Clinical trial results:
Evaluation of postoperative administration of tranexamic acid on reducing blood loss after hip prothesis 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 biginning ot 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 biginning ot 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 ot 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 surgey.
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 aterial 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: - 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: - 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: o Dr Pierre LAMBERT o 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: - The addition of a co-investigator: o Dr Jean-Yves BIEN
07 September 2015	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. To date 120 patients have been included out of the 168 planned.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported