



Clinical trial results:

A RANDOMISED, MULTICENTRE, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY ON THE EFFICACY AND SAFETY OF A THERAPEUTIC STRATEGY OF POST PARTUM HAEMORRHAGE COMPARING EARLY ADMINISTRATION OF HUMAN FIBRINOGEN VERSUS PLACEBO IN PATIENTS TREATED WITH INTRAVENOUS PROSTAGLANDINS FOLLOWING VAGINAL DELIVERY.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-002484-26 |
| Trial protocol | FR |
| Global end of trial date | 06 August 2018 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 18 June 2020 |
| First version publication date | 18 June 2020 |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | FIDEL |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02155725 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | LFB Biomédicaments |
| Sponsor organisation address | 3, Avenue des tropiques, LES ULIS, France, 91940 |
| Public contact | Medical Director france, LFB Biomédicaments, 33 169827229, zitounis@lfb.fr |
| Scientific contact | Medical Director france, LFB Biomédicaments, 33 169827229, zitounis@lfb.fr |

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 | 20 May 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 06 August 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 August 2018 |
| 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 assess the benefits of a therapeutic strategy that associates an early administration of human fibrinogen concentrate in the management of PPH on the reduction of bleeding after the initiation of prostaglandins intravenous infusion.

Protection of trial subjects:

This study was conducted in compliance with good clinical practice (GCP) as described in the International Conference on Harmonisation (ICH) document "Guidance for Industry-E6 Good Clinical Practice: Consolidated Guidance". These practices were consistent with the principles stated in the Declaration of Helsinki. All other applicable regulations were followed.

Due to the context of emergency, consent was obtained after a concise information from the patient or a member of her family or a reliable person, depending on the patient's level of consciousness. In all cases, as soon as the patient regained competence, she received full information about the study and a post-inclusion consent to continue the study was requested.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 10 April 2014 |
| 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 | France: 448 |
| Worldwide total number of subjects | 448 |
| EEA total number of subjects | 448 |

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) | 448 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Between 10 April 2014 and 20 June 2018, 448 patients from 30 sites signed an informed consent.

Pre-assignment

Screening details: -

Pre-assignment period milestones

| | |
|------------------------------|-----|
| Number of subjects started | 448 |
| Number of subjects completed | 437 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|-------------------------------------|
| Reason: Number of subjects | treated with another IMP: 1 |
| Reason: Number of subjects | not treated: 5 |
| Reason: Number of subjects | no emergency consent signed: 2 |
| Reason: Number of subjects | no post inclusion consent signed: 1 |
| Reason: Number of subjects | refused to continue the study: 2 |

Period 1

| | |
|------------------------------|--|
| Period 1 title | Treatment period |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|----------------|
| Arm title | Clotfact group |
|------------------|----------------|

Arm description: -

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Clotfact |
| Investigational medicinal product code | |
| Other name | Fibrinogen concentrate |
| Pharmaceutical forms | Powder and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Fibrinogen: 3g; 2 vials of 1.5g/100 mL, each vial of powder will be reconstituted with 100 mL of sterile water for injection.

Route of administration: IV administration with a flow rate \leq 20 mL/min

| | |
|------------------|---------------|
| Arm title | Placebo group |
|------------------|---------------|

Arm description: -

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo: 2 vials of 100 mL, each vial of powder will be reconstituted with 100 mL of sterile water for injection.

Route of administration: IV administration with a flow rate ≤ 20 mL/min

| Number of subjects in period 1^[1] | Clotfact group | Placebo group |
|---|----------------|---------------|
| Started | 224 | 213 |
| Completed | 224 | 213 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 448 patients from 30 sites signed an informed consent but only 437 patients included after the pre-assignment period.

Period 2

| | |
|------------------------------|--|
| Period 2 title | Follow-up period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst |

Blinding implementation details:

During this follow-up period, no new randomisation for the patients, but the blind is maintained.

Arms

| | |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Clotfact group |

Arm description: -

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Clotfact |
| Investigational medicinal product code | |
| Other name | Fibrinogen concentrate |
| Pharmaceutical forms | Powder and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

No injection during this period.

| | |
|--|--|
| Arm title | Placebo group |
| Arm description: - | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for infusion |
| Routes of administration | Intravenous use |

No injection during this period

| Number of subjects in period 2 | Clottafact group | Placebo group |
|---------------------------------------|------------------|---------------|
| Started | 224 | 213 |
| Completed | 207 | 202 |
| Not completed | 17 | 11 |
| Patient refusal to continue | 3 | - |
| Consent withdrawn by subject | - | 5 |
| Last visit not done | 10 | 4 |
| Protocol deviation | 4 | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Clottafact group |
|-----------------------|------------------|

| |
|--------------------------------|
| Reporting group description: - |
|--------------------------------|

| | |
|-----------------------|---------------|
| Reporting group title | Placebo group |
|-----------------------|---------------|

| |
|--------------------------------|
| Reporting group description: - |
|--------------------------------|

| Reporting group values | Clottafact group | Placebo group | Total |
|------------------------|------------------|---------------|-------|
| Number of subjects | 224 | 213 | 437 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 224 | 213 | 437 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 30.5 | 30.3 | |
| standard deviation | ± 5.6 | ± 5.4 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 224 | 213 | 437 |
| Male | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | Clotfact group |
| Reporting group description: - | |
| Reporting group title | Placebo group |
| Reporting group description: - | |
| Reporting group title | Clotfact group |
| Reporting group description: - | |
| Reporting group title | Placebo group |
| Reporting group description: - | |
| Subject analysis set title | PP Set Clotfact |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Patients with no missing data for the primary criterion. | |
| Subject analysis set title | PP Set Placebo |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Patients with no missing data for the primary criterion. | |
| Subject analysis set title | ITT Set Clotfact |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All patients treated with Clotfact. | |
| Subject analysis set title | ITT Set Placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All patients treated with Placebo. | |
| Subject analysis set title | FAS Set Clotfact |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Patients treated with Clotfact of the ITT Set with no missing data for the primary criteria. | |
| Subject analysis set title | FAS Set Placebo |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Patients treated with Placebo of the ITT Set with no missing data for the primary criteria. | |

Primary: Failure rate of PPH management

| | |
|--|--------------------------------|
| End point title | Failure rate of PPH management |
| End point description: The primary efficacy variable is a binary (Failure versus Success) composite endpoint. Failure is defined when a patient: - loses at least 4 g/dL of Hb compared to the reference Hb level , AND/OR - requires the transfusion of at least 2 units of packed RBCs. | |
| End point type | Primary |
| End point timeframe: Evaluation of the two criteria that form the primary endpoint within the 48 h following the administration of IMP. | |

| End point values | PP Set Clotfact | PP Set Placebo | FAS Set Clotfact | FAS Set Placebo |
|--|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 195 ^[1] | 193 ^[2] | 220 ^[3] | 210 ^[4] |
| Units: number of patients with failure | 75 | 80 | 88 | 89 |

Notes:

[1] - 38,5 % of patients in failure

[2] - 41,5 % of patients in failure

[3] - 40,0 % of patients in failure

[4] - 42,4 % of patients in failure

Statistical analyses

| Statistical analysis title | Failure rate |
|-----------------------------------|--------------|
|-----------------------------------|--------------|

Statistical analysis description:

Logistic regression adjusting for baseline fibrinogen level and centre.

| | |
|---|------------------------------------|
| Comparison groups | FAS Set Clotfact v FAS Set Placebo |
| Number of subjects included in analysis | 430 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9563 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.9889 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6633 |
| upper limit | 1.4744 |

Secondary: Patients with at least administration of 2 units of RBCs

| | |
|--|--|
| End point title | Patients with at least administration of 2 units of RBCs |
| End point description: | |
| Considering failure as the fact of requiring at least 2 units of RBCs. | |
| End point type | Secondary |
| End point timeframe: | |
| from H0 to Day 2 | |

| End point values | FAS Set Clotfact | FAS Set Placebo | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 220 ^[5] | 210 ^[6] | | |
| Units: number of patients | 51 | 52 | | |

Notes:

[5] - 23,4 % of patients with administration of at least 2 RBCs.

[6] - 25,0 % of patients with administration of at least 2 RBCs.

Statistical analyses

| Statistical analysis title | Failure on the administration of RBCs |
|--|---------------------------------------|
| Statistical analysis description: | |
| Failure on individual component of the primary endpoint defined as administration of 2 units of RBCs | |
| Comparison groups | FAS Set Clotfact v FAS Set Placebo |
| Number of subjects included in analysis | 430 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9786 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.0064 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6321 |
| upper limit | 1.6022 |

Secondary: Patients with lost of at least 4 g/dL of Hb

| End point title | Patients with lost of at least 4 g/dL of Hb |
|---|---|
| End point description: | |
| Considering failure as the fact of having lost at least 4 g/dL of Hb. | |
| End point type | Secondary |
| End point timeframe: | |
| From reference value to Day 2 | |

| End point values | FAS Set Clotfact | FAS Set Placebo | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 220 ^[7] | 210 ^[8] | | |
| Units: number of patients | 42 | 41 | | |

Notes:

[7] - 19,1 % of patients with lost of at least 4 g/dL of Hb.

[8] - 19,5 % of patients with lost of at least 4 g/dL of Hb.

Statistical analyses

| | |
|--|------------------------------------|
| Statistical analysis title | Failure on the loss of Hb |
| Statistical analysis description: | |
| Failure on individual component of the primary endpoint defined as a loss of at least 4 g/dL of Hb | |
| Comparison groups | FAS Set Clotfact v FAS Set Placebo |
| Number of subjects included in analysis | 430 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9474 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.0169 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6177 |
| upper limit | 1.6741 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events are reported from the inclusion to the end of the study.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Clotfact group |
|-----------------------|----------------|

Reporting group description: -

| | |
|-----------------------|---------------|
| Reporting group title | Placebo group |
|-----------------------|---------------|

Reporting group description: -

| Serious adverse events | Clotfact group | Placebo group | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 10 / 224 (4.46%) | 10 / 213 (4.69%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood pressure ambulatory increased | | | |
| subjects affected / exposed | 1 / 224 (0.45%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood uric acid increased | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aneurysm | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 224 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood pressure inadequately controlled | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 1 / 224 (0.45%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 224 (0.45%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| HELLP syndrome | | | |
| subjects affected / exposed | 1 / 224 (0.45%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Postpartum haemorrhage | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retained placenta or membranes | | | |
| subjects affected / exposed | 1 / 224 (0.45%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Discomfort | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 224 (0.45%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Broad ligament haematoma | | | |
| subjects affected / exposed | 1 / 224 (0.45%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metrorrhagia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 224 (0.45%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine haematoma | | | |
| subjects affected / exposed | 1 / 224 (0.45%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine necrosis | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine rupture | | | |
| subjects affected / exposed | 1 / 224 (0.45%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Acute fatty liver of pregnancy | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 224 (0.45%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Psychological trauma | | | |
| subjects affected / exposed | 1 / 224 (0.45%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Amniotic cavity infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 224 (0.45%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometritis decidual | | | |
| subjects affected / exposed | 1 / 224 (0.45%) | 1 / 213 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 224 (0.45%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 224 (0.45%) | 0 / 213 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Clotfact group | Placebo group | |
|---|-------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 95 / 224 (42.41%) | 106 / 213 (49.77%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 224 (1.34%) | 6 / 213 (2.82%) | |
| occurrences (all) | 3 | 6 | |
| Hypotension | | | |
| subjects affected / exposed | 5 / 224 (2.23%) | 4 / 213 (1.88%) | |
| occurrences (all) | 5 | 4 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 224 (0.89%) | 3 / 213 (1.41%) | |
| occurrences (all) | 3 | 3 | |
| Headache | | | |

| | | | |
|---|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 5 / 224 (2.23%) 6 | 7 / 213 (3.29%) 8 | |
| General disorders and administration site conditions | | | |
| Hyperthermia | | | |
| subjects affected / exposed | 2 / 224 (0.89%) | 5 / 213 (2.35%) | |
| occurrences (all) | 2 | 5 | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 3 / 213 (1.41%) | |
| occurrences (all) | 0 | 3 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 4 / 224 (1.79%) | 6 / 213 (2.82%) | |
| occurrences (all) | 4 | 6 | |
| Pyrexia | | | |
| subjects affected / exposed | 11 / 224 (4.91%) | 12 / 213 (5.63%) | |
| occurrences (all) | 11 | 12 | |
| Malaise | | | |
| subjects affected / exposed | 2 / 224 (0.89%) | 4 / 213 (1.88%) | |
| occurrences (all) | 2 | 4 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 224 (1.79%) | 1 / 213 (0.47%) | |
| occurrences (all) | 4 | 1 | |
| Constipation | | | |
| subjects affected / exposed | 9 / 224 (4.02%) | 4 / 213 (1.88%) | |
| occurrences (all) | 9 | 4 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 21 / 224 (9.38%) | 29 / 213 (13.62%) | |
| occurrences (all) | 21 | 29 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 4 / 213 (1.88%) | |
| occurrences (all) | 0 | 4 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 224 (0.45%) | 4 / 213 (1.88%) | |
| occurrences (all) | 1 | 4 | |
| Reproductive system and breast disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Metrorrhagia | | | |
| subjects affected / exposed | 6 / 224 (2.68%) | 3 / 213 (1.41%) | |
| occurrences (all) | 6 | 3 | |
| Nipple disorder | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 4 / 213 (1.88%) | |
| occurrences (all) | 0 | 4 | |
| Oedema genital | | | |
| subjects affected / exposed | 2 / 224 (0.89%) | 5 / 213 (2.35%) | |
| occurrences (all) | 2 | 5 | |
| Uterine pain | | | |
| subjects affected / exposed | 4 / 224 (1.79%) | 0 / 213 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Vulval oedema | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 4 / 213 (1.88%) | |
| occurrences (all) | 0 | 4 | |
| Hepatobiliary disorders | | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 3 / 224 (1.34%) | 0 / 213 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 3 / 224 (1.34%) | 1 / 213 (0.47%) | |
| occurrences (all) | 3 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 224 (1.34%) | 4 / 213 (1.88%) | |
| occurrences (all) | 3 | 4 | |
| Infections and infestations | | | |
| Endometritis decidual | | | |
| subjects affected / exposed | 4 / 224 (1.79%) | 5 / 213 (2.35%) | |
| occurrences (all) | 4 | 5 | |
| Puerperal pyrexia | | | |
| subjects affected / exposed | 7 / 224 (3.13%) | 4 / 213 (1.88%) | |
| occurrences (all) | 7 | 4 | |
| Urinary tract infection | | | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 224 (1.79%) | 0 / 213 (0.00%) | |
| occurrences (all) | 4 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 10 February 2015 | In a purpose to facilitate the emergency procedure, the information sheet and the informed consent have been simplified in terms of both content and form, without modifying the meaning and the purpose of the provided information. |
| 21 December 2017 | The purpose of this amendment was to update the patient information leaflet (emergency and post-inclusion) according to the new version of the Clottafact SPC . |
| 29 March 2018 | The purpose of this amendment is to update the patient information leaflet (emergency and post-inclusion) according to the new version of the Clottafact SPC. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|--|---------------|
| 01 February 2018 | Interruption of inclusions due to IMP shortage | 19 March 2018 |

Notes:

Limitations and caveats

None reported