



Clinical trial results: The Impact of Target Temperature Management on Drug Metabolism Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2018-002226-22 |
| Trial protocol | AT |
| Global end of trial date | 17 June 2020 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 17 June 2022 |
| First version publication date | 17 June 2022 |
| Summary attachment (see zip file) | Publicaiton (1-s2.0-S0753332221013603-main-2.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-----|
| Sponsor protocol code | 2.0 |
|-----------------------|-----|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Medical University of Vienna |
| Sponsor organisation address | Währinger Gürtel 18-20, Vienna, Austria, 1090 |
| Public contact | Department of Emergency Medicine, Medical University of Vienna, +43 14040019640, post_akh_ls_6d@akhwien.at |
| Scientific contact | Department of Emergency Medicine, Medical University of Vienna, +43 14040019640, post_akh_ls_6d@akhwien.at |

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 | 01 February 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 June 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 June 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To compare the half-life of pantoprazole during cooling and after rewarming

Protection of trial subjects:

The study was of an observational nature and only patients, who received pantoprazole as part of their standard treatment, were included. Thus, no patient received a drug other than their standard treatment. Blood sampling was performed using existing central or peripheral venous or arterial catheters.

Background therapy:

Patients received standard of care after cardiac arrest. The study did not interfere with standard of care at any time.

Evidence for comparator:

We compared the pharmacokinetics of pantoprazole during three periods after cardiac arrest within the same patient:

- 1) mild therapeutic hypothermia
- 2) after rewarming, at ICU
- 3) after recovery, at normal ward.

No comparator substance (e.g. placebo) was used within the study.

| | |
|---|-------------|
| Actual start date of recruitment | 25 May 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 | Austria: 16 |
| Worldwide total number of subjects | 16 |
| EEA total number of subjects | 16 |

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) | 13 |
| From 65 to 84 years | 3 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening depended mainly on in- and exclusion criteria, but also on availability of the study team.

Period 1

| | |
|------------------------------|-----------------------|
| Period 1 title | Main (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | No |
| Arm title | Target Temperature Management |

Arm description:

all patients received a 40mg bolus infusion of pantoprazole as soon as target temperature (32-34 degrees Celsius) was reached

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | pantoprazole |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

40mg intravenous bolus infusion

| | |
|------------------|-----------|
| Arm title | Rewarming |
|------------------|-----------|

Arm description:

40mg bolus infusion as soon as normal body temperature was reached

| | |
|--|----------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | pantoprazole |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

40mg intravenous bolus infusion

| | |
|------------------|-----------|
| Arm title | Recovered |
|------------------|-----------|

Arm description:

After patients have almost completely recovered and were treated at the normal ward, the third study period was conducted. Patients received a 40mg intravenous bolus of pantoprazole.

| | |
|--|----------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | pantoprazole |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

40mg intravenous bolus infusion

| Number of subjects in period 1 | Target Temperature Management | Rewarming | Recovered |
|---------------------------------------|-------------------------------|-----------|-----------|
| Started | 16 | 16 | 10 |
| Completed | 16 | 16 | 10 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------|
| Reporting group title | Main |
|-----------------------|------|

Reporting group description:

16 patients were eligible for inclusion and completed the TTM period (=target temperature management), the rewarming period (=after rewarming at the ICU) and 10 of these 16 patients entered the recovered period (=at normal ward). Six patients either died or had poor neurologic outcome and couldn't provide informed consent for participation in period 3. For period 1 and 2 the EC waived informed consent.

| Reporting group values | Main | Total | |
|--|----------|-------|--|
| Number of subjects | 16 | 16 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 13 | 13 | |
| From 65-84 years | 3 | 3 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| median | 53 | | |
| inter-quartile range (Q1-Q3) | 46 to 62 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 3 | 3 | |
| Male | 13 | 13 | |

Subject analysis sets

| | |
|----------------------------|--------------|
| Subject analysis set title | Per Protocol |
|----------------------------|--------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

All patients who completed the three trials (each patient took part in up to three periods, that were compared with each other)

| Reporting group values | Per Protocol | | |
|--|--------------|--|--|
| Number of subjects | 10 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 9 | | |
| From 65-84 years | 1 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| median | 53 | | |
| inter-quartile range (Q1-Q3) | 46,25 to 60,5 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 3 | | |
| Male | 7 | | |

End points

End points reporting groups

| | |
|--|-------------------------------|
| Reporting group title | Target Temperature Management |
| Reporting group description: all patients received a 40mg bolus infusion of pantoprazole as soon as target temperature (32-34 degrees Celsius) was reached | |
| Reporting group title | Rewarming |
| Reporting group description: 40mg bolus infusion as soon as normal body temperature was reached | |
| Reporting group title | Recovered |
| Reporting group description: After patients have almost completely recovered and were treated at the normal ward, the third study period was conducted. Patients received a 40mg intravenous bolus of pantoprazole. | |
| Subject analysis set title | Per Protocol |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All patients who completed the three trials (each patient took part in up to three periods, that were compared with each other) | |

Primary: terminal elimination half-life

| | |
|--|--------------------------------|
| End point title | terminal elimination half-life |
| End point description: | |
| End point type | Primary |
| End point timeframe: 24h per period | |

| End point values | Target Temperature Management | Rewarming | Recovered | |
|---------------------------------------|-------------------------------|------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 ^[1] | 10 | 10 | |
| Units: h | | | | |
| median (inter-quartile range (Q1-Q3)) | 2.4 (1.8 to 4.8) | 2.8 (2.1 to 6.8) | 1.2 (0.9 to 2.3) | |

Notes:

[1] - only patients who completed all three periods were included in the final analysis

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Friedman ANOVA |
| Statistical analysis description: comparing the three periods, including 10 patients who completed the three periods. | |
| Comparison groups | Target Temperature Management v Rewarming v Recovered |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | < 0.001 ^[3] |
| Method | ANOVA |

Notes:

[2] - included n=10 who completed all three study periods

[3] - a significant difference was found

Secondary: Area under the time-concentration curve

| | |
|--|---|
| End point title | Area under the time-concentration curve |
| End point description: Area under the time concentration curve from 0-24h of pantoprazole after 40mg bolus infusion | |
| End point type | Secondary |
| End point timeframe: 24 hours per period | |

| End point values | Target Temperature Management | Rewarming | Recovered | |
|---------------------------------------|-------------------------------|-------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 ^[4] | 10 ^[5] | 10 ^[6] | |
| Units: ng/mL*h | | | | |
| median (inter-quartile range (Q1-Q3)) | 12.7 (9.6 to 22.6) | 9.8 (7.6 to 18.6) | 7.2 (5.9 to 9.5) | |

Notes:

[4] - only 10 subjects completed all three periods for the comparison of the pharmacokinetics

[5] - only 10 subjects completed all three periods for the comparison of the pharmacokinetics

[6] - only 10 subjects completed all three periods for the comparison of the pharmacokinetics

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Friedman ANOVA |
| Statistical analysis description: comparison of all three groups in one analysis | |
| Comparison groups | Target Temperature Management v Rewarming v Recovered |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[7] |
| P-value | = 0.027 ^[8] |
| Method | ANOVA |

Notes:

[7] - n=10 because the same ten subjects completed all three periods

[8] - there was a significant difference between the three study periods

Secondary: Volume of Distribution

| | |
|--|------------------------|
| End point title | Volume of Distribution |
| End point description: three study periods were compared with each other. 10 patients completed the three periods and were therefore eligible for comparison. The Volume of distribution is presented in the unit L (Liters). | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 24h per period | |

| End point values | Target Temperature Management | Rewarming | Recovered | |
|---------------------------------------|-------------------------------|---------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 ^[9] | 10 ^[10] | 10 ^[11] | |
| Units: Liters | | | | |
| median (inter-quartile range (Q1-Q3)) | 11.4 (10.2 to 12.7) | 16.5 (14.3 to 21.2) | 12.5 (8 to 15.6) | |

Notes:

[9] - only 10 subjects completed all three periods for the comparison of the pharmacokinetics

[10] - only 10 subjects completed all three periods for the comparison of the pharmacokinetics

[11] - only 10 subjects completed all three periods for the comparison of the pharmacokinetics

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Friedman ANOVA |
| Statistical analysis description: | |
| all three periods were compared with each other using a Friedman ANOVA | |
| Comparison groups | Target Temperature Management v Rewarming v Recovered |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 ^[12] |
| Method | ANOVA |

Notes:

[12] - there was a significant difference between the three study periods.

Secondary: Clearance

| | |
|--|-----------|
| End point title | Clearance |
| End point description: | |
| The main comparison was performed in 10 patients, who completed all three study periods. | |
| End point type | Secondary |
| End point timeframe: | |
| 0-24h after each dose, | |

| End point values | Target Temperature Management | Rewarming | Recovered | |
|---------------------------------------|-------------------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 ^[13] | 10 ^[14] | 10 ^[15] | |
| Units: L/h | | | | |
| median (inter-quartile range (Q1-Q3)) | 2.9 (1.7 to 4.0) | 3.9 (2.0 to 4.9) | 5.5 (3.9 to 6.5) | |

Notes:

[13] - Ten patients completed the three study periods and were included in the final analysis

[14] - Ten patients completed the three study periods and were included in the final analysis

[15] - Ten patients completed the three study periods and were included in the final analysis

Statistical analyses

| | |
|-----------------------------------|----------------|
| Statistical analysis title | Friedman Anova |
|-----------------------------------|----------------|

Statistical analysis description:

all three periods were compares in one statistical test - a Friedman ANOVA

| | |
|---|---|
| Comparison groups | Target Temperature Management v Rewarming v Recovered |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.027 ^[16] |
| Method | ANOVA |

Notes:

[16] - There was a significant difference between the three study periods.

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

First visit of each patient to last visit of each individual patient. This was depending on the clinical course of the patients and lasted up to 19 days until all three study periods were completed.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|-----|
| Dictionary version | 3.0 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Full Analysis Set |
|-----------------------|-------------------|

Reporting group description:

Due to the observational nature of the study and the critical illness of the patients, only serious adverse events were documented.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: This was a non-interventional, observational study in patients who have undergone a successful cardiopulmonary resuscitation. Pantoprazole was part of their standard of care and we quantified pharmacokinetics. Thus, we have only recorded serious adverse events, but no non-serious adverse events.

| Serious adverse events | Full Analysis Set | | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 16 (37.50%) | | |
| number of deaths (all causes) | 5 | | |
| number of deaths resulting from adverse events | 0 | | |
| Nervous system disorders | | | |
| Hypoxic brain damage | Additional description: In five subjects treating physicians diagnosed a hypoxic brain damage after initial cardiac arrest. Because of poor prognosis treatment was withdrawn. There was no causal relationship with the study. Of note, pantoprazole was part of standard of care | | |
| subjects affected / exposed | 5 / 16 (31.25%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 5 | | |
| Hepatobiliary disorders | | | |
| Hypoxic hepatitis | Additional description: In one patient a hypoxic hepatitis was diagnosed after initial cardiac arrest. There was no causal relationship with the study or the study drug. Pantoprazole was part of standard of care. | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | Additional description: Two patients developed an acute kidney failure after initial cardiac arrest. There was no causal relationship with the study or the study drug. Of note, pantoprazole was part of the standard of care. | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 1 %

| | | | |
|---|-------------------|--|--|
| Non-serious adverse events | Full Analysis Set | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 06 February 2019 | <p>The study was initially submitted as an interventional trial in patients undergoing cardiopulmonary resuscitation. The IMPs included paracetamol, erythromycin and pantoprazole. However, as we couldn't provide sufficient evidence for the individual benefit of the participating subjects, we were only able to conduct a non-interventional study investigating the pharmacokinetics of pantoprazole. Hence, due to the non-interventional nature of the study, the Ethics Committee did not demand a EudraCT entry. However, since the current EudraCT entry was still opened, we decided to enter study data as far as possible.</p> <p>The Amendment date relates to the last change of the study protocol, which in its final version describes a non-interventional study focusing on the pharmacokinetics of pantoprazole.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

16 patients were included in total. However, six couldn't participate in the last period due to death or poor neurologic outcome. Hence, the final population consists of 10 patients.

Notes: