Clinical trial results:
CLINICAL STUDY TO INVESTIGATE THE EFFICACY, SAFETY AND IMMUNOGENICITY OF WILATE IN CHILDREN < 6 YEARS OF AGE WITH INHERITED VON WILLEBRAND DISEASE

Summary

EudraCT number	2005-001426-84
Trial protocol	DE FR CZ
Global end of trial date	01 August 2009

Results information

Result version number	v1 (current)
This version publication date	05 August 2016
First version publication date	05 August 2016

Trial information

Trial identification

Sponsor protocol code	WIL-14

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 Development, Octapharma Pharmazeutika Produktionsgesellschaft mbH, +43 1610320,
Scientific contact	Clinical Research and Development, Octapharma Pharmazeutika Produktionsgesellschaft mbH, +43 1610320,

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 December 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 August 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the efficacy of Wilate for the prevention and/or treatment of bleeding episodes and in surgical procedures in children <6 years of age.

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, lab-values, viral safety testing, vital signs and physician´s and parent´s assessment of tolerability were recorded. Inhibitors against VWF and FVIII were determined prior to first treatment and after 3, 6, 9 and 12 months of study participation, as well as in suspicion of inhibitor development. Thrombogenicity markers (F1+2, D-dimers) were determined at baseline and every 3 months and in all patients undergoing surgical procedures. Viral testing was performed before the first Wilate infusion and every 3 months thereafter.

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	02 April 2006
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	Czech Republic: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Poland: 5
Worldwide total number of subjects	17
EEA total number of subjects	17

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)	7
Children (2-11 years)	10
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients with defined inherited VWD of any type who require or are suspected to require treatment with Wilate and who are well known to the respective centres were eligible for inclusion into the study. Previously treated and previously untreated patients were eligible for the study.

Period 1

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

Arms

Arm title	VWF/FVIII containing human coagulation concentrate

Arm description:

Subjects were treated according to their individual clinical situation: prophylactically, for bleeding episodes because of a minor or major surgery.

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

Dosage and administration details:

The number of administrations and the actual dose for treatment or prevention of spontaneous bleeding episodes or for treatment before, during and after surgical procedures depended on the clinical situation of the patient, e.g. the severity of the disease and the actual bleeding or the type of surgery. Single administrations, multiple doses and treatment as continuous infusion may have been appropriate. Bolus infusion: Wilate should be injected intravenously at a maximum speed of 4 mL per minute, using an aseptic technique. Continuos infusion: preparation of the product was idential to bolus infusion. The solution was then transferred into plastic bags provided by the supplier of the infusion pump.

Number of subjects in period 1	VWF/FVIII containing human coagulation concentrate
Started	17
Completed	15
Not completed	2
subjects did not require treatment	2

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	17	17	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	7	7	
Children (2-11 years)	10	10	
Gender categorical Units: Subjects			
Female	5	5	
Male	12	12	

Subject analysis sets

Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-treat (ITT) data set comprised all patients included in the study who received at least one dose of Wilate, and this population was included in the statistical evaluation. Safety population was identical to the ITT population.

Reporting group values	Intention-to-treat		
Number of subjects	15		
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	5		
Children (2-11 years)	10		
Gender categorical Units: Subjects			
Female	5		
Male	10		

End points

End points reporting groups

Reporting group title	VWF/FVIII containing human coagulation concentrate

Reporting group description:

Subjects were treated according to their individual clinical situation: prophylactically, for bleeding episodes because of a minor or major surgery.

Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-treat (ITT) data set comprised all patients included in the study who received at least one dose of Wilate, and this population was included in the statistical evaluation. Safety population was identical to the ITT population.

Primary: Amount of IMP required

End point title	Amount of IMP required[1]

End point description:

The average dose for all sites combined was investigated. In general, across all bleeding sites, more severe bleeding episodes required higher mean doses.

End point type	Primary

End point timeframe:

at the 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: The endpoint was evaluated by descriptive statistics only, including mean and standard deviation.

End point values	Intention-to-treat			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: Average dose/body weight (IU/kg)				
arithmetic mean (standard deviation)	35.87 (± 15.15)			

Statistical analyses

No statistical analyses for this end point

Primary: Overall efficacy assessment of investigators

End point title	Overall efficacy assessment of investigators[2]

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: This endpoint was evaluated by descriptive statistics only (absolute and relative frequencies).

End point values	Intention-to-treat			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: number of patients				
Excellent: haemostasis achieved	9			
Good: slight oozing and adequate control of bleed	6			
Moderate: moderate bleeding or control of bleed	0			
None: severe uncontrolled or intensity not changed	0			
Missing/NA/ND	0			

Statistical analyses

No statistical analyses for this end point

Primary: Overall efficacy assessment of patients

End point title	Overall efficacy assessment of patients[3]

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: This endpoint was evaluated by descriptive statistics only (absolute and relative frequencies).

End point values	Intention-to-treat			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: number of patients				
Excellent: haemostasis achieved	9			
Good: slight oozing and adequate control of bleed	4			
Moderate: moderate bleeding or control of bleed	0			
None: severe uncontrolled or intensity not changed	0			
Missing/NA/ND	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of bleeding episodes

End point title	Number of bleeding episodes[4]

End point description:

Estimate and Pearson-Clopper 95 % confidence interval for the frequeny of major bleeding episodes
Subjects included in ITT analysis, N=15

Incidence: 4
Total: 68
Incidence estimate (%): 5.88

two-sided CI: 1.63 - 14.38

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: Statistical information is entered in the endpoint description. The system does not allow statistical data to be entered in the statisticial analysis section for studies with 1 treatment arm.

End point values	Intention-to-treat			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: Bleeding episodes				
Others	15			
Joint	7			
Ankle	1			
Muscle	5			
Oral	15			
Epistaxis	22			
Gastrointestinal	2			
Ecchymosis	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 hours SAE reporting requirement.
Waiver from 24 hours SAE reporting: hospitalization for the treatment of a (disease-related) BE.

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.
AEs were evalutaed at each patient visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

Reporting group title	all patients exposed to treatment (ITI, safety set)

Reporting group description: -

Serious adverse events	all patients exposed to treatment (ITI, safety set)		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 15 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Accident, Head Injury			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Torticollis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Catheter Sepsis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	all patients exposed to treatment (ITI, safety set)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 15 (93.33%)		
Investigations			
Parvovirus B19 test positive			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	5		
Fibrin D dimer			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hepatic enzyme increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Prothrombin level increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			

Accident subjects affected / exposed occurrences (all) Head injury subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Vascular disorders Haemorrhage subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	4 / 15 (26.67%) 5		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Haematemesis subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 4 2 / 15 (13.33%) 3 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	6		
Bronchial obstruction			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Dermatitis allergic			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dermatitis diaper			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Torticollis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 15 (46.67%)		
occurrences (all)	10		
Acute tonsilitis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Bronchitis			

subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Pharyngitis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	5		
Catheter sepsis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Erythema infectiosum			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Varicella			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2006	Addition of an optional PK investigation and a follow-up recovery investigation in patients with severe or type 3 VWD Addition of thrombogenicity marker (F1+2, D-dimers) determination Addition of 3 new investigators and study centres from France and removal of 4 investigators and study centres from Germany
03 July 2007	Addition of a new investigator and study centre from Germany Addition of a second central laboratory and reassignment of blood coagulation and viral marker assessments between the two laboratories
05 September 2007	Addition of 2 new investigators and study centres, one from Germany and one from the Czech Republic
07 January 2008	Addition of an appendix listing participating study centres, with new centres indicated in italics Prolongation of the study duration Addition of two external CROs, one to monitor centres in France and one in the Czech Republic

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported