



## Clinical trial results:

### Effect of preoperative intravenous highdose methylprednisolone on orthostatic intolerance, sleeping pattern, glucose homeostasis and immune signaling in patients scheduled for total hip-arthroplasty

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2015-000102-19  |
| Trial protocol           | DK              |
| Global end of trial date | 02 January 2017 |

#### Results information

|                                   |  |
|-----------------------------------|--|
| Result version number             | v1 (current)   |
| This version publication date     | 22 May 2022  |
| First version publication date    | 22 May 2022  |
| Summary attachment (see zip file) | Orthostatic hypotension and intolerance (Lindberg-Larsen et al. 2018 OH ad OI.pdf) |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | HL_VL_01_2015 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02445898 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Copenhagen university Hospital Rigshospitalet  |
| Sponsor organisation address | Blegdamsvej 9, Copenhagen, Denmark, 2100   |
| Public contact               | Viktoria Oline Lindberg-Larsen, Section for Surgical Pathophysiology, Rigshospitalet, 0045 28791991, viktorina_oline@hotmail.com |
| Scientific contact           | Viktoria Oline Lindberg-Larsen, Section for Surgical Pathophysiology, Rigshospitalet, 0045 28791991, viktorina_oline@hotmail.com |

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 May 2017      |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 28 December 2016 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 02 January 2017  |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the effect of intravenous highdose injection of methylprednisolone on orthostatic hypotension and intolerance in patients undergoing total hip-arthroplasty

Protection of trial subjects:

All trial patients followed standard treatment regarding surgery and postoperative regime. Information regarding physical testing and extra blood sampling was given prior til inclusion.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 01 September 2015 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Denmark: 59 |
| Worldwide total number of subjects   | 59          |
| EEA total number of subjects         | 59          |

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)                      | 20 |
| From 65 to 84 years                       | 39 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Patient were recruited at the ambulatory at Bispebjerg University Hospital visit when planned for total hip arthroplasty surgery.

190 patients were screened for inclusion, 64 patients were included, and 59 patients completed the study. The 5 patients excluded the trial due to protocol violations, primarily conversion to general anesthesia.

### Pre-assignment

Screening details:

- Age 55-80 years
- Hip osteoarthritis
- Planned for primary total hip arthroplasty (THA)
- Able to speak and understand Danish
- Have given informed consent

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 59 |
| Number of subjects completed | 59 |

### Period 1

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

Blinding implementation details:

A research assistant not otherwise involved in the trial performed a computer-generated random allocation sequence (1:1 allocation rate) concealed in 64 consecutively numbered, opaque, sealed envelopes determining active treatment or placebo. On the morning of surgery the envelopes were opened consecutively, and the trial drug was prepared by 2 anesthetist nurses not otherwise involved in the collection of trial data.

### Arms

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

Arm description:

Isotonic saline (2 mL)

|  |  |
|--|--|
| Arm type                               | Placebo                                |
| Investigational medicinal product name | Isotonic saline                        |
| Investigational medicinal product code | PL1                                    |
| Other name                             |  |
| Pharmaceutical forms                   | Concentrate for solution for injection |
| Routes of administration               | Intravenous use                        |

Dosage and administration details:

2 mL isotonic saline administered IV after induction of anaesthesia

|                    |                   |
|--------------------|-------------------|
| <b>Arm title</b>   | Steroid           |
| Arm description: - |                   |
| Arm type           | Active comparator |

|  |  |
|--|--|
| Investigational medicinal product name | Solu-Medrol  |
| Investigational medicinal product code | PR1  |
| Other name                             |  |
| Pharmaceutical forms                   | Concentrate and solvent for solution for injection |
| Routes of administration               | Intravenous use                                    |

Dosage and administration details:

125 mg Solu-Medrol administered IV after induction of anaesthesia

| <b>Number of subjects in period 1</b> | Placebo | Steroid |
|---------------------------------------|---------|---------|
| Started                               | 30      | 29      |
| Completed                             | 30      | 29      |

## Baseline characteristics

### Reporting groups

|  |         |
|--|---------|
| Reporting group title                                  | Placebo |
| Reporting group description:<br>Isotonic saline (2 mL) |         |
| Reporting group title                                  | Steroid |
| Reporting group description: -                         |         |

| Reporting group values  | Placebo           | Steroid           | Total |
|---|-------------------|-------------------|-------|
| Number of subjects  | 30                | 29                | 59    |
| Age categorical<br>Units: Subjects  |                   |                   |       |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation     | 67.2<br>± 6.7     | 67.4<br>± 5.4     | -     |
| Gender categorical<br>Units: Subjects                                       |                   |                   |       |
| Female  | 12                | 17                | 29    |
| Male  | 18                | 12                | 30    |
| ASA<br>Units: Subjects  |                   |                   |       |
| ASA1  | 6                 | 6                 | 12    |
| ASA2  | 24                | 22                | 46    |
| ASA3  | 0                 | 1                 | 1     |
| BMI<br>Units: BMI<br>arithmetic mean<br>standard deviation                  | 27.5<br>± 4.3     | 26.9<br>± 4.1     | -     |
| Hemoglobin<br>Units: g/dL<br>arithmetic mean<br>standard deviation          | 8.7<br>± 0.6      | 8.7<br>± 0.7      | -     |
| C-reactive protein<br>Units: mg/l<br>median<br>inter-quartile range (Q1-Q3) | 2.5<br>1.0 to 4.0 | 1.0<br>1.0 to 3.0 | -     |

## End points

### End points reporting groups

|  |         |
|--|---------|
| Reporting group title                                  | Placebo |
| Reporting group description:<br>Isotonic saline (2 mL) |         |
| Reporting group title                                  | Steroid |
| Reporting group description: -                         |         |

### Primary: Orthostatic hypotension 6 hrs

|   |                               |
|---|-------------------------------|
| End point title   | Orthostatic hypotension 6 hrs |
| End point description:  |                               |
| End point type  | Primary                       |
| End point timeframe:<br>Orthostatic challenge 6 hrs postoperatively |                               |

| End point values            | Placebo         | Steroid         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 30              | 29              |  |  |
| Units: project patients     |                 |                 |  |  |
| OH                          | 11              | 11              |  |  |

### Statistical analyses

|   |                   |
|---|-------------------|
| Statistical analysis title              | RR                |
| Comparison groups                       | Placebo v Steroid |
| Number of subjects included in analysis | 59                |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | non-inferiority   |
| P-value                                 | < 0.05            |
| Method                                  | Fisher exact      |

### Secondary: Orthostatic intolerance 6 hrs

|   |                               |
|---|-------------------------------|
| End point title   | Orthostatic intolerance 6 hrs |
| End point description:  |                               |
| End point type  | Secondary                     |
| End point timeframe:<br>Orthostatic challenge 6 hrs postoperatively |                               |

| <b>End point values</b>     | Placebo         | Steroid         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 30              | 29              |  |  |
| Units: project patients     |                 |                 |  |  |
| OI                          | 13              | 9               |  |  |

### Statistical analyses

|   |                   |
|---|-------------------|
| <b>Statistical analysis title</b>       | RR                |
| Comparison groups                       | Placebo v Steroid |
| Number of subjects included in analysis | 59                |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | non-inferiority   |
| P-value                                 | < 0.05            |
| Method                                  | Fisher exact      |

### Secondary: Orthostatic hypotension 24 hrs

|  |                                |
|--|--------------------------------|
| End point title                              | Orthostatic hypotension 24 hrs |
| End point description:                       |                                |
| End point type                               | Secondary                      |
| End point timeframe:                         |                                |
| Orthostatic challenge 24 hrs postoperatively |                                |

| <b>End point values</b>     | Placebo         | Steroid         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 30              | 29              |  |  |
| Units: project patients     |                 |                 |  |  |
| OH                          | 5               | 2               |  |  |

### Statistical analyses

|                                   |                   |
|-----------------------------------|-------------------|
| <b>Statistical analysis title</b> | RR                |
| Comparison groups                 | Placebo v Steroid |

|   |                 |
|---|-----------------|
| Number of subjects included in analysis | 59              |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority |
| P-value                                 | < 0.05          |
| Method                                  | Fisher exact    |

### Secondary: Orthostatic intolerance 24 hrs

|  |                                |
|--|--------------------------------|
| End point title                              | Orthostatic intolerance 24 hrs |
| End point description:                       |                                |
| End point type                               | Secondary                      |
| End point timeframe:                         |                                |
| Orthostatic challenge 24 hrs postoperatively |                                |

| End point values            | Placebo         | Steroid         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 30              | 29              |  |  |
| Units: project patients     |                 |                 |  |  |
| OI                          | 5               | 1               |  |  |

### Statistical analyses

|   |                   |
|---|-------------------|
| <b>Statistical analysis title</b>       | RR                |
| Comparison groups                       | Placebo v Steroid |
| Number of subjects included in analysis | 59                |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | non-inferiority   |
| P-value                                 | < 0.05            |
| Method                                  | Fisher exact      |



## Adverse events

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

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Timeframe for reporting adverse events:

From time of trial medication administration until 20 hrs after administration (5 x T½)

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Adverse event reporting additional description:

Following postoperative conditions will not be registered as AEs, as they are common following anaesthesia and surgery:

Moderate hypotension (MAP <60 mmHg)

Shivering

Pain from the surgical field

Urine retention

Intraoperative bleeding

nausea and vomiting

Dizziness

Fatigue

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

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### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 10 |
|--------------------|----|

Frequency threshold for reporting non-serious adverse events: 2 %

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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: There were no adverse events in the small clinical trial

## 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

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29573263>

<http://www.ncbi.nlm.nih.gov/pubmed/32719355>