Clinical trial results:
International clinical study to investigate the efficacy and safety of Wiloctin in patients with inherited von willebrand disease (vWD)

Summary

EudraCT number	2006-002857-54
Trial protocol	DE
Global end of trial date	02 March 2007

Results information

Result version number	v1 (current)
This version publication date	23 November 2017
First version publication date	23 November 2017

Trial information

Trial identification

Sponsor protocol code	TMAE-104

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	Clinical Research and Develpment, Octapharma Pharmazeutika Produktionsgesellschaft mbH, 0043 1610320,
Scientific contact	Clinical Research and Develpment, Octapharma Pharmazeutika Produktionsgesellschaft mbH, 0043 1610320, clinical.department@octapharma.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	11 July 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 March 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to confirm the clinical efficacy of WILOCTIN using surrogate markers, i.e. the plasma levels of FVIII:C, vWF:Ag, vWF:CBA and vWF:RCoF before and after administration.

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 risk factors associated with the investigational medicinal product.
Throughout the study safety was assessed, such as occurrence of AEs, safety labs, assessment of viral markers, vital signs and physical examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 January 2002
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	Poland: 23
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Norway: 1
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	7
Adolescents (12-17 years)	3
Adults (18-64 years)	27
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Defined inherited VWD, types 1 to 3; aged > 6 and < 85 years; not sufficiently responding to DDAVP treatment; written informed consent freely given.

Period 1

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

Arms

Arm title	WILATE (formerly called Wiloctin)

Arm description:

Dosing of WILATE (formerly called Wiloctin) and frequency of treatment was determined according to the clinical needs of the subjects and the opinion of the treating physician. WILATE was administered intravenously. Twenty eight different WILATE batches were used during the study.

Arm type	Experimental
Investigational medicinal product name	WILATE, plasma derived VWF: FVIII concentrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

WILATE was to be injected intravenously at a speed of 2-3 mL per minute, using aseptic technique. At the end of the infusion, the injection line was to be flushed with 0.9 % sodium chloride. WILATE could also be administered by continuous infusion

Number of subjects in period 1	WILATE (formerly called Wiloctin)
Started	41
Completed	41

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	41	41	
Age categorical Units: Subjects			
Age total	41	41	
Age continuous Units: years			
arithmetic mean	36.2		
full range (min-max)	5 to 73	-	
Gender categorical Units: Subjects			
Female	23	23	
Male	18	18	

End points

End points reporting groups

Reporting group title	WILATE (formerly called Wiloctin)
Reporting group description:	
Dosing of WILATE (formerly called Wiloctin) and frequency of treatment was determined according to the clinical needs of the subjects and the opinion of the treating physician. WILATE was administered intravenously. Twenty eight different WILATE batches were used during the study.	
Subject analysis set title	VWD Type 3 PK Analysis Baseline
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
surrogate markers, i.e. plasma levels of FVIII:C, FVIII:C chromo, VWF:Ag, VWF:CB and VWF:RCo at Baseline	
Subject analysis set title	VWD Type 3 PK Analysis > 6M
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
surrogate markers, i.e. plasma levels of FVIII:C, FVIII:C chromo, VWF:Ag, VWF:CB and VWF:RCo t > 6M	
Subject analysis set title	VWD Type 3 Recovery (nominal) Analysis Baseline
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
surrogate markers, i.e. plasma levels of FVIII:C, FVIII:C chromo, VWF:Ag and VWF:RCo at Baseline	
Subject analysis set title	VWD Type 3 Recovery (nominal) Analysis >6M
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
surrogate markers, i.e. plasma levels of FVIII:C, FVIII:C chromo, VWF:Ag and VWF:RCo at Baseline	
Subject analysis set title	VWD Type 3 Recovery (actual) Analysis Baseline
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
surrogate markers, i.e. plasma levels of FVIII:C, FVIII:C chromo and VWF:RCo at Baseline	
Subject analysis set title	VWD Type 3 Recovery (actual) Analysis >6M
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
surrogate markers, i.e. plasma levels of FVIII:C, FVIII:C chromo and VWF:RCo at Baseline	

Primary: Median Half Life

End point title	Median Half Life[1]
End point description:	
surrogate markers, i.e. plasma levels of FVIII:C, FVIII:C chromo, VWF:Ag, VWF:CB and VWF:RCo at Baseline and >6M	
End point type	Primary
End point timeframe:	
Baseline and >6M.	

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: Primarily descriptive statistical methods were used to analyse the data. Statistical tests of hypotheses and confidence intervals were of explanatory nature only.

End point values	VWD Type 3 PK Analysis Baseline	VWD Type 3 PK Analysis > 6M		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6		
Units: hours				
number (not applicable)				
VWF: RCo	18.96	15.75		
VWF: Ag	9.44	9.66		
VWF:CB	12.46	13.42		
FVIII: C chromo	16.84	16.35		
FVIII:C	24.21	18.57		

Statistical analyses

No statistical analyses for this end point

Primary: Median Recovery (nominal)

End point title	Median Recovery (nominal)[2]

End point description:

surrogate markers, i.e. plasma levels of FVIII:C, FVIII:C chromo, VWF:Ag and VWF:RCo at Baseline and >6M

End point type	Primary

End point timeframe:

Baseline and >6M

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: Primarily descriptive statistical methods were used to analyse data. Statistical tests of hypotheses and confidence intervals were of explanatory nature only.

End point values	VWD Type 3 Recovery (nominal) Analysis Baseline	VWD Type 3 Recovery (nominal) Analysis >6M		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6		
Units: %/IU/kg				
number (not applicable)				
VWF: RCo	1.47	1.41		
VWF: Ag	1.35	1.63		
FVIII: C chromo	1.72	1.61		
FVIII:C	1.76	1.67		

Statistical analyses

No statistical analyses for this end point

Primary: Median Recovery (actual)

End point title	Median Recovery (actual)[3]

End point description:

surrogate markers, i.e. plasma levels of FVIII:C, FVIII:C chromo and VWF:RCo at Baseline and >6M

End point type	Primary

End point timeframe:

Baseline and >6M

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: Primarily descriptive statistical methods were used to analyse the data. Statistical tests of hypotheses and confidence intervals were of explanatory nature only.

End point values	VWD Type 3 Recovery (actual) Analysis Baseline	VWD Type 3 Recovery (actual) Analysis >6M		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6		
Units: %/IU/kg				
number (not applicable)				
VWF: RCo	1.85	1.75		
FVIII: C chromo	1.76	1.67		
FVIII:C	1.8	1.74		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: throughout the study period	
Adverse event reporting additional description: AEs were to be categorised according to intensity, duration, frequency and time of occurrence	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups	
Reporting group title	Safety Set
Reporting group description: All subjects who had received at least one treatment with WILATE	

Serious adverse events	Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 41 (29.27%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Parvovirus B19 serology positive			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Scratch			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			

subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Catheter site haemorrhage			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
multi-organ failure			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences causally related to treatment / all	0 / 30		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mouth haemorrhage			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pancreatitis acute			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Synovitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
catheter related infection			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Parotitis			
subjects affected / exposed	1 / 41 (2.44%)		
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 Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 41 (60.98%)		

Nervous system disorders Headache subjects affected / exposed occurrences (all)	 3 / 41 (7.32%) 4		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 5 / 41 (12.20%) 10		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	 3 / 41 (7.32%) 6		
Gastrointestinal disorders Gastrointestinal haemorrhage subjects affected / exposed occurrences (all)	 5 / 41 (12.20%) 30		
Infections and infestations Pharyngitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 9 / 41 (21.95%) 18 4 / 41 (9.76%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2001	Amendment I : In order to confirm the available information on the pharmacokinetic properties of Wiloctin, it has been proposed to include a pharmacokinetic evaluation of Wiloctin in some patients (e.g. before the patients have to undergo a planned surgery). Therefore, Octapharma decided to amend the study protocol, and to include a pharmacokinetic assessment in around 10 patients.
16 October 2006	Amendment VI: Due to the submission of the study in Germany, it is necessary to amend the individual duration of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported