Clinical trial results:
Pharmacokinetics of WILATE® and Haemate® P in von Willebrand type 3 patients - a prospective, randomised, controlled, open-labelled, 2-arm cross-over study.

Summary

EudraCT number	2008-001910-25
Trial protocol	SK
Global end of trial date	14 January 2010

Results information

Result version number	v1 (current)
This version publication date	06 January 2017
First version publication date	06 January 2017

Trial information

Trial identification

Sponsor protocol code	WIL-21

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Octapharma AG
Sponsor organisation address	Seidenstraße 2, Lachen, Switzerland, CH-8853
Public contact	Bruce Schwartz, Octapharma USA, Inc. , +1 (201)604-1112, bruce.schwartz@octapharma.com
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 June 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 January 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the half-life of WILATE® in terms of the ristocetin cofactor activity (VWF:RCo), the FVIII coagulant activity (FVIII:C), the VWF antigen (VWF:Ag), and collagen binding activity (VWF:CB) of WILATE® and to compare these parameters with those for Haemate® P.

Protection of trial subjects:

This trial was conducted in accordance to the principles of GCP, ensuring that the rights, safety and well-being of patients are protected and in consistency with the declaration of Helsinki. Inclusion and exclusion criteria were carefully defined in order to protect subjects from contraindications, interactions with other medication and safety factors associated with the investigational medicinal product. Throughout the study safety was assessed, such as occurrence of AEs, labvalues, vital signs and physical examinations.

Background therapy:

NA

Evidence for comparator:

Haemate® P (CSL Behring GmbH): Vials of approximately 600 IU VWF:RCo.
A dose of at least 40 IU VWF:RCo/kg body weight was given intravenously by bolus administration. One batch of Haemate® P was used (20566911G).

Haemate® P is a commercially available product. Each vial of Haemate® P had a labelled (nominal) potency of 600 IU of VWF:RCo and 250 IU FVIII:C (VWF:RCo/FVIII:C ratio of ~2.4:1) that was to be reconstituted in 5 mL water for injections.

Actual start date of recruitment	28 August 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 9
Worldwide total number of subjects	9
EEA total number of subjects	9

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)	2
Adults (18-64 years)	7
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Defined inherited VWD type 3, Male or female patients ≥ 12 years of age with a body weight ≥ 32 kg and ≤ 125 kg, Negative for Hepatitis B surface antigen (HBsAg), Any human immunodeficiency virus (HIV)-positive patients had to have a baseline CD4+ cell count of > 200/mm3, and a platelet count of > 100,000/dL, freely given informed consent.

Pre-assignment

Screening details:

Patients were randomly assigned to receive either WILATE® or Haemate® P in Period 1. After a washout period of at least 7 days, but not more than 4 weeks, patients were switched to the other study drug for Period 2. Randomisation took place before study drug administration and patient satisied all of the inclusion criteria for Period 1, Visit 2.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Period 1

Arm description:

Patients were randomly assigned to receive either WILATE® or Haemate® P in Period 1, and then switched to the other study drug for Period 2. Randomisation took place before study drug administration, i.e., when the patient satisfied all of the entry criteria required for inclusion in Period 1 Visit 2.

Arm type	Experimental
Investigational medicinal product name	VWF/FVIII containing human coagulation concentrate
Investigational medicinal product code	
Other name	Wilate(R), plasma derived VWF:FVIII concentrate
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single dose of at least 40 IU VWF:RCo/kg body weight of WILATE® (using the labelled potency) was administered intravenously by bolus administration in each study period. The dose of WILATE® selected for the study is in line with that previously used in clinical studies. A single, bolus, intravenous dose of approximately 50 IU VWF:RCo/kg body weight has been previously administered to patients with VWD (studies TMAE-105, TMAE-109 TMAE-104 and TMAE-106) and a single, intravenous, bolus dose of at least 40 IU VWF:RCo/kg body weight of WILATE® was administered in study WIL-12.

Investigational medicinal product name	VWF/FVIII containing human coagulation concentrate
Investigational medicinal product code	
Other name	Haemate(R)P
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single dose of at least 40 IU VWF:RCo/kg body weight of Haemate® P (using the labelled potency) was administered intravenously by bolus administration in each study period.

Arm title	Period 2

Arm description:

Patients were randomly assigned to receive either WILATE® or Haemate® P in Period 1, and then switched to the other study drug for Period 2. Randomisation took place before study drug administration, i.e., when the patient satisfied all of the entry criteria required for inclusion in Period 1 Visit 2.

Arm type	Experimental
Investigational medicinal product name	VWF/FVIII containing human coagulation concentrate
Investigational medicinal product code	
Other name	Wilate(R), plasma derived VWF:FVIII concentrate
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single dose of at least 40 IU VWF:RCo/kg body weight of WILATE® (using the labelled potency) was administered intravenously by bolus administration in each study period. The dose of WILATE® selected for the study is in line with that previously used in clinical studies. A single, bolus, intravenous dose of approximately 50
IU VWF:RCo/kg body weight has been previously administered to patients with VWD (studies TMAE-105, TMAE-109 TMAE-104 and TMAE-106) and a single, intravenous,
bolus dose of at least 40 IU VWF:RCo/kg body weight of WILATE® was administered in study WIL-12.

Investigational medicinal product name	VWF/FVIII containing human coagulation concentrate
Investigational medicinal product code	
Other name	Haemate(R)P
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single dose of at least 40 IU VWF:RCo/kg body weight of WILATE® or Haemate® P (using the labelled potency) was administered intravenously by bolus administration in each study period.

Number of subjects in period 1	Period 1	Period 2
Started	9	9
Completed	9	9

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	9	9	
Age categorical Units: Subjects			
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	7	7	
Gender categorical Units: Subjects			
Female	8	8	
Male	1	1	

End points

End points reporting groups

Reporting group title	Period 1

Reporting group description:

Patients were randomly assigned to receive either WILATE® or Haemate® P in Period 1, and then switched to the other study drug for Period 2. Randomisation took place before study drug administration, i.e., when the patient satisfied all of the entry criteria required for inclusion in Period 1 Visit 2.

Reporting group title	Period 2

Reporting group description:

Patients were randomly assigned to receive either WILATE® or Haemate® P in Period 1, and then switched to the other study drug for Period 2. Randomisation took place before study drug administration, i.e., when the patient satisfied all of the entry criteria required for inclusion in Period 1 Visit 2.

Subject analysis set title	PK-evaluable population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK-evaluable population consisted of all patients in the ITT/safety population who had concentration data at baseline (before the injection) and at least four post-infusion time points for both study periods. Of the 9 patients originally enrolled, 1 was excluded from the PK-evaluable set as she was suspected not to be a VWD type 3 patient.

Primary: VWF:RCo - Terminal half-lives (h) in the PK-evaluable population

End point title	VWF:RCo - Terminal half-lives (h) in the PK-evaluable population[1]

End point description:

End point type	Primary

End point timeframe:

end of the study

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: Confidence interval of VWF:RCo of t1/2 in the PK-evaluable population:

Estimated ratio of geometric means of Wilate(R) vs Haemate(R)P (%): 102.3
Two-sided 90% CI (%): 85.5 - 122.5
p-value: 0.8161

End point values	PK-evaluable population			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: T1/2 (h) of VWF:RCo (modified)				
arithmetic mean (standard deviation)				
Wilate(R)	10.5 (± 2.6)			
Haemate(R)P	10.2 (± 2.2)			

Statistical analyses

No statistical analyses for this end point

Primary: VWF:Ag - Terminal half-lives (h) in the PK-evaluable population

End point title	VWF:Ag - Terminal half-lives (h) in the PK-evaluable

End point description:

End point type	Primary

End point timeframe:

at the end of the study

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Confidence interval of VWF:RCo of t1/2 in the PK-evaluable population:

Estimated ratio of geometric means of Wilate(R) vs Haemate(R)P (%): 93.9
Two-sided 90% CI (%): 81.0 - 109.0
p-value: 0.4504

End point values	PK-evaluable population			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: t1/2 (h) of VWF:AG				
arithmetic mean (standard deviation)				
Wilate(R)	15.7 (± 3.2)			
Haemate(R)P	16.9 (± 4.6)			

Statistical analyses

No statistical analyses for this end point

Primary: VWF:CB - Terminal half-lives (h) in the PK-evaluable population

End point title	VWF:CB - Terminal half-lives (h) in the PK-evaluable

End point description:

End point type	Primary

End point timeframe:

at the end of the study

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Confidence interval of VWF:RCo of t1/2 in the PK-evaluable population:

Estimated ratio of geometric means of Wilate(R) vs Haemate(R)P (%): 102.7
Two-sided 90% CI (%): 86.1 - 122.5
p-value: 0.7813

End point values	PK-evaluable population			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: t1/2 (h) of VWF:CB				
arithmetic mean (standard deviation)				
Wilate(R)	9.6 (± 1.5)			

Haemate(R)P	9.5 (± 2.2)			

Statistical analyses

No statistical analyses for this end point

Primary: FVIII:C - Terminal half-lives (h) in the PK-evaluable population

End point title	FVIII:C - Terminal half-lives (h) in the PK-evaluable

End point description:

End point type	Primary

End point timeframe:

at the end of the study

Notes:

[4] - 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: Confidence interval of VWF:RCo of t1/2 in the PK-evaluable population:

Estimated ratio of geometric means of Wilate(R) vs Haemate(R)P (%): 101.7
Two-sided 90% CI (%): 83.5 - 124.0
p-value: 0.8712

End point values	PK-evaluable population			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: t1/2 (h) of FVIII:C (Chromogenic)				
arithmetic mean (standard deviation)				
Wilate(R)	18.9 (± 5.8)			
Haemate(R)P	19.5 (± 7.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed throughout the whole study.

Adverse event reporting additional description:

All SAEs, whether suspected to be related to study treatment or not, are reported by telephone, fax or e-mail immediately to the responsible Clinical Project Manager, study monitor, or to the responsible local CRO.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Overall Trail

Reporting group description: -

Serious adverse events	Overall Trail		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Overall Trail		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)		
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2008	Amendment 1 • Changed to a single-centre study design
03 March 2009	Amendment 2 • Addition of VWF multimer analysis • Inclusion of an additional 3 patients for a total of 9 patients • Changed to a multi-centre study design • Inclusion of the 900 IU FVIII batch size of WILATE® as an investigational product • Specification that noncompartmental PK analysis will be performed • Calculation of PK parameters using actual potency of drug
21 July 2009	Amendment 3 • Changed to a single-centre study design

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported