# Clinical trial results:
# A multi-centre randomised, double-blind, placebo-controlled trial of pre-hospital treatment with tranexamic acid for severely injured patients at risk of acute traumatic coagulopathy.

## Summary

| | |
|---|---|
| EudraCT number | 2019-004118-33 |
| Trial protocol | DE |
| Global end of trial date | 14 June 2023 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 07 October 2023 |
| First version publication date | 07 October 2023 |
| Summary attachment (see zip file) | ClinicalStudy Report (20230418_PATCH_Synospe_ClinicalStudyReport_final.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | PATCH_Trauma |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02187120 |
| WHO universal trial number (UTN) | U1111-1169-6738 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | University Witten/Herdecke |
| Sponsor organisation address | Alfred-Herrhausen-Str. 50, Witten, Germany, D-58448 |
| Public contact | IFOM, Institut für Forschung in der Operativen Medizin, 0049 02219895726, patch@uni-wh.de |
| Scientific contact | IFOM, Institut für Forschung in der Operativen Medizin, 0049 02219895726, patch@uni-wh.de |

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 | 20 December 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 December 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 June 2023 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To determine the effect of early administration of TXA, compared to placebo, on mortality and favourable outcomes (moderate disability or good recovery) at six months in severely injured adults at risk of ATC who are treated in advanced trauma systems.
To determine the effect of early administration of TXA, compared to placebo, on coagulation and fibrinolysis, and on clinical outcomes that are mediated through other putative inflammatory, immune, and neurological effects of plasmin.
To determine whether early administration of TXA, compared to placebo, is associated with excessive vascular occlusive events, especially among potentially higher risk patients (eg >50 years old).

Protection of trial subjects:

Upon arrival at the scene of injury, EMS clinicians will follow usual resuscitation protocols to address immediate life-threatening conditions of the airway, breathing or circulation.

Review and consider any protocol modifications or ancillary studies proposed by the study investigators after the main trial begins to ensure that these do not negatively impact on the main trial. Protocol modifications will be considered in the context of their potential impact on scientific integrity and subject safety;

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 July 2020 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Germany: 8 |
| Country: Number of subjects enrolled | Australia: 1299 |
| Worldwide total number of subjects | 1307 |
| EEA total number of subjects | 8 |

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) | 1307 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Adult patients (age ≥18 years);
• Injured through any mechanism;
• COAST score ≥3;
• First dose of study drug can be administered within three hours of injury; and
• Patients to be transported to a participating trauma centre

### Pre-assignment

Screening details:

Upon arrival at the scene of injury, EMS clinicians trained in study procedures decided whether the patient is eligible for inclusion in the trial. Patients assessed as meeting the inclusion criteria at any time during the prehospital period, with no exclusion criteria, were randomised.

### Period 1

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

Blinding implementation details:

All trial personnel and participants will be blinded to treatment allocation. An independent pharmaceutical packaging company will be responsible for labelling ampoules containing TXA or sodium chloride (placebo) and preparing trial packs. The independent pharmaceutical packaging will contain the study code to determine which patients received TXA or placebo and this will not be available to trial investigators until completion of the trial.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

As soon as possible after injury, EMS clinicians administered a 10 ml ampoule containing 0.9 % w/v Sodium Chloride via iv injection (ampoules containing Sodium Chloride appear identical to ampoules containing TXA). After the patient arrived at hospital,
clinicians administered a second 10 ml ampoule containing 0.9 % w/v Sodium Chloride added to up to 1 litre 0.9 % w/v Sodium Chloride infused iv over 8 h.

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

Dosage and administration details:

0.9% sodium chloride;
Mode of administration: slow intravenous injection and infused intravenously;
pre-hospital administration of tranexamic acid followed by an infusion over 8 hours

| | |
|---|---|
| **Arm title** | Experimental intervention - TXA |

Arm description:

As soon as possible after injury, emergency medical services (EMS)
clinicians administered 1 g Tranexamic Acid (TXA; 10 ml ampoule containing 100 mg/ml TXA in water for injection) via iv injection. After the patient arrived at hospital, clinicians administered 1 g TXA (10 ml ampoule containing 100 mg/ml TXA in water for injection) added to up to 1 litre 0.9 % w/v Sodium Chloride infused iv over 8 h.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | TXA |
| Investigational medicinal product code | |
| Other name | Cyclokapron |
| Pharmaceutical forms | Injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1g TXA (in 10 ml water) and 1g TXA (in 1000 ml 0.9 % NaCl);
Mode of administration: slow intravenous injection and infused intravenously;
after injury, emergency medical services (EMS) clinicians administered 1 g Tranexamic Acid;
After the patient arrived at hospital, clinicians administered 1 g TXA

| **Number of subjects in period 1** | Placebo | Experimental intervention - TXA |
|---|---|---|
| Started | 646 | 661 |
| Completed | 559 | 572 |
| Not completed | 87 | 89 |
| Consent withdrawn by subject | 26 | 31 |
| Lost to follow-up | 61 | 58 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall Period |
|---|---|

Reporting group description: -

| Reporting group values | Overall Period | Total | |
|---|---|---|---|
| Number of subjects | 1307 | 1307 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 1307 | 1307 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 44.15 | | |
| standard deviation | ± 19.3 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Male | 918 | 918 | |
| female | 382 | 382 | |
| Not recorded | 7 | 7 | |

### Subject analysis sets

| Subject analysis set title | Primary outcomes - extended GOS-E |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The ITT population consist of all randomised patients. Dichotomised Glasgow Outcome Scale Extended (GOSE) at 6 months: A favourable outcome is
defined as GOSE scores 5-8 (moderate disability or good recovery) as opposed to GOSE scores 1-4 (died=1, severe disability 2-4).

The binary primary outcome of favourable GOSE (scores 5-8) was compared between treatment groups using a risk ratio together with a 95% confidence interval and p-value, estimated by a logbinomial regression model. If model convergence was not achieved, then Poisson regression with robust standard errors was applied.

| Subject analysis set title | Primary outcomes - extended GOS-E |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

The PP population will consist of all randomised patients with the exception of those who did not receive both doses of study drug or received open label TXA or did not meet the inclusion/exclusion criteria: age <18 years, had a COAST score <3, received their study drug >3 hours after injury, were pregnant, were residents at an aged care facility or did not attend a participating study centre.

| Subject analysis set title | Secondary outcomes -24h |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Mortality at:
- 24 hours;
- 28 days;
- 6 months.

| Subject analysis set title | Secondary outcomes -28 days |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Mortality at:
• 24 hours;
• 28 days;
• 6 months.

| Subject analysis set title | Secondary outcomes -6month |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Mortality at:
• 24 hours;
• 28 days;
• 6 months.

| **Reporting group values** | Primary outcomes - extended GOS-E | Primary outcomes - extended GOS-E | Secondary outcomes -24h |
|---|---|---|---|
| Number of subjects | 1300 | 847 | 1300 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 1307 | 847 | 1307 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 44.15 | 44.75 | 44.15 |
| standard deviation | ± 19.3 | ± 18.85 | ± 19.3 |
| Gender categorical<br>Units: Subjects | | | |
| Male | 918 | 602 | 918 |
| female | 382 | 245 | 382 |
| Not recorded | | | |

| **Reporting group values** | Secondary outcomes -28 days | Secondary outcomes -6month | |
|---|---|---|---|
| Number of subjects | 1300 | 1300 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 1307 | 1307 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 44.15 | 44.15 | |
| standard deviation | ± 19.3 | ± 19.3 | |
| Gender categorical<br>Units: Subjects | | | |
| Male | 918 | 918 | |
| female | 382 | 382 | |
| Not recorded | | | |

## End points

### End points reporting groups

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

Reporting group description:

As soon as possible after injury, EMS clinicians administered a 10 ml ampoule containing 0.9 % w/v Sodium Chloride via iv injection (ampoules containing Sodium Chloride appear identical to ampoules containing TXA). After the patient arrived at hospital,
clinicians administered a second 10 ml ampoule containing 0.9 % w/v Sodium Chloride added to up to 1 litre 0.9 % w/v Sodium Chloride infused iv over 8 h.

| Reporting group title | Experimental intervention - TXA |
|---|---|

Reporting group description:

As soon as possible after injury, emergency medical services (EMS)
clinicians administered 1 g Tranexamic Acid (TXA; 10 ml ampoule containing 100 mg/ml TXA in water for injection) via iv injection. After the patient arrived at hospital, clinicians administered 1 g TXA (10 ml ampoule containing 100 mg/ml TXA in water for injection) added to up to 1 litre 0.9 % w/v Sodium Chloride infused iv over 8 h.

| Subject analysis set title | Primary outcomes - extended GOS-E |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The ITT population consist of all randomised patients. Dichotomised Glasgow Outcome Scale Extended (GOSE) at 6 months: A favourable outcome is
defined as GOSE scores 5-8 (moderate disability or good recovery) as opposed to GOSE scores 1-4 (died=1, severe disability 2-4).

The binary primary outcome of favourable GOSE (scores 5-8) was compared between treatment groups using a risk ratio together with a 95% confidence interval and p-value, estimated by a logbinomial regression model. If model convergence was not achieved, then Poisson regression with robust standard errors was applied.

| Subject analysis set title | Primary outcomes - extended GOS-E |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

The PP population will consist of all randomised patients with the exception of those who did not receive both doses of study drug or received open label TXA or did not meet the inclusion/exclusion criteria: age <18 years, had a COAST score <3, received their study drug >3 hours after injury, were pregnant, were residents at an aged care facility or did not attend a participating study centre.

| Subject analysis set title | Secondary outcomes -24h |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Mortality at:
- 24 hours;
- 28 days;
- 6 months.

| Subject analysis set title | Secondary outcomes -28 days |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Mortality at:
- 24 hours;
- 28 days;
- 6 months.

| Subject analysis set title | Secondary outcomes -6month |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Mortality at:
- 24 hours;
- 28 days;
- 6 months.

| Primary: GOS-E | |
|---|---|
| End point title | GOS-E |
| End point description: | |

| | |
|---|---|
| End point type | Primary |
| End point timeframe: | |
| 6 month | |

| End point values | Placebo | Experimental intervention - TXA | Primary outcomes - extended GOS-E | Primary outcomes - extended GOS-E |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 559 | 572 | 1131 | 727 |
| Units: Subject | 646 | 661 | 1300 | 1300 |

**Statistical analyses**

| Statistical analysis title | Primary outcome analysis – favourable 6-month GOSE |
|---|---|
| Comparison groups | Placebo v Experimental intervention - TXA |
| Number of subjects included in analysis | 1131 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.95 |
| Method | log-binomial regression |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1.12 |
| Variability estimate | Standard deviation |

| Secondary: Death within 24hr | |
|---|---|
| End point title | Death within 24hr |
| End point description: | |

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: | |
| 24 hours after injury | |

| End point values | Placebo | Experimental intervention - TXA | Secondary outcomes -24h | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 559 | 572 | 1297 | |
| Units: Subject | 643 | 657 | 1300 | |

**Statistical analyses**

| Statistical analysis title | secondary endpoint analyses - 24hr |
|---|---|
| Comparison groups | Placebo v Experimental intervention - TXA |
| Number of subjects included in analysis | 1131 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | log-binomial regression |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 0.94 |
| Variability estimate | Standard deviation |

**Secondary: Death within 28 days**

| End point title | Death within 28 days |
|---|---|
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 28 days after injury | |

| End point values | Placebo | Experimental intervention - TXA | Secondary outcomes -28 days | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 559 | 572 | 1290 | |
| Units: Subject | 643 | 657 | 1300 | |

**Statistical analyses**

| **Statistical analysis title** | secondary endpoint analyses - 28 days |
|---|---|
| Comparison groups | Placebo v Experimental intervention - TXA |
| Number of subjects included in analysis | 1131 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | log-binomial regression |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 0.99 |

**Secondary: Death within 6 month**

| End point title | Death within 6 month |
|---|---|
| End point description: | |
| End point type | Secondary |
| End point timeframe: death by 6 month after injury | |

| **End point values** | Placebo | Experimental intervention - TXA | Secondary outcomes - 6month | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 559 | 572 | 1277 | |
| Units: Subject | 643 | 657 | 1300 | |

**Statistical analyses**

| **Statistical analysis title** | secondary endpoint analyses - 6 month |
|---|---|
| Comparison groups | Placebo v Experimental intervention - TXA |
| Number of subjects included in analysis | 1131 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | log-binomial regression |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.83 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.03 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

overal period: 6 month
July 2014 - March 2021

Adverse event reporting additional description:

Any untoward medical occurrence in study participant which does not necessarily have to have a causal relationship with the study drug, but which was of concern to the organisation/site principal investigator's clinical judgement. Ae´s in this study included (but were not limited to) vascular occlusive events, seizures, cardiac arrest, anaphylax

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

### Dictionary used

| | |
|---|---|
| Dictionary name | CPMP/ICH/377/95 |
| Dictionary version | July 2000 |

### Reporting groups

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

Reporting group description:

As soon as possible after injury, EMS clinicians administered a 10 ml ampoule containing 0.9 % w/v Sodium Chloride via iv injection (ampoules containing Sodium Chloride appear identical to ampoules containing TXA). After the patient arrived at hospital,
clinicians administered a second 10 ml ampoule containing 0.9 % w/v Sodium Chloride added to up to 1 litre 0.9 % w/v Sodium Chloride infused iv over 8 h.

| | |
|---|---|
| Reporting group title | Experimental intervention - TXA |

Reporting group description:

As soon as possible after injury, emergency medical services (EMS) clinicians administered 1 g Tranexamic Acid (TXA; 10 ml ampoule containing 100 mg/ml TXA in water for injection) via iv injection. After the patient arrived at hospital, clinicians administered 1 g TXA (10 ml ampoule containing 100 mg/ml TXA in water for injection) added to up to 1 litre 0.9 % w/v Sodium Chloride infused iv over 8 h.

| **Serious adverse events** | Placebo | Experimental intervention - TXA | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 643 (0.62%) | 3 / 657 (0.46%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Complication of procedure | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | 0 / 657 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 643 (0.31%) | 2 / 657 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Heparin-induced thrombocytopenia (HITS) | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | 0 / 657 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 643 (0.00%) | 1 / 657 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo | Experimental intervention - TXA | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 643 (1.24%) | 16 / 657 (2.44%) | |
| Injury, poisoning and procedural complications | | | |
| Others | | | |
| subjects affected / exposed | 8 / 643 (1.24%) | 16 / 657 (2.44%) | |
| occurrences (all) | 19 | 25 | |

## 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? No

### Limitations and caveats

None reported

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/3731424