rVWF [N=13]	0.75 (0.58 to 1.01)			
--------------------	---------------------	--	--	--

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Area under the plasma concentration/time curve from time 0 to infinity (AUC0-∞/Dose) of VWF:Ag

End point title	PK80 - Area under the plasma concentration/time curve from time 0 to infinity (AUC0-∞/Dose) of VWF:Ag ^[52]
-----------------	---

End point description:

Area under the plasma concentration curve (AUC) from time 0 to infinity of von Willebrand Factor Antigen (VWF:Ag) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[52] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: (hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	66.6 (50.4 to 89.4)			
PK2 of rVWF [N=13]	86.9 (54.9 to 100.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of VWF:Ag

End point title	PK80 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of VWF:Ag ^[53]
-----------------	---

End point description:

Area under the plasma concentration curve (AUC) from time 0 to 96 hours of von Willebrand Factor Antigen (VWF:Ag) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[53] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: (hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	61.3 (48.8 to 73.7)			
PK2 of rVWF [N=13]	77.4 (53 to 87.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Mean Residence Time of VWF:Ag

End point title	PK80 - Mean Residence Time of VWF:Ag ^[54]
-----------------	--

End point description:

Mean Residence Time (MRT) of von Willebrand Factor Antigen (VWF:Ag) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[54] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: hours				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	38.4 (31.9 to 48.1)			
PK2 of rVWF [N=13]	36.9 (30 to 50.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Clearance of VWF:Ag

End point title	PK80 - Clearance of VWF:Ag ^[55]
-----------------	--

End point description:

Clearance (CL) of von Willebrand Factor Antigen (VWF:Ag) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[55] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: dL/kg/hours				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	0.015 (0.011 to 0.02)			
PK2 of rVWF [N=13]	0.012 (0.01 to 0.018)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Incremental Recovery of VWF:Ag

End point title	PK80 - Incremental Recovery of VWF:Ag ^[56]
-----------------	---

End point description:

Incremental Recovery (IR) at the maximum plasma concentration Area under the plasma concentration curve (AUC) from time 0 to infinity of von Willebrand Factor Antigen (VWF:Ag) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[56] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: (U/dL)/(U VWF: RCo/kg)				
median (confidence interval 0%)				
PK1 of rVWF [N=15]	2.2 (1.9 to 2.6)			
PK2 of rVWF [N=13]	2.4 (2 to 2.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Elimination Phase Half-Life of VWF:Ag

End point title	PK80 - Elimination Phase Half-Life of VWF:Ag ^[57]
-----------------	--

End point description:

Elimination Phase Half-Life (T_{1/2}) of von Willebrand Factor Antigen (VWF:Ag) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg

rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[57] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: hours				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	27.5 (22.5 to 34)			
PK2 of rVWF [N=13]	24.8 (21.1 to 37.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Volume of Distribution at Steady State of VWF:Ag

End point title	PK80 - Volume of Distribution at Steady State of VWF:Ag ^[58]
-----------------	---

End point description:

Volume of Distribution at Steady State (V_{ss}) of von Willebrand Factor Antigen (VWF:Ag) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[58] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: dL/kg				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	0.55 (0.46 to 0.61)			
PK2 of rVWF [N=13]	0.5 (0.41 to 0.57)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Area under the plasma concentration/time curve from time 0 to infinity (AUC0-∞/Dose) of VWF:CB

End point title	PK80 - Area under the plasma concentration/time curve from time 0 to infinity (AUC0-∞/Dose) of VWF:CB ^[59]
-----------------	---

End point description:

Area under the plasma concentration curve (AUC) from time 0 to infinity of von Willebrand Factor Collagen Binding (VWF:CB) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[59] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: (hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	73.9 (57.3 to 96.2)			
PK2 of rVWF [N=13]	90.8 (66 to 105.2)			

Statistical analyses

Secondary: PK80 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of VWF:CB

End point title	PK80 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of VWF:CB ^[60]
-----------------	---

End point description:

Area under the plasma concentration curve (AUC) from time 0 to 96 hours of von Willebrand Factor Collagen Binding (VWF:CB) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[60] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: (hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	71.9 (57 to 89.8)			
PK2 of rVWF [N=13]	88.1 (63.8 to 96.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Mean Residence Time of VWF:CB

End point title	PK80 - Mean Residence Time of VWF:CB ^[61]
-----------------	--

End point description:

Mean Residence Time (MRT) of von Willebrand Factor Collagen Binding (VWF:CB) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[61] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: hours				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	30.9 (24.3 to 35)			
PK2 of rVWF [N=13]	28.7 (25.6 to 37.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Clearance of VWF:CB

End point title	PK80 - Clearance of VWF:CB ^[62]
-----------------	--

End point description:

Clearance (CL) of von Willebrand Factor Collagen Binding (VWF:CB) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[62] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: dL/kg/hours				
median (confidence interval 95%)				

PK1 of rVWF [N=15]	0.014 (0.01 to 0.017)			
PK2 of rVWF [N=13]	0.011 (0.01 to 0.015)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Incremental Recovery of VWF:CB

End point title	PK80 - Incremental Recovery of VWF:CB ^[63]
-----------------	---

End point description:

Incremental Recovery (IR) at the maximum plasma concentration Area under the plasma concentration curve (AUC) from time 0 to infinity of von Willebrand Factor Collagen Binding (VWF:CB) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[63] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: (U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	3.1 (2.8 to 3.6)			
PK2 of rVWF [N=13]	3.7 (2.7 to 4)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Elimination Phase Half-Life of VWF:CB

End point title	PK80 - Elimination Phase Half-Life of VWF:CB ^[64]
-----------------	--

End point description:

Elimination Phase Half-Life (T_{1/2}) of von Willebrand Factor Collagen Binding (VWF:CB) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[64] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: hours				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	18.8 (16.6 to 24.9)			
PK2 of rVWF [N=13]	20.9 (17.8 to 23.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Volume of Distribution at Steady State of VWF:CB

End point title	PK80 - Volume of Distribution at Steady State of VWF:CB ^[65]
-----------------	---

End point description:

Volume of Distribution at Steady State (Vss) of von Willebrand Factor Collagen Binding (VWF:CB) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[65] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: dL/kg				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	0.39 (0.34 to 0.46)			
PK2 of rVWF [N=13]	0.36 (0.33 to 0.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80 - Area under the plasma concentration/time curve from time 0 to infinity (AUC0-∞/Dose) of FVIII:C

End point title	PK80 - Area under the plasma concentration/time curve from time 0 to infinity (AUC0-∞/Dose) of FVIII:C ^[66]
-----------------	--

End point description:

Area under the plasma concentration curve (AUC) from time 0 to infinity of Factor VIII activity (FVIII:C) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only). PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[66] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: (hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	96.8 (64 to 126.5)			
PK2 of rVWF [N=13]	94.8 (60.4 to 106.5)			

Statistical analyses

Secondary: PK80 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of FVIII:C

End point title	PK80 - Area under the plasma concentration/time curve from time 0 to 96 hours (AUC0-96h/Dose) of FVIII:C ^[67]
-----------------	--

End point description:

Area under the plasma concentration curve (AUC) from time 0 to 96 hours of Factor VIII activity (FVIII:C) after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

Category title includes number of subjects [N] who provided data for the category.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[67] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: (hours*U/dL)/(U VWF: RCo/kg)				
median (confidence interval 95%)				
PK1 of rVWF [N=15]	81.7 (54.7 to 104.3)			
PK2 of rVWF [N=13]	71.8 (49.6 to 89.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK80- Ratio of intra-subject PK of VWF:RCo, VWF:Ag and VWF:CB at baseline and after 6 months

End point title	PK80- Ratio of intra-subject PK of VWF:RCo, VWF:Ag and VWF:CB at baseline and after 6 months ^[68]
-----------------	--

End point description:

Area under the plasma concentration curve (AUC) from time 0 to infinity per dose (AUC0-∞/dose) for von Willebrand Factor Ristocetin cofactor (VWF:RCo), von Willebrand Factor Antigen (VWF:Ag) and von Willebrand Factor Collagen Binding (VWF:CB). Each parameter was compared between the two PK assessments after infusion of 80 IU/kg recombinant von Willebrand Factor: von Willebrand Factor Ristocetin cofactor (VWF:RCo rVWF) [rVWF] for subjects in the PK80 arm (subjects from Arm 3 with PK80 data only).

PK assessment conducted at first infusion of 80 IU/kg rVWF [PK1] and the second infusion of 80 IU/kg rVWF after subjects were treated on demand for bleeding episodes for at least 6 months since their first infusion of study product [PK2].

13 subjects had data available for this endpoint i.e. data for PK1 and PK2.

End point type	Secondary
----------------	-----------

End point timeframe:

PK evaluations at pre-infusion, then at 15, 30 and 60 mins, and 3, 6, 12, 24, 30, 48, 72 and 96 hrs post-infusion.

PK evaluation timeframe for 28 ± 3 days after first infusion of study product which includes PK evaluation for both infusions and washout.

Notes:

[68] - 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: Per protocol, descriptive statistics were collected for this endpoint.

End point values	PK80 Arm			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: ratio of AUC _{0-∞} /dose				
geometric mean (confidence interval 90%)				
AUC _{0-∞} /dose - VWF:RCo	0.9587 (0.8466 to 1.0857)			
AUC _{0-∞} /dose - VWF:Ag	1.0914 (1.0132 to 1.1757)			
AUC _{0-∞} /dose - VWF:CB	1.0666 (1.0004 to 1.1372)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

for 12 months after first infusion of recombinant von Willebrand Factor (rVWF) with or without recombinant Factor VIII (rVWF:rFVIII)

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	17.1
--------------------	------

Reporting groups

Reporting group title	Safety Analysis Set
-----------------------	---------------------

Reporting group description:

The Safety Analysis Set comprises of subjects who were treated with study product at least once during the study.

Serious adverse events	Safety Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 37 (18.92%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mesenteric haematoma			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Heart rate increased			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 37 (27.03%)		
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Laceration subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 4		
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3 2 / 37 (5.41%) 2		
General disorders and administration site conditions Infusion site paraesthesia subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3 2 / 37 (5.41%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain	3 / 37 (8.11%) 3		

subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 November 2011	Exclusion criteria updated to ensure specific cohort of patients plus hypersensitivity of study product components. New study arm added (PK80 analysis). Update for safety stopping rules.
10 August 2012	Clarification on procedure for enabling home treatment of bleeding episodes. Inclusion criteria updated to better reflect real life clinical practice for this cohort of patients. Option to use premixed or sequential infusion of study product (when administered together with recombinant Factor VIII).
26 July 2013	Final report to be done after completion of study Parts A and B.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported