Clinical trial results:
EFFICACY AND SAFETY STUDY OF WILFACTIN ADMINISTERED BY CONTINUOUS INFUSION IN PATIENTS WITH SEVERE VON WILLEBRAND DISEASE UNDERGOING MAJOR SURGICAL PROCEDURES

Summary

EudraCT number	2007-004116-32
Trial protocol	FR BE
Global end of trial date	07 March 2013

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	22 July 2015

Trial information

Trial identification

Sponsor protocol code	Protocol WIL1-0609

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	LFB Biotechnologies
Sponsor organisation address	3 Avenue des Tropiques - LES ULIS, COURTABOEUF, France, 91930
Public contact	Global Clinical Development Leader, LFB Biotechnologies, 33 169825656,
Scientific contact	Global Clinical Development Leader, LFB Biotechnologies, 33 169825656,

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	03 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 March 2013
Global end of trial reached?	Yes
Global end of trial date	07 March 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the efficacy of continuous infusion of WILFACTIN for the prevention of perioperative bleeding in subjects with severe von Willebrand Disease undergoing elective major surgery.

Protection of trial subjects:

Blood sampling usually done for laboratory testing presents a potential discomfort and the associated risks are slight pain at the site, feeling light-headed, bruising and, exceptionally, local infection as well as bleeding from the site of the puncture. However, all precautionary measures will be taken to minimizes potential side effects.
Continuous infusion, through a catheter placed in a vein in the arm, is also advantageous in that it avoids repeat injections and minimises pain and injury in the vein due to many needle punctures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 December 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	Poland: 2
Country: Number of subjects enrolled	France: 4
Worldwide total number of subjects	6
EEA total number of subjects	6

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)	5

From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, six (6) subjects have been enrolled by in 3 centers in France (Besancon, Lyon, and Rennes) and 1 center in Poland (Warsaw) between 08 December 2008 and 23 January 2013

Pre-assignment

Screening details:

During the "pre-surgical period", informed consent was to be obtained and screening procedures conducted to confirm eligibility. Screening was to be done no longer than 8 weeks prior to the surgery. Main medical and surgical history, including bleeding history was recorded.

Pre-assignment period milestones

Number of subjects started	6
Number of subjects completed	6

Period 1

Period 1 title	Preoperative pharmacokinetic study
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	WILFACTIN

Arm description: -

Arm type	Experimental
Investigational medicinal product name	WILFACTIN
Investigational medicinal product code	vWF SD-35-DH
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single dose of 60 IU VWF:RCo/kg by bolus injection.

Number of subjects in period 1	WILFACTIN
Started	6
Completed	6

Period 2

Period 2 title	Surgery by continuous infusion
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	WILFACTIN

Arm description: -

Arm type	Experimental
Investigational medicinal product name	WILFACTIN
Investigational medicinal product code	vWF SD-35-DH
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The pre-Continuous infusion period started with:
▪ An extra bolus injection of vWF SD-35-DHD 12-24 hours before surgery (on D-1) if the subject's baseline FVIII:C levels was < 0.5 IU/mL.
▪ A loading dose 2 hours before the surgery on D0 in all subjects
The Continuous Infusion (CI) period started immediately after the end of loading dose (H0) and lasted until the day of satisfactory healing of the surgical wound (Dn). This period lasted at least 6 days (144 hours) and could be longer depending on the type of surgery and its outcome.
.

Number of subjects in period 2	WILFACTIN
Started	6
Completed	6

Baseline characteristics

Reporting groups

Reporting group title	Preoperative pharmacokinetic study

Reporting group description: -

Reporting group values	Preoperative pharmacokinetic study	Total	
Number of subjects	6	6	
Age categorical Units: Subjects			
Adults (18-75 years)	6	6	
Age continuous Units: years			
median	49.5		
full range (min-max)	32 to 75	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	3	3	

Subject analysis sets

Subject analysis set title	TTS (Total Treated Set)
Subject analysis set type	Full analysis

Subject analysis set description:

All patients included in the study analysed in the TTS

Reporting group values	TTS (Total Treated Set)		
Number of subjects	6		
Age categorical Units: Subjects			
Adults (18-75 years)	6		
Age continuous Units: years			
median	49.5		
full range (min-max)	32 to 75		
Gender categorical Units: Subjects			
Female	3		
Male	3		

End points

End points reporting groups

Reporting group title	WILFACTIN
Reporting group description: -	
Reporting group title	WILFACTIN
Reporting group description: -	
Subject analysis set title	TTS (Total Treated Set)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients included in the study analysed in the TTS	

Primary: Overall hemostatic efficacy assessment

End point title	Overall hemostatic efficacy assessment[1]
End point description:	
End point type	Primary
End point timeframe:	
The primary endpoint was the overall hemostatic efficacy assessment by the investigator after 6 days (6 × 24 hours = 144 hours) of CI (at D7) using a 4-point scale.	
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: Descriptive analysis	

End point values	TTS (Total Treated Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: 4-point scale				
Excellent	100			
Good	0			
Moderate	0			
None	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Clinical safety was assessed throughout the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Total Treated Set

Reporting group description: -

Serious adverse events	Total Treated Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Pseudomonal sepsis	Additional description: Pseudomonas sepsis with abdominal entrance 6 days following orthopaedic surgery. The AE resolved without sequelae.		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection	Additional description: Fortuitis discovery of infection (staphylococcus epidermidis) on the defectice knee prosthesis (device) to be removed for re-alloplasty. The AE resolved without sequelae.		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Total Treated Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Investigations			
Blood pressure increased	Additional description: 1 blood pressure increased assessed as not related to the study drug 1 blood pressure increased assessed as possibly related to the study drug		

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Transaminases increased	Additional description: Not related to the study drug		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Anaemia postoperative	Additional description: Not related to the study drug		
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	3		
Vascular disorders			
Haematoma	Additional description: Not related to the study drug		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nervous system disorders			
Sciatica	Additional description: Not related to te study drug		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Infusion site reaction	Additional description: Probable relationship with the study drug		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Venipuncture site inflammation	Additional description: Possibly related to the study drug		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Vessel puncture site haematoma	Additional description: Not related to the study drug		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea	Additional description: Not related to the study drug		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Dyspepsia	Additional description: Not related to the study drug		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Psychiatric disorders			

Insomnia	Additional description: Not related to the study drug		
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2011	-To extend the study duration, -To modulate the use of the corrective factor at initiation of continuous infusion (dose for safety margin), as newly describe in the European "Guideline on the clinical investigation of recombinant and human plasma-derived-factor VIII products", EMEA/CHMP/BPWP/144533/2009 (23 July 2009) -To specify change of Director of Medical and Development Director. -To updated the French Patient information and Consent Form sheets by providing the latest information of French regulation regarding the reference methodology for personal data processing in biomedical clinical studies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported