



Clinical trial results: Evaluation of postoperative administration of tranexamic acid on reducing blood loss after hip prosthesis surgery.

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2013-000791-15 |
| Trial protocol | FR |
| Global end of trial date | 27 January 2016 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 05 September 2019 |
| First version publication date | 05 September 2019 |
| Summary attachment (see zip file) | PORTO_Anesthesiology (PORTO_Anesthesiology.pdf) |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | 1308015 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02252497 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | CHU SAINT-ETIENNE |
| Sponsor organisation address | Boulevard Pasteur, LILLE, France, |
| Public contact | FORT, CHU de Saint-Etienne, 33 0477828374, j.noel.fort@chu-st-etienne.fr |
| Scientific contact | FORT, CHU de Saint-Etienne, 33 0477828374, j.noel.fort@chu-st-etienne.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 | 19 August 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 January 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 January 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective is to compare the blood loss during a hip replacement surgery and during the next 4 days, between 2 groups. First group will receive 1g of tranexamic acid (Exacyl) before the surgery. Second group will receive 1g of tranexamic acid (Exacyl) before the surgery, and 1g in a 8h-perfusion during the surgery.

Protection of trial subjects:

The safety of both groups will be assessed by comparing the number of expected and unexpected serious adverse events that occur in each of the two groups.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 01 September 2013 |
| 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: 168 |
| Worldwide total number of subjects | 168 |
| EEA total number of subjects | 168 |

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) | 75 |
| From 65 to 84 years | 81 |
| 85 years and over | 12 |

Subject disposition

Recruitment

Recruitment details:

Subjects were only recruited in France, at chu St-Etienne between April 2014 and December 2015

Pre-assignment

Screening details:

No screenig in this study

Period 1

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

Blinding implementation details:

The study was conducted in double-blind:

- the syringes was prepared by another service
- tranexamic acid and NaCl were indistinguishable

As a result, neither investigators nor patients were aware of the treatment administered. In addition, the dosages of tranexamic acid concentrations were performed blindly in the randomization group.

Arms

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

Arm description:

Patients received 1g of tranexamic acid (Exacyl) before the surgery then 1g of tranexamic acid for 8 hours.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tranexamic acid |
| Investigational medicinal product code | |
| Other name | Exacyl |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Intravenous infusion of 1g of tranexamic acid for 8 hours.

| | |
|------------------|---------------|
| Arm title | Control group |
|------------------|---------------|

Arm description:

Patients received 1g of tranexamic acid (Exacyl) before the surgery then physiological serum (NACL) for 8 hours.

| | |
|--|-----------------------|
| Arm type | Placebo |
| Investigational medicinal product name | NACL |
| Investigational medicinal product code | |
| Other name | Physiological serum |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Intravenous infusion of physiological serum (NACL) for 8 hours.

| Number of subjects in period 1 | Exacyl group | Control group |
|---------------------------------------|--------------|---------------|
| Started | 84 | 84 |
| Completed | 84 | 83 |
| Not completed | 0 | 1 |
| Consent withdrawn by subject | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--|---------------|
| Reporting group title | Exacyl group |
| Reporting group description: Patients received 1g of tranexamic acid (Exacyl) before the surgery then 1g of tranexamic acid for 8 hours. | |
| Reporting group title | Control group |
| Reporting group description: Patients received 1g of tranexamic acid (Exacyl) before the surgery then physiological serum (NACL) for 8 hours. | |

| Reporting group values | Exacyl group | Control group | Total |
|--|--------------|---------------|-------|
| Number of subjects | 84 | 84 | 168 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Adults | 84 | 83 | 167 |
| Not recorded | 0 | 1 | 1 |
| Age continuous | | | |
| Units: years | | | |
| median | 65.5 | 68.2 | |
| inter-quartile range (Q1-Q3) | 58.7 to 73.0 | 56.8 to 78.4 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 47 | 39 | 86 |
| Male | 37 | 44 | 81 |
| Not recorded | 0 | 1 | 1 |

Subject analysis sets

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

Subject analysis set description:

The statistical analysis was done using SAS-Windows software® version 9.4 installed on PC. The graphical representations were made using the R version 3.2.1 software.

No interim analysis was performed. The protocol provided for a safety analysis for half of the patients included to assess by a monitoring committee the frequency of expected and unexpected SAE occurring in each treatment group. After the inclusion of 80 patients, only 3 SAE were registered that did not require a supervisory committee meeting.

The final analysis was performed on the 167 patients included in the study, with 1 patient withdrawing consent on the day of surgery, according to the principle of intention-to-treat (ITT).

| Reporting group values | Final analysis | | |
|---|----------------|--|--|
| Number of subjects | 167 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 75 | | |
| From 65-84 years | 81 | | |
| 85 years and over | 11 | | |
| Adults | 167 | | |
| Not recorded | 1 | | |
| Age continuous | | | |
| Units: years | | | |
| median | 66.2 | | |
| inter-quartile range (Q1-Q3) | 58.0 to 75.6 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 86 | | |
| Male | 81 | | |
| Not recorded | 1 | | |

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | Exacyl group |
| Reporting group description: Patients received 1g of tranexamic acid (Exacyl) before the surgery then 1g of tranexamic acid for 8 hours. | |
| Reporting group title | Control group |
| Reporting group description: Patients received 1g of tranexamic acid (Exacyl) before the surgery then physiological serum (NACL) for 8 hours. | |
| Subject analysis set title | Final analysis |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The statistical analysis was done using sAS-Windows software® version 9.4 installed on PC. The graphical representations were made using the R version 3.2.1 software. No interim analysis was performed. The protocol provided for a safety analysis for half of the patients included to assess by a monitoring committee the frequency of expected and unexpected SAE occurring in each treatment group. After the inclusion of 80 patients, only 3 SAE were registered that did not require a supervisory committee meeting. The final analysis was performed on the 167 patients included in the study, with 1 patient withdrawing consent on the day of surgery, according to the principle of intention-to-treat (ITT). | |

Primary: Calculated volume of blood loss since the start of the intervention at Day 4 (in ml)

| | |
|---|--|
| End point title | Calculated volume of blood loss since the start of the intervention at Day 4 (in ml) |
| End point description: | |
| End point type | Primary |
| End point timeframe: The primary endpoint is the calculated blood loss between the beginning of the surgery (day 1) and day 4. | |

| End point values | Exacyl group | Control group | Final analysis | |
|--------------------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 84 | 83 | 167 | |
| Units: millilitre(s) | | | | |
| arithmetic mean (standard deviation) | 918.6 (± 337.8) | 888.4 (± 366.4) | 903.6 (± 351.6) | |

Statistical analyses

| | |
|---|------------------|
| Statistical analysis title | Primary Endpoint |
| Statistical analysis description: A description of the included population was conducted using the following statistical methods: - Quantitative data: number of data available, average, standard deviation, median, 1st and 3rd quartiles (Q1 and Q3), minimum and maximum. - Qualitative data: absolute and relative frequencies (expressed in %). The comparability of the two treatment groups to inclusion was verified on demographics and initial | |

characteristics.

| | |
|---|--------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.58 |
| Method | Student test |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 30.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -76.7 |
| upper limit | 137.2 |

Notes:

[1] - No statistical tests were conducted, with differences to be evaluated in clinical terms. In order to compare the two treatment groups on perioperative blood loss, total blood loss volumes were calculated. They were compared by a Student t test or in the case of a non-normal distribution variable, by a rank test. Normality was pre-verified by a Shapiro-Wilk test. The difference in averages was also presented with its 95% confidence interval (IC 95%).

Secondary: The blood loss during the surgery

| | |
|--|-----------------------------------|
| End point title | The blood loss during the surgery |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Hemoglobin at the beginning of the surgery D1, at the end of the surgery D1. | |

| End point values | Exacyl group | Control group | Final analysis | |
|--------------------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 84 | 83 | 167 | |
| Units: millilitre(s) | | | | |
| arithmetic mean (standard deviation) | 166.6 (± 206.0) | 165.4 (± 222.8) | 166.0 (± 213.9) | |

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | The blood loss during the surgery |
| Statistical analysis description: | |
| The blood loss since the beginning of the surgery until the end of the surgery. | |
| With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated. | |
| Comparison groups | Exacyl group v Control group |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | = 0.97 |
| Method | Student test |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -64 |
| upper limit | 66.2 |

Notes:

[2] - For the determination of risk factors for blood loss, a multivariate linear regression was performed. Initially, univariate analyses adjusted to the treatment group were implemented on each of these factors: for quantitative factors, which were continuously tested, univariate analyses by linear regression were qualitative factors, univariate analyses of variance have been implemented.

Secondary: The postoperative blood loss, between the end of the surgery and the day after

| | |
|---|--|
| End point title | The postoperative blood loss, between the end of the surgery and the day after |
| End point description: | |
| The postoperative blood loss, between the end of the surgery and the day after. | |
| End point type | Secondary |
| End point timeframe: | |
| Since the end of surgery until 24 hours later. | |

| End point values | Exacyl group | Control group | Final analysis | |
|---------------------------------------|------------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 84 | 83 | 167 | |
| Units: millilitre(s) | | | | |
| median (inter-quartile range (Q1-Q3)) | 288.7 (111.5 to 436.9) | 236.4 (38.4 to 386.9) | 265.3 (73.6 to 422.0) | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | The postoperative blood loss until 24 hours |
| Statistical analysis description: | |
| The blood loss between the end of the surgery and 24 hours later. | |
| Comparison groups | Exacyl group v Control group |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | = 0.4 |
| Method | Logrank |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -61.8 |
| upper limit | 113.7 |

Notes:

[3] - With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

Secondary: Blood loss from the end of surgery to Day 4

| | |
|---|---|
| End point title | Blood loss from the end of surgery to Day 4 |
| End point description: | |
| The postoperative blood loss, between the end of the surgery (day 1) and day 4. | |
| End point type | Secondary |
| End point timeframe: | |
| Between the end of the surgery (day 1) and day 4. | |

| End point values | Exacyl group | Control group | Final analysis | |
|---------------------------------------|------------------------|------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 84 | 83 | 167 | |
| Units: millilitre(s) | | | | |
| median (inter-quartile range (Q1-Q3)) | 480.9 (221.1 to 687.7) | 398.0 (137.9 to 634.8) | 418.2 (174.4 to 683.7) | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Blood loss from the end of surgery to Day 4 |
| Statistical analysis description: | |
| With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated | |
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[4] |
| P-value | = 0.53 |
| Method | Logrank |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.6 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -128.2 |
| upper limit | 133.4 |

Notes:

[4] - No comment.

Secondary: Hemoglobin since the beginning of the intervention until Day 4

| | |
|---|--|
| End point title | Hemoglobin since the beginning of the intervention until Day 4 |
| End point description: Hemoglobin since the beginning of the intervention until Day 4 | |
| End point type | Secondary |
| End point timeframe: hemoglobin at the beginning of the surgery D1, at the end of the surgery D1, at the day after the surgery (D2) and at D4. | |

| End point values | Exacyl group | Control group | Final analysis | |
|--|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 84 | 83 | 167 | |
| Units: g/dl | | | | |
| arithmetic mean (standard deviation) | | | | |
| pre-operative hemoglobin | 14.2 (± 1.5) | 14.2 (± 1.5) | 14.2 (± 1.5) | |
| Hemoglobin at the beginning of the surgery | 13.1 (± 1.4) | 13.2 (± 1.4) | 13.1 (± 1.4) | |
| Hemoglobin at the end of the surgery | 12.6 (± 1.5) | 12.7 (± 1.4) | 12.7 (± 1.5) | |
| Hemoglobin at Day 1 | 11.9 (± 1.5) | 12.1 (± 1.2) | 12.0 (± 1.4) | |
| "Corrected" hemoglobin at Day 1 | 11.9 (± 1.5) | 12.1 (± 1.3) | 12.0 (± 1.4) | |
| Hemoglobin at Day 4 | 11.4 (± 1.4) | 11.5 (± 1.3) | 11.5 (± 1.3) | |
| "Corrected" hemoglobin at Day 4 | 11.4 (± 1.5) | 11.5 (± 1.3) | 11.4 (± 1.4) | |
| loss of hemoglobin at D4 compared to pre-operative | 2.8 (± 1.0) | 2.7 (± 1.1) | 2.8 (± 1.1) | |

Statistical analyses

| | |
|--|------------------------------|
| Statistical analysis title | Pre-operative hemoglobin |
| Statistical analysis description: With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated. | |
| Comparison groups | Exacyl group v Control group |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | = 0.88 |
| Method | Student test |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.45 |
| upper limit | 0.45 |

Notes:

[5] - No comment.

| | |
|-----------------------------------|--|
| Statistical analysis title | Hemoglobin at the beginning of the surgery |
|-----------------------------------|--|

Statistical analysis description:

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|--------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.32 |
| Method | Student test |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.49 |
| upper limit | 0.35 |

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | Hemoglobin at the end of the surgery |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|--------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[6] |
| P-value | = 0.58 |
| Method | Student test |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.07 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.52 |
| upper limit | 0.37 |

Notes:

[6] - No comment.

| | |
|-----------------------------------|---------------------|
| Statistical analysis title | Hemoglobin at Day 1 |
|-----------------------------------|---------------------|

Statistical analysis description:

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|--------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[7] |
| P-value | = 0.15 |
| Method | Student test |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.2 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.62 |
| upper limit | 0.22 |

Notes:

[7] - No comment.

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | "Corrected" hemoglobin at Day 1 |
|-----------------------------------|---------------------------------|

Statistical analysis description:

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|--------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[8] |
| P-value | = 0.38 |
| Method | Student test |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.19 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.61 |
| upper limit | 0.24 |

Notes:

[8] - No comment.

| | |
|-----------------------------------|---------------------|
| Statistical analysis title | Hemoglobin at Day 4 |
|-----------------------------------|---------------------|

Statistical analysis description:

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|--------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[9] |
| P-value | = 0.23 |
| Method | Student test |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.54 |
| upper limit | 0.28 |

Notes:

[9] - No comment.

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | "Corrected" hemoglobin at Day 4 |
|-----------------------------------|---------------------------------|

Statistical analysis description:

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|--------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[10] |
| P-value | = 0.54 |
| Method | Student test |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.55 |
| upper limit | 0.29 |

Notes:

[10] - No comment.

| | |
|-----------------------------------|--|
| Statistical analysis title | Loss of hemoglobin at D4 compared to pre-operative |
|-----------------------------------|--|

Statistical analysis description:

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|-------------------|------------------------------|
| Comparison groups | Exacyl group v Control group |
|-------------------|------------------------------|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[11] |
| P-value | = 0.44 |
| Method | Student test |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.2 |
| upper limit | 0.45 |

Notes:

[11] - No comment.

Secondary: Transfusion between the beginning of the surgery and day 4

| | |
|------------------------|---|
| End point title | Transfusion between the beginning of the surgery and day 4 |
| End point description: | Transfusion between the beginning of the surgery and day 4. |
| End point type | Secondary |
| End point timeframe: | Between the beginning of the surgery and day 4. |

| End point values | Exacyl group | Control group | Final analysis | |
|--|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 84 | 83 | 167 | |
| Units: Number | | | | |
| Since the beginning of the surgery until day 4 | 1 | 1 | 2 | |
| Beginning of the surgery until - end of study | 3 | 3 | 6 | |
| During the surgery | 0 | 0 | 0 | |
| Since the recovery room until 24 hours | 0 | 1 | 1 | |
| Since 24 hours until Day 4 | 1 | 0 | 1 | |
| Since Day 4 until the exit from the hospital | 1 | 1 | 2 | |
| Exit from the hospital until- End of the follow-up | 1 | 2 | 3 | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Since the beginning of the surgery an day 4 |
| Statistical analysis description: | At least one transfusion since the beginnig of the surgery and post-operative day 4. |

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using

Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[12] |
| P-value | = 1 |
| Method | Chi-squared |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.06 |
| upper limit | 15.5 |

Notes:

[12] - No comment.

| | |
|-----------------------------------|---|
| Statistical analysis title | Beginning of the surgery until - end of study |
|-----------------------------------|---|

Statistical analysis description:

At least one transfusion since the beginning of the surgery until the end of the study.

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[13] |
| P-value | = 1 |
| Method | Chi-squared |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.21 |
| upper limit | 4.76 |

Notes:

[13] - No comment.

| | |
|-----------------------------------|--------------------|
| Statistical analysis title | During the surgery |
|-----------------------------------|--------------------|

Statistical analysis description:

Transfusion during the surgery.

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated

| | |
|-------------------|------------------------------|
| Comparison groups | Control group v Exacyl group |
|-------------------|------------------------------|

| | |
|---|---------------|
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Chi-squared |

| | |
|-----------------------------------|--|
| Statistical analysis title | Since the recovery room until 24 hours |
|-----------------------------------|--|

Statistical analysis description:

Transfusion since the recovery room until 24 hours.

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5 |
| Method | Chi-squared |

| | |
|-----------------------------------|----------------------------|
| Statistical analysis title | Since 24 hours until Day 4 |
|-----------------------------------|----------------------------|

Statistical analysis description:

Transfusion since 24 hours until Day 4.

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Chi-squared |

| | |
|-----------------------------------|--|
| Statistical analysis title | Since Day 4 until the exit from the hospital |
|-----------------------------------|--|

Statistical analysis description:

Transfusion since Day 4 until the exit from the hospital.

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|-------------------|------------------------------|
| Comparison groups | Exacyl group v Control group |
|-------------------|------------------------------|

| | |
|---|-----------------|
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Chi-squared |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.06 |
| upper limit | 15.5 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Exit from the hospital until- End of the follow-up |
|-----------------------------------|--|

Statistical analysis description:

Transfusion since the exit from the hospital until the end of the follow-up.

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.62 |
| Method | Chi-squared |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.05 |
| upper limit | 5.34 |

Secondary: Incidence of symptomatic thromboembolic events and death at 6 weeks

| | |
|-----------------|---|
| End point title | Incidence of symptomatic thromboembolic events and death at 6 weeks |
|-----------------|---|

End point description:

The endpoint is a composite endpoint consisting venous events (deep vein thrombosis or pulmonary embolism), arterial events (acute coronary syndrome, stroke ischemic acute lower limb ischemia) and death from all causes.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At 6 weeks after the surgery.

| End point values | Exacyl group | Control group | Final analysis | |
|--|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 84 | 83 | 167 | |
| Units: Number | | | | |
| symptomatic thromboembolic events-death at 6 weeks | 0 | 2 | 2 | |
| thromboembolic venous events at 6 weeks | 0 | 2 | 2 | |
| thromboembolic arterial events at 6 weeks | 0 | 0 | 0 | |
| Death at 6 weeks | 0 | 0 | 0 | |

Statistical analyses

| Statistical analysis title | Symptomatic thromboembolic events and death |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Symptomatic thromboembolic events and death at 6 weeks.

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[14] |
| P-value | = 0.25 |
| Method | Chi-squared |

Notes:

[14] - No comment.

| Statistical analysis title | Venous thromboembolic events at 6 weeks |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[15] |
| P-value | = 0.25 |
| Method | Chi-squared |

Notes:

[15] - No comment.

Secondary: The postoperative blood loss in the surgical drain until the 24th postoperative hour

| | |
|-----------------|--|
| End point title | The postoperative blood loss in the surgical drain until the 24th postoperative hour |
|-----------------|--|

End point description:

To evaluate the effect of blood levels of blood loss, the criterion will be the postoperative blood loss measured in the surgical drain placed intraarticular until the 24th postoperative hour.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Since the surgery until the 24th post-operative hour. | |

| End point values | Exacyl group | Control group | Final analysis | |
|---------------------------------------|------------------------|------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 84 | 83 | 167 | |
| Units: millilitre(s) | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Blood loss in the drain at 1 hour | 60.0 (35.0 to 100.0) | 60.0 (30.0 to 80.0) | 60.0 (30.0 to 90.0) | |
| Blood loss in the drain at 2 hours | 80.0 (40.0 to 125.0) | 80.0 (40.0 to 100.0) | 80.0 (40.0 to 120.0) | |
| Blood loss in the drain at 3 hours | 90.0 (50.0 to 150.0) | 100.0 (50.0 to 120.0) | 100.0 (50.0 to 140.0) | |
| Blood loss in the drain at 4 hours | 100.0 (60.0 to 170.0) | 110.0 (50.0 to 150.0) | 110.0 (60.0 to 160.0) | |
| Blood loss in the drain at 8 hours | 150.0 (100.0 to 235.0) | 155.0 (90.0 to 220.0) | 150.0 (100.0 to 230.0) | |
| Blood loss in the drain at 12 hours | 180.0 (120.0 to 270.0) | 200.0 (100.0 to 270.0) | 190.0 (120.0 to 270.0) | |
| Blood loss in the drain at 16 hours | 205.0 (140.0 to 310.0) | 230.0 (130.0 to 300.0) | 210.0 (140.0 to 310.0) | |
| Blood loss in the drain at 20 hours | 230.0 (170.0 to 350.0) | 260.0 (150.0 to 340.0) | 250.0 (170.0 to 350.0) | |
| Blood loss in the drain at 24 hours | 265.0 (200.0 to 390.0) | 300.0 (170.0 to 390.0) | 290.0 (190.0 to 390.0) | |

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Blood loss in the drain at 1 hour |
| Statistical analysis description: | |
| With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated. | |
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[16] |
| P-value | = 0.34 |
| Method | Logrank |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 9.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.98 |
| upper limit | 24.55 |

Notes:

[16] - No comment.

| | |
|--|------------------------------------|
| Statistical analysis title | Blood loss in the drain at 2 hours |
| Statistical analysis description: With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated. | |
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[17] |
| P-value | = 0.64 |
| Method | Logrank |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 7.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.55 |
| upper limit | 24.86 |

Notes:

[17] - No comment.

| | |
|--|------------------------------------|
| Statistical analysis title | Blood loss in the drain at 3 hours |
| Statistical analysis description: With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated. | |
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6 |
| Method | Logrank |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 8.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.77 |
| upper limit | 28.45 |

| | |
|--|------------------------------------|
| Statistical analysis title | Blood loss in the drain at 4 hours |
| Statistical analysis description: With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated. | |
| Comparison groups | Exacyl group v Control group |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.58 |
| Method | Logrank |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 11.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.68 |
| upper limit | 33.5 |

| | |
|-----------------------------------|------------------------------------|
| Statistical analysis title | Blood loss in the drain at 8 hours |
|-----------------------------------|------------------------------------|

Statistical analysis description:

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|--------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.95 |
| Method | Logrank |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 6.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.03 |
| upper limit | 35.4 |

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | Blood loss in the drain at 12 hours |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|--------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[18] |
| P-value | = 0.92 |
| Method | Logrank |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.56 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -31.01 |
| upper limit | 36.12 |

Notes:

[18] - No comment.

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | Blood loss in the drain at 16 hours |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|--------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[19] |
| P-value | = 0.77 |
| Method | Logrank |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.88 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -39.9 |
| upper limit | 34.13 |

Notes:

[19] - No comment.

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | Blood loss in the drain at 20 hours |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|--------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[20] |
| P-value | = 0.99 |
| Method | Logrank |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.35 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -38.08 |
| upper limit | 42.78 |

Notes:

[20] - No comment.

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | Blood loss in the drain at 24 hours |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

With regard to secondary objectives, if the variables were quantitative, tests identical to those used for the main criterion were implemented. For qualitative variables, the two groups were compared using Fisher's exact test. Relative risk (RR) and 95% confidence interval (IC 95%) were also estimated.

| | |
|---|--------------------------------|
| Comparison groups | Exacyl group v Control group |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[21] |
| P-value | = 0.89 |
| Method | Logrank |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -41.03 |
| upper limit | 45.55 |

Notes:

[21] - No comment.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At 6 weeks.

The investigator was required to report to the promoter:

- any unexpected SAE within 24 hours of its appearance,
- any SAE expected within 8 days of its appearance.

whether or not this SAE was related to the experimental drug.

Adverse event reporting additional description:

Any serious adverse event/effect (SAE) contained in the Summary of product characteristics was considered as an expected SAE. The following events were also considered as expected SAE:

- hemorrhage, hematoma regardless of the site
- venous or arterial thromboembolic complication
- infectious complications
- post-op operative complication

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 10.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Exacyl group |
|-----------------------|--------------|

Reporting group description:

Non-serious adverse events:

A total of 22 patients (13.2%) had at least one non-serious adverse event, 12 (14.3%) in the Exacyl group .

Serious adverse events:

A total of 6 patients (3.6%) had at least one serious adverse event (SAE), 2 (2.4%) in the Exacyl group .

In this group one patient presented a vascular condition and an other one presented gastrointestinal problems.

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

Reporting group description:

Non-serious adverse events:

A total of 22 patients (13.2%) had at least one non-serious adverse event, 10 (12.0%) in the placebo group.

Serious adverse events:

A total of 6 patients (3.6%) had at least one serious adverse event (SAE), 4 (4.8%) in the placebo group.

In this group:

- two patients presented a vascular condition
- one patient presented a heart condition
- and an other one presented musculoskeletal and connective tissue disorders.

| Serious adverse events | Exacyl group | Placebo group | |
|---|---|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | 4 / 83 (4.82%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Vascular disorders | | | |
| vascular condition | Additional description: - Stitches hemorrhage for the patient of the Exacyl group - Hemorrhagic duodenal ulcer for one of the patients of the placebo group - Deep Vein Thrombosis for the other patient of the placebo group | | |

| | | | |
|---|--|----------------|--|
| subjects affected / exposed | 1 / 84 (1.19%) | 2 / 83 (2.41%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| heart condition | Additional description: Bradycardia | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| gastrointestinal problems | Additional description: Obstruction of the small intestine | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| musculoskeletal and connective tissue disorders | Additional description: mixed infection | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 1.19 %

| Non-serious adverse events | Exacyl group | Placebo group | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 84 (14.29%) | 10 / 83 (12.05%) | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 4 / 83 (4.82%) | |
| occurrences (all) | 5 | 5 | |
| Surgical and medical procedures | | | |
| Wall hematoma | | | |
| subjects affected / exposed | 8 / 84 (9.52%) | 6 / 83 (7.23%) | |
| occurrences (all) | 14 | 14 | |
| Complication of the prosthesis | | | |
| subjects affected / exposed | 3 / 84 (3.57%) | 2 / 83 (2.41%) | |
| occurrences (all) | 5 | 5 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 14 October 2013 | This amendment is a substantial change in the protocol because it concerns: <ul style="list-style-type: none">- The accuracy of the second sample for the dosage of tranexamic acid, which will be 20 minutes after the Exacyl bolus.- The accuracy of the timing of the samples for dosages of tranexamic acid and hemoglobin at the end of the procedure, which will be done after plugging in the drains- The accuracy of the time of the 4th sample for the dosage of tranexamic acid, which will take place 3 hours after the exacyl bolus- The accuracy of the time of the 5th and final sample for the dosage of tranexamic acid, which will take place at the end of the infusion of Exacyl or placebo |
| 16 June 2014 | This amendment is a substantial change in the protocol because it concerns: <ul style="list-style-type: none">- the modification of a non-inclusion criterion. Indeed, following an update of the Summary of characteristics of the Exacyl , the contraindications have been modified, including the "history of confirmed arterial or venous thrombotic accident" which has become "Acute Venous or Arterial Thrombosis". This criterion has therefore been updated in the protocol.- The addition of 2 co-investigators:<ul style="list-style-type: none">o Dr Pierre LAMBERTo Dr Nicolas BARBE- The addition of an experimenter: Julien LANOISELE |
| 09 February 2015 | This amendment is a substantial change in the protocol because it concerns: <ul style="list-style-type: none">- The addition of a co-investigator:<ul style="list-style-type: none">o Dr Jean-Yves BIEN |
| 07 September 2015 | <p>This amendment constitutes a substantial change in the protocol as it relates to the extension of the inclusion period for a period of 1 year, until 31 August 2016, bringing the end of the follow-up to 31 October 2016. The purpose of this extension is to allow for the inclusion of all planned patients.</p> <p>To date 120 patients have been included out of the 168 planned.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported