



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 minimize 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 full range (min-max) | 49.5 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 full range (min-max) | 49.5 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 defective 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 subjects affected / exposed occurrences (all) | Additional description: Not related to the study drug | | |
| | 2 / 6 (33.33%) | | |
| | 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|--|
| 19 May 2011 | <ul style="list-style-type: none">-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