



## Clinical trial results: CUstodiol vs RInger: whaT Is the Best Agent?

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2014-003818-92  |
| Trial protocol           | IT              |
| Global end of trial date | 17 January 2018 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 29 May 2021  |
| First version publication date | 29 May 2021  |

### Trial information

#### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | CURITIBA-TRIAL |
|-----------------------|----------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02327611 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | IRCCS Ospedale San Raffaele   |
| Sponsor organisation address | Via Olgettina, 60, Milano, Italy, 20133                               |
| Public contact               | UO Chirurgia Vascolare, IRCCS Ospedale San Raffaele, 0039 0226437377, |
| Scientific contact           | UO Chirurgia Vascolare, IRCCS Ospedale San Raffaele, 0039 0226437377, |

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                       | 17 January 2018 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 17 January 2018 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 17 January 2018 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

Compare the efficacy of renal perfusion with Custodiol versus enriched Ringer's solution for renal protection in patients undergoing open thoracoabdominal aortic aneurysm (TAAA) repair

Protection of trial subjects:

Approval by the local Ethics Committee was obtained before the beginning of the study and written informed consent was obtained from all patients at time of enrolment. Patients care was carried out by a multidisciplinary team.

Except for the solutions used during the perfusion, the trial did not affect any other aspect of patient treatment, which was left to standard clinical practice.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 22 February 2015 |
| 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 | Italy: 90 |
| Worldwide total number of subjects   | 90        |
| EEA total number of subjects         | 90        |

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)                      | 30 |
| From 65 to 84 years                       | 60 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

#### Recruitment details:

This prospective, single-center, randomized, double-blind, controlled, parallel trial involved 90 adult patients who were to undergo TAAA open repair surgery requiring renal perfusion. Patients were enrolled between February 2015 and January 2017. One year of follow up was completed in January 2018.

### Pre-assignment

#### Screening details:

Patients who have participated in experimental trials during the previous 3 months, undergoing emergency/urgency intervention, patient uncooperative and/or affected by mental disease, with allergy/intolerance to the study drug, patient receiving chronic dialysis before surgery, and pregnant or breastfeeding women were excluded

### Period 1

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

#### Blinding implementation details:

A computer-generated permuted block (up to a size of 10 and a 1:1 allocation) randomization sequence was used. Treatment allocation was prepared by an independent operator not otherwise involved in the trial. The patient was randomized upon operative room arrival by a CURITIBA trial staff member who prepared the blinded treatment and was not in any way involved in the clinical management of the patient. Both solutions are colorless, thus impossible to distinguish.

### Arms

|  |   |
|--|---|
| Are arms mutually exclusive?           | Yes   |
| <b>Arm title</b>                       | Custodiol Renal Perfusion                         |
| Arm description: -                     |   |
| Arm type                               | Experimental                                      |
| Investigational medicinal product name | Custodiol   |
| Investigational medicinal product code |   |
| Other name                             | Custodiol HTK, Histidine-tryptophan-ketoglutarate |
| Pharmaceutical forms                   | Solution for organ preservation                   |
| Routes of administration               | Intraarterial use                                 |

#### Dosage and administration details:

Patients randomized in the Custodiol arm received, upon renal artery clamping, a renal perfusion with cold (4°C) Custodiol.

During renal ischemic time, a total of 1.5 mL of Custodiol per gram of estimated kidney weight were administered, thus implying an average of 400 mL of Custodiol for a 70-kg patient

|  |   |
|--|---|
| <b>Arm title</b>                       | Ringer Renal Perfusion                              |
| Arm description: -                     |   |
| Arm type                               | Active comparator                                   |
| Investigational medicinal product name | Ringer's lactate                                    |
| Investigational medicinal product code |   |
| Other name                             | Lactated Ringer's solution, Sodium lactate solution |
| Pharmaceutical forms                   | Solution for infusion                               |
| Routes of administration               | Intraarterial use                                   |

#### Dosage and administration details:

Patients randomized in the enriched Ringer's lactate arm received a renal perfusion with cold (4°C) Ringer's lactate solution enriched with 125 mg per liter of methylprednisolone and 12.5 g per liter of mannitol.

| <b>Number of subjects in period 1</b> | Custodiol Renal Perfusion | Ringer Renal Perfusion |
|---------------------------------------|---------------------------|------------------------|
| Started                               | 45                        | 45                     |
| Completed                             | 44                        | 44                     |
| Not completed                         | 1                         | 1                      |
| Intraoperative clinical reasons       | 1                         | 1                      |

## Baseline characteristics

### Reporting groups

|                                |                           |
|--------------------------------|---------------------------|
| Reporting group title          | Custodiol Renal Perfusion |
| Reporting group description: - |                           |
| Reporting group title          | Ringer Renal Perfusion    |
| Reporting group description: - |                           |

| Reporting group values             | Custodiol Renal Perfusion | Ringer Renal Perfusion | Total |
|------------------------------------|---------------------------|------------------------|-------|
| Number of subjects                 | 45                        | 45                     | 90    |
| Age categorical<br>Units: Subjects |                           |                        |       |

|   |                |                |    |
|---|----------------|----------------|----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 63.7<br>± 9.82 | 66.4<br>± 9.21 | -  |
| Gender categorical<br>Units: Subjects                                   |                |                |    |
| Female  | 33             | 29             | 62 |
| Male  | 12             | 16             | 28 |

## End points

### End points reporting groups

|                                |                           |
|--------------------------------|---------------------------|
| Reporting group title          | Custodiol Renal Perfusion |
| Reporting group description: - |                           |
| Reporting group title          | Ringer Renal Perfusion    |
| Reporting group description: - |                           |

### Primary: Reduction of Acute renal failure (AKI)

|                        |  |
|------------------------|--|
| End point title        | Reduction of Acute renal failure (AKI)   |
| End point description: | Make a significant reduction of acute renal failure (AKI - Defined according to the diagram 2013.9 KDIGO) in postoperative surgical patients who receive renal perfusion with Custodiol vs standard perfusion with Ringer's lactate solution |
| End point type         | Primary  |
| End point timeframe:   | 28 days after surgery  |

| End point values            | Custodiol Renal Perfusion | Ringer Renal Perfusion |  |  |
|-----------------------------|---------------------------|------------------------|--|--|
| Subject group type          | Reporting group           | Reporting group        |  |  |
| Number of subjects analysed | 45                        | 45                     |  |  |
| Units: number of patients   |                           |                        |  |  |
| Any AKI (AKIN 1 + 2+ 3)     | 22                        | 34                     |  |  |
| AKIN stage 0                | 23                        | 11                     |  |  |
| AKIN stage 1                | 11                        | 18                     |  |  |
| AKIN stage 2                | 7                         | 7                      |  |  |
| AKIN stage 3                | 4                         | 9                      |  |  |
| Severe AKI (AKIN 2 +3)      | 11                        | 16                     |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | AKI Intention-to-treat analysis                    |
| Comparison groups                       | Custodiol Renal Perfusion v Ringer Renal Perfusion |
| Number of subjects included in analysis | 90   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| P-value                                 | < 0.05   |
| Method                                  | Wilcoxon (Mann-Whitney)                            |

### Secondary: Length of stay in the Intensive care Unit (ICU)

|                        |   |
|------------------------|---|
| End point title        | Lenght of stay in the Intensive care Unit (ICU) |
| End point description: |   |
| End point type         | Secondary                                       |
| End point timeframe:   |   |
| 60 days after surgery  |   |

| End point values                      | Custodirol Renal Perfusion | Ringer Renal Perfusion |  |  |
|---------------------------------------|----------------------------|------------------------|--|--|
| Subject group type                    | Reporting group            | Reporting group        |  |  |
| Number of subjects analysed           | 45                         | 45                     |  |  |
| Units: day                            |                            |                        |  |  |
| median (inter-quartile range (Q1-Q3)) | 1 (1 to 2)                 | 1 (1 to 2)             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Lenght of hospitalization

|                        |                           |
|------------------------|---------------------------|
| End point title        | Lenght of hospitalization |
| End point description: |                           |
| End point type         | Secondary                 |
| End point timeframe:   |                           |
| 60 days after surgery  |                           |

| End point values                      | Custodirol Renal Perfusion | Ringer Renal Perfusion |  |  |
|---------------------------------------|----------------------------|------------------------|--|--|
| Subject group type                    | Reporting group            | Reporting group        |  |  |
| Number of subjects analysed           | 45                         | 45                     |  |  |
| Units: day                            |                            |                        |  |  |
| median (inter-quartile range (Q1-Q3)) | 15 (13 to 20)              | 15 (13 to 18)          |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: In-hospital mortality

|                        |                       |
|------------------------|-----------------------|
| End point title        | In-hospital mortality |
| End point description: |                       |

|                        |           |
|------------------------|-----------|
| End point type         | Secondary |
| End point timeframe:   |           |
| During hospitalization |           |

| End point values            | Custodiol Renal Perfusion | Ringer Renal Perfusion |  |  |
|-----------------------------|---------------------------|------------------------|--|--|
| Subject group type          | Reporting group           | Reporting group        |  |  |
| Number of subjects analysed | 45                        | 45                     |  |  |
| Units: number of patients   | 4                         | 6                      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 1-year survival

|                        |                 |
|------------------------|-----------------|
| End point title        | 1-year survival |
| End point description: |                 |
| End point type         | Secondary       |
| End point timeframe:   |                 |
| 1 year after surgery   |                 |

| End point values                 | Custodiol Renal Perfusion | Ringer Renal Perfusion |  |  |
|----------------------------------|---------------------------|------------------------|--|--|
| Subject group type               | Reporting group           | Reporting group        |  |  |
| Number of subjects analysed      | 45                        | 45                     |  |  |
| Units: percent                   |                           |                        |  |  |
| number (confidence interval 95%) | 91.1 (83 to 99)           | 84.4 (74 to 95)        |  |  |

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Until the end of the annual follow-up

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 20 |
|--------------------|----|

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Custodiol Renal Perfusion |
|-----------------------|---------------------------|

Reporting group description: -

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Ringer Renal Perfusion |
|-----------------------|------------------------|

Reporting group description: -

| Serious adverse events                            | Custodiol Renal Perfusion | Ringer Renal Perfusion |  |
|---|---------------------------|------------------------|--|
| Total subjects affected by serious adverse events |                           |                        |  |
| subjects affected / exposed                       | 0 / 44 (0.00%)            | 0 / 44 (0.00%)         |  |
| number of deaths (all causes)                     | 5                         | 6                      |  |
| number of deaths resulting from adverse events    | 0                         | 0                      |  |

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

| Non-serious adverse events                            | Custodiol Renal Perfusion | Ringer Renal Perfusion |  |
|---|---------------------------|------------------------|--|
| Total subjects affected by non-serious adverse events |                           |                        |  |
| subjects affected / exposed                           | 0 / 44 (0.00%)            | 0 / 44 (0.00%)         |  |

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: No non-serious adverse event associated to the IMPs were recorded

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 04 March 2015 | Changes and clarifications regarding the randomization procedure<br>Changes to some study procedures (e.g. sample collection, markers analysis, data recording) |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24377947>