



## Clinical trial results:

### Infusion of hypertonic solutions: A risk factor for delirium after cardiac surgery? A randomised double blinded controlled trial.

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2018-002385-39 |
| Trial protocol           | SE             |
| Global end of trial date | 26 June 2020   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 03 June 2021 |
| First version publication date | 03 June 2021 |

#### Trial information

##### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | HSPOD |
|-----------------------|-------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |                                                                                         |
|------------------------------|-----------------------------------------------------------------------------------------|
| Sponsor organisation name    | County Council of Västerbotten                                                          |
| Sponsor organisation address | Heart Center, University Hospital of Umeå, Umeå, Sweden,                                |
| Public contact               | Fredrik Holmner, County Council of Västerbotten, 046 0907853650, fredrik.holmner@vll.se |
| Scientific contact           | Fredrik Holmner, County Council of Västerbotten, 046 0907853650, fredrik.holmner@vll.se |

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:

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**Results analysis stage**

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|                                                      |              |
|------------------------------------------------------|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 26 June 2020 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 26 June 2020 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 26 June 2020 |
| Was the trial ended prematurely?                     | No           |

Notes:

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**General information about the trial**

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Main objective of the trial:

Are hypertonic solutions a risk factor for delirium after cardiac surgery?

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Protection of trial subjects:

All patients was informed about the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. Personal data was processed in a legal, correct and open manner, collected for specific, explicit and legitimate purposes, adequate and relevant, correct and updated. Personal data are stored in a form that allows identification of the data patient for a longer time than is necessary and was treated in a manner that ensures appropriate security.

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Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 26 April 2019 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Sweden: 205 |
| Worldwide total number of subjects   | 205         |
| EEA total number of subjects         | 205         |

Notes:

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**Subjects enrolled per age group**

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|                                           |   |
|-------------------------------------------|---|
| 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) | 1   |
| From 65 to 84 years  | 204 |
| 85 years and over    | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Patients were enrolled consecutively and upon availability at Umeå Heart Centre, Umeå University Hospital, Sweden, between April 2019 and June 2020

### Pre-assignment

Screening details:

205 patients were included, 200 were randomised

### 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, Data analyst |

### Arms

|                              |            |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes        |
| <b>Arm title</b>             | Test group |

Arm description:

Cardiac surgical patients requiring cardiopulmonary bypass randomised to:

Priming of the heart-lung machine: Ringer-Acetate 1000 ml + Mannitol 60 g + Sodium Chloride 160 mmol + Heparin 10 000 IU

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Experimental      |
| Investigational medicinal product name | Ringer-Acetate    |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Infusion          |
| Routes of administration               | Intraarterial use |

Dosage and administration details:

1000 ml administered at commence of cardiopulmonary bypass as a single dose. Included in the prime composition used to fill the components of the heart-lung machine.

|                                        |                   |
|----------------------------------------|-------------------|
| Investigational medicinal product name | Mannitol          |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Infusion          |
| Routes of administration               | Intraarterial use |

Dosage and administration details:

60 g administered at commence of cardiopulmonary bypass as a single dose. Included in the prime composition used to fill the components of the heart-lung machine.

|                                        |                                                       |
|----------------------------------------|-------------------------------------------------------|
| Investigational medicinal product name | Sodium chloride                                       |
| Investigational medicinal product code |                                                       |
| Other name                             |                                                       |
| Pharmaceutical forms                   | Concentrate for concentrate for solution for infusion |
| Routes of administration               | Intraarterial use                                     |

Dosage and administration details:

160 mmol administered at commence of cardiopulmonary bypass as a single dose. Included in the prime composition used to fill the components of the heart-lung machine.

|                                        |         |
|----------------------------------------|---------|
| Investigational medicinal product name | Heparin |
| Investigational medicinal product code |         |
| Other name                             |         |

|                                                                                                                                                                         |                                                             |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| Pharmaceutical forms                                                                                                                                                    | Concentrate and solvent for solution for injection/infusion |
| Routes of administration                                                                                                                                                | Intraarterial use                                           |
| Dosage and administration details:                                                                                                                                      |                                                             |
| 10 000 IU administered at commence of cardiopulmonary bypass as a single dose. Included in the prime composition used to fill the components of the heart-lung machine. |                                                             |
| <b>Arm title</b>                                                                                                                                                        | Comparison group                                            |
| Arm description:                                                                                                                                                        |                                                             |
| Cardiac surgical patients requiring cardiopulmonary bypass randomised to:                                                                                               |                                                             |
| Priming of the heart-lung machine: Ringer-Acetate 1400 ml + Heparin 10 000 IU                                                                                           |                                                             |
| Arm type                                                                                                                                                                | Active comparator                                           |
| Investigational medicinal product name                                                                                                                                  | Ringer-Acetate                                              |
| Investigational medicinal product code                                                                                                                                  |                                                             |
| Other name                                                                                                                                                              |                                                             |
| Pharmaceutical forms                                                                                                                                                    | Infusion                                                    |
| Routes of administration                                                                                                                                                | Intraarterial use                                           |
| Dosage and administration details:                                                                                                                                      |                                                             |
| 1400 ml administered at commence of cardiopulmonary bypass as a single dose. Included in the prime composition used to fill the components of the heart-lung machine.   |                                                             |
| Investigational medicinal product name                                                                                                                                  | Heparin                                                     |
| Investigational medicinal product code                                                                                                                                  |                                                             |
| Other name                                                                                                                                                              |                                                             |
| Pharmaceutical forms                                                                                                                                                    | Concentrate and solvent for solution for injection/infusion |
| Routes of administration                                                                                                                                                | Intraarterial use                                           |
| Dosage and administration details:                                                                                                                                      |                                                             |
| 10 000 IU administered at commence of cardiopulmonary bypass as a single dose. Included in the prime composition used to fill the components of the heart-lung machine. |                                                             |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Test group | Comparison group |
|-----------------------------------------------------|------------|------------------|
| Started                                             | 100        | 100              |
| Completed                                           | 98         | 97               |
| Not completed                                       | 2          | 3                |
| Consent withdrawn by subject                        | -          | 3                |
| Lost to follow-up                                   | 1          | -                |
| Protocol deviation                                  | 1          | -                |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 205 patients were included, only 200 were randomised due to change of ECC method after inclusion (heparin coated CPB system)

## Baseline characteristics

### Reporting groups

| Reporting group title                                                                                                                                                                                                                 | Test group       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Reporting group description:<br>Cardiac surgical patients requiring cardiopulmonary bypass randomised to:<br>Priming of the heart-lung machine: Ringer-Acetate 1000 ml + Mannitol 60 g + Sodium Chloride 160 mmol + Heparin 10 000 IU |                  |
| Reporting group title                                                                                                                                                                                                                 | Comparison group |
| Reporting group description:<br>Cardiac surgical patients requiring cardiopulmonary bypass randomised to:<br>Priming of the heart-lung machine: Ringer-Acetate 1400 ml + Heparin 10 000 IU                                            |                  |

| Reporting group values                                | Test group | Comparison group | Total |
|-------------------------------------------------------|------------|------------------|-------|
| Number of subjects                                    | 100        | 100              | 200   |
| Age categorical<br>Units: Subjects                    |            |                  |       |
| In utero                                              | 0          | 0                | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0          | 0                | 0     |
| Newborns (0-27 days)                                  | 0          | 0                | 0     |
| Infants and toddlers (28 days-23 months)              | 0          | 0                | 0     |
| Children (2-11 years)                                 | 0          | 0                | 0     |
| Adolescents (12-17 years)                             | 0          | 0                | 0     |
| Adults (18-64 years)                                  | 1          | 0                | 1     |
| From 65-84 years                                      | 99         | 100              | 199   |
| 85 years and over                                     | 0          | 0                | 0     |
| Gender categorical<br>Units: Subjects                 |            |                  |       |
| Female                                                | 30         | 24               | 54    |
| Male                                                  | 70         | 76               | 146   |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                       |                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Reporting group title                                                                                                                                                                                                                 | Test group       |
| Reporting group description:<br>Cardiac surgical patients requiring cardiopulmonary bypass randomised to:<br>Priming of the heart-lung machine: Ringer-Acetate 1000 ml + Mannitol 60 g + Sodium Chloride 160 mmol + Heparin 10 000 IU |                  |
| Reporting group title                                                                                                                                                                                                                 | Comparison group |
| Reporting group description:<br>Cardiac surgical patients requiring cardiopulmonary bypass randomised to:<br>Priming of the heart-lung machine: Ringer-Acetate 1400 ml + Heparin 10 000 IU                                            |                  |

### Primary: Delirium

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Delirium |
| End point description:<br>Assessment delirium is performed by executing the following test battery: <ol style="list-style-type: none"><li>1. Mini Mental State Examination (MMSE)</li><li>2. Geriatric Depression Scale-15 (GDS-15)</li><li>3. Katz ADL-stair case test</li><li>4. Barthel index</li><li>5. NRS Pain</li><li>6. Organic Brain Syndrome Scale (OBS)</li><li>7. The Nursing Delirium Screening Scale (Nu-DESC)</li><li>8. Richmond agitation sedation scale (RASS)</li><li>9. Glasgow coma scale (GCS)</li></ol> |          |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Primary  |
| End point timeframe:<br>Assessed before and 1 day and 3 days after surgery                                                                                                                                                                                                                                                                                                                                                                                                                                                     |          |

| End point values            | Test group      | Comparison group |  |  |
|-----------------------------|-----------------|------------------|--|--|
| Subject group type          | Reporting group | Reporting group  |  |  |
| Number of subjects analysed | 98              | 97               |  |  |
| Units: number of patients   | 98              | 97               |  |  |

### Statistical analyses

|                            |                                   |
|----------------------------|-----------------------------------|
| Statistical analysis title | Difference postoperative delirium |
| Comparison groups          | Test group v Comparison group     |

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 195                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other <sup>[1]</sup>    |
| P-value                                 | < 0.05                  |
| Method                                  | Wilcoxon (Mann-Whitney) |

Notes:

[1] - The standard test for categorical variables with a large sample size will be analysed by the Chi-square test. Fisher's test will be executed in test situations, when the cell frequency in a contingency table is small, typically less than 5. In addition, differences of test scores between test and comparison group for the employed tests will be reported and analysed statistically using the Mann-Whitney u-test. Test scores represent data on the ordinal scale.

## Secondary: Plasma osmolality

|                 |                   |
|-----------------|-------------------|
| End point title | Plasma osmolality |
|-----------------|-------------------|

End point description:

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

End point timeframe:

Plasma osmolality is measured intraoperatively and twice postoperatively (day 1 and day 3).

| End point values            | Test group      | Comparison group |  |  |
|-----------------------------|-----------------|------------------|--|--|
| Subject group type          | Reporting group | Reporting group  |  |  |
| Number of subjects analysed | 98              | 97               |  |  |
| Units: mmol                 |                 |                  |  |  |
| number (not applicable)     | 98              | 97               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the time a patient receives the first dose of study treatment until 24 hours thereafter.

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

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |   |
|--------------------|---|
| Dictionary version | 5 |
|--------------------|---|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Test group |
|-----------------------|------------|

Reporting group description:

Cardiac surgical patients requiring cardiopulmonary bypass randomised to:

Priming of the heart-lung machine: Ringer-Acetate 1000 ml + Mannitol 60 g + Sodium Chloride 160 mmol + Heparin 10 000 IU

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Comparison group |
|-----------------------|------------------|

Reporting group description:

Cardiac surgical patients requiring cardiopulmonary bypass randomised to:

Priming of the heart-lung machine: Ringer-Acetate 1400 ml + Heparin 10 000 IU

| Serious adverse events                            | Test group      | Comparison group |  |
|---------------------------------------------------|-----------------|------------------|--|
| Total subjects affected by serious adverse events |                 |                  |  |
| subjects affected / exposed                       | 0 / 100 (0.00%) | 0 / 100 (0.00%)  |  |
| number of deaths (all causes)                     | 0               | 0                |  |
| number of deaths resulting from adverse events    | 0               | 0                |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events                            | Test group                                                            | Comparison group |  |
|-------------------------------------------------------|-----------------------------------------------------------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                                                                       |                  |  |
| subjects affected / exposed                           | 5 / 100 (5.00%)                                                       | 2 / 100 (2.00%)  |  |
| Investigations                                        |                                                                       |                  |  |
| Creatine urine increased                              |                                                                       |                  |  |
| subjects affected / exposed                           | 1 / 100 (1.00%)                                                       | 1 / 100 (1.00%)  |  |
| occurrences (all)                                     | 1                                                                     | 1                |  |
| Injury, poisoning and procedural complications        |                                                                       |                  |  |
| other                                                 | Additional description: Increasing pressure drop, membrane oxygenator |                  |  |
| subjects affected / exposed                           | 2 / 100 (2.00%)                                                       | 1 / 100 (1.00%)  |  |
| occurrences (all)                                     | 2                                                                     | 1                |  |
| Vascular disorders                                    |                                                                       |                  |  |

|                                                                                                |                      |                      |  |
|------------------------------------------------------------------------------------------------|----------------------|----------------------|--|
| Unstable blood pressure<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 100 (1.00%)<br>1 | 0 / 100 (0.00%)<br>0 |  |
| Nervous system disorders<br>Encephalopathy<br>subjects affected / exposed<br>occurrences (all) | 1 / 100 (1.00%)<br>1 | 0 / 100 (0.00%)<br>0 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported