Clinical trial results:
Pharmacokinetics of Tranexamic Acid after oral, intramuscular or intravenous administration: a prospective, randomised, cross-over trial in healthy volunteers.

Summary

EudraCT number	2019-000285-38
Trial protocol	FR
Global end of trial date	14 October 2020

Results information

Result version number	v1 (current)
This version publication date	08 September 2022
First version publication date	08 September 2022
Summary attachment (see zip file)	Publication (PHARMACO-TXA_Publication_20211031.pdf)

Trial information

Trial identification

Sponsor protocol code	APHP190020

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03777488
WHO universal trial number (UTN)	-
Other trial identifiers	code sponsor LSHTM: 2018/KEP/205

Notes:

Sponsors

Sponsor organisation name	LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE
Sponsor organisation address	Keppel Street, LONDON, United Kingdom, WC1E 7HT
Public contact	Collette Barrow , LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE , 44 0207 299 4684, woman2@lshtm.ac.uk
Scientific contact	Pr. Haleema Shakur-Still, LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE , Haleema.Shakur-Still@lshtm.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

- Inclusion / exclusion criteria;
- At the inclusion visit, all women must have a pregnancy test (urine βhCG) done which must be negative to continue. Participants medical history will be checked to ensure there are no changes since V0 visit;
- After drug administration, pain assessment using a Visual Analogue Scale (VAS) and vital signs were recorded during 8 hours;
- The patient is seen the next day.

Background therapy:

No background therapy.

Evidence for comparator:

Not applicable

Actual start date of recruitment	03 June 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	15
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Healthy volunteers will be recruited by advertisement in universities or website to the general public. A first contact by phone or mail 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.

Pre-assignment

Screening details:

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

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tranexamic acid Group 1

Arm description:

Participants will receive tranexamic acid in the following order:
- First Dose: Intravenous
- Second Dose: Intramuscular
- Third Dose: Oral

Arm type	Experimental
Investigational medicinal product name	tranexamic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution, Solution for injection
Routes of administration	Intramuscular use, Intravenous use, Oral use

Dosage and administration details:

Drug: Tranexamic Acid 1 gram intravenously
Intravenous tranexamic acid crossover to oral and intramuscular arms

Drug: Tranexamic acid 2 grams oral solution
Oral tranexamic acid crossover to intravenous and intramuscular arms

Drug: Tranexamic acid 1 gram intramuscular
Intramuscular tranexamic acid crossover to oral and intravenous arms

Arm title	Tranexamic acid Group 2

Arm description:

Participants will receive tranexamic acid in the following order:
First Dose: Intravenous
Second Dose: Oral
Third Dose: Intramuscular

Arm type	Experimental

Investigational medicinal product name	tranexamic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution, Solution for injection
Routes of administration	Intramuscular use, Intravenous use, Oral use

Dosage and administration details:

Drug: Tranexamic Acid 1 gram intravenously
Intravenous tranexamic acid crossover to oral and intramuscular arms

Drug: Tranexamic acid 2 grams oral solution
Oral tranexamic acid crossover to intravenous and intramuscular arms

Drug: Tranexamic acid 1 gram intramuscular
Intramuscular tranexamic acid crossover to oral and intravenous arms

Arm title	Tranexamic acid Group 3

Arm description:

Participants will receive tranexamic acid in the following order:
First Dose: Intramuscular
Second Dose: Intravenous
Third Dose: Oral

Arm type	Experimental
Investigational medicinal product name	tranexamic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution, Solution for injection
Routes of administration	Intramuscular use, Intravenous use, Oral use

Dosage and administration details:

Drug: Tranexamic Acid 1 gram intravenously
Intravenous tranexamic acid crossover to oral and intramuscular arms

Drug: Tranexamic acid 2 grams oral solution
Oral tranexamic acid crossover to intravenous and intramuscular arms

Drug: Tranexamic acid 1 gram intramuscular
Intramuscular tranexamic acid crossover to oral and intravenous arms

Arm title	Tranexamic acid Group 4

Arm description:

Participants will receive tranexamic acid in the following order:
First Dose: Intramuscular
Second Dose: Oral
Third Dose: Intravenous

Arm type	Experimental
Investigational medicinal product name	tranexamic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution, Solution for injection
Routes of administration	Intramuscular use, Intravenous use, Oral use

Dosage and administration details:

Drug: Tranexamic Acid 1 gram intravenously
Intravenous tranexamic acid crossover to oral and intramuscular arms

Drug: Tranexamic acid 2 grams oral solution
Oral tranexamic acid crossover to intravenous and intramuscular arms

Drug: Tranexamic acid 1 gram intramuscular
Intramuscular tranexamic acid crossover to oral and intravenous arms

Arm title	Tranexamic acid Group 5

Arm description:

Participants will receive tranexamic acid in the following order:
First Dose: Oral
Second Dose: Intravenous
Third Dose: Intramuscular

Arm type	Experimental
Investigational medicinal product name	tranexamic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution, Solution for injection
Routes of administration	Intramuscular use, Intravenous use, Oral use

Dosage and administration details:

Drug: Tranexamic Acid 1 gram intravenously
Intravenous tranexamic acid crossover to oral and intramuscular arms

Drug: Tranexamic acid 2 grams oral solution
Oral tranexamic acid crossover to intravenous and intramuscular arms

Drug: Tranexamic acid 1 gram intramuscular
Intramuscular tranexamic acid crossover to oral and intravenous arms

Arm title	Tranexamic acid Group 6

Arm description:

Participants will receive tranexamic acid in the following order:
First Dose: Oral
Second Dose: Intramuscular
Third Dose: Intravenous

Arm type	Experimental
Investigational medicinal product name	tranexamic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution, Solution for injection
Routes of administration	Intramuscular use, Intravenous use, Oral use

Dosage and administration details:

Drug: Tranexamic Acid 1 gram intravenously
Intravenous tranexamic acid crossover to oral and intramuscular arms

Drug: Tranexamic acid 2 grams oral solution
Oral tranexamic acid crossover to intravenous and intramuscular arms

Drug: Tranexamic acid 1 gram intramuscular
Intramuscular tranexamic acid crossover to oral and intravenous arms

Number of subjects in period 1	Tranexamic acid Group 1	Tranexamic acid Group 2	Tranexamic acid Group 3
Started	3	2	3
Completed	3	2	3

Number of subjects in period 1	Tranexamic acid Group 4	Tranexamic acid Group 5	Tranexamic acid Group 6
Started	2	2	3
Completed	2	2	3

Baseline characteristics

Reporting groups

Reporting group title	Tranexamic acid Group 1

Reporting group description:

Participants will receive tranexamic acid in the following order:
- First Dose: Intravenous
- Second Dose: Intramuscular
- Third Dose: Oral

Reporting group title	Tranexamic acid Group 2

Reporting group description:

Participants will receive tranexamic acid in the following order:
First Dose: Intravenous
Second Dose: Oral
Third Dose: Intramuscular

Reporting group title	Tranexamic acid Group 3

Reporting group description:

Participants will receive tranexamic acid in the following order:
First Dose: Intramuscular
Second Dose: Intravenous
Third Dose: Oral

Reporting group title	Tranexamic acid Group 4

Reporting group description:

Participants will receive tranexamic acid in the following order:
First Dose: Intramuscular
Second Dose: Oral
Third Dose: Intravenous

Reporting group title	Tranexamic acid Group 5

Reporting group description:

Participants will receive tranexamic acid in the following order:
First Dose: Oral
Second Dose: Intravenous
Third Dose: Intramuscular

Reporting group title	Tranexamic acid Group 6

Reporting group description:

Participants will receive tranexamic acid in the following order:
First Dose: Oral
Second Dose: Intramuscular
Third Dose: Intravenous

Reporting group values	Tranexamic acid Group 1	Tranexamic acid Group 2	Tranexamic acid Group 3
Number of subjects	3	2	3
Age categorical			
The 11 female and four male study participants had a median age of 25 yr and a median BW of 64.2 kg.			
Units: Subjects			
Adults (18-64 years)	3	2	3
Gender categorical			
The 11 female and four male study participants had a median age of 25 yr and a median BW of 64.2 kg.			
Units: Subjects			

Female	3	2	2
Male	0	0	1

Reporting group values	Tranexamic acid Group 4	Tranexamic acid Group 5	Tranexamic acid Group 6
Number of subjects	2	2	3
Age categorical			
The 11 female and four male study participants had a median age of 25 yr and a median BW of 64.2 kg.			
Units: Subjects			
Adults (18-64 years)	2	2	3
Gender categorical			
The 11 female and four male study participants had a median age of 25 yr and a median BW of 64.2 kg.			
Units: Subjects			
Female	1	1	2
Male	1	1	1

Reporting group values	Total		
Number of subjects	15		
Age categorical			
The 11 female and four male study participants had a median age of 25 yr and a median BW of 64.2 kg.			
Units: Subjects			
Adults (18-64 years)	15		
Gender categorical			
The 11 female and four male study participants had a median age of 25 yr and a median BW of 64.2 kg.			
Units: Subjects			
Female	11		
Male	4		

End points

End points reporting groups

Reporting group title	Tranexamic acid Group 1

Reporting group description:

Participants will receive tranexamic acid in the following order:
- First Dose: Intravenous
- Second Dose: Intramuscular
- Third Dose: Oral

Reporting group title	Tranexamic acid Group 2

Reporting group description:

Participants will receive tranexamic acid in the following order:
First Dose: Intravenous
Second Dose: Oral
Third Dose: Intramuscular

Reporting group title	Tranexamic acid Group 3

Reporting group description:

Participants will receive tranexamic acid in the following order:
First Dose: Intramuscular
Second Dose: Intravenous
Third Dose: Oral

Reporting group title	Tranexamic acid Group 4

Reporting group description:

Participants will receive tranexamic acid in the following order:
First Dose: Intramuscular
Second Dose: Oral
Third Dose: Intravenous

Reporting group title	Tranexamic acid Group 5

Reporting group description:

Participants will receive tranexamic acid in the following order:
First Dose: Oral
Second Dose: Intravenous
Third Dose: Intramuscular

Reporting group title	Tranexamic acid Group 6

Reporting group description:

Participants will receive tranexamic acid in the following order:
First Dose: Oral
Second Dose: Intramuscular
Third Dose: Intravenous

Primary: Serum tranexamic acid concentrations versus time profiles for each route of administration (Oral, intramuscular and intravenous)

End point title	Serum tranexamic acid concentrations versus time profiles for each route of administration (Oral, intramuscular and intravenous)[1]

End point description:

The median time to reach a concentration of 10 mg.L-1 was 1 min for the IV route, 3.5 min for the IM route, and 66 min for the oral route, although with the oral route the target concentration was reached in only 11 of 15 patients. The median maximum concentration was 54.6, 34.3, and 12.7 mg.L-1 for the IV, IM, and oral routes, respectively.

Note: standard deviation is non applicable so set to 0.

End point type	Primary

End point timeframe:

24 hours

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Final data analysis involved determination of pharmacokinetic parameters over time. No formal statistical analysis was required relating to the primary endpoint.

End point values	Tranexamic acid Group 1	Tranexamic acid Group 2	Tranexamic acid Group 3	Tranexamic acid Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	2	3	2
Units: µg/mL				
arithmetic mean (standard deviation)	54.6 (± 0)	54.6 (± 0)	54.6 (± 0)	54.6 (± 0)

End point values	Tranexamic acid Group 5	Tranexamic acid Group 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	3		
Units: µg/mL				
arithmetic mean (standard deviation)	54.6 (± 0)	54.6 (± 0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

3 months maximum

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Tranexamic acid Group 1

Reporting group description:

Participants will receive tranexamic acid in the following order:
- First Dose: Intravenous
- Second Dose: Intramuscular
- Third Dose: Oral

Reporting group title	Tranexamic acid Group 2

Reporting group description:

Participants will receive tranexamic acid in the following order:
First Dose: Intravenous
Second Dose: Oral
Third Dose: Intramuscular

Reporting group title	Tranexamic acid Group 3

Reporting group description:

Participants will receive tranexamic acid in the following order:
First Dose: Intramuscular
Second Dose: Intravenous
Third Dose: Oral

Reporting group title	Tranexamic acid Group 4

Reporting group description:

Participants will receive tranexamic acid in the following order:
First Dose: Intramuscular
Second Dose: Oral
Third Dose: Intravenous

Reporting group title	Tranexamic acid Group 5

Reporting group description:

Participants will receive tranexamic acid in the following order:
First Dose: Oral
Second Dose: Intravenous
Third Dose: Intramuscular

Reporting group title	Tranexamic acid Group 6

Reporting group description:

Participants will receive tranexamic acid in the following order:
First Dose: Oral
Second Dose: Intramuscular
Third Dose: Intravenous

Serious adverse events	Tranexamic acid Group 1	Tranexamic acid Group 2	Tranexamic acid Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0

Serious adverse events	Tranexamic acid Group 4	Tranexamic acid Group 5	Tranexamic acid Group 6
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Tranexamic acid Group 1	Tranexamic acid Group 2	Tranexamic acid Group 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	3 / 3 (100.00%)
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Reproductive system and breast disorders			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	1
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			

Musculoskeletal and connective tissue disorders			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Infections and infestations			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Non-serious adverse events	Tranexamic acid Group 4	Tranexamic acid Group 5	Tranexamic acid Group 6
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	1 / 2 (50.00%)	1 / 3 (33.33%)
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	2 / 2 (100.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Reproductive system and breast disorders			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Infections and infestations subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 2 (0.00%) 0	0 / 3 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 March 2020	Interruption of inclusions during the first COVID-19 lockdown. No patient were in follow-up during this period	12 June 2020

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Main limitations are related to the study population, as young and healthy volunteers were included. We therefore did not investigate the effect of age or BW through a wide range, or the effect of renal impairment and other clinical conditions.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34998508