

**Clinical trial results:****Prospective, Open-Label, Multi-Center, Phase III Clinical Study To Investigate The Efficacy And Safety Of Human Factor VWF/VIII Concentrate (Wilate) In Subjects With Inherited Type 3 Von Willebrand Disease (VWD) Who Undergo Major Surgical Procedures.****Summary**

EudraCT number	2010-021162-30
Trial protocol	BG IT
Global end of trial date	12 March 2014

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information**Trial identification**

Sponsor protocol code	WIL-24
-----------------------	--------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01365546
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 Produktionsges.m.b.H, Oberlaaer Strasse 235, A-1100 Vienna, Austria, 0043 1610320, clinical.department@octapharma.com
Scientific contact	Clinical Research and Development, Octapharma Pharmazeutika Produktionsges.m.b.H, Oberlaaer Strasse 235, A-1100 Vienna, Austria, 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	25 July 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the overall hemostatic efficacy of Wilate in preventing excessive intra- and post-operative bleeding in pediatric and adult subjects with Type 3 VWD who require a Von Willebrand Factor (VWF) product and undergo a major surgical procedure.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles of the Declaration of Helsinki, and ICH-GCP (Note for Guidance CPMP/ICH/135/95), and national regulatory requirements ensuring that the rights, safety and well-being of patients are protected and in consistency with the 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, vital signs and physical examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 August 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	Poland: 2
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	India: 13
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Oman: 2
Worldwide total number of subjects	41
EEA total number of subjects	16

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)	3
Adults (18-64 years)	33
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Gene defect, race, family/inhibitor history, viral status, co-morbidity & concomitant medications, medical history, vital signs, body weight and height were documented, physical examination performed. In/Exclusion criteria checked. Pt should not have taken any VWF-containing product for at least 3 days prior to the screening.

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
------------------	--------

Arm description:

Wilate was administered before, during and after surgical procedures according to the patient's individual IVR, the guidelines defined in the protocol and the patient's clinical condition. For baseline IVR investigations, Wilate was administered at a dose of 60 VWF:RCo IU/kg (labeled potency).

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:

All pt received 60 IU/kg of wilate® for the in vivo recovery (IVR) investigation at study start to calculate the recommended dosing for surgeries. In addition the following guidelines were given: Major surgery: A loading dose of 40–60 VWF:RCo IU/kg within 3 h of start of procedure to achieve peak plasma VWF:RCo level of 100%. A maintenance dose of 20–40 VWF:RCo IU/kg or half of the loading dose every 12–24 h. Trough levels of VWF:RCo were to be maintained at > 50% for at least 6 days. At least 2 maintenance doses were to be administered within the first 24 h after the start of surgery. Minor surgery: A loading dose of 30–60 VWF:RCo IU/kg within 3 h of start of procedure to achieve peak plasma VWF:RCo level of 50%. A maintenance dose of 20–40 VWF:RCo IU/kg or half of the loading dose every 12–24 h. Trough levels of VWF:RCo were to be maintained at > 30% for at least 2 days. These dosing recommendations were adjusted based on baseline recovery and the individual clinical situation.

Number of subjects in period 1	Wilate
Started	41
Completed	30
Not completed	11
Consent withdrawn by subject	1
No evaluable surgery performed	9
Withdrawn due to study termination	1

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			
Adolescence	3	3	
Adults	38	38	
Age continuous Units: years			
arithmetic mean	39		
full range (min-max)	12 to 83	-	
Gender categorical Units: Subjects			
Female	29	29	
Male	12	12	

Subject analysis sets

Subject analysis set title	ITT population
----------------------------	----------------

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

Subject analysis set description:

The intention to treat (ITT) data set consists of all surgical procedures in the safety analysis data set that were performed in subjects with the underlying disease (VWD), and for which any data were collected after treatment with Wilate®.

Subject analysis set title	Safety population
----------------------------	-------------------

Subject analysis set type	Safety analysis
---------------------------	-----------------

Subject analysis set description:

The safety analysis population consists of all subjects who receive at least part of one dose of Wilate®. The safety analysis data set consists of all surgical procedures and planned surgical procedures for which the subject received at least part of one dose of Wilate®. If a subject is administered Wilate® in anticipation of a planned surgical procedure and the procedure is not performed, the patient is included in the safety analysis data set but is not counted in the sample size of the trial with respect to the primary or hemostatic endpoints.

Reporting group values	ITT population	Safety population	
Number of subjects	30	41	
Age categorical Units: Subjects			
Adolescence			
Adults			
Age continuous Units: years			
arithmetic mean	38.3	39	
full range (min-max)	12 to 74	12 to 83	

Gender categorical			
Units: Subjects			
Female	21	29	
Male	9	12	

End points

End points reporting groups

Reporting group title	Wilate
Reporting group description:	
Wilate was administered before, during and after surgical procedures according to the patient's individual IVR, the guidelines defined in the protocol and the patient's clinical condition. For baseline IVR investigations, Wilate was administered at a dose of 60 VWF:RCo IU/kg (labeled potency).	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intention to treat (ITT) data set consists of all surgical procedures in the safety analysis data set that were performed in subjects with the underlying disease (VWD), and for which any data were collected after treatment with Wilate®.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis population consists of all subjects who receive at least part of one dose of Wilate®. The safety analysis data set consists of all surgical procedures and planned surgical procedures for which the subject received at least part of one dose of Wilate®. If a subject is administered Wilate® in anticipation of a planned surgical procedure and the procedure is not performed, the patient is included in the safety analysis data set but is not counted in the sample size of the trial with respect to the primary or hemostatic endpoints.	

Primary: overall hemostatic efficacy of Wilate in surgeries.

End point title	overall hemostatic efficacy of Wilate in surgeries. ^[1]
End point description:	
The primary endpoint is the overall hemostatic efficacy of Wilate® in the treatment in VWD subjects who undergo a surgical procedure, based on both the intra-operative assessment of the surgeon and the assessment by the Investigator covering the post-surgical period from the end of the procedure to 24 hours following the last infusion, both of which use a 4-point ordinal hemostatic efficacy scales. The primary analysis focused on the overall proportion of surgical episodes declared as successful treatment (rated as per the composite assessment algorithm). An independent data monitoring committee (IDMC) conducted an independent adjudication of all hemostatic efficacy results and adjudicated the Investigator's and surgeon's assessments of the intra- and post-operative assessments ("secondary adjudication"). The primary endpoint (success or failure) was derived from the adjudicated intra- and post-operative assessments according to an agreed composite assessment algorithm.	
End point type	Primary
End point timeframe:	
post surgery, 24 hours after the last infusion	

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 proportion of surgeries with successful treatment were calculated and the following null and alternative primary hypotheses tested: H0: $p_0 < 0.6$ versus Ha: $p_0 \geq 0.6$ where p_0 represents the overall proportion of successfully treated surgical episodes. Result is documented in section END POINT of this report. This is a single arm study, so no comparison between groups was done.

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	30 ^[2]			
Units: proportion				
number (confidence interval 98.75%)	0.967 (0.784 to 1)			

Notes:

[2] - subjects in this case refers to the number of surgical procedures (30 procedures in 28 patients)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The condition of the patients was monitored throughout the study . At each (scheduled or unscheduled) study visit, AEs were documented by the investigator

Assessment type

Systematic

Dictionary used

Dictionary name

MedDRA

Dictionary version

14.0

Reporting groups

Reporting group title

All patients exposed to treatment (Safety Set)

Reporting group description: -

Serious adverse events	All patients exposed to treatment (Safety Set)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 41 (4.88%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Gastritis erosive			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal haemorrhage			
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	All patients exposed to treatment (Safety Set)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 41 (70.73%)		

Investigations Haemoglobin decreased subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 6		
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	8 / 41 (19.51%) 10		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 4		
General disorders and administration site conditions Pain subjects affected / exposed occurrences (all) pyrexia subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 4 4 / 41 (9.76%) 4		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	6 / 41 (14.63%) 7 6 / 41 (14.63%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2012	After discussion with the FDA, a protocol amendment was implemented and the study design was changed to accept all VWD types as well as minor surgeries, with the requirement that at least 10 patients would have VWD Type 3 and at least at least 20 surgeries would be major. This version was sent to FDA for comments only. It was never sent or implemented at any other participating country or site.
10 December 2012	Includes all changes of Amendment, dated 24-Sep-2012 and changes as discussed with the FDA on 19-Nov-2012 as questions arose during the course of the study from Regulatory Authorities and study centers regarding the number of subjects to be enrolled. Therefore, the text regarding the number of subjects was re-worded and clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported