# Clinical trial results:
# Does LOW Dose DEXmedetomidine After Cardiopulmonary Bypass Separation Decrease the Incidence of DELirium: A Double-blind Randomized Placebocontrolled Study (LOWDEXDEL Study)

## Summary

| | |
|---|---|
| EudraCT number | 2017-002007-97 |
| Trial protocol | BE |
| Global end of trial date | 30 August 2019 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 17 February 2021 |
| First version publication date | 17 February 2021 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 2017/24JUL/374 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03388541 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Cliniques universitaires Saint-Luc |
| Sponsor organisation address | Avenue Hippocrate, 10, Brussels, Belgium, 1200 |
| Public contact | Mona Momeni, Cliniques universitaires Saint-Luc, 0032 27647029, mona.momeni@uclouvain.be |
| Scientific contact | Mona Momeni, Cliniques universitaires Saint-Luc, 0032 27647029, mona.momeni@uclouvain.be |

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 | 28 October 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 August 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 August 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To analyze whether the addition of a low dose DEXMEDETOMDINE to a sedation regimen based on propofol decreases the incidence of in-hospital delirium compared to propofol sedation with placebo in patients ≥ 60 years undergoing cardiac surgery

Protection of trial subjects:

Any serious adverse events that would have occurred due to the study drug would have been reported to the IDMC. The patients are very closely monitored during the whole period when they receive Dexmedetomidine but also afterwards as they stay during several hours in the ICU. Otherwise, strict rules were followed to protect the subjects. In any case data regarding the patients were kept anonymous.

Background therapy:

DEXMEDETOMIDINE was started at a dose of 0.4µg/kg/h (5ml/h) at the moment of the closure of the chest and continued during 10 hours.

Evidence for comparator:

Placebo (NaCl 0.9%) was started at a continuous infusion of 5ml/h at the closure of the chest and was continued during 10 hours

| | |
|---|---|
| Actual start date of recruitment | 07 December 2017 |
| 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 | Belgium: 420 |
| Worldwide total number of subjects | 420 |
| EEA total number of subjects | 420 |

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) | 0 |
| From 65 to 84 years | 408 |
| 85 years and over | 12 |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were recruited from one single center (Cliniques Universitaires Saint Luc)

### Pre-assignment

Screening details:

Following written informed consent and before commencing treatment with Dexmedetomidine or Placebo, the patients were screened with Mini Mental State Examination test in order to evaluate the cognitive status of the patient.

### 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, Monitor, Carer, Assessor |

Blinding implementation details:

Randomization and blinding performed by research Pharmacy of Cliniques Universitaires Saint Luc

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | DEXDOR |

Arm description:

Patients receiving continuous IV infusion of dexmedetomidine

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | DEXMEDETOMIDINE |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

The drug was prepared at such that 5 ml/h corresponded to 0.4 µg/kg/h

| | |
|---|---|
| **Arm title** | PLACEBO |

Arm description:

Patients receiving continuous IV infusion of NaCl0.9%

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Sodium Chloride |
| Investigational medicinal product code | |
| Other name | Isotonic saline solution, Normal saline solution, Physiological saline solution |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

The drug was prepared without addition of any other substances and infused at a continuous IV infusion of 5 mL/H.

| **Number of subjects in period 1** | DEXDOR | PLACEBO |
|---|---|---|
| Started | 210 | 210 |
| Completed | 205 | 203 |
| Not completed | 5 | 7 |
| Consent withdrawn by subject | 2 | 2 |
| Change in surgical plan | 2 | 2 |
| died before administration of study drug | - | 1 |
| Study drug not prepared | 1 | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | DEXDOR |
| Reporting group description: | |
| Patients receiving continuous IV infusion of dexmedetomidine | |
| Reporting group title | PLACEBO |
| Reporting group description: | |
| Patients receiving continuous IV infusion of NaCl0.9% | |

| Reporting group values | DEXDOR | PLACEBO | Total |
|---|---|---|---|
| Number of subjects | 210 | 210 | 420 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (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) | 0 | 0 | 0 |
| From 65-84 years | 205 | 203 | 408 |
| 85 years and over | 5 | 7 | 12 |
| Age continuous<br>Units: years | | | |
| median | 71 | 70 | |
| full range (min-max) | 66 to 75 | 65 to 76 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 57 | 48 | 105 |
| Male | 153 | 162 | 315 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | DEXDOR |
| Reporting group description: | |
| Patients receiving continuous IV infusion of dexmedetomidine | |
| Reporting group title | PLACEBO |
| Reporting group description: | |
| Patients receiving continuous IV infusion of NaCl0.9% | |

### Primary: Postoperative in-hospital delirium

| | |
|---|---|
| End point title | Postoperative in-hospital delirium |

End point description:

The primary outcome was the incidence of POD at any time during the patient's hospital stay. Delirium assessment in the ICU was performed once the Richmond Agitation-Sedation Scale was -3 and was based on the Confusion Assessment Method for intubated patients in the ICU (CAM-ICU). The nurses in the ICU evaluated POD every 8 hours with the French version of the CAM-ICU. Delirium assessment at the ward was performed twice a day (08.00 AM and 08.00 PM) with the CAM. Because POD is a fluctuating state, often presenting in the ward and at night, the chart review method was used to detect any episode of POD that was not diagnosed otherwise. The medical chart of the patients was checked for any notifications made by nurses or physicians suggesting for the occurrence of POD (e.g. aggressive, confusion, having been tied, use of haloperidol, hallucinations, inappropriate behaviour,..). Trained study staff then reviewed the medical chart.

| | |
|---|---|
| End point type | Primary |
| End point timeframe: | |
| After surgical intervention | |

| End point values | DEXDOR | PLACEBO | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 205 | 203 | | |
| Units: percent | 18 | 19 | | |

### Statistical analyses

| Statistical analysis title | Full study |
|---|---|

Statistical analysis description:

The primary outcome was the incidence of POD at any time during the patient’s hospital stay. Delirium assessment in the ICU was performed once the Richmond Agitation Sedation Scale was ≥ 3 and was based on the Confusion Assessment Method for initiated patients in the ICU (CAM-ICU). The nurses in the ICU evaluated ÖD every 8 hours with French version of the CAM-ICU. Delerium Assessment at the ward was performed twice a day (8/00 AM and 08:00 PM). With the CAM. Because POD is fluctuating state, of

| | |
|---|---|
| Comparison groups | DEXDOR v PLACEBO |

| | |
|---|---|
| Number of subjects included in analysis | 408 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | = 0.687 |
| Method | Chi-squared |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 1.54 |

Notes:

[1] - This is a superiority trial with an alternative hypothesis being that adding a low dose DEX to propofol sedation would result in a different risk of POD compared to propofol with PL.

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| After surgical intervention | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 10.0 |

| Reporting groups | |
|---|---|
| Reporting group title | DEXDOR |
| Reporting group description: | |
| Patients receiving continuous IV infusion of dexmedetomidine | |
| Reporting group title | PLACEBO |
| Reporting group description: | |
| Patients receiving continuous IV infusion of NaCl0.9% | |

| Serious adverse events | DEXDOR | PLACEBO | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 205 (0.00%) | 0 / 203 (0.00%) | |
| number of deaths (all causes) | 1 | 10 | |
| number of deaths resulting from adverse events | 0 | 0 | |

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

| Non-serious adverse events | DEXDOR | PLACEBO | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 178 / 205 (86.83%) | 153 / 203 (75.37%) | |
| Vascular disorders | | | |
| Surgical revision | | | |
| subjects affected / exposed | 12 / 205 (5.85%) | 8 / 203 (3.94%) | |
| occurrences (all) | 1 | 1 | |
| Cardiac disorders | | | |
| Hypotension requiring norepinephrine | | | |
| subjects affected / exposed | 178 / 205 (86.83%) | 153 / 203 (75.37%) | |
| occurrences (all) | 1 | 1 | |
| Epicardial pacing | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 116 / 205 (56.59%) | 97 / 203 (47.78%) | |
| occurrences (all) | 1 | 1 | |
| Permanent pace maker | | | |
| subjects affected / exposed | 6 / 205 (2.93%) | 2 / 203 (0.99%) | |
| occurrences (all) | 1 | 1 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 6 / 205 (2.93%) | 10 / 203 (4.93%) | |
| occurrences (all) | 1 | 1 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 26 November 2018 | An amendment was asked in order to increase the number of patients to include, as the incidence of POD in the Placebo group was lower than expected. We had initially planned to include a total number of 270 patients |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported