Pharmacokinetics of **T**rane**x**amic **Ac**id after oral, intramuscular or intravenous administration: a prospective, randomised, cross-over trial in healthy volunteers.

PharmacoTXA trial

INTERVENTIONAL RESEARCH PROTOCOL
OF A MEDICINAL PRODUCT FOR HUMAN USE

Sponsor Protocol Number	2018/KEP/205
NCT (clinicaltrials.gov) Number	NCT03777488
EudraCT Number	2019-000285-38
APHP Protocole Number	APHP190020

PROTOCOL VERSIONS:		
NUMBER	DATE	DETAILS/ REASON FOR CHANGE
1.0	04/04/2019	First submitted version
1.1	16/05/2019	Replies to ANSM
1.2	19/06/2019	Further replies to ANSM
1.3	24/07/19	Replies to EC
2.0	10/06/2020	Extension of recruitment period

TRIAL SPONSORSHIP, ORGANISATION & RESPONSIBILITIES

TRIAL PRODUCT	TRANEXAMIC ACID
PROTOCOL NUMBER	2018/KEP/205
FULL TITLE	Pharmacokinetics of Tranexamic Acid after oral, intramuscular or intravenous administration: a prospective, randomised, cross-over study in healthy volunteers.
ACRONYM	PharmacoTXA trial
EudraCT NUMBER	2019-000285-38

RESPONSIBLE PERSONS' CONTACT DETAILS

Sponsor: Clinical Trials Unit, Faculty of Epidemiology London School of Hygiene and Tropical Medicine, Keppel Street London, WC1E 7HT, UK	**Sponsor Representative:** Assistance Publique-Hôpitaux de Paris (AP-HP) Clinical Research and Innovation Delegation (DRCI) Hôpital Saint Louis 1 avenue Claude Vellefaux, 75010 PARIS	**Responsible for monitoring the trial:** Unité de Recherche Clinique (URC) Paris Descartes Necker Cochin Hôpital Necker-Enfants Malades 149, rue de Sèvres - 75743 Paris cedex 15
Haleema Shakur-Still Professor of Global Health Clinical Trials Ian Roberts Professor of Epidemiology and Public Health Patricia Henley Sponsor Legal Representative	Project Manager: **Christophe AUCAN**	URC Coordinator: Pr Jean-Marc TRELUYER URC project advisor: Laure CHOUPEAUX URC Data Manager: Fabrice GOURMELON
Trial site: Centre d'Investigation Clinique (CRC) Hôpital Necker-Enfants Malades 149, rue de Sèvres - 75743 Paris cedex 15	**Site Laboratory details**: Laboratoire de Biologie Médicale Hôpital Necker-Enfants Malades 149, rue de Sèvres - 75743 Paris cedex 15	**Pharmacy details**: Pharmacie secteur « Essais Cliniques » Hôpital Necker-Enfants Malades 149, rue de Sèvres - 75743 Paris cedex 15
Site Principal Investigator: Dr Michaela SEMERARO	Hematology responsible: Pr E. MACINTYRE Biochemistry responsible : Pr J-L. BEAUDEUX	Clinical Trial pharmacist: Sylvain AUVITY
Coordinating Investigator	**PK Laboratory/analysis** UFR Sciences de la Santé Simone Veil, Université Versailles Saint Quentin, 2 avenue de la source de la Bièvre, 78180 Montigny le Bretonneux Unité de Recherche Clinique Paris Descartes Necker Cochin	
Dr Grassin Delyle Université Versailles Saint Quentin	**Dr Grassin Delyle :** Université Versailles Saint Quentin / Hôpital Foch **Dr Saïk Urien :** Unité de Recherche Clinique Paris Descartes Necker Cochin	

PROTOCOL AUTHORISATION SIGNATURES:

We confirm that this study will be carried out in accordance with the protocol, current good clinical trial practices, and all relevant ethical, statutory and regulatory requirements.

NAME & ADDRESS	ROLE	SIGNATURE	DATE (dd/mm/yy)

TABLE OF CONTENTS

1 SUMMARY 6

2 SCIENTIFIC JUSTIFICATION FOR THE TRIAL 10

2.1 EXISTING KNOWLEDGE RELATING TO THE CONDITION UNDER INVESTIGATION 10
2.2 SUMMARY OF RELEVANT PRE-CLINICAL AND CLINICAL TRIALS 10
2.3 HYPOTHESIS FOR THE STUDY 14
2.4 DESCRIPTION OF THE POPULATION OF TRIAL SUBJECTS AND JUSTIFICATION FOR THE CHOICE OF SUBJECTS 14
2.5 NAME AND DESCRIPTION OF THE INVESTIGATIONAL MEDICINAL PRODUCT(S) 15
2.6 DESCRIPTION AND JUSTIFICATION OF THE DOSAGE, ROUTE OF ADMINISTRATION, ADMINISTRATION SCHEDULE AND TREATMENT DURATION 15
2.7 SUMMARY OF THE KNOWN AND FORESEEABLE BENEFITS AND RISKS FOR THE STUDY PARTICIPANTS 15

3 OBJECTIVES 16

3.1 PRIMARY OBJECTIVE 16
3.2 SECONDARY OBJECTIVES 16

4 DESCRIPTION OF THE TRIAL 16

4.1 CONCISE DESCRIPTION OF THE PRIMARY AND SECONDARY ENDPOINTS 16
4.2 RESEARCH METHODOLOGY 17

5 PROCEDURE FOR THE TRIAL 20

5.1 SCREENING VISIT (V0) 20
5.2 INCLUSION VISIT (V1) 21
5.3 FOLLOW-UP VISITS 23
5.4 END OF STUDY VISIT 27
5.5 EXPECTED LENGTH OF PARTICIPATION, CHRONOLOGY AND DURATION OF THE STUDY. 27
5.6 TABLE OR DIAGRAM SUMMARISING THE CHRONOLOGY OF THE STUDY 28
5.7 DISTINCTION BETWEEN STANDARD CARE AND RESEARCH 29
5.8 BIOLOGICAL SAMPLES 29
5.9 TERMINATION AND EXIT RULES 29

6 ELIGIBILITY CRITERIA 32

6.1 INCLUSION CRITERIA 32
6.2 EXCLUSION CRITERIA 32
6.3 RECRUITMENT METHODS 33

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS 33

7.1 THE INVESTIGATIONAL MEDICINAL PRODUCT 33
7.2 TRACEABILITY INFORMATION FOR THE INVESTIGATIONAL MEDICINAL PRODUCT 34
7.3 AUTHORISED AND PROHIBITED TREATMENTS (MEDICINAL, NON-MEDICINAL, SURGICAL), INCLUDING EMERGENCY MEDICATIONS 34
7.4 METHODS FOR MONITORING COMPLIANCE WITH THE TREATMENT 35

8 EFFICACY ASSESSMENT 35

8.1 DESCRIPTION OF PARAMETERS FOR ASSESSING EFFICACY ENDPOINTS 35
8.2 ANTICIPATED METHODS AND TIMETABLE FOR MEASURING, COLLECTING AND ANALYSING THE EFFICACY DATA 35

9 SPECIFIC COMMITTEES FOR THE TRIAL 35

9.1 SCIENTIFIC COMMITTEE 35

10 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE STUDY 36

10.1 SAFETY ENDPOINTS 36
10.2 ANTICIPATED METHODS AND TIMETABLE FOR MEASURING, COLLECTING AND ANALYSING THE SAFETY ENDPOINTS 36
10.3 RECORDING AND REPORTING ADVERSE EVENTS 36
11 DATA MANAGEMENT 46
11.1 DATA COLLECTION 46
11.2 IDENTIFICATION OF DATA RECORDED DIRECTLY IN THE CRFS WHICH WILL BE CONSIDERED AS SOURCE DATA 46
11.3 RIGHT TO ACCESS SOURCE DATA AND DOCUMENTS 47
11.4 DATA PROCESSING AND STORAGE OF DOCUMENTS AND DATA 48
11.5 OWNERSHIP OF THE DATA 48
12 STATISTICAL ASPECTS 48
12.1 PLANNED STATISTICAL METHODS, INCLUDING THE TIMETABLE FOR ANY PLANNED INTERIM ANALYSES 48
12.2 HYPOTHESES FOR CALCULATING THE REQUIRED NUMBER OF SUBJECTS, AND THE RESULT 50
13 QUALITY CONTROL AND ASSURANCE 50
13.1 GENERAL ORGANISATION 50
13.2 QUALITY CONTROL 51
13.3 CASE REPORT FORM 52
13.4 MANAGEMENT OF NON-COMPLIANCES 52
13.5 AUDITS/INSPECTIONS 53
13.6 PRINCIPAL INVESTIGATOR'S DECLARATION OF RESPONSIBILITY 53
14 ETHICAL AND LEGAL CONSIDERATIONS 54
14.1 METHODS FOR INFORMING AND OBTAINING CONSENT FROM THE RESEARCH PARTICIPANTS 54
14.2 PROHIBITION OF CONCOMITANT CLINICAL STUDIES PARTICIPATION AND EXCLUSION PERIOD AFTER THE TRIAL, IF APPLICABLE 55
14.3 COMPENSATION FOR SUBJECTS 55
14.4 REGISTRATION ON THE NATIONAL REGISTER OF SUBJECTS PARTICIPATING IN HUMAN RESEARCH TRIALS ON THE PRODUCTS LISTED IN ARTICLE L. 5311-1 OF THE FRENCH PUBLIC HEALTH CODE 55
14.5 LEGAL OBLIGATIONS 55
15 FUNDING AND INSURANCE 57
15.1 SOURCES OF FUNDING FOR THE TRIAL 57
15.2 INSURANCE 57
16 PUBLICATION 57
16.1 MENTION OF AP-HP AFFILIATION FOR PROJECTS SPONSORED OR MANAGED BY AP-HP 58
16.2 MENTION OF THE AP-HP MANAGER (DRCD) IN THE ACKNOWLEDGEMENTS OF THE TEXT 58
16.3 MENTION OF THE FUNDER IN THE ACKNOWLEDGEMENTS OF THE TEXT 58
17 BIBLIOGRAPHY 59
18 LIST OF ADDENDA 62
18.1 LIST OF INVESTIGATORS 62
18.2 SERIOUS ADVERSE EVENTS REPORT FORM 62
18.3 PREGNANCY REPORT FORM 62
18.4 INCLUDE THE SCP 62

1 SUMMARY

Full title	Pharmacokinetics of tranexamic acid after oral, intramuscular or intravenous administration: a prospective, randomised, cross-over pharmacokinetic study in healthy volunteers
Acronym	PharmacoTXA
Coordinating Investigator	Stanislas Grassin Delyle
Sponsor	London School of Hygiene & Tropical Medicine
Scientific justification	Intravenous administration of tranexamic acid (TXA) safely reduces death due to bleeding in patients with trauma and post-partum haemorrhage (PPH) [1-3]. In both situations, most deaths occur soon after bleeding onset and treatment delay reduces the survival benefit [4]. One of the main barriers to rapid treatment is the need for an intravenous (IV) injection. Paramedics who are trained to insert intravenous lines are not always available and even when they are, securing IV access can be difficult in shocked patients with collapsed veins. Although TXA is available for oral (tablet or oral solution) and intravenous use, there has been little research into different routes of administration. Intramuscular injection would be easier and faster to administer and would require less training than IV use and the use of the oral solution may reduce the time needed to reach therapeutic levels when compared to a later IV administration. Because TXA has a wide therapeutic index, an initial IM injection could be followed by an IV TXA when this becomes possible. Although the pharmacokinetics of TXA after tablet and intravenous administration have been well studied, there have been few studies of IM use or the use of oral TXA solutions. Clinical trials with tranexamic acid have shown its efficacy in several indications and reduced mortality in trauma and postpartum haemorrhage patients when administered within 3 hours [1,2,4,5]. Our hypothesis is that the pharmacokinetics of tranexamic acid after intramuscular injection or the oral solution may be suitable for early use of this molecule in emergency situations, including in remote areas around the world where a parenteral approach is not readily available or in contexts where medical personnel are not available.
Main objective and primary endpoint	Main objective: to determine the pharmacokinetics of tranexamic acid in healthy volunteers using a population approach after oral, intramuscular or intravenous administration. Primary endpoint: serum tranexamic acid concentrations versus time profiles for each administration route

Secondary objectives and endpoints	Secondary objectives: - To evaluate the local and systemic tolerance profile with the different routes of administration. - To determine the feasibility of measuring tranexamic acid in dry blood spots Secondary endpoints: - Average pain score and duration of pain after administration (visual analogue scale) for each administration route at visits V1, V3, V5 - Reaction at site of injection (redness, swelling, induration, tenderness, ecchymosis, necrosis, nerve injury, infection) for IM and IV administration route at visits V1, V2, V3, V4, V5, V6, - Vital signs (blood pressure, heart rate and respiratory rate) after administration for each administration route at visits V1, V2, V3, V4, V5, V6 - Solicited adverse events (fever, nausea, vomiting, diarrhoea, visual impairment, seizure) - Number of participants with solicited local and systemic adverse events - Number of participants reporting one or more adverse events and serious adverse events - Correlation between serum and dry blood spot concentrations for each administration route at visits V1, V3, V5
Design of the trial	Phase I/II, Single-centre, prospective, randomised, cross-over trial
Population of trial subjects	Healthy volunteers
Inclusion criteria	• Adult healthy volunteers both men and non-pregnant women • ≥18-≤45-year-old • Body mass index between ≥18 and ≤30 kg/m2, and bodyweight between ≥50 and ≤100 kg • Coagulation test results of fibrinogen, D-dimers, prothrombin time and a partial thromboplastin time within normal limits at screening (see protocol for details) • Normal renal function based on medical history and laboratory tests (laboratory test of serum creatinine should in the range of 0.6–1.1 mg/dL for women and 0.7–1.3 mg/dL for men. Glomerular filtration rate (GFR) should be 90 mL/min/1.73m^2 or greater (adjusting for age, sex, weight and ethnicity) • If a woman, must have a negative urine β-human chorionic gonadotropin (βhCG) pregnancy test at screening and inclusion visits • Provision of signed informed consent prior to any study specific procedure • People with public healthcare insurance (France)
Exclusion criteria	• Previous thrombotic event or pre-existing pro-thrombotic disease

	• Any history of seizures • Any chronic or active cardiovascular or renal disease • Planned general anaesthesia or surgery in the 3 months following inclusion • Pregnant and/or breastfeeding • Visual disturbance • Haematuria • Known allergy or contraindications to the study drugs or any of the excipients of the formulations • Use of any prescription or non-prescription medication (including hormonal contraception) within 7 days before the first dose of the study drug is scheduled • Inability to give informed consent • Previous participation during the year in clinical studies compensated for an amount incompatible with participation in this study, verified by recording in the national register of subjects participating in human research trials • Legal criteria: - People deprived of liberty by judicial or administrative decision - Adult protected bylaw (France)
Investigational medicinal product(s)	Tranexamic acid (Exacyl®), 0.5 g/5 ml, injectable solution: Each volunteer will receive one x 1g intravenous injection and one x 1g intramuscular injection. Tranexamic acid (Exacyl®), 1.0 g/10 ml, oral solution: Each volunteer will receive one x 2g oral solution.
Comparator treatment	Not Applicable
Interventions added for the trial	- Drug administration - Blood samples for pharmacokinetic study
Risks added by the trial	The most frequent risks associated with the administration of tranexamic acid through the intravenous, intramuscular and oral routes are digestive disorders (diarrhoea, nausea, vomiting; appearing in >1/100 and <1/10 patients); allergic dermatitis (>1/1000 and <1/100). Cases of visual impairment or convulsions have been reported with tranexamic acid, but only at high doses or during cardiac surgery. In the present study, the doses (1g through the parenteral routes and 2g through the oral route) are lower than doses used in routine clinical practice. Insertion of intravenous cannula for intravenous administration of TXA and blood sampling may cause pain (common), bruising (rare), local allergic reaction secondary to disinfectant or adhesive plaster, vagal malaise and possibly infection (very rare). Intramuscular injection procedure of a large volume may cause pain (common), Local reaction at site of injection (site: redness (common), swelling (common), tenderness (common),

	ecchymosis (common), induration (rare), necrosis (very rare), nerve injury (very rare), infection (rare) and systemic events (allergic reaction (very rare), infection (very rare). One study of subfascial and intramuscular infiltration of 2g of tranexamic in 67 elderly patients having surgery for peritrochanteric fracture reported no adverse effects up to 2 weeks. Since TXA is eliminated mainly in the urine, only patients with normal renal function will be included in the trial. Therefore no risk of drug accumulation is anticipated.
Scope of the trial	To determine doses and routes to be used in subsequent trials in postpartum women and patients with severe bleeding after trauma and to assess the safety of administration of tranexamic acid by intramuscular injection
Number of subjects included	30 healthy volunteers to be screened 15 healthy volunteers to be select and randomised for the pharmacological study
Number of sites	1
Duration of the trial	- Duration of the inclusion period: 16 months - Duration of the research period for each participant: 7 days of participation over a period of 3 months maximum - Total duration of the research period: 19 months
Number of enrolments expected per site and per month	1
Statistical analysis	Tranexamic acid time-courses will be analysed using the nonlinear mixed effect modelling software program Monolix 2019R1 version. All other data will be analysed using STATA.
Sources of funding for the trial	Funding is by the London school of Hygiene & Tropical Medicine from a grant provided to them by the Bill and Melinda Gates Foundation and Wellcome.
Trial will have a Data Monitoring Committee	No

2 SCIENTIFIC JUSTIFICATION FOR THE TRIAL

2.1 Existing knowledge relating to the condition under investigation

Tranexamic acid (TXA) reduces bleeding by inhibiting the enzymatic breakdown of fibrin blood clots (fibrinolysis) [6]. Plasminogen produced by the liver is converted into the fibrinolytic enzyme plasmin by tissue plasminogen activator (tPA). Plasminogen and tPA bind to c-terminal lysine residues on fibrin leading to localised plasmin formation and fibrin cleavage [7]. TXA is a molecular analogue of lysine that inhibits fibrinolysis by competing with fibrin for the lysine binding sites in plasminogen. TXA inhibits the capacity of plasminogen and plasmin to bind to fibrin, hence preserving blood clots from plasmin-mediated lysis [6].

Intravenous administration of TXA safely reduces death due to bleeding in patients with trauma and post-partum haemorrhage (PPH) [1-3]. In both situations, most deaths occur soon after bleeding onset and treatment delay reduces the survival benefit [4]. One of the main barriers to rapid treatment is the need for an intravenous (IV) injection. Paramedics who are trained to insert intravenous lines are not always available and even when they are, securing IV access can be difficult in shocked patients with collapsed veins. Although TXA is available for oral (tablet or oral solution) and intravenous use, there has been little research into different routes of administration. Intramuscular injection would be easier and faster to administer and would require less training than IV use and the use of the oral solution may reduce the time needed to reach therapeutic levels when compared to a later IV administration. Because TXA has a wide therapeutic index, an initial IM injection or oral administration could be followed by an IV TXA when this becomes possible.

2.2 Summary of relevant pre-clinical and clinical trials

Although the pharmacokinetics of TXA after tablet and intravenous administration have been well studied, there have been few studies of IM use or of the use of oral TXA solutions. A systematic search identified two pharmacokinetic studies of IM TXA conducted in 1975 and 1986 that included six (male) participants [8,9]. These showed that the bioavailability of TXA after IM injection is over 95% with therapeutic TXA levels (>10 mg/L) achieved within 30 minutes of administration, but there was a wide variability between the two studies, with T_{max}

around 0.5 or 1 hr, and C_{max} of approximatively 20 or 12 µg/ml for the same 500 mg dose. A individual-patient data metanalysis confirming this excellent intramuscular bioavailability was recently published by our team [10].
One study of subfascial and intramuscular infiltration of 2g of TXA in 67 elderly patients having surgery for peritrochanteric fracture reported no adverse effects up to 2 weeks. However, this study did not report on the bioavailability of intramuscular TXA [11].

Larger well-designed studies with a greater sample-size would be helpful to better describe the pharmacokinetics trough the IM route and to confirm the bioavailability, which would suggest that IM may be a feasible alternative to IV use when IV administration is either impractical or would result in treatment delay. We will examine the pharmacokinetics of TXA after IM injection and after use of an oral TXA solution.

With respect to safety in healthy volunteers, TXA (1g IV) was previously administered to 49 healthy volunteers treated with rivaroxaban in a study aimed at assessing the effects of 4-factor prothrombin complex concentrate and tranexamic acid on bleeding parameters and pharmacodynamics after a punch biopsy procedure (NCT02561923). No serious adverse events were reported in this study and none of the subjects withdrew from the study due to adverse events. No clinically relevant laboratory changes, vital signs abnormalities, physical examination abnormalities, or ECG abnormalities were reported during the study [12]. The pharmacokinetics of TXA was also reported in 6 previous studies in healthy volunteers with doses ranging from 0.5 to 2 g, including 2 studies with an intramuscular administration, with no specific report of adverse events [8,9,13-16].

Ethnic origin is known to have an impact on the glomerular filtration rate, which should modify the drug pharmacokinetics, especially for tranexamic acid due to its 100% kidney elimination. Hence, nonblack ethnicity is an independent factor associated with a lower glomerular filtration rate [17].

TXA has been in clinical use for over 40 years for a variety of clinical conditions where there is haemorrhage or a risk of haemorrhage. Both intravenous and oral routes (tablets and solution)

have marketed authorisation in France. In summary, clinical trials of TXA has been carried out in the following bleeding conditions:

Obstetric haemorrhage:

Treatment of postpartum haemorrhage: A systematic review identified two trials involving 20,212 women and showed that 1 gram of intravenous TXA (plus an additional 1 gram if bleeding continued up to 24 hours) reduces the risk of death due to bleeding after postpartum haemorrhage (PPH) compared to placebo. There is no evidence for an increase in risk of thromboembolic events, seizures or any other side effects associated with TXA [18]. Based on this evidence, the WHO recommends the early use of TXA (within 3 hours of birth) in women with PPH [19].

Prevention of postpartum haemorrhage: A systematic review including 26 randomised trial of TXA for the prevention of PPH found that most trials are small and unreliable [20]. One exception is the placebo-controlled TRAAP trial which enrolled 4079 women who were giving birth vaginally in French hospitals [21]. There was no statistically significant difference in the primary outcome of blood loss ≥500 mL. Fewer woman in the TXA group received additional uterotonics and fewer experienced clinically significant PPH according to care provider. The rates of nausea and vomiting were higher in the TXA group compared to the placebo group.

Traumatic haemorrhage:

The CRASH-2 trial involving 20,211 trauma patients found that TXA reduced the risk of death from bleeding by 15% compared to placebo. The trial also found that early administration of TXA in trauma patients (≤3 hr) was more effective in reducing deaths from bleeding than late administration (>3 hr). There was no evidence for an increase in risk of thromboembolic events, seizures or any other side effects associated with TXA [3].

Gastrointestinal bleeding

A systematic review including eight randomised trials found that patients with acute upper gastrointestinal bleeding may benefit from the administration of TXA [22].

Two small trials have assessed the effect of oral TXA in patients with lower gastrointestinal bleeding. In one trial the proportion of stools containing visible blood was lower when patients received TXA [23]. However, in the second trial there were no statistically significant differences between the TXA and placebo groups for any of the outcomes assessed [24].

Surgical haemorrhage

A systematic review of 129 randomised trials found that TXA reduced the risk of receiving a blood transfusion by 38% and the amount of blood loss by 34% in patients undergoing surgery. The effect of TXA on risk of thromboembolic events was uncertain [25].

Intracranial haemorrhage

Spontaneous intracerebral haemorrhage: A systematic review including nine randomised controlled trials suggest that TXA reduces the risk of rebleeding. However, long term use of TXA may increase the risk of cerebral ischaemia in these patients. There is some evidence that shorter treatment might reduce rebleeding without an increase in the risk of ischaemia [26].

A trial of TXA in patients with spontaneous intracerebral haemorrhage observed no statistically significant differences in functional status or death at day 90. There were fewer deaths at day 7 in the TXA group [27].

Traumatic brain injury: The results of two randomised trials in patients with traumatic brain injury showed that TXA reduced intracranial haemorrhage growth compared to placebo. However, the effect of TXA on risk of death and thromboembolic events is uncertain [28-30].

Pulmonary haemorrhage

A systematic review including two small randomised trials found that TXA reduced the amount and duration of blood loss in patients with haemoptysis [31]. Another recent trial also suggests that using inhaled TXA can be safe and effective to control bleeding in patients with non-massive hemoptysis [32].

Menorrhagia

Randomised trials of oral TXA show that TXA reduces blood loss and improves indicators of quality of life in women with menorrhagia [33].

Ocular haemorrhage

Randomised trials of oral TXA shows that it reduces the risk of secondary haemorrhage in patients with hyphema [34].

Topical use of tranexamic acid

One concern with administering TXA intramuscularly is local tissue reaction. The evidence from a systematic review which investigated the efficacy and safety of topically applied tranexamic acid in major surgery (where the drug is applied directly into joints, surgical wounds and body organs) identified 67 studies involving 6,034 patients. There were no major differences between topical and intravenous tranexamic acid with respect to safety [35].

2.3 Hypothesis for the trial

Clinical trials with tranexamic acid have shown its efficacy in several indications and reduced mortality in trauma and postpartum haemorrhage patients when administered within 3 hours [1,2,4,5]. Our hypothesis is that the pharmacokinetics of tranexamic acid after intramuscular injection or the oral solution may be suitable for early use of this molecule in emergency situations, including in remote areas around the world where a parenteral approach is not readily available or in contexts where medical personnel are not available.

2.4 Description of the population of trial subjects and justification for the choice of subjects

Fifteen healthy volunteers will be included in an age range compatible with motherhood for women. This study in healthy volunteers will allow a description of the drug pharmacokinetics and a comparison of the three different administration routes in people without any specific medical condition. Subsequent trials will be planned in specific populations such as trauma patients or postpartum women. For these reasons, we will include in the present study both men and women, in an age range compatible with motherhood for women.

2.5 Name and description of the investigational medicinal product(s)

Patient will receive the marketed forms of tranexamic acid:

- Exacyl® (Sanofi Aventis) 0.5 g/5 ml injectable solution
- Exacyl® (Sanofi Aventis) 1 g/10 ml oral solution.

See Section 7 for further information about the product.

2.6 Description and justification of the dosage, route of administration, administration schedule and treatment duration

Each volunteer will receive one dose of medication through each of the three routes (oral, intravenous, intramuscular), on three separate days. The selected doses are 1g for the intravenous and intramuscular routes and 2g for the oral route due to the 100% intramuscular bioavailability and 50% oral bioavailability [10].

See Section 7 for further information about the administration of the product.

2.7 Summary of the known and foreseeable benefits and risks for the study participants

There is no benefit for participants. The foreseeable risks are those related to IMP and the routes of administration. The most frequent risks associated with the administration of tranexamic acid through the intravenous, intramuscular and oral routes are:

- digestive disorders (diarrhoea, nausea, vomiting; appearing in >1/100 and <1/10 patients)
- allergic dermatitis (>1/1000 and <1/100)

Cases of visual impairment or convulsions have been reported with tranexamic acid, but only at high doses or during cardiac surgery. In the present study, the doses (1g through the parenteral routes and 2g through the oral route) are lower than doses used in routine clinical practice.

Insertion of intravenous cannula for intravenous administration of TXA and blood sampling may cause pain (common), bruising (rare), local allergic reaction secondary to disinfectant or adhesive plaster, vagal malaise and possibly infection (very rare).

Intramuscular injection procedure of a large volume may cause pain (common), Local reaction at site of injection (including Injection site redness (common), Injection site swelling (common), Injection site tenderness (common), Injection site ecchymosis (common), Injection site induration (rare), injection site necrosis (very rare), injection site nerve injury

(very rare), injection site infection (rare) and systemic events (allergic reaction (very rare), infection (very rare). One study of subfascial and intramuscular infiltration of 2g of tranexamic in 67 elderly patients having surgery for peritrochanteric fracture reported no adverse effects up to 2 weeks [11]. One concern with administering TXA intramuscularly is local tissue reaction. The evidence from a systematic review which investigated the efficacy and safety of topically applied tranexamic acid in major surgery (where the drug is applied directly into joints, surgical wounds and body organs) identified 67 studies involving 6,034 patients. There were no major differences between topical and intravenous tranexamic acid with respect to safety [35].

Since TXA is eliminated mainly in the urine, only participants with normal renal function will be included in the trial. Normal renal function is defined as a laboratory test of serum creatinine in the range of 0.6–1.1 mg/dL for women and 0.7–1.3 mg/dL for men and a glomerular filtration rate (GFR) of 90 mL/min/1.73m^2 or greater (adjusting for age, sex, weight and ethnicity). Therefore no risk of drug accumulation is anticipated.

3 OBJECTIVES

3.1 Primary objective

- To determine the pharmacokinetics of tranexamic acid in healthy volunteers using a population approach after oral, intramuscular or intravenous administration

3.2 Secondary objectives

- To evaluate the local and systemic safety profile with the different routes of administration.
- To determine the feasibility of measuring tranexamic acid in dry blood spots

4 DESCRIPTION OF THE TRIAL

4.1 Concise description of the primary and secondary endpoints

4.1.1 Primary endpoint

- Serum tranexamic acid concentrations versus time profiles for each route of administration.

4.1.2 Secondary endpoints

- Average pain score and duration of pain after administration (visual analogue scale) for each administration route at visits V1, V3, V5
- Reaction at site of injection (redness, swelling, induration, tenderness, ecchymosis, necrosis, nerve injury, infection) for IM and IV administration route at visits V1, V2, V3, V4, V5, V6,
- Vital signs (blood pressure, heart rate and respiratory rate) after administration for each administration route at visits V1, V2, V3, V4, V5, V6
- Solicited adverse events (fever, nausea, vomiting, diarrhoea, visual impairment, seizure)
- Number of participants with solicited local and systemic adverse events
- Number of participants reporting one or more adverse events and serious adverse events
- Correlation between serum and dry blood spot concentrations for each administration route at visits V1, V3, V5

4.2 Research methodology

4.2.1 Design of the trial

This research study is a phase I/II, single-centre, prospective, randomised, cross-over trial in healthy volunteers.

The design will be as follows:

The volunteers will be randomized into each of the 6 treatment groups (2-3 patients per group). The volunteers will receive tranexamic acid through the intravenous, intramuscular or oral route, in 6 different orders depending of the group, on three separate days (see Figure 1). The order used for the different routes of administration in each volunteer is not a factor that could influence the results of this pharmacokinetic study. Nevertheless, in order to reflect the best of all the variability that could be introduced into the system, the design selected for the study includes the 6 possible groups with regard to the sequence of routes of administration. Since the planned number of volunteers is 15, the groups consist of 2 or 3 volunteers alternately. This will not affect the final analysis, since the different groups will not be compared with each other, only the 3 routes of administration (oral, intravenous and

intramuscular) will be compared, each with a total of 15 patients. Any randomized participant who has not received all three drug doses will be replaced and the replacement will be allocated to the same randomisation group.

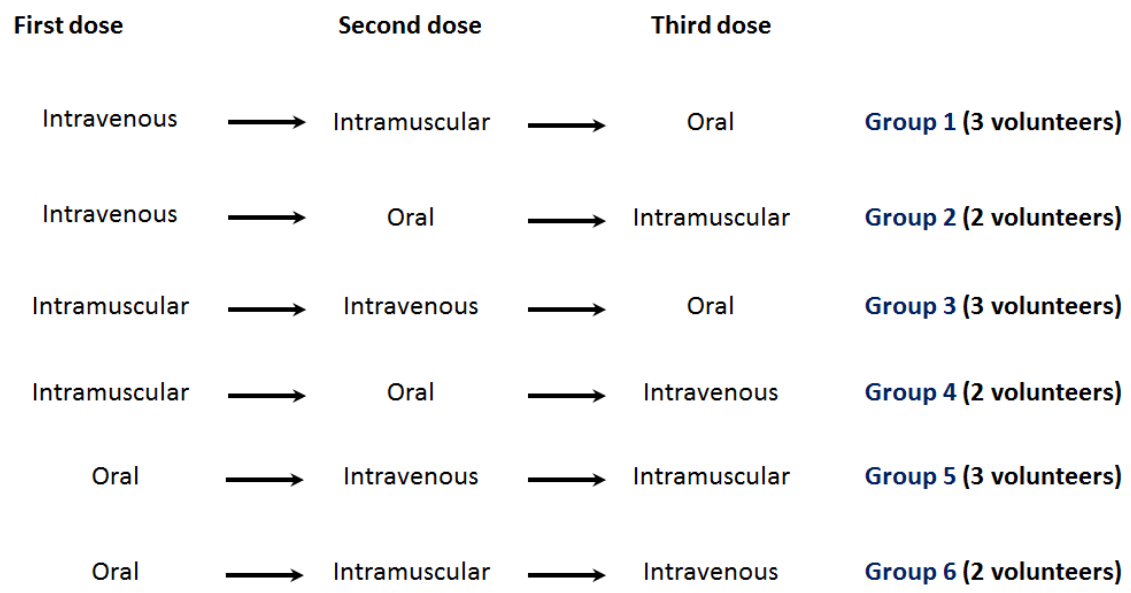

Figure 1: *Overview of randomisation groups*

4.2.2 Number of participating sites

This research is a single centre study which will take place at the Clinical Investigation Centre of Necker Hospital, Paris, France.

4.2.3 Identification of the participants

At inclusion the investigator will assign the patient an inclusion number as follows:

- the first three digits correspond to the centre number, e.g. 001 to 999
- the following four digits correspond to the patient sequential entry number (for example, the third patient screened in centre 001 will be patient 001 0003). The participants will be identified by their inclusion number and initials (participant last and first name initials) for the entire duration of the trial.

4.2.4 Randomisation

Randomisation will be done centrally by using a web-based access to the randomisation system which will be provided by AP-HP. Volunteers will be randomized into each of 6 treatment groups (2-3 patients per group). See section 4.2.1 for overview of treatment groups.

5 PROCEDURE FOR THE TRIAL

Before any examination or intervention may be carried out for the trial, the investigator must obtain the *free, informed and written consent of the participant.*
Participants in the clinical studies described in article L.1121-1(1° paragraph) of the Code de la Santé Publique are eligible for prior medical examination appropriate for the trial.

All visits (except End of Study visit which is telephone follow-up) will take place at Clinical Investigation Centre, Necker Hospital, Paris.

5.1 Screening visit (V0)

Healthy volunteers will be recruited by advertisement in universities or website to the general public.

A first contact by phone or mail with healthy volunteer who wants to participate will be done by investigator in order to verify main eligibility criteria and give information about the study.

If volunteer agrees to consider participation, an appointment for screening visit will be scheduled.

The screening visit will take place between 1 and 7 days before the inclusion visit.

During the screening visit (V0):

Consent: Informed consent must be signed by the participant before any research activity is carried out. An investigator trained on the trial Protocol will provide full information to the participant and will answer all questions the participant may have regarding the study. Once the participant has had all of their questions answered and are willing to proceed, their written consent will be obtained. The participant will be given a copy of the written consent to keep.

Whose consent must be obtained?	Who informs the individual and collects their consent?	When is the individual informed?	When is the individual's consent taken?
The trial participant	The investigator trained on the trial protocol	By mail or phone before screening visit (at the latest when taking appointment for screening visit)	At screening visit

Eligibility assessments:

- Demographic data (including ethnic origin) will be collected. It is necessary to collect information on ethnic origin because this is known to have an impact on the glomerular filtration rate, which could modify the drug pharmacokinetics of tranexamic acid, as it is eliminated 100% by the kidneys.
- Medical History and concomitant treatment are collected to assess eligibility.
- Following Examinations will be performed:
    - **Physical examination** including **weight and height**
    - **Vital signs** (including Blood pressure, heart rate, respiratory rate)
    - **Laboratory tests**:
        - Haematology tests (full blood count)
        - Renal function test (urea, creatinine and GFR calculated according to the CKD-EPI formula [36])
        - Coagulation tests (fibrinogen, D-dimers, prothrombin time and partial thromboplastin time)
        - For women: pregnancy test (urine βhCG)

5.2 Inclusion visit (V1)

All **inclusion and exclusion criteria** have to be checked by physician, to ensure laboratory tests done at the screening visit are within normal values and for women, the pregnancy test is negative.

If a volunteer meets all inclusion and has no exclusion criteria and s/he consents to participate, the participant is considered **enrolled.** The investigator will randomize her/him to one of six groups (see Section 4.2.1).

Visit V1 (=1st drug administration):

- All women must have a **pregnancy test** (urine βhCG) done which must be negative to continue this visit.
- Participants medical history will be checked to ensure there are no changes since V0 visit.
- Baseline blood pressure, heart rate and respiratory rate will be recorded
- T_{-1}: One blood sample will be taken for pharmacokinetics immediately prior to drug administration (0,5 mL venous blood taken in a dry tube without anti-coagulant)

- T_0: Drug Administration (PO, IV or IM) (as per randomization)
- **Pain assessment** using a Visual Analogue Scale (VAS) will be recorded immediately after drug administration and at 2 hourly intervals up to 8 hours. The VAS used will be the Numerical Pain Rating Scale where individuals rate their pain on a ten-point numerical scale. The scale is composed of 0 (no pain at all) to 9 (worst imaginable pain). The duration of any pain associated with IV or IM administration will be assessed once at 8 hours. Participants will be offered pain relief if needed in the form of simple analgesia (paracetamol).

  The duration of any pain associated with IV or IM administration will be assessed once at 8 hours.
- Blood samples for **pharmacokinetics** (*0,5 mL of venous blood in dry tube without anti-coagulant)* will be taken at the following times after drug administration:
  - T0+ 5min (only for IV route)
  - T0+30min
  - T0+1h
  - T0+2h
  - T0+3h
  - T0+4h
  - T0+5h
  - T0+6h
  - T0+8h (only for IM and PO routes)
- **Dry Blood Spot:** At one time-point (any time-point between T0+ 5min and T0+8h), a capillary blood sample will be taken at a finger with a lancet and a drop of blood will be placed on Mitra® device. An aliquot of 200µL of whole blood will be taken and aliquoted from the venous blood sample taken at the same time.
- **Reaction at site of injection:** Each injection site will be checked visually for local reaction and any other complications (including redness, swelling, induration, tenderness, ecchymosis, necrosis, nerve injury, infection) every fifteen minutes after administration for the first one hour then every two hours up to 8 hours after each injection and once at each subsequent visit. Reaction will be measured in millimetre, and time of occurrence will be recorded.

- Participants will have their **vital signs** (blood pressure, heart rate and respiratory rate) monitored and recorded at every fifteen minutes after administration for the first one hour then every two hours after drug administration.
- All **adverse events** and **concomitant treatments** will be recorded. The following adverse events will be elicited specifically (fever, nausea, vomiting, diarrhoea, visual impairment, seizure).

5.3 Follow-up visits

Wash-out period between 2 drug doses is at least 48-hrs (but could be more). All the doses have to be completed within 3 months after the first dose.

Visit V2 (=visit V1 +24h):

- **Pain assessment** using a Visual Analog Scale will be recorded at T_0 +24h (+/- 1 hour). The VAS used will be the Numerical Pain Rating Scale where individuals rate their pain on a ten-point numerical scale. The scale is composed of 0 (no pain at all) to 9 (worst imaginable pain). Participants will be offered pain relief if needed in the form of simple analgesia (paracetamol).
- **Vital signs** (blood pressure, heart rate and respiratory rate) recorded at T_0 +24h (+/- 1 hour).
- Blood samples for **pharmacokinetics (***0,5 mL of venous blood in dry tube without anti-coagulant)* will be taken at T_0 +24h.
- **Reaction at site of injection:** Each injection site will be checked visually for local reaction and any other complications (including redness, swelling, induration, tenderness, ecchymosis, necrosis, nerve injury, infection) at T_0+24h (+/- 1 hour). Reaction will be measured in millimetre, and time of occurrence will be recorded.
- All the **adverse events** and **concomitant treatments** are collected

Visit V3 (=2nd drug administration (must be ≥ 48 hours from V1 T_0):

- All women must have a **pregnancy test** (urine βhCG) done which must be negative to continue this visit.
- Participants medical history will be checked to ensure there are no changes since V0 visit.
- Baseline blood pressure, heart rate and respiratory rate will be recorded

- T_{-1}: One blood sample will be taken for pharmacokinetics immediately prior to drug administration (0,5 mL venous blood taken in a dry tube without anti-coagulant)
- T_0: Drug Administration (PO, IV or IM) (as per randomization)
- **Pain assessment** using a Visual Analogue Scale (VAS) will be recorded immediately after drug administration and at 2 hourly intervals up to 8 hours. The VAS used will be the Numerical Pain Rating Scale where individuals rate their pain on a ten-point numerical scale. The scale is composed of 0 (no pain at all) to 9 (worst imaginable pain). The duration of any pain associated with IV or IM administration will be assessed once at 8 hours. Participants will be offered pain relief if needed in the form of simple analgesia (paracetamol).

  The duration of any pain associated with IV or IM administration will be assessed once at 8 hours.
- Blood samples for **pharmacokinetics** (*0,5 mL of venous blood in dry tube without anti-coagulant)* will be taken at the following times after drug administration:
  - T0+ 5min (only for IV route)
  - T0+30min
  - T0+1h
  - T0+2h
  - T0+3h
  - T0+4h
  - T0+5h
  - T0+6h
  - T0+8h (only for IM and PO routes)
- **Dry Blood Spot:** At one time-point (any time-point between T0+ 5min and T0+8h), a capillary blood sample will be taken at a finger with a lancet and a drop of blood will be placed on Mitra® device. An aliquot of 200µL of whole blood will be taken and aliquoted from the venous blood sample taken at the same time.
- **Reaction at site of injection:** Each injection site will be checked visually for local reaction and any other complications (including redness, swelling, induration, tenderness, ecchymosis, necrosis, nerve injury, infection) every fifteen minutes after administration for the first one hour then every two hours up to 8 hours after each injection and once at each subsequent visit. Reaction will be measured in millimetre, and time of occurrence will be recorded.

- Participants will have their **vital signs** (blood pressure, heart rate and respiratory rate) monitored and recorded at every fifteen minutes after administration for the first one hour then every two hours after drug administration.
- All the **adverse events** and **concomitant treatments** will be recorded.

Visit V4 (=visit V3 +24h):

- **Pain assessment** using a Visual Analog Scale will be recorded at T_0 +24h (+/- 1 hour). The VAS used will be the Numerical Pain Rating Scale where individuals rate their pain on a ten-point numerical scale. The scale is composed of 0 (no pain at all) to 9 (worst imaginable pain). Participants will be offered pain relief if needed in the form of simple analgesia (paracetamol).
- **Vital signs** (blood pressure, heart rate and respiratory rate) recorded at T_0 +24h (+/- 1 hour).
- Blood samples for **pharmacokinetics (***0,5 mL of venous blood in dry tube without anti-coagulant)* will be taken at T_0 +24h.
- **Reaction at site of injection:** Each injection site will be checked visually for local reaction and any other complications (including redness, swelling, induration, tenderness, ecchymosis, necrosis, nerve injury, infection) at T_0+24h (+/- 1 hour). Reaction will be measured in millimetre, and time of occurrence will be recorded.
- All the **adverse events** and **concomitant treatments** are collected.

Visit V5 (=3rd drug administration):

- All women must have a **pregnancy test** (urine βhCG) done which must be negative to continue this visit.
- Participants medical history will be checked to ensure there are no changes since V_0 visit.
- Baseline blood pressure, heart rate and respiratory rate will be recorded
- T_{-1}: One blood sample will be taken for pharmacokinetics immediately prior to drug administration (0,5 mL venous blood taken in a dry tube without anti-coagulant)
- T_0: Drug Administration (PO, IV or IM) (as per randomization)
- **Pain assessment** using a Visual Analogue Scale (VAS) will be recorded immediately after drug administration and at 2 hourly intervals up to 8 hours. The VAS used will be the Numerical Pain Rating Scale where individuals rate their pain on a ten-point numerical scale. The scale is composed of 0 (no pain at all) to 9 (worst imaginable pain). The duration

of any pain associated with IV or IM administration will be assessed once at 8 hours. Participants will be offered pain relief if needed in the form of simple analgesia (paracetamol).

The duration of any pain associated with IV or IM administration will be assessed once at 8 hours.

- Blood samples for **pharmacokinetics** (*0,5 mL of venous blood in dry tube without anti-coagulant)* will be taken at the following times after drug administration:
    - T0+ 5min (only for IV route)
    - T0+30min
    - T0+1h
    - T0+2h
    - T0+3h
    - T0+4h
    - T0+5h
    - T0+6h
    - T0+8h (only for IM and PO routes)
- **Dry Blood Spot:** At one time-point (any time-point between T0+ 5min and T0+8h), a capillary blood sample will be taken at a finger with a lancet and a drop of blood will be placed on Mitra® device. An aliquot of 200µL of whole blood will be taken and aliquoted from the venous blood sample taken at the same time.
- **Reaction at site of injection:** Each injection site will be checked visually for local reaction and any other complications (including redness, swelling, induration, tenderness, ecchymosis, necrosis, nerve injury, infection) every fifteen minutes after administration for the first one hour then every two hours up to 8 hours after each injection and once at each subsequent visit. Reaction will be measured in millimetre, and time of occurrence will be recorded.
- Participants will have their **vital signs** (blood pressure, heart rate and respiratory rate) monitored and recorded at every fifteen minutes after administration for the first one hour then every two hours after drug administration.
- All the **adverse events** and **concomitant treatments** will be recorded.

Visit V6 (=visit V5 +24h):

- **Pain assessment** using a Visual Analog Scale will be recorded at T_0 +24h (+/- 1 hour). The VAS used will be the Numerical Pain Rating Scale where individuals rate their pain on a ten-point numerical scale. The scale is composed of 0 (no pain at all) to 9 (worst imaginable pain). Participants will be offered pain relief if needed in the form of simple analgesia (paracetamol).
- **Vital signs** (blood pressure, heart rate and respiratory rate) recorded at T_0 +24h (+/- 1 hour).
- Blood samples for **pharmacokinetics (***0,5 mL of venous blood in dry tube without anti-coagulant)* will be taken at T_0 +24h.
- **Reaction at site of injection:** Each injection site will be checked visually for local reaction and any other complications (including redness, swelling, induration, tenderness, ecchymosis, necrosis, nerve injury, infection) at T_0+24h (+/- 1 hour). Reaction will be measured in millimetre, and time of occurrence will be recorded.
- All the **adverse events** and **concomitant treatments** are collected.
- **Laboratory tests**:
    - Haematology tests (full blood count)
    - Renal function test (urea, creatinine and GFR)
    - Coagulation tests (fibrinogen, D-dimers, prothrombin time and partial thromboplastin time)
    - For women: pregnancy test (urine βhCG)

5.4 End of study visit

Due to the low toxicity of the molecule and its half-life ranging from 1 to 10 hours (depending on patient populations), healthy volunteers who participated in the study and received at least one administration of tranexamic acid will have a telephone follow-up after the end of the study. They will be contacted by **telephone 48 hours after the last administration** to check for any adverse events.

5.5 Expected length of participation, chronology and duration of the study.

Maximum period between screening and enrolment	7 days
Inclusion period	16 months
Duration of participation for each participant	Screen + 3x 2 days + 1 phone contact = over 3 months
Total study period	19 months

Table summarising the chronology of the study

Action	**Visit V0** Screening	**Visit V1** Inclusion	**Visit V2** V1+24h	**Visit V3**	**Visit V4** V3+24h	**Visit V5**	**Visit V6** V5+24h	**End of Study**
Verification of Eligibility Criteria	X	X						
Signature of Informed Consent	X							
Demographic data	X							
Medical History	X							
Physical Examination, including **weight and height**	X							
Vital signs (including Blood pressure, heart rate, respiratory rate)	x	x	x	x	x	x	x	
Randomisation		x						
Drug Administration (PO, IM or IV)		X		X		X		
Pain (Visual Analogue Scale and duration of pain)		X	X	X	X	X	X	
Reaction at injection sites		X	X	X	X	X	X	
Laboratory Tests	X	X		X		X	X	
Haematology tests (full blood count)	x						x	
Renal function test (urea, creatinine, GFR)	x						x	
Coagulation tests (fibrinogen, D-dimers, prothrombin time and partial thromboplastin time)	x						x	
For women: pregnancy test (urine βhCG)	x	x		x		x	x	
Pharmacokinetic		X	X	X	X	X	X	
1 sample immediately prior to drug administration		x		x		x		
8 samples from T0+5min to T0+8h		x		x		x		
1 sample at T0+24h			x		x		x	
Dry Blood Spot: 1 capillary sample at any time-point between T0+5min and T0+8h and one 200 µL whole blood aliquot of the venous sample taken at the same time		X		X		X		
Concomitant treatments	X	X	X	X	X	X	X	
Adverse Event		X	X	X	X	X	X	X
Telephone Follow-Up								X

5.6 Distinction between standard care and research

This study includes only healthy volunteers. All procedures are related to the trial.

5.7 Biological samples

5.8.1 Pharmacokinetics study

Serum PK samples: each dosage requires 0,5 ml of blood in dry tube without anticoagulant. The PK sample will then be centrifuged for 10 min at 4 000 rpm then the serum will be frozen at -20°C

The samples will be kept frozen at -20°C in the Clinical Investigation Centre of Necker Hospital. Once all the samples have been collected, they will be sent frozen to the mass spectrometry platform of the UFR Sciences de la Santé Simone Veil, University Versailles Saint Quentin, 2 avenue de la source de la Bièvre, 78180 Montigny le Bretonneux, France to perform the analysis under the supervision of Dr Grassin-Delyle.

Dry Blood Spot: for each participant, at visit 1, 3 and 5, at one time-point (any time-point between T0+ 5min and T0+8h), a capillary blood sample will be taken at a finger with a lancet and a drop of blood will be placed on Mitra® device. An aliquot of 200µL of whole blood will be taken and aliquoted from the venous blood sample taken at the same time. The filter papers will be kept at ambient temperature in the Clinical Investigation Centre of Necker Hospital during the study period. Once all the samples have been collected, they will be sent in the same time than serum PK samples to the UFR Sciences de la Santé Simone Veil, University Versailles Saint Quentin.

The inclusion number will be used to identify the sample, no identifying data will be transferred to the laboratory.

Once all analysis for this trial has been completed, all blood samples will be destroyed.

5.8 Termination and exit rules

5.8.1 Criteria and procedures for prematurely terminating the study treatment

- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the subject's source file and the case report form (CRF)

- Premature termination of treatment, but the participant remains enrolled in the study until the end of the subject's participation: the investigator must document the reason
- Premature termination of treatment and exit from the study. The investigator must:
    - Document the reason(s)
    - Collect all endpoints at the moment the subject exits from the study, if the subject agrees
    - Schedule further follow-up visits, especially in case of a serious adverse event.

5.8.2 Criteria and procedure for premature withdrawals and exits from the study

- Participants may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interest. For the safety of participants, if any of the following adverse events occur during the course of the trial, the investigator should permanently withdraw the participant: (1) allergic reaction to tranexamic acid (2) any thromboembolic event (3) any renal impairment (4) any visual disturbances attributed to tranexamic acid. If more than 5 patients were withdrawn from the study for safety reasons, the study would be terminated.

Participants lost to follow-up (that is, the participant cannot be located): The investigator must make every effort to reconnect with the participant (and record her/his attempts in the source file), at least to determine whether the participant is alive or dead.

If a participant exits the trial prematurely or withdraws consent, data collected prior to the date of premature exit will be used.

The case report form must list the various reasons why the subject exited or was withdrawn from the study:

- ☐ Adverse reaction
- ☐ Other medical problem
- ☐ Subject's personal reasons
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

5.8.3 Monitoring participants after the premature termination of treatment

In case of adverse events, the investigator must notify AP-HP and monitor the participants until the end of her/his participation in the research. If treatment is stopped prematurely due to a serious adverse event, a serious adverse event report will be sent by email (eig-vigilance.drc@aphp.fr) to DRCI. The serious adverse event will be monitored until it is resolved.

5.8.4 Procedure for replacing participants

Participants who have signed a consent form but fail to meet the eligibility criteria after screening visit, will not be considered enrolled and must not be randomized or initiated on treatment. These participants will be replaced in order to have 15 randomized.

Randomized participants who have not received all three drug doses will be replaced. In this case, the replacement will be allocated to the same randomisation group.

5.8.5 Full or partial cancellation of the study

LSHTM (the sponsor), or the Competent Authority (ANSM) may prematurely discontinue all or part of the trial, temporarily or permanently, in the following situations:

- if unexpected facts or new information about the product, in light of which the objectives of the study or clinical programme are unlikely to be achieved.
- LSHTM reserves the right to permanently suspend enrolment at any time if the enrolment targets have not been met.

If the study is cancelled prematurely, AP-HP will inform the Competent Authority (ANSM) and the Institutional Review Board of its decision within 15 days, together with justification for the decision.

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Adult healthy volunteers both men and non-pregnant women
- ≥18-≤45-year-old
- Body mass index between ≥18 and ≤30 kg/m2, and bodyweight between ≥50 and ≤100 kg
- Coagulation test results of fibrinogen, D-dimers, prothrombin time and a partial thromboplastin time within normal limits at screening

	Normal limits
fibrinogen	*[1.5 - 3.5 g/L]*
D-dimers	*< 500 ng/mL*
prothrombin time	*> 70 %*
partial thromboplastin time	*< 1.2*

- Normal renal function based on medical history and laboratory tests (laboratory test of serum creatinine should in the range of 0.6–1.1 mg/dL for women and 0.7–1.3 mg/dL for men. Glomerular filtration rate (GFR) should be 90 mL/min/1.73m^2 or greater (adjusting for age, sex, weight and ethnicity)
- If a woman, must have a negative urine β-human chorionic gonadotropin (βhCG) pregnancy test at screening and inclusion visits
- Provision of signed informed consent prior to any study specific procedure
- People with public healthcare insurance

6.2 Exclusion criteria

- Previous thrombotic event or pre-existing pro-thrombotic disease
- Any history of seizures
- Any chronic or active cardiovascular or renal disease
- Planned general anaesthesia or surgery in the 3 months following inclusion
- Pregnant and/or breastfeeding
- Visual disturbance
- Haematuria
- Known allergy or contraindication to the study drugs or any of the excipients of the formulations

- Use of any prescription or non-prescription medication (including hormonal contraception) within 7 days before the first dose of the study drug is scheduled
- Inability to give informed consent
- Previous participation during the year in clinical studies compensated for an amount incompatible with participation in this study, verified by recording in the national register of subjects participating in human research trials.
- Legal criteria:
  - Patient deprived of liberty by judicial or administrative decision
  - Adult protected by law

6.3 Recruitment methods

Healthy volunteers will be recruited by advertisement in universities or website

Total number of participants to be randomized and received at least one dose and have one post dose PK sample.	15
Number of sites	1
Enrolment period (months)	16
Number of participants/site	15
Number of participants/site/month	1

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

7.1 The investigational medicinal product

7.1.1 Tranexamic Acid

Patient will receive the marketed forms of tranexamic acid (Exacyl®):

- Exacyl® (Sanofi Aventis) 0.5 g/5 ml injectable solution IV
- Exacyl® (Sanofi Aventis) 1 g/10 ml oral solution

Storage conditions: each package contains 5 vials which will be stored at ambient temperature at Necker Hospital Pharmacy, Paris, France.

Labeling: each vial will be labelled for “research use only”

Dosing: Each volunteer will receive one dose tranexamic acid through each of the three routes on three separate days. The selected doses and routes are:

- Intravenous route: 1 g (2 vials x 5 mL, total volume 10 mL) will be given by in slow infusion at a rate of approximately 1 mL/min by trial personnel trained to administer IV injections.
- Intramuscular route: 1 g (2 vials x 5 mL). Each 5mL will be injected separately to the deltoid muscle of the arms or the vastus lateralis muscle of the thighs. IM injections will only be administered by trial personnel trained to administer these. Each injection will be given using the Z-track method. The Z-track is a method of administrating an IM injection that prevents the medication being tracked through the subcutaneous tissue, sealing the medication in the muscle, and minimizing irritation from the medication. Using the Z-track technique, the skin is pulled laterally, away from the injection site, before the injection; then the medication is injected, the needle is withdrawn, and the skin is released [37]. The site of each injection will be recorded.
- Oral route: 2 g (2 vials x 10 mL) will be swallowed.

7.2 Traceability information for the investigational medicinal product

The investigational medicinal products will be purchased and managed by the Pharmacy at Necker Hospital, Paris. The lot number and expiry date of each dose of drug and the inclusion number of the participant will be recorded on a Drug Accountability Log. Date, time and name of person administering each dose will be recorded.

7.3 Authorised and prohibited treatments (medicinal, non-medicinal, surgical), including emergency medications

Prohibited Medication/Class of drug:	**Usage:**
Any other prescription or non-prescription medication	*NA*

The following medications and procedures are allowed during the study:

Rescue/Supportive Medication/Class of drug:	**Usage:**
Any emergency drug which would be required for volunteer care	*Emergency treatment*

7.4 Methods for monitoring compliance with the treatment

A single dose per route (oral, intramuscular and intravenous) of TXA will be administered by investigators at the hospital. If a dose is not administered, the reason for this will be recorded in the CRF.

8 EFFICACY ASSESSMENT

8.1 Description of parameters for assessing efficacy endpoints

Due to its very high specificity, mass spectrometry is recognized as a reference method for drug analysis. Our team is experienced in mass spectrometry and has a record of publication in the development of new methods, including tranexamic acid [38-43]. Tranexamic acid will be measured in samples with liquid chromatography coupled to mass spectrometry according to an analytical method validated following the EMA guideline on bioanalytical method validation [40,43].

8.2 Anticipated methods and timetable for measuring, collecting and analysing the efficacy data

Drug concentration is collected at Visits V1, V2, V3, V4, V5 and V6: for more details see sections 5.2 and 5.3.

9 SPECIFIC COMMITTEES FOR THE TRIAL

9.1 Scientific committee

A Protocol Development Committee comprising members from the Sponsor (LSHTM), APHP and coordinating investigator has been convened.

Membership:

- Stanislas Grassin Delyle
- Ian Roberts
- Michaela Semeraro
- Haleema Shakur-Still
- Jean-Marc Tréluyer

Operation procedures:

Their role will be to ensure that the trial design is appropriate and all ethical, regulatory and scientific aspects of the trial have been considered. In the event the protocol requires amending, this committee will review and recommend any changes. The final decision for any amendment to the Protocol resides with the Sponsor.

10 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE STUDY

10.1 Safety endpoints

Safety Endpoints are:

- ✓ Number of participants with solicited local and systemic adverse events.
- ✓ Average pain score reported by participants during intramuscular administration (visual analogic scale)
- ✓ Duration of pain from intramuscular administration (hours)
- ✓ Local reaction at site of injection (redness, swelling, induration, tenderness, ecchymosis, necrosis, nerve injury, infection)
- ✓ Systemic events (fever, nausea, vomiting, seizure, diarrhoea, visual impairment)
- ✓ Vital signs (blood pressure, heart rate and respiratory rate) after administration

Number of participants reporting one or more adverse events and serious adverse events

10.2 Anticipated methods and timetable for measuring, collecting and analysing the safety endpoints

Safety Endpoints are recorded at each visit: for more details see sections 5.2 and 5.3.

- ✓ Pain is assessed by Visual Analog Scale (intensity from 0 to 9)
- ✓ Reaction at site of injection is assessed by visual inspection (measure in mm of the surface in case of reaction, and time of occurrence)

10.3 Recording and reporting adverse events

10.3.1 Definitions

According to Article R1123-46 of the French Public Health Code:

- **Adverse event**

Any untoward medical occurrence in a trial subject, which does not necessarily have a causal relationship with the clinical trial or with the investigational product.

- **Adverse reaction to an investigational medicinal product**

Any adverse event occurred in a trial subject, which has a causal relationship with the clinical trial or with the investigational medicinal product

- **Serious adverse event or reaction**

Any adverse event or reaction that at any dose of medication, results in death, threatens the life of the research subject, requires hospitalisation or prolongs hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity.

- **Unexpected adverse reaction to an investigational medicinal product**

Any adverse reaction to the product, whose nature, severity, frequency or outcome is inconsistent with the safety information described in the Reference Safety Information (summary of product characteristics, or the investigator's brochure if the product is not authorised).

<u>According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for clinical trial sponsors (ANSM)</u>:

- **Emerging safety issue**

Any new safety information that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.

For the clinical trials involving the first administration or use of an investigational medicinal product in healthy volunteers, any serious adverse reaction.

Examples:

a) any clinically significant increase in the frequency of an expected serious adverse reaction

b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial that are notified by the investigator to the sponsor together with follow-up reports

c) any new safety issue relating to the conduct of the clinical trial or the development of the investigational medicinal product, that may impact the safety of the trial subjects.

Examples:

- a serious adverse event likely to be related to the interventions and the trial's diagnostic procedures and which may impact the conduct of the clinical trial,

- a significant risk on the trial subjects such as ineffectiveness of the investigational medicinal product in treating a life-threatening illness under investigation,
- significant safety results from a recently completed non-clinical study (such as a carcinogenicity study),
- the premature termination, or temporary suspension, of a trial conducted on the same investigational medicinal product in another country, for safety reasons,
- an unexpected serious adverse reaction associated with a non-experimental medication required for the conduct of the clinical trial, (e.g. challenge agents, rescue treatment)

d) any suspected unexpected serious adverse reaction (SUSAR) reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication.

10.3.2 The role of the investigator

The investigator must **assess the seriousness criteria of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF).
The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the severity** of the adverse events by using:

- Common Terminology Criteria for Adverse Events [National Cancer Institute]

The investigator must assess the **causal relationship** between the serious adverse events and the investigational medicinal product(s).

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not ruled out).

These terms are defined as follows (extracted from the WHO-UMC causality categories, version dated 17/04/2012).

Table 1: WHO-UMC causality categories (extract)

Causality term	Assessment criteria*
Certain	· Event or laboratory test abnormality, with plausible time relationship to drug intake ** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable / Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake ** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake ** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with
** Or study procedures

10.3.2.1 Serious adverse events that require a notification without delay by the investigator to the sponsor via AP-HP.

As per article R.1123-49 of the French Public Health Code (CSP), the investigator must notify the sponsor representative (APHP) **without delay on the day when the investigator becomes aware** of any serious adverse event which occurs during a trial as described in Article L.1121-1(1) CSP.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening
3- requires inpatient hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

10.3.2.2 Specific features of the protocol

10.3.2.2.1 Other events that require the investigator to notify the sponsor via AP-HP without delay

- Adverse events judged as being "medically significant"

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of these adverse events, according to the same modalities and within the same timeline as for serious adverse events (see above).

- ***In utero exposure:*** The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any pregnancy that occurs during the trial, even if not associated with an adverse event.

  If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be reported to the sponsor.

  The events are reported using a special form, appended to the protocol.

  - Exposure **via breastfeeding**

Exposure via breastfeeding occurs if an infant or child could have been exposed *via* the breast milk of a mother being treated with an investigational medicinal product.

Even if such exposure is not associated with an adverse event, the investigator must always notify the sponsor without delay on the day when the investigator becomes aware of any exposure via breastfeeding.

10.3.2.3 Period during which the investigator must send notification of SAEs to the sponsor represented by AP-HP without delay

The investigator notifies the sponsor without delay of all the serious adverse events listed in the corresponding section:

- starting from the date on which the subject signs the consent form
- throughout the whole follow-up period intended by the trial
- until 48 hours after the end of the subject's treatment with the investigational medicinal product.
- indefinitely, if the SAE is likely to be due to the investigational medicinal product

10.3.2.4 Procedures and deadlines for notifying the sponsor

The investigator should initially complete a SAE reporting form (contained in the case report form). This report must be signed by the investigator.

The investigator must complete every section of the SAE form so that the sponsor via AP-HP can carry out the appropriate assessment.

The initial report sent to the sponsor represented by AP-HP must be rapidly followed up by one or more additional written reports describing the course of the event and any complementary information.

Whenever possible, the investigator will provide the sponsor represented by AP-HP with any documents that may be useful for medical assessment of the case (medical reports, laboratory test results, results of additional exams, etc.). These documents must be anonymized. In addition, the investigator must state the study acronym and the inclusion number and initials of the study participant on each paper of the attached document.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has terminated his/her participation in the trial.

The initial report, the SAE follow-up reports, and all other documents must be sent to AP-HP by e-mail (**eig-vigilance.drc@aphp.fr**). It is possible to send the SAE to the AP-HP's Safety department by fax No. **+33 (0)1 44 84 17 99** only in case of unsuccessful attempt to send the SAE by e-mail. This is to avoid duplicated reports.

For trials which use e-CRF:

- the investigator completes the SAE report form in the e-CRF, then validates, prints and signs the form before sending it by e-mail;
- In case of failure to connect to the e-CRF, the investigator should complete, sign and send the SAE report form to the safety Department. As soon as the connection is restored, the investigator must complete the SAE report form in the e-CRF.

The investigator must comply with all requests for additional information from AP-HP.

For all questions relating to an adverse event report, the safety Department can be contacted via email at vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the initial notification and follow-up report forms for pregnancy exposure during trial participation".

The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy ends, and must notify the sponsor of the outcome of the pregnancy, using this form.

If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.

The initial pregnancy report form, the SAE follow-up forms and any other documents will be sent to the sponsor using the same modalities as described above.

If it was the father who was exposed, the investigator must obtain the mother's permission before collecting information about the pregnancy.

10.3.3 Role of the sponsor

The sponsor, represented by AP-HP, shall continuously assess the safety of the investigational medicinal product throughout the trial.

10.3.3.1 Analysis and declaration of serious adverse events

The sponsor assesses through AP-HP's Safety Department:

- the **seriousness** of all reported adverse events,
- the **causal relationship** between these adverse events and investigational medicinal product and/or study procedures and any other treatments,

  All serious adverse events for which the investigator and/or the sponsor suspect a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expectedness assessment** of the serious adverse reactions

  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, is considered unexpected.

  The sponsor, acting through AP-HP's Safety Department by delegation, assesses the expectedness of the serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal product(s) refer to the SmPC for:

- EXACYL 0,5 g/5 ml sol inj IV, enclosed in appendix 4.
- EXACYL 1 g/10 ml sol buv, enclosed in appendix 5.

No specific safety problems can be anticipated in the population of healthy volunteers from this open-label study, who will each receive 3 doses of the drug over a short period of time, at doses well below those used in clinical routine in some centres.

Indeed, tranexamic acid has had a marketing authorization for several decades and is used daily in hospitals in a number of indications, as well as in pre-hospital settings in emergency situations.

This drug has a very favourable benefit/risk ratio and a wide therapeutic range. The only adverse reactions that it can cause frequently are digestive (SPC), without any severity criteria.

The only differences between the intravenous and intramuscular routes are related to the site of administration itself and possible pharmacokinetic differences. With regard to the administration site, the risks associated with intramuscular injections are well known and the intramuscular administration itself will be carried out by a team experienced in clinical research, in an adapted structure (CIC). At the pharmacokinetic level, the routine route of administration used in hospitals is the intravenous route, which by definition has the maximum bioavailability. The exposure of patients by the IM route will therefore be at most identical to that obtained by the IV route, which is already suggested by the data available in the literature. Tranexamic acid does not undergo any hepatic metabolism, no drug interaction related to this hepatic metabolism can occur, especially since the study population will not receive any treatment. The elimination of tranexamic acid is 100% renal and the renal function of the study population will be verified beforehand.

In conclusion, there is no pharmacokinetic or pharmacodynamic argument to suggest any risk to the patients in the proposed study.

For trials conducted on healthy volunteers, the sponsor represented by AP-HP will report without delay to the ANSM all serious adverse events and reactions (whether they are expected or not)

Any suspected unexpected serious adverse reaction must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).

The sponsor represented by AP-HP must notify all the investigators about any information that could adversely affect the safety of the trial subjects.

10.3.3.2 Analysis and declaration of other safety data

This relates to any emerging safety issue that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.

For the clinical trials involving the first administration of a medicinal product in healthy volunteers, emerging safety issue is defined as all serious adverse reactions occurring in trial participants.

The sponsor represented by AP-HP by delegation will inform the competent authority and the Ethics Committee without delay after becoming aware of the emerging safety issue and, if applicable, describe what urgent safety measures have been taken.

The sponsor represented by APHP will report to the *Directeur général de l'Agence Régionale de Santé* any emerging safety issue occurring in healthy volunteers taking part in a clinical trial and any urgent safety measures that have been taken by the sponsor.

Following the initial declaration of any emerging safety issue, the sponsor represented by AP-HP will report to ANSM any additional relevant information about the emerging safety issues in the form of a follow-up report, which must be sent no later than 8 days upon knowledge of the sponsor.

In all cases, AP-HP will inform the Sponsor (LSHTM) of all serious adverse events and any emerging safety issues within 24 hours of it becoming aware of any reports/issues. Written copies of all information will be provided to the Sponsor (LSHTM) by AP-HP.

10.3.3.3 Annual safety report

The sponsor (LSHTM) must prepare once yearly throughout the trial duration an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:

- an analysis of safety data concerning trial participants
- a description of the participants included in the trial (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- cumulative summary tabulation of all the serious adverse events that have occurred since the beginning of the clinical trial,

The DSUR will be transmitted to ANSM on the 6 November each year until final closeout. The Sponsor has several ongoing trials of tranexamic acid which reports annually across the European Union. The anniversary date for reporting is 6 November.

10.3.4 Data Safety Monitoring Board (DSMB)

There is no need to create a DSMB for this trial. Tranexamic acid is a marketed product with robust safety and efficacy data available for both the oral and intravenous routes. Although there is less data available on the intramuscular route, we do not anticipate any safety issues. Also the trial includes only 15 participants and will be completed within a short timeframe.

11 DATA MANAGEMENT

11.1 Data collection

Information required in the research protocol must be collected in the case report form (CRF) and an explanation must be given by the investigator for each missing data. Data must be reported in the electronic CRF when they are available, for clinical or para-clinical data. Correction of discordant data on CRF will be asked through queries. In the CRF, the changes in the data will be tracked. Anonymization of the patients will be ensured using a code number and initials, reported on each document needed for the research, or by erasing nominative data on copies of source documents.

11.2 Identification of data recorded directly in the crfs which will be considered as source data

None

11.3 Right to access source data and documents

11.3.1.1 Access to data

In accordance with GCP:

- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures.
- the investigators will ensure the persons in charge of monitoring and auditing the clinical trial and of quality control have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.3.1.2 Source documents

The source documents are any original document or item that proves the existence or accuracy of a data-point or fact recorded during the trial. Source documents will be kept by the investigator, or by the hospital in the case of hospital medical records, for the statutory period. The sponsor requires source documents to be kept for 15 years after the end of trial declaration.

11.3.1.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular the identity of the participants and the results obtained.

These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the French Criminal Code).

During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised.

Under no circumstances will the names and addresses of the subjects be shown.

Only the participant’s initials will be recorded, along with an identification code specific to the study.

The sponsor will ensure that each participant has agreed in writing for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.4 Data processing and storage of documents and data

11.4.1 Data entry

Data will be entered electronically via a web browser provided by Clinical Research Unit of Necker Hospital, APHP.

11.4.2 Data processing (CNIL) outside of France

Data will be sent within the European Union or to an "acceptable" country: United Kingdom.

11.4.3 Archiving

The specific documents for a clinical trial on a medicinal product for human use will be archived by the investigator and the sponsor for 15 years after the end of the trial.

11.5 Ownership of the data

LSHTM is the owner of the data of this trial. The data cannot be used or disclosed to a third party without its prior permission.

12 STATISTICAL ASPECTS

12.1 Planned statistical methods, including the timetable for any planned interim analyses

There are no planned interim analyses.

Safety Population: All participants who receive study medication (TXA oral, IV, IM) will be included in the Safety Population.

Pharmacokinetic Population: All participants who receive one dose of TXA and have at least 1 blood sample to determine serum concentrations of TXA will be included in the PK data analysis.

Safety Parameters: Individual and summary vital signs, pain scale scores, skin reaction measurement and clinical laboratory data will be presented in tabular form with mean, median, standard deviation and range (minimum and maximum) as appropriate.

For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Frequencies and percentages will be presented by dose group for participants who had a shift to low and for those who had a shift to high from baseline to any post-dosing assessment. The number and percentage of participants in each dose group with normal and abnormal physical examination results will be presented for evaluations at baseline and final visit. For each body system, changes in findings from baseline to final visit (no change, normal to abnormal, or abnormal to normal) will be tabulated for each dose group.

Individual and summary blood pressures, pulse, and respiration rate, and clinical laboratory data (haematology, serum biochemistry, coagulation,) will be presented in tabular form with mean, median, standard deviation and range (minimum and maximum) as appropriate.

Adverse events will be tabulated and summarised according to the current version of Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded by System Organ Class and Preferred Term using the MedDRA dictionary. Safety analyses will be carried out using STATA (newest version)

Pharmacokinetic analysis: Tranexamic acid time-courses will be analysed using the nonlinear mixed effect modelling software program Monolix 2019R1 version (www.lixoft.eu) [44], according to previous works from our team [45-48]. Briefly, parameters will be estimated by computing the maximum likelihood estimator of the parameters without any approximation of the model (no linearization) using the stochastic approximation expectation maximization (SAEM) algorithm combined to a Markov Chain Monte Carlo (MCMC) procedure (to ensure full convergence, the MCMC will be fixed to 20 and the iteration number to 1000). Different error models will be investigated (i.e. multiplicative, proportional and/or additive error models) to describe residual variabilities (expressed as σ, square root of σ^2), and the between-subject variabilities (expressed as ω, square root of the variance ω^2) will be ascribed to an exponential model. The Bayesian information criterion (BIC) will be used to test different hypotheses regarding the model, i.e.

i) covariate effect(s) on pharmacokinetic parameter(s),

ii) residual variability model (proportional versus proportional plus additive model)

and iii) structure of the variance-covariance matrix for the ω parameters.

Main covariates of interest in the population will be age, bodyweight (BW) and renal function. Parameter estimates will be standardised for a mean standard covariate using an allometric model: $P_i = P_{STD} \times (COV_i/COV_{STD})^{PWR}$ where P_{STD} is the standard value of parameter and P_i and COV_i are the parameter and covariate values of the i^{th} individual. The PWR exponents may be estimated from the data. However, for bodyweight, allometric scaling theory dictates that these are typically 0.75 and 1 for clearance and volumes terms respectively [49]. The goodness-of-fit of each model will be evaluated by visual inspection of the individual concentration-time courses, the observed-predicted (population and individual) concentration scatter plots and the prediction-corrected visual predictive checks.

12.2 Hypotheses for calculating the required number of subjects, and the result

According to PFIM 3.2.1 software [50] and based on the population pharmacokinetic parameters determined in a meta-analysis of the different pharmacokinetic studies published in healthy volunteers[10], a sample size of 15 healthy volunteers will allow to estimate accurately the pharmacokinetic parameters of the 3 administration tranexamic acid routes (Relative Standard Errors < 30%). Optimal blood sampling times were also evaluated and are as follows: immediately prior to dosing and 5 min, 30 min and 1, 2, 3, 4, 5, 6, 24 hours after intravenous administration. Regarding the IM and oral administration, the sampling times will be as follows: immediately prior to dosing and 0.5, 1, 2, 3, 4, 5, 6, 8 and 24 hours after the tranexamic acid administration.

13 QUALITY CONTROL AND ASSURANCE

Every clinical study managed by AP-HP is ranked according to the projected risk incurred by the study participants using a classification system specific to AP-HP-sponsored clinical trials.

13.1 General organisation

The sponsor (LSHTM) represented by APHP must ensure the safety and respect of individuals who have agreed to participate in the trial. The sponsor must have a quality assurance system (via APHP) for monitoring the implementation of the study at the research centres.

For this purpose, the sponsor shall appoint appropriately qualified staff, trained in monitoring activities, whose role is to carry out regular follow-up visits at the study sites, after completing their initial visits.

The purpose of monitoring the study, as defined in the Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the research subjects are safe, protected and their rights are being met
- the data being recorded is accurate, complete and consistent with the source documents
- the study is carried out in accordance with the current version of the protocol, with GCP and with all statutory and regulatory requirements.

13.1.1 Strategy for site opening

There is only one study site in this trial. An audit of the trial site facilities by the Sponsor (LSHTM) will be carried out before the trial can be opened. Recruitment to the trial can only start once the Sponsor has confirmation that all necessary approvals for the conduct of the trial are in place and the site has been trained on the protocol.

13.1.2 Scope of site monitoring

For this study, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, the sponsor, in agreement with the coordinating investigator, has agreed on a logistical score and impact and the corresponding study monitoring level of: D level (higher level for APHP).

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor (via APHP) will be responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI and in accordance with Good Clinical Practice as well as with the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent
- compliance with the study protocol and its procedures
- quality of the data collected in the case report forms: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

13.3 Case report form

All information required by the protocol must be entered in the case report forms. The data must be collected as and when it is obtained, and clearly recorded in these case report forms. A reason must be given for any missing data.

The trial site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given instructions for using this tool.

Using on-line case report forms means the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, there are consistency checks to ensure the data are verified immediately upon being entered. The investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result the investigator or any other individual involved in conducting the study failing to comply with the protocol, standard operating procedures, good clinical practice or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

The sponsor has its own procedures for managing these non-compliances. All non-compliances must be reported to the Sponsor as soon as possible, and no later than 24 hours of identifying a non-compliance has occurred.

Any serious or potential serious breaches identified by the trial site or AP-HP (represented by DRCI) must be reported to the Sponsor (LSHTM) without delay on the day (within 24 hours) it is identified aware of these)

A “serious breach” is a breach which is likely to effect to a significant degree –

a) The safety or physical or mental integrity of the subjects of the trial; or

b) The scientific value of the trial

The sponsor is responsible for reporting all serious breaches to the relevant Regulatory Authority and Ethics Committee.

13.5 Audits/inspections

The Sponsor (LSHTM) will also be responsible for auditing all aspects of the trial. Audits will include the Sites (Unité de Recherche Clinique et Centre d'Investigation Clinique Paris Descartes Necker Cochin, including the Pharmacy, CIC) and Clinical Research and Innovation Delegation (DRCI). AP-HP audits will be carried out where appropriate.

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the basis of medical secrecy.

An audit can be carried out at any time by independent individuals appointed by the sponsor. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the trial agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study.

13.6 Principal investigator's declaration of responsibility

Before starting the trial, each investigator must be trained on Good Clinical Practice and must give DRCI a signed and dated copy of his/her curriculum vitæ and RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

Each investigator will agree to comply with legislation and to conduct the trial in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at the participating site will sign a declaration of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their co-workers will sign a delegation form specifying each person's role. The Site principal investigator is responsible for ensuring that all co-workers delegated trial related tasks are fully trained.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing and obtaining consent from the research participants

In accordance with Article L.1122-1-1 of the French Public Health Code, no research can be carried out on a person without his/her free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code.

The person’s free and informed written consent will be obtained by the investigator, or by a doctor representing the investigator, before the person is enrolled on the trial.

The information sheet and a copy of the consent form, signed and dated by the research subject and by the investigator or the doctor representing the investigator, will be given to the individual prior to being enrolled on the trial.

In addition, the investigator will specify in the research participant’s medical file the methods used for obtaining their consent as well as the methods used for providing information with a view to obtaining consent. The investigator will retain the original signed and dated consent form. A third copy will be sent to DRCI.

14.2 Prohibition of concomitant clinical studies participation and exclusion period after the trial, if applicable

Whilst participating in this trial, participants may not take part in any other interventional clinical study.

14.3 Compensation for participants

Participants will receive a total of 750€ in compensation for the inconveniences relating to the trial.

14.4 Registration on the national register of subjects participating in human research trials on the products listed in article l. 5311-1 of the French public health code

Healthy volunteers participating in this study will be registered by Clinical Investigation Centre of Necker Hospital on with the organization, 'Volunteers for Biomedical Research' (https://vrb.sante.gouv.fr/vrb/) to prevent them from participating in multiple studies at the same time.

14.5 Legal obligations

14.5.1 The sponsor's role

The London School of Hygiene and Tropical Medicine, London, UK is the Sponsor of this trial. Assistance Publique Hôpitaux de Paris (AP-HP) has agreed to carry out the sponsorship requirements for this study. AP-HP has delegated responsibilities to its Clinical Research and Innovation Delegation (DRCI) in order to conduct the study in accordance with Article L.1121-1 of the French Public Health Code. LSHTM reserves the right to terminate the study at any time for medical or administrative reasons. In this case, AP-HP and the Site principal investigator will be informed accordingly.

14.5.2 Request for approval from the Institutional Review Board

AP-HP is responsible for obtaining prior approval from the Institutional Review Board for its clinical trials of medicinal products for human use, within the scope of the Board's authority and in accordance with statutory and regulatory requirements.

14.5.3 Request for approval from the ANSM

AP-HP is responsible for obtaining prior authorisation from Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) for this clinical trial of medicinal products for human use, within the scope of the ANSM's authority and in accordance with statutory and regulatory requirements.

14.5.4 Procedures relating to data protection and individual liberties

The data files used for this research is implemented according to French regulation (amended data protection act) and European regulation (General regulation on data protection – RGPD

Declaration of compliance with the MR 001 "Reference Method"

This research is governed by the CNIL 'Reference Method for processing personal data for clinical studies' (MR-001, amended). AP-HP confirms that it has signed a declaration of compliance with this "Reference Method".

14.5.5 Modifications to the trial

Any substantial amendment which may be needed to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to implementing the amendment, approval from the Institutional Review Board and authorisation from the ANSM, within the scope of their respective authorities.
The information sheet and the consent form can be revised if necessary, in particular if there is substantial amendment to the study or if adverse reactions occur.

14.5.6 Final study report

The final study report referred to in CSP Article R.1123-67 is written and signed by the sponsor, AP-HP and the Site investigator. A report summary, meeting the competent authority's guidelines, has to be sent to the competent authority and Institutional Review Board within one year of the end of the trial i.e. the end of the participation of the last study participant.

15 FUNDING AND INSURANCE

15.1 Sources of funding for the trial

LSHTM has received funding from the Wellcome (WT208870/Z/17/Z) and the Bill & Melinda Gates Foundation (OPP1176150) for this study. The study is being conducted as an academic collaboration between LSHTM, Assistance Publique-Hôpitaux de Paris (AP-HP), Unité de Recherche Clinique et Centre d'Investigation Clinique Paris Descartes Necker Cochin and UFR Sciences de la Santé Simone Veil, University Versailles Saint Quentin.

15.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own third party liability as well as the third-party liability of all the doctors involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the study participant and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GERLING through BIOMEDIC-INSURE, covering its own third party liability and that of any collaborator (doctor or research staff), in accordance with Article L.1121-10 of CSP.

16 PUBLICATION

As Sponsor, LSHTM has the right and responsibility to ensure the results of this study is published. As this study is being conducted as an academic collaboration between LSHTM, Assistance Publique-Hôpitaux de Paris (AP-HP), Unité de Recherche Clinique et Centre d'Investigation Clinique Paris Descartes Necker Cochin and UFR Sciences de la Santé Simone Veil, University Versailles Saint Quentin, 2 avenue de la source de la Bièvre, 78180 Montigny le Bretonneux, France, all parties who contribute significantly to this study will be named in the final publication.

16.1 Mention of AP-HP affiliation for projects sponsored or managed by AP-HP

If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is not important. Each of these affiliations must be identified by an address and separated by a semicolon. The AP-HP institution must feature under the acronym "**AP-HP**" first in the address, specifically followed by: ***AP-HP**, hospital, department, city, postcode, France*

16.2 Mention of the AP-HP manager (DRCI) in the acknowledgements of the text

"The sponsor was supported in the management of this trial in France by *Assistance Publique – Hôpitaux de Paris* (Clinical Research and Development Department)"

- 'The authors thank URC-CIC Paris Descartes Necker Cochin for the implementation, conduct and data management of the study".

16.3 Mention of the funder in the acknowledgements of the text

LSHTM has a legal responsibility to acknowledge in all relevant publications that they received funding from the Wellcome (WT208870/Z/17/Z) and the Bill & Melinda Gates Foundation (OPP1176150) for this study.

This study has been registered on the http://clinicaltrials.gov/ website under *registration number* NCT03777488

17 BIBLIOGRAPHY

1. Collaborators WT Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **389:** 2105-16.
2. Collaborators C-, Roberts I, Shakur H, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011; **377:** 1096-101, 101 e1-2.
3. Collaborators C-t, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010; **376:** 23-32.
4. Gayet-Ageron A, Prieto-Merino D, Ker K, et al. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. *Lancet* 2018; **391:** 125-32.
5. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010; **376:** 23-32.
6. McCormack PL Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. *Drugs* 2012; **72:** 585-617.
7. Okamoto S, Okamoto U Aminomethyl-cyclohexane carboxylic acid, AMCHA, a new potent inhibitor of the fibrinolysis. *Keio Journal of Medicine* 1962; **11:** 105-15.
8. Puigdellivol E, Carral ME, Moreno J, Pla-Delfina JM, Jane F Pharmacokinetics and absolute bioavailability of intramuscular tranexamic acid in man. *International Journal of Clinical Pharmacology, Therapy, and Toxicology* 1985; **23:** 298-301.
9. Sano M, Hakusui H, Kojima C, Akimoto T Absorption and Excretion of Tranexamic Acid following Intravenous, Intramuscular and Oral Administrations in Healthy Volunteers. *Japanese Journal of Clinical Pharmacology and Therapeutics* 1976; **7:** 375-82.
10. Grassin-Delyle S, Semeraro M, Foissac F, et al. Tranexamic acid through intravenous, intramuscular and oral routes: an individual participant data meta-analysis of pharmacokinetic studies in healthy volunteers. *Fundamental and Clinical Pharmacology* 2019.
11. Virani SR, Dahapute AA, Panda I, Bava SS Role of Local Infiltration of Tranexamic Acid in Reducing Blood Loss in Peritrochanteric Fracture Surgery in the Elderly Population. *Malays Orthop J* 2016; **10:** 26-30.
12. . Clinical Study Report 39039039NAP1004, 2017.
13. Eriksson O, Kjellman H, Pilbrant A, Schannong M Pharmacokinetics of tranexamic acid after intravenous administration to normal volunteers. *European Journal of Clinical Pharmacology* 1974; **7:** 375-80.
14. Pilbrant A, Schannong M, Vessman J Pharmacokinetics and bioavailability of tranexamic acid. *European Journal of Clinical Pharmacology* 1981; **20:** 65-72.
15. Chang Q, Yin OQ, Chow MS Liquid chromatography-tandem mass spectrometry method for the determination of tranexamic acid in human plasma. *Journal of Chromatography. B: Analytical Technologies in the Biomedical and Life Sciences* 2004; **805:** 275-80.
16. Sindet-Pedersen S Distribution of tranexamic acid to plasma and saliva after oral administration and mouth rinsing: a pharmacokinetic study. *Journal of Clinical Pharmacology* 1987; **27:** 1005-8.
17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Annals of Internal Medicine* 1999; **130:** 461-70.

18. Shakur H, Beaumont D, Pavord S, Gayet-Ageron A, Ker K, Mousa HA Antifibrinolytic drugs for treating primary postpartum haemorrhage. *The Cochrane Database of Systematic Reviews* 2018; **2:** CD012964.
19. Vogel JP, Oladapo OT, Dowswell T, Gulmezoglu AM Updated WHO recommendation on intravenous tranexamic acid for the treatment of post-partum haemorrhage. *Lancet Glob Health* 2018; **6:** e18-e9.
20. Ker K, Shakur H, Roberts I Does tranexamic acid prevent postpartum haemorrhage? A systematic review of randomised controlled trials. *BJOG: An International Journal of Obstetrics and Gynaecology* 2016; **123:** 1745-52.
21. Sentilhes L, Winer N, Azria E, et al. Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. *New England Journal of Medicine* 2018; **379:** 731-42.
22. Bennett C, Klingenberg SL, Langholz E, Gluud LL Tranexamic acid for upper gastrointestinal bleeding. *The Cochrane Database of Systematic Reviews* 2014**:** CD006640.
23. Hollanders D, Thomson JM, Schofield PF Tranexamic acid therapy in ulcerative colitis. *Postgraduate Medical Journal* 1982; **58:** 87-91.
24. Smith SR, Murray D, Pockney PG, Bendinelli C, Draganic BD, Carroll R Tranexamic Acid for Lower GI Hemorrhage: A Randomized Placebo-Controlled Clinical Trial. *Diseases of the Colon and Rectum* 2018; **61:** 99-106.
25. Ker K, Edwards P, Perel P, Shakur H, Roberts I Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012; **344:** e3054.
26. Roos YB, Rinkel GJ, Vermeulen M, Algra A, van Gijn J Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. *The Cochrane Database of Systematic Reviews* 2003**:** CD001245.
27. Sprigg N, Flaherty K, Appleton JP, et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet* 2018; **391:** 2107-15.
28. Zehtabchi S, Abdel Baki SG, Falzon L, Nishijima DK Tranexamic acid for traumatic brain injury: a systematic review and meta-analysis. *American Journal of Emergency Medicine* 2014; **32:** 1503-9.
29. Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, Thinkamrop B, Phuenpathom N, Lumbiganon P Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. *BMC Emergency Medicine* 2013; **13:** 20.
30. CRASH-2 Collaborators IBS Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *BMJ* 2011; **343:** d3795.
31. Prutsky G, Domecq JP, Salazar CA, Accinelli R Antifibrinolytic therapy to reduce haemoptysis from any cause. *The Cochrane Database of Systematic Reviews* 2016; **11:** CD008711.
32. Wand O, Guber E, Guber A, Epstein Shochet G, Israeli-Shani L, Shitrit D Inhaled Tranexamic Acid for Hemoptysis Treatment: A Randomized Controlled Trial. *Chest* 2018.
33. Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M Antifibrinolytics for heavy menstrual bleeding. *The Cochrane Database of Systematic Reviews* 2018; **4:** CD000249.
34. Gharaibeh A, Savage HI, Scherer RW, Goldberg MF, Lindsley K Medical interventions for traumatic hyphema. *The Cochrane Database of Systematic Reviews* 2013**:** CD005431.
35. Montroy J, Hutton B, Moodley P, et al. The efficacy and safety of topical tranexamic acid: A systematic review and meta-analysis. *Transfusion Medicine Reviews* 2018.
36. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Annals of Internal Medicine* 2009; **150:** 604-12.
37. Hopkins U, Arias CY Large-volume IM injections: A review of best practices. *Oncology Nurse Advisor* 2013.

38. Alvarez JC, Abe E, Etting I, Le Guen M, Devillier P, Grassin-Delyle S Quantification of remifentanil and propofol in human plasma: a LC-MS/MS assay validated according to the EMA guideline. *Bioanalysis* 2015; **7:** 1675-84.
39. Alvarez JC, Charbit B, Grassin-Delyle S, Demolis JL, Funck-Brentano C, Abe E Human plasma quantification of droperidol and ondansetron used in preventing postoperative nausea and vomiting with a LC/ESI/MS/MS method. *Journal of Chromatography. B: Analytical Technologies in the Biomedical and Life Sciences* 2011; **879:** 186-90.
40. Grassin Delyle S, Abe E, Batisse A, et al. A validated assay for the quantitative analysis of tranexamic acid in human serum by liquid chromatography coupled with electrospray ionization mass spectrometry. *Clinica Chimica Acta* 2010; **411:** 438-43.
41. Ribot M, Polito A, Grassin-Delyle S, Annane D, Alvarez JC Human plasma quantification of fludrocortisone using liquid chromatography coupled with atmospheric pressure chemical ionization mass spectrometry after low-dosage administration. *Clinica Chimica Acta* 2013; **420:** 109-13.
42. Grassin Delyle S, Abe E, Devillier P, Alvarez JC Determination of rimonabant in human plasma and hair by liquid chromatography-mass spectrometry. *Journal of Chromatography. B: Analytical Technologies in the Biomedical and Life Sciences* 2008; **872:** 115-20.
43. Fabresse N, Fall F, Etting I, Devillier P, Alvarez JC, Grassin-Delyle S LC-MS/MS determination of tranexamic acid in human plasma after phospholipid clean-up. *Journal of Pharmaceutical and Biomedical Analysis* 2017; **141:** 149-56.
44. Kuhn E, Lavielle M Maximum likelihood estimation in nonlinear mixed effects models. *Computational Statistics and Data Analysis* 2005; **49:** 1020-38.
45. Gertler R, Gruber M, Grassin-Delyle S, et al. Pharmacokinetics of tranexamic acid in neonates and infants undergoing cardiac surgery. *British Journal of Clinical Pharmacology* 2017.
46. Grassin-Delyle S, Couturier R, Abe E, Alvarez JC, Devillier P, Urien S A practical tranexamic acid dosing scheme based on population pharmacokinetics in children undergoing cardiac surgery. *Anesthesiology* 2013; **118:** 853-62.
47. Grassin-Delyle S, Theusinger OM, Albrecht R, et al. Optimisation of the dosage of tranexamic acid in trauma patients with population pharmacokinetic analysis. *Anaesthesia* 2018; **73:** 719-29.
48. Grassin-Delyle S, Tremey B, Abe E, et al. Population pharmacokinetics of tranexamic acid in adults undergoing cardiac surgery with cardiopulmonary bypass. *British Journal of Anaesthesia* 2013; **111:** 916-24.
49. Anderson BJ, Holford NH Mechanism-based concepts of size and maturity in pharmacokinetics. *Annual Review of Pharmacology and Toxicology* 2008; **48:** 303-32.
50. Bazzoli C, Retout S, Mentre F Design evaluation and optimisation in multiple response nonlinear mixed effect models: PFIM 3.0. *Computer Methods and Programs in Biomedicine* 2010; **98:** 55-65.

18 LIST OF ADDENDA

18.1 Addenda 1: List of investigators

18.2 Addenda 2: Serious adverse events report form

18.3 Addenda 3: Pregnancy report form

18.4 Addenda 4: SmPC, EXACYL 0,5 g/5 ml sol inj IV

18.5 Addenda 5: SmPC, EXACYL 1 g/10 ml sol buv