Clinical trial results:
TRAnexamic Acid for Preventing postpartum hemorrhage following a vaginal delivery : a multicenter randomised, double blind placebo controlled trial

Summary

EudraCT number	2014-001748-39
Trial protocol	FR
Global end of trial date	30 March 2017

Results information

Result version number	v1 (current)
This version publication date	24 April 2019
First version publication date	24 April 2019
Summary attachment (see zip file)	Résume_Rapport_Final_TRAAP (Résume_Rapport_Final_TRAAP.doc)

Trial information

Trial identification

Sponsor protocol code	PHRC2013-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02302456
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU d'Angers
Sponsor organisation address	4 rue Larrey, ANGERS, France, 49933
Public contact	Direction de la Recherche, CHU d'Angers, 33 241356329, Adeline.Morvan@chu-angers.fr
Scientific contact	Direction de la Recherche, CHU d'Angers, 33 241356329, Adeline.Morvan@chu-angers.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	13 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2017
Global end of trial reached?	Yes
Global end of trial date	30 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of a low dose of TXA (1g) after vaginal delivery, within 2 minutes after delivery of the child, versus placebo on the incidence of PPH, defined by blood loss ≥ 500 ml, measured with a graduated collector bag.

Protection of trial subjects:

Le rapport bénéfices/risques n'a pas été modifié au cours de l'étude. Seules 2 suspicions d'effets indésirables ont été déclarées au cours de l'étude dont 1 SUSAR (cytolyse hépatique dont l'imputabilité reste incertaine). L'acide tranexamique à la dose de 1g en préventif de l'HPP n'a pas augmenté le risque thrombotique en post-partum chez les patientes incluses et traitées par le médicament expérimental. Aucun cas de nécrose corticale ou d'effet sur le rein n'a été déclaré au cours de l'étude (risque attendu pour des doses supérieures supérieures à 2g dans l'HPP ; une mise à jour du RCP a été faite en conséquence).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 February 2015
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: 4079
Worldwide total number of subjects	4079
EEA total number of subjects	4079

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)	4079

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

En France, 4074 patientes ont été inclus dans l'étude entre le 16/02/2015 et le 09/12/2016.
14 centres français ont participé à l'étude

Pre-assignment

Screening details:

4074 patientes ont été incluses et randomisées.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Bras Acide Tranexamique

Arm description: -

Arm type	Experimental
Investigational medicinal product name	ACIDE TRANEXAMIQUE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intracavernous use

Dosage and administration details:

Tranexamic acid (TXA) 1g-10ml
It is in the form of a conditioned injectable solution, for blind application, in 10 mL type 1 glass vial, at a concentration of 100 mg/mL
The route of administration is the Slow Intravenous Strict

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Chlorure de sodium 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Chlorure de sodium 0.9% (Sodium : 154 mmol/l et Chlorure : 154 mmol/l) - 10ml
Administration : voie intraveineuse lente

Number of subjects in period 1	Bras Acide Tranexamique	Placebo
Started	2040	2039
Completed	1467	1480
Not completed	573	559
Consent withdrawn by subject	10	13
exclusion criteria	11	12
caesarian delivery	74	68
Protocol deviation	478	466

Baseline characteristics

Reporting groups	
Reporting group title	Bras Acide Tranexamique
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Bras Acide Tranexamique	Placebo	Total
Number of subjects	2040	2039	4079
Age categorical Units: Subjects			
Adults (18-64 years)	2040	2039	4079
Gender categorical Units: Subjects			
Female	2040	2039	4079

Subject analysis sets	
Subject analysis set title	Modified intention to treat
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Groups don't show significant differences in the characteristics of inclusion or compliance with the assigned intervention and other aspects of managing third stage of labor

Reporting group values	Modified intention to treat		
Number of subjects	3891		
Age categorical Units: Subjects			
Adults (18-64 years)	3891		
Gender categorical Units: Subjects			
Female	3891		

End points

End points reporting groups

Reporting group title	Bras Acide Tranexamique
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Modified intention to treat
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Groups don't show significant differences in the characteristics of inclusion or compliance with the assigned intervention and other aspects of managing third stage of labor

Primary: Postpartum Hemorrhage

End point title	Postpartum Hemorrhage

End point description:

A graduated bag (with 100-ml graduations) to collect and measure postpartum vaginal blood loss objectively was placed just after delivery and remained in place for at least 15 minutes and until the birth attendant considered that the bleeding had stopped.

End point type	Primary

End point timeframe:

at least 15 minutes and until the birth attendant considered that the bleeding had stopped.

End point values	Bras Acide Tranexamique	Placebo	Modified intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	2040	2039	3891	
Units: millilitre(s)	2040	2039	3891	

Attachments (see zip file)	Supplementary-Appendix Final.pdf Publication_NEJM.pdf

Statistical analyses

Statistical analysis title	Modified intention to treat analysis
Comparison groups	Placebo v Bras Acide Tranexamique
Number of subjects included in analysis	4079
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Kruskal-wallis

Secondary: the impact of TXA (1 g) after vaginal delivery on postpartum blood loss	
End point title	the impact of TXA (1 g) after vaginal delivery on postpartum blood loss

End point description:

To assess the impact of TXA (1 g) after vaginaldelivery on postpartum blood loss : Other outcome measures describing postpartum blood loss, such as mean measured total postpartum blood loss, incidence of severe PPH, defined by blood loss ≥ 1000 mL, proportion of women requiring supplementary uterotonic agent, transfusion, arterial embolization, or emergency surgery for PPH, and mean peripartum change in hemoglobin and hematocrit

End point type	Secondary

End point timeframe:

From 15 minutes to two days after the delivery

End point values	Bras Acide Tranexamique	Placebo	Modified intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	2040	2039	3891	
Units: millilitre(s)	2040	2039	3891	

Attachments (see zip file)	Supplementary-Appendix Final.pdf Publication_NEJM.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: potential adverse effects of TXA	
End point title	potential adverse effects of TXA

End point description:

The hemodynamic parameters, gastrointestinal side effects, renal, hepatic and coagulation function, venous or arterial thrombosis

End point type	Secondary

End point timeframe:

within 3 months following delivery

End point values	Bras Acide Tranexamique	Placebo	Modified intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	2040	2039	3891	
Units: mmHg	2040	2039	3891	

Attachments (see zip file)	Supplementary-Appendix Final.pdf Publication_NEJM.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: women ’s satisfaction and psychological status

End point title	women ’s satisfaction and psychological status

End point description:

End point type	Secondary

End point timeframe:

60 days after the delivery

End point values	Bras Acide Tranexamique	Placebo	Modified intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	2040	2039	3891	
Units: questionnaire	2040	2039	3891	

Attachments (see zip file)	Supplementary-Appendix Final.pdf Publication_NEJM.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Within 12 weeks after the delivery

Adverse event reporting additional description:

The following parameters will be collected :
- Hemodynamic parameters
- Potential moderate adverse effects of TXA in the work room
- Biological parameters: urea, creatinine, prothrombin time , activated partial thromboplastin time, fibrinogen, ALT, AST, billirubin J2
- Potential serious adverse events up to 12 weeks postpartum

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Tranaxemic Acid

Reporting group description:

The last 6 weeks of pregnancy: initial information
During the work: information, selection and inclusion
During the third phase of the work: treatment, with a masked ampoule of 10 mL of the study product (TXA or placebo according to the randomization list) that will be administered IV to the patient
From the time of delivery and during the 2 hours of surveillance in the work room: first follow-up step with measurement of blood loss and tolerance parameters.
At D2, second stage of follow-up: blood sampling and determination of hemoglobin and hematocrit, and parameters of renal and hepatic function and coagulation. A self-questionnaire is to be completed by the participants.
At 8 weeks postpartum, send a self-administered mailer to patients with a pre-stamped envelope.
At 12 weeks postpartum: Telephone contact for thromboembolic events and any unexpected adverse reactions.

Reporting group title	Placebo

Reporting group description:

The last 6 weeks of pregnancy: initial information
During the work: information, selection and inclusion
During the third phase of the work: treatment, with a masked ampoule of 10 mL of the study product (TXA or placebo according to the randomization list) that will be administered IV to the patient
From the time of delivery and during the 2 hours of surveillance in the work room: first follow-up step with measurement of blood loss and tolerance parameters.
At D2, second stage of follow-up: blood sampling and determination of hemoglobin and hematocrit, and parameters of renal and hepatic function and coagulation. A self-questionnaire is to be completed by the participants.
At 8 weeks postpartum, send a self-administered mailer to patients with a pre-stamped envelope.
At 12 weeks postpartum: Telephone contact for thromboembolic events and any unexpected adverse reactions.

Serious adverse events	Tranaxemic Acid	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 2040 (0.88%)	25 / 2039 (1.23%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	0 / 2040 (0.00%)	1 / 2039 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive episodes			
subjects affected / exposed	0 / 2040 (0.00%)	1 / 2039 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian vein thrombosis			
subjects affected / exposed	0 / 2040 (0.00%)	2 / 2039 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 2040 (0.05%)	1 / 2039 (0.05%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Anaemia, postpartum			
subjects affected / exposed	0 / 2040 (0.00%)	1 / 2039 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpartum haemorrhage			
subjects affected / exposed	5 / 2040 (0.25%)	5 / 2039 (0.25%)	
occurrences causally related to treatment / all	0 / 10	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	1 / 2040 (0.05%)	0 / 2039 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eclampsia			
subjects affected / exposed	1 / 2040 (0.05%)	0 / 2039 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Malaise			
subjects affected / exposed	0 / 2040 (0.00%)	1 / 2039 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Retinal vasculitis			
subjects affected / exposed	0 / 2040 (0.00%)	1 / 2039 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 2040 (0.00%)	1 / 2039 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthmatic crisis			
subjects affected / exposed	0 / 2040 (0.00%)	1 / 2039 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute delirium			
subjects affected / exposed	0 / 2040 (0.00%)	1 / 2039 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
postpartum depression			
subjects affected / exposed	1 / 2040 (0.05%)	0 / 2039 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 2040 (0.00%)	2 / 2039 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 2040 (0.05%)	0 / 2039 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensorimotor disorder			
subjects affected / exposed	1 / 2040 (0.05%)	0 / 2039 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal vasculitis			
subjects affected / exposed	0 / 2040 (0.00%)	1 / 2039 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	1 / 2040 (0.05%)	0 / 2039 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 2040 (0.05%)	0 / 2039 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 2040 (0.05%)	0 / 2039 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic pain			
subjects affected / exposed	1 / 2040 (0.05%)	0 / 2039 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			

subjects affected / exposed	1 / 2040 (0.05%)	0 / 2039 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Sacroiliitis			
subjects affected / exposed	0 / 2040 (0.00%)	1 / 2039 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Postpartum sepsis			
subjects affected / exposed	0 / 2040 (0.00%)	1 / 2039 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 2040 (0.05%)	0 / 2039 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingitis			
subjects affected / exposed	0 / 2040 (0.00%)	1 / 2039 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal infection			
subjects affected / exposed	1 / 2040 (0.05%)	0 / 2039 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometritis			
subjects affected / exposed	0 / 2040 (0.00%)	2 / 2039 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometritis bacterial			
subjects affected / exposed	0 / 2040 (0.00%)	1 / 2039 (0.05%)	
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: 0 %

Non-serious adverse events	Tranaxemic Acid	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	744 / 2040 (36.47%)	701 / 2039 (34.38%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 2040 (0.00%)	1 / 2039 (0.05%)	
occurrences (all)	1	1	
superficial vein thrombosis			
subjects affected / exposed	1 / 2040 (0.05%)	3 / 2039 (0.15%)	
occurrences (all)	4	4	
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 2040 (0.05%)	0 / 2039 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	57 / 2040 (2.79%)	58 / 2039 (2.84%)	
occurrences (all)	115	115	
Pregnancy, puerperium and perinatal conditions			
Postpartum haemorrhage			
subjects affected / exposed	116 / 2040 (5.69%)	154 / 2039 (7.55%)	
occurrences (all)	270	270	
puerperium haemorrhage			
subjects affected / exposed	2 / 2040 (0.10%)	4 / 2039 (0.20%)	
occurrences (all)	6	6	
General disorders and administration site conditions			
Headache			
subjects affected / exposed	29 / 2040 (1.42%)	32 / 2039 (1.57%)	
occurrences (all)	61	61	
Malaise			

subjects affected / exposed	22 / 2040 (1.08%)	31 / 2039 (1.52%)	
occurrences (all)	53	53	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	6 / 2040 (0.29%)	10 / 2039 (0.49%)	
occurrences (all)	16	16	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	88 / 2040 (4.31%)	49 / 2039 (2.40%)	
occurrences (all)	137	137	
vomiting			
subjects affected / exposed	69 / 2040 (3.38%)	37 / 2039 (1.81%)	
occurrences (all)	106	106	
Hepatobiliary disorders			
other	Additional description: whose : increased liver enzymes		
subjects affected / exposed	368 / 2040 (18.04%)	343 / 2039 (16.82%)	
occurrences (all)	713	713	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2014	amendment 1 concerned minor amendments to the protocol following a request by the CCTIRS
20 February 2015	amendment 2 concerned the deletion of the troponin
24 February 2015	Amendment 3 concerned the opening of two new centers, Nantes University Hospital and Bicêtre University Hospital in Paris.
19 May 2015	amendment 4 concerned the change of two principal investigators of already opened centers, the principal investigator of the University Hospital of Caen and the principal investigator of Port Royal Maternity Hospital Cochin in Paris.
13 October 2015	amendment 6 concerned the opening of a new participating center, the Montpellier University Hospital Center
19 October 2015	amendment 5 concerned the opening of three new participating centers, the Trousseau Hospital in Paris, the Saint Joseph Hospital in Marseille and the Maternité Notre Dame de Bon Secours in Paris. This amendment also related to the addition of the fibrinogen assay, the extension of the stability period of the Experimental Medicinal Product (ME) and the modification of the primary packaging of ME
13 November 2015	amendment 8 concerned the amendment of the charter of the Independent Supervisory Committee (CIS)
17 November 2015	amendment 7 concerned the opening of a new participating center, the Hôpital Mère-Mère-Enfant at the Hospices Civiles de Lyon
15 December 2015	Amendment 9 concerned the opening of a new participating center, the Vendee Hospital at La Roche-sur-Yon
19 January 2016	amendment 10 concerned the opening of a new participating center, the CH of Pau and the addition of an investigator to a participating center, at the level of the Civil Hospitals of Lyon-Hôpital Croix Rousse
19 April 2016	Amendment 11 concerned the closure of a participating center, Lille University Hospital.
14 June 2016	amendment 12 concerned the extension of the inclusion period by 6 additional months
24 October 2016	Amendment 13 concerned amendments to the protocol for updates.
13 December 2016	Amendment 14 dealt with increasing the number of participants to include, from 4000 patients to 4080

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30134136