



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 β hCG) 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: <ul style="list-style-type: none">• 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 occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Infections and infestations Infections and infestations subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 1 / 3 (33.33%) 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 occurrences (all) | 2 / 2 (100.00%) 3 | 0 / 2 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| General disorders and administration site conditions General disorders and administration site conditions subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 2 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Reproductive system and breast disorders Reproductive system and breast disorders alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 1 / 2 (50.00%) 2 | 0 / 3 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 3 (0.00%) 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>