# Clinical trial results:
# The Effect of Sildenafil (REVATIO®) on Post Cardiac Surgery Acute Kidney Injury: A Randomised, Placebo-controlled Phase IIb Clinical Trial: The REVAKI-2 Trial

## Summary

| | |
|---|---|
| EudraCT number | 2015-003259-24 |
| Trial protocol | GB |
| Global end of trial date | 20 September 2018 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 26 October 2019 |
| First version publication date | 26 October 2019 |
| Summary attachment (see zip file) | Study Manuscript (proof) (REVAKI-2 PDF Proof.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 0360 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | ISRCTN18386427 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | University of Leicester |
| Sponsor organisation address | University Road, Leicester, United Kingdom, |
| Public contact | Research Manager, Mrs Tracy Kumar, 44 01162583039, tk98@le.ac.uk |
| Scientific contact | Research Manager, Mrs Tracy Kumar, 44 01162583039, tk98@le.ac.uk |

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 | 18 June 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 September 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 September 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The REVAKI-2 Trial proposes to test the hypothesis that postoperative acute kidney injury (AKI) will be less in cardiac surgery patients identified as being at increased risk of developing AKI preoperatively, by the administration of sildenafil, a PDE-5 inhibitor

Protection of trial subjects:

Exclusion criteria applied regarding contra-indication for the investigation product.

Research bloods attempted to be taken at the same time as routine clinical blood tests to minimise risk of pain, bruising, blood clots, and infections.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 December 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research |
| Long term follow-up duration | 3 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 129 |
| Worldwide total number of subjects | 129 |
| EEA total number of subjects | 129 |

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 | 125 |
| 85 years and over | 4 |

## Subject disposition

### Recruitment

Recruitment details:

There were 129 patients recruited and randomised between September 2015 and September 2018 which made up the analysis population, 60 of whom were allocated to Sildenafil and 69 to Placebo.

### Pre-assignment

Screening details:

Potential research participants were identified by qualified study staff from clinical and theatre lists and hospital medical notes and referrals from other trusts.

### 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 |

Blinding implementation details:

The active drug or placebo according to randomisation will be prepared by the unblinded researchers. This will be prepared in a clinical area whereby the unblinded researchers are the only team members aware of the allocated treatment. The blinded team will not handle the supply or returns of the investigational medicinal product. Both active drug (bolus and infusion) and placebo (bolus and infusion) will be clearly labelled as REVAKI-2 sildenafil/placebo and are identical in appearance.

### Arms

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

Arm description:

Sildenafil citrate 12.5mg in 65mls of 5% dextrose solution was administered intravenously over 150 minutes starting at the time of skin incision.

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

Dosage and administration details:

Sildenafil citrate 12.5mg in 65mls of 5% dextrose solution was administered intravenously over 150 minutes starting at the time of skin incision.

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

. In the Placebo group, a 5% dextrose solution was administered to the same volume and timing as the intervention (Sildenafil citrate 12.5mg in 65mls of 5% dextrose solution was administered intravenously over 150 minutes starting at the time of skin incision).

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Dextrose |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

. In the Placebo group, a 5% dextrose solution was administered to the same volume and timing as the intervention (Sildenafil citrate 12.5mg in 65mls of 5% dextrose solution was administered intravenously

over 150 minutes starting at the time of skin incision.)

| **Number of subjects in period 1** | Sildenafil | Placebo |
|---|---|---|
| Started | 60 | 69 |
| Completed | 55 | 62 |
| Not completed | 5 | 7 |
| Adverse event, serious fatal | 1 | 3 |
| Lost to follow-up | 4 | 4 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | overall trial |

Reporting group description: -

| Reporting group values | overall trial | Total | |
|---|---|---|---|
| Number of subjects | 129 | 129 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 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 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 72 | | |
| full range (min-max) | 52 to 88 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 24 | 24 | |
| Male | 105 | 105 | |

## End points

### End points reporting groups

| Reporting group title | Sildenafil |
|---|---|

Reporting group description:

Sildenafil citrate 12.5mg in 65mls of 5% dextrose solution was administered intravenously over 150 minutes starting at the time of skin incision.

| Reporting group title | Placebo |
|---|---|

Reporting group description:

. In the Placebo group, a 5% dextrose solution was administered to the same volume and timing as the intervention (Sildenafil citrate 12.5mg in 65mls of 5% dextrose solution was administered intravenously over 150 minutes starting at the time of skin incision).

### Primary: Serum Creatinine

| End point title | Serum Creatinine[1][2] |
|---|---|

End point description:

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

End point timeframe:

pre-operation to 96 hours post-surgery

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Please see manuscript attachment

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Please see manuscript attachment

| End point values | Sildenafil | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 60 | | | |
| Units: µmol.L-1 | | | | |
| number (confidence interval 95%) | 0.88 (-5.82 to 7.59) | | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information[1] | |
|---|---|
| Timeframe for reporting adverse events:<br>consent to 3 month follow-up | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 14 |

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

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: Please see manuscript attachment

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 12 September 2016 | List of expected adverse events was updated. Concomitant medication timing was updated |
| 13 June 2017 | The AKI risk score used in the inclusion criteria was amended. The blood volumes to be collected were updated. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported