

**Clinical trial results:****A Prospective Randomized Double Blind Multicenter Phase III Study Comparing two Methods of Cardioplegia in Aortic Valve Surgery Custodiol-N versus Custodiol****Summary**

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2012-003776-40   |
| Trial protocol           | DE               |
| Global end of trial date | 06 December 2019 |

**Results information**

|                                   |   |
|-----------------------------------|---|
| Result version number             | v1 (current)                              |
| This version publication date     | 28 April 2022                             |
| First version publication date    | 28 April 2022                             |
| Summary attachment (see zip file) | CSRCustodiol-N_AVS (20200121SYNOPSIS.pdf) |

**Trial information****Trial identification**

|                       |                       |
|-----------------------|-----------------------|
| Sponsor protocol code | CL-N-CSM-AV-III/05/12 |
|-----------------------|-----------------------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02098772 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Dr. Franz Köhler Chemie GmbH  |
| Sponsor organisation address | Werner-von - Siemens-Str. 14-28, Bensheim, Germany, 64625                                 |
| Public contact               | Dr. Roman Petrov, Dr. Franz Köhler Chemie GmbH, +49 625110830, r.petrov@koehler-chemie.de |
| Scientific contact           | Dr. Roman Petrov, Dr. Franz Köhler Chemie GmbH, +49 625110830, r.petrov@koehler-chemie.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                       | 04 December 2020 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 06 December 2019 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 06 December 2019 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The objective of this investigation is to compare the cardioprotective effects and safety of two cardioplegic solutions, Custodiol and Custodiol-N in patients undergoing aortic valve surgery +/- bypass surgery.

Protection of trial subjects:

Patients were monitored for adverse events. Safety laboratory examinations were performed according to protocol.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 01 March 2014 |
| 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 | Germany: 530 |
| Worldwide total number of subjects   | 530          |
| EEA total number of subjects         | 530          |

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)                      | 169 |
| From 65 to 84 years                       | 359 |
| 85 years and over                         | 2   |

## Subject disposition

### Recruitment

Recruitment details:

To obtain a sample for analysis per protocol of 394 patients a total of 530 patients with aortic valve disease was scheduled to be enrolled. One patient included did not receive treatment at all, one other patient received not the treatment randomised to.

### Pre-assignment

Screening details:

The study population was selected from patients of either sex who were to undergo surgery for aortic valve replacement (with or without coronary bypass surgery).

### Period 1

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

### Arms

|  |                       |
|--|-----------------------|
| Are arms mutually exclusive?           | Yes                   |
| <b>Arm title</b>                       | Custodiol             |
| Arm description: -                     |                       |
| Arm type                               | Active comparator     |
| Investigational medicinal product name | Custodiol             |
| Investigational medicinal product code | B05CX10               |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Infusion              |

Dosage and administration details:

During aortic valve surgery, after cross clamping of the aorta on cardiopulmonary bypass, the Custodiol® or Custodiol-N solution, was infused into the root of the aorta at a temperature of 4 - 6°C.

|  |                       |
|--|-----------------------|
| <b>Arm title</b>                       | Custodiol-N           |
| Arm description: -                     |                       |
| Arm type                               | Experimental          |
| Investigational medicinal product name | Custodiol-N           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Infusion              |

Dosage and administration details:

During aortic valve surgery, after cross clamping of the aorta on cardiopulmonary bypass, the Custodiol® or Custodiol-N solution, was infused into the root of the aorta at a temperature of 4 - 6°C.

| <b>Number of subjects in period 1</b> | Custodiol | Custodiol-N |
|---------------------------------------|-----------|-------------|
| Started                               | 265       | 265         |
| Completed                             | 265       | 263         |
| Not completed                         | 0         | 2           |
| Adverse event, serious fatal          | -         | 1           |
| Protocol deviation                    | -         | 1           |

## Baseline characteristics

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### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Treatment |
|-----------------------|-----------|

Reporting group description:

This reporting group equals the full analysis data set

---

| Reporting group values | Treatment | Total |  |
|------------------------|-----------|-------|--|
| Number of subjects     | 530       | 530   |  |
| Age categorical        |           |       |  |
| Units: Subjects        |           |       |  |
| Adults (18-64 years)   | 168       | 168   |  |
| From 65-84 years       | 360       | 360   |  |
| 85 years and over      | 2         | 2     |  |
| Gender categorical     |           |       |  |
| Units: Subjects        |           |       |  |
| Female                 | 181       | 181   |  |
| Male                   | 349       | 349   |  |

## End points

### End points reporting groups

|  |                                       |
|--|---------------------------------------|
| Reporting group title  | Custodiol                             |
| Reporting group description: -   |                                       |
| Reporting group title  | Custodiol-N                           |
| Reporting group description: -   |                                       |
| Subject analysis set title   | Custodiol per protocol analysis set   |
| Subject analysis set type  | Per protocol                          |
| Subject analysis set description:<br>The per protocol analysis set: 205 patients for the Custodiol® group and 206 for the Custodiol-N group. |                                       |
| Subject analysis set title   | Custodiol-N per protocol analysis set |
| Subject analysis set type  | Per protocol                          |
| Subject analysis set description:<br>The per protocol analysis set: 205 patients for the Custodiol® group and 206 for the Custodiol-N group. |                                       |

### Primary: Peak CK-MB value

|   |                  |
|---|------------------|
| End point title   | Peak CK-MB value |
| End point description:  |                  |
|   |                  |
| End point type  | Primary          |
| End point timeframe:<br>CK-MB peak value from 4 to 24 hours (measurements 4, 8, 12, 16, 20, 24 hours ± 30 min) after release of the aortic cross clamp. |                  |

| End point values                     | Custodiol       | Custodiol-N     |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 265             | 263             |  |  |
| Units: Units                         |                 |                 |  |  |
| arithmetic mean (standard deviation) | 65.1 (± 110.7)  | 58.1 (± 38.2)   |  |  |

### Statistical analyses

|  |                                      |
|--|--------------------------------------|
| Statistical analysis title   | CK-MB peak value (full analysis set) |
| Statistical analysis description:<br>Primary analysis was performed taking the logarithm of 4h-24h-peak CK-MB values as primary endpoint. The null hypothesis was: "No effect of Custodiol-N over Custodiol® with respect to CKMB peak value". |                                      |
| Comparison groups  | Custodiol v Custodiol-N              |
| Number of subjects included in analysis  | 528                                  |
| Analysis specification   | Pre-specified                        |
| Analysis type  | non-inferiority <sup>[1]</sup>       |
| P-value  | = 0.4815                             |
| Method   | likelihood ratio test (5% level)     |

Notes:

[1] - Likelihood ratio test +at the 5 per cent level of the treatment group parameter in a linear model.  
Missing log (CK-MB) values were handled by multiple imputation before deriving peak values.

### Primary: Peak CK-MB (per protocol set)

|                 |                               |
|-----------------|-------------------------------|
| End point title | Peak CK-MB (per protocol set) |
|-----------------|-------------------------------|

End point description:

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Within 24 h from opening of aortic cross clamp

| End point values                     | Custodiol per protocol analysis set | Custodiol-N per protocol analysis set |  |  |
|--------------------------------------|-------------------------------------|---------------------------------------|--|--|
| Subject group type                   | Subject analysis set                | Subject analysis set                  |  |  |
| Number of subjects analysed          | 205                                 | 206                                   |  |  |
| Units: U/L                           |                                     |                                       |  |  |
| arithmetic mean (standard deviation) | 59.6 (± 42.7)                       | 58.4 (± 38.6)                         |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | CK-MB 24h peak value (per protocol data set)                                |
| Comparison groups                       | Custodiol-N per protocol analysis set v Custodiol per protocol analysis set |
| Number of subjects included in analysis | 411   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority   |
| P-value                                 | = 0.9122  |
| Method                                  | likelihood ratio test (5% level)  |

### Secondary: Adrenaline requirement on SICU within 24 hours (cumulative dose)

|                 |  |
|-----------------|--|
| End point title | Adrenaline requirement on SICU within 24 hours (cumulative dose) |
|-----------------|--|

End point description:

Values provided for full analysis set

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Within 24 h after opening of aortic cross clamp

| End point values                     | Custodiol       | Custodiol-N     |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 263             | 262             |  |  |
| Units: µg/kg body mass               |                 |                 |  |  |
| arithmetic mean (standard deviation) | 3.88 (± 35.57)  | 9.04 (± 78.24)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Dobutamine requirement on SICU within 24 hours (cumulative dose)

|   |  |
|---|--|
| End point title   | Dobutamine requirement on SICU within 24 hours (cumulative dose) |
| End point description:<br>Data for full analysis set provided.                |  |
| End point type  | Secondary  |
| End point timeframe:<br>Within 24 h following oopening of aortic cross clamp. |  |

| End point values                     | Custodiol       | Custodiol-N     |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 263             | 262             |  |  |
| Units: µg/kg body mass               |                 |                 |  |  |
| arithmetic mean (standard deviation) | 3.88 (± 35.57)  | 9.04 (± 78.24)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Noradrenaline requirement on SICU within 24 hours (cumulative dose)

|   |   |
|---|---|
| End point title   | Noradrenaline requirement on SICU within 24 hours (cumulative dose) |
| End point description:<br>Values for full analysis set provided. Data in the Custodiol-N group were distorted by one single patient for whom a dose of 317 mg per kg body weight were documented. |   |
| End point type  | Secondary   |
| End point timeframe:<br>Within 24 h after opening of aortic cross clamp.  |   |



| End point values                     | Custodioli       | Custodioli-N       |  |  |
|--------------------------------------|------------------|--------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group    |  |  |
| Number of subjects analysed          | 264              | 260                |  |  |
| Units: µg/kg body mass               |                  |                    |  |  |
| arithmetic mean (standard deviation) | 75.81 (± 380.37) | 842.46 (± 9811.41) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: 5-day peak value of Troponin-T

|  |                                |
|--|--------------------------------|
| End point title  | 5-day peak value of Troponin-T |
| End point description:   |                                |
| Due to a confusion of the unit there was one single peak value of 841000 pg/mL in the Custodioli-N group, after removing this single value, the mean value for the remaining group was 1271.3 pg/mL. |                                |
| End point type   | Secondary                      |
| End point timeframe:   |                                |
| 4, 8, 12, 16, 20, 24 hours ± 30 min and on the days 2, 3, 4 and 5 after release of the aortic cross clamp  |                                |

| End point values                     | Custodioli        | Custodioli-N       |  |  |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group    |  |  |
| Number of subjects analysed          | 265               | 263                |  |  |
| Units: pg/mL                         |                   |                    |  |  |
| arithmetic mean (standard deviation) | 1227.4 (± 1262.7) | 4465.4 (± 51796.4) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: CK-MB area under the curve

|  |                            |
|--|----------------------------|
| End point title  | CK-MB area under the curve |
| End point description:   |                            |
| End point type   | Secondary                  |
| End point timeframe:   |                            |
| Between 4 and 24 hours after removal of the aortic cross-clamp |                            |

| End point values                     | Custodiol              | Custodiol-N            |  |  |
|--------------------------------------|------------------------|------------------------|--|--|
| Subject group type                   | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed          | 265                    | 263                    |  |  |
| Units: area under curve              |                        |                        |  |  |
| arithmetic mean (standard deviation) | 1009.5 ( $\pm$ 1199.6) | 924.08 ( $\pm$ 593.61) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Troponin T area under the curve

|  |                                 |
|--|---------------------------------|
| End point title  | Troponin T area under the curve |
| End point description:   |                                 |
| End point type   | Secondary                       |
| End point timeframe:   |                                 |
| Between 4 and 24 hours after removal of the aortic cross-clamp |                                 |

| End point values                     | Custodiol            | Custodiol-N           |  |  |
|--------------------------------------|----------------------|-----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group       |  |  |
| Number of subjects analysed          | 265                  | 263                   |  |  |
| Units: area under the curve          |                      |                       |  |  |
| arithmetic mean (standard deviation) | 16020 ( $\pm$ 14870) | 64972 ( $\pm$ 796589) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Need of defibrillation

|  |                        |
|--|------------------------|
| End point title                                  | Need of defibrillation |
| End point description:                           |                        |
| End point type                                   | Secondary              |
| End point timeframe:                             |                        |
| Up to day 5 after opening of aortic cross clamp. |                        |

| End point values                        | Custodiol       | Custodiol-N     |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                      | Reporting group | Reporting group |  |  |
| Number of subjects analysed             | 265             | 261             |  |  |
| Units: patients needing defibrillations |                 |                 |  |  |
| 0 defibrillations needed                | 256             | 252             |  |  |
| 1 defibrillation needed                 | 7               | 7               |  |  |
| 2 defibrillations needed                | 1               | 1               |  |  |
| 3 defibrillations needed                | 0               | 1               |  |  |
| 4 defibrillations needed                | 1               | 0               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Requirement for intraaortic ball pump treatment (IABP)

|                 |  |
|-----------------|--|
| End point title | Requirement for intraaortic ball pump treatment (IABP) |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Within 5 days from surgery

| End point values             | Custodiol       | Custodiol-N     |  |  |
|------------------------------|-----------------|-----------------|--|--|
| Subject group type           | Reporting group | Reporting group |  |  |
| Number of subjects analysed  | 265             | 263             |  |  |
| Units: patients needing IABP | 1               | 2               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Blood pressure

|                 |                |
|-----------------|----------------|
| End point title | Blood pressure |
|-----------------|----------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Within 5 days from surgery

| End point values                     | Custodiol       | Custodiol-N     |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 265             | 263             |  |  |
| Units: mmHg                          |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| systolic                             | 135.8 (± 18.8)  | 136.5 (± 19.4)  |  |  |
| diastolic                            | 77.0 (± 11.3)   | 77.2 (± 10.9)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Length of surgical intensive care unit (SICU) stay

|                        |  |
|------------------------|--|
| End point title        | Length of surgical intensive care unit (SICU) stay |
| End point description: |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Following surgery      |  |

| End point values                     | Custodiol       | Custodiol-N     |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 265             | 262             |  |  |
| Units: days                          |                 |                 |  |  |
| arithmetic mean (standard deviation) | 2.6 (± 3.8)     | 2.4 (± 4.2)     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of mechanical ventilation (intubation to extubation)

|   |   |
|---|---|
| End point title   | Duration of mechanical ventilation (intubation to extubation) |
| End point description:  |   |
| The duration 24 h and 4 min was displayed as 24.67h; 27 h 55 min as 27.92h. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Following surgery   |   |

| End point values                     | Custodiol       | Custodiol-N     |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 264             | 261             |  |  |
| Units: hours                         |                 |                 |  |  |
| arithmetic mean (standard deviation) | 24.67 (± 31.7)  | 27.92 (± 54.52) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Occurrence of cardiac arrhythmias

|                             |                                   |
|-----------------------------|-----------------------------------|
| End point title             | Occurrence of cardiac arrhythmias |
| End point description:      |                                   |
| End point type              | Secondary                         |
| End point timeframe:        |                                   |
| Within 5 days after surgery |                                   |

| End point values            | Custodiol       | Custodiol-N     |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 265             | 263             |  |  |
| Units: arrhythmias          |                 |                 |  |  |
| no arrhythmia               | 168             | 159             |  |  |
| 1 episode of arrhythmia     | 72              | 73              |  |  |
| 2 episodes                  | 17              | 20              |  |  |
| 3 episodes                  | 4               | 4               |  |  |
| 4 episodes                  | 2               | 5               |  |  |
| 5 episodes                  | 2               | 2               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Repeated patient transfer to intensive care unit

|                             |  |
|-----------------------------|--|
| End point title             | Repeated patient transfer to intensive care unit |
| End point description:      |  |
| End point type              | Secondary  |
| End point timeframe:        |  |
| Within 6 days after surgery |  |

| <b>End point values</b>     | Custodiol       | Custodiol-N     |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 265             | 263             |  |  |
| Units: number of patients   | 2               | 5               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mortality

|                 |           |
|-----------------|-----------|
| End point title | Mortality |
|-----------------|-----------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Within 30 days from surgery

| <b>End point values</b>     | Custodiol       | Custodiol-N     |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 265             | 263             |  |  |
| Units: number of fatalities | 4               | 3               |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

30 days from surgery

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Custodiol safety data set |
|-----------------------|---------------------------|

Reporting group description:

One patient randomised to Custodiol-N received Custodiol instead and was excluded from efficacy analysis. However, for safety analysis, this patient was analysed in the Custodiol-group

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Custodiol-N safety data set |
|-----------------------|-----------------------------|

Reporting group description: -

| Serious adverse events                            | Custodiol safety data set | Custodiol-N safety data set |  |
|---|---------------------------|-----------------------------|--|
| Total subjects affected by serious adverse events |                           |                             |  |
| subjects affected / exposed                       | 34 / 266 (12.78%)         | 28 / 263 (10.65%)           |  |
| number of deaths (all causes)                     | 4                         | 3                           |  |
| number of deaths resulting from adverse events    | 2                         | 1                           |  |
| Investigations                                    |                           |                             |  |
| Investigations                                    |                           |                             |  |
| subjects affected / exposed                       | 1 / 266 (0.38%)           | 1 / 263 (0.38%)             |  |
| occurrences causally related to treatment / all   | 1 / 2                     | 0 / 1                       |  |
| deaths causally related to treatment / all        | 0 / 0                     | 0 / 0                       |  |
| Injury, poisoning and procedural complications    |                           |                             |  |
| Injury, poisoning and procedural complications    |                           |                             |  |
| subjects affected / exposed                       | 4 / 266 (1.50%)           | 3 / 263 (1.14%)             |  |
| occurrences causally related to treatment / all   | 0 / 5                     | 0 / 3                       |  |
| deaths causally related to treatment / all        | 0 / 0                     | 0 / 0                       |  |
| Vascular disorders                                |                           |                             |  |
| Vascular disorders                                |                           |                             |  |
| subjects affected / exposed                       | 1 / 266 (0.38%)           | 2 / 263 (0.76%)             |  |
| occurrences causally related to treatment / all   | 0 / 1                     | 0 / 2                       |  |
| deaths causally related to treatment / all        | 0 / 0                     | 0 / 0                       |  |
| Cardiac disorders                                 |                           |                             |  |

|   |   |                  |  |
|---|---|------------------|--|
| Cardiac disorders                               |   |                  |  |
| subjects affected / exposed                     | 9 / 266 (3.38%)   | 12 / 263 (4.56%) |  |
| occurrences causally related to treatment / all | 1 / 10  | 0 / 16           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0            |  |
| Nervous system disorders                        |   |                  |  |
| Nervous system disorders                        | Additional description: One fatality in the Cutodiol-N group was documented as cerebral infarction. |                  |  |
| subjects affected / exposed                     | 3 / 266 (1.13%)   | 1 / 263 (0.38%)  |  |
| occurrences causally related to treatment / all | 0 / 3   | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 1            |  |
| Blood and lymphatic system disorders            |   |                  |  |
| Blood and lymphatic system disorders            |   |                  |  |
| subjects affected / exposed                     | 1 / 266 (0.38%)   | 0 / 263 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0            |  |
| Hepatobiliary disorders                         |   |                  |  |
| Hepatobiliary disorders                         |   |                  |  |
| subjects affected / exposed                     | 1 / 266 (0.38%)   | 0 / 263 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1   | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |   |                  |  |
| Pleural effusion                                |   |                  |  |
| subjects affected / exposed                     | 0 / 266 (0.00%)   | 1 / 263 (0.38%)  |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0            |  |
| Renal and urinary disorders                     |   |                  |  |
| Acute kidney injury                             |   |                  |  |
| subjects affected / exposed                     | 1 / 266 (0.38%)   | 1 / 263 (0.38%)  |  |
| occurrences causally related to treatment / all | 0 / 1   | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0            |  |
| Product issues                                  |   |                  |  |
| Device malfunction                              |   |                  |  |
| subjects affected / exposed                     | 3 / 266 (1.13%)   | 0 / 263 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3   | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0            |  |



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

| <b>Non-serious adverse events</b>                     | Custodiol safety data set | Custodiol-N safety data set |  |
|---|---------------------------|-----------------------------|--|
| Total subjects affected by non-serious adverse events |                           |                             |  |
| subjects affected / exposed                           | 241 / 266 (90.60%)        | 248 / 263 (94.30%)          |  |
| Investigations  |                           |                             |  |
| Investigations  |                           |                             |  |
| subjects affected / exposed                           | 79 / 266 (29.70%)         | 83 / 263 (31.56%)           |  |
| occurrences (all)                                     | 162                       | 151                         |  |
| Injury, poisoning and procedural complications        |                           |                             |  |
| Injury, poisoning and procedural complications        |                           |                             |  |
| subjects affected / exposed                           | 70 / 266 (26.32%)         | 67 / 263 (25.48%)           |  |
| occurrences (all)                                     | 88                        | 85                          |  |
| Vascular disorders                                    |                           |                             |  |
| Vascular disorders                                    |                           |                             |  |
| subjects affected / exposed                           | 56 / 266 (21.05%)         | 41 / 263 (15.59%)           |  |
| occurrences (all)                                     | 63                        | 43                          |  |
| Cardiac disorders                                     |                           |                             |  |
| Cardiac disorders                                     |                           |                             |  |
| subjects affected / exposed                           | 114 / 266 (42.86%)        | 136 / 263 (51.71%)          |  |
| occurrences (all)                                     | 168                       | 194                         |  |
| Blood and lymphatic system disorders                  |                           |                             |  |
| Blood and lymphatic system disorders                  |                           |                             |  |
| subjects affected / exposed                           | 91 / 266 (34.21%)         | 91 / 263 (34.60%)           |  |
| occurrences (all)                                     | 124                       | 128                         |  |
| General disorders and administration site conditions  |                           |                             |  |
| General disorders and administrations site conditions |                           |                             |  |
| subjects affected / exposed                           | 42 / 266 (15.79%)         | 41 / 263 (15.59%)           |  |
| occurrences (all)                                     | 51                        | 47                          |  |
| Gastrointestinal disorders                            |                           |                             |  |
| Gastrointestinal disorders                            |                           |                             |  |
| subjects affected / exposed                           | 45 / 266 (16.92%)         | 41 / 263 (15.59%)           |  |
| occurrences (all)                                     | 62                        | 54                          |  |
| Respiratory, thoracic and mediastinal disorders       |                           |                             |  |

|  |                           |                           |  |
|--|---------------------------|---------------------------|--|
| Respiratory, thoracic and mediastinal disorders<br>subjects affected / exposed<br>occurrences (all)  | 190 / 266 (71.43%)<br>325 | 183 / 263 (69.58%)<br>321 |  |
| Psychiatric disorders<br>Psychiatric disorders<br>subjects affected / exposed<br>occurrences (all)   | 70 / 266 (26.32%)<br>78   | 61 / 263 (23.19%)<br>67   |  |
| Musculoskeletal and connective tissue disorders<br>Musculoskeletal and connective tissue disorders<br>subjects affected / exposed<br>occurrences (all) | 18 / 266 (6.77%)<br>18    | 17 / 263 (6.46%)<br>17    |  |
| Infections and infestations<br>Infections and infestations<br>subjects affected / exposed<br>occurrences (all)   | 22 / 266 (8.27%)<br>22    | 13 / 263 (4.94%)<br>13    |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 28 April 2014    | New formulation of IMP  |
| 13 May 2015      | Specification trial medication, new risk assessment   |
| 21 April 2016    | Changes in protocol (resulted in version 22.03.2016) following updated IB (version 04-2016) |
| 09 January 2017  | Increase number of patients   |
| 16 November 2017 | change of time for perfusion of the heart   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported