

# Pharmacokinetic profile, safety and tolerability of Sildenafil (REVATIO®) in cardiac surgery patients with chronic kidney disease

<b>Submission date</b> 20/11/2012	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered
		<input type="checkbox"/> Protocol
<b>Registration date</b> 10/01/2014	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan
		<input checked="" type="checkbox"/> Results
<b>Last Edited</b> 26/10/2016	<b>Condition category</b> Urological and Genital Diseases	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

### Background and study aims

We are carrying out a study of 36 patients with kidney disease who are scheduled to have heart surgery. Our goal is to find the ideal dose of the drug named Sildenafil (REVATIO®) to protect the kidneys during heart surgery with a heart-lung machine. We want to look at the levels of Sildenafil in the bloodstream, and the way the body removes it. Other aims of this study are to find out how safe this medicine is and what side effects it causes, if any.

### Who can participate?

Adult men or women with kidney disease, having heart surgery at three study centres in England can take part in this study.

### What does the study involve?

Over a period of six months patients who are planned to undergo heart surgery at a participating centre will be asked to take part in the trial. If they provide consent, patients will receive a single dose of Sildenafil during surgery. The amount of Sildenafil given to the participants will be increased with each six participants; there will be six groups in total. This will enable us to find the optimum dose to protect the kidneys during surgery. Blood samples will be collected at regular intervals during surgery to study the levels of the medication in the bloodstream and how quickly it is removed by the body. Blood and urine samples will also be collected at regular intervals during the hospital stay after the operation and tested for several chemicals that will give us an idea of how well different parts of the body, e.g. your brain, heart and kidneys, worked during and after the operation. At the end of the study, we will compare the amount of medication in the bloodstream and how long it stayed present between the six different groups. We will also compare measures of well-being and kidney function between groups.

### What are the possible benefits and risks of participating?

We believe that this drug has the potential to benefit patients at risk of postoperative acute

kidney injury, who would otherwise be at higher risk, and has a very low risk profile. Potential participants will need to weigh up the possibility of benefit from the intervention against the risk of harm.

Where is the study run from?

The study has been set up by the University of Leicester and University of Oxford, UK in collaboration with the British Heart Foundation.

When is study starting and how long is it expected to run for?

The recruitment started mid-2013. Participants will be enrolled on the study for a period of six weeks, until they return to hospital for a routine follow-up appointment.

Who is funding the study?

This study is funded by the British Heart Foundation, UK.

Who is the main contact?

Miss Veerle Verheyden, vv46@le.ac.uk

Professor Gavin Murphy, gjm19@le.ac.uk

## Contact information

### Type(s)

Scientific

### Contact name

Miss Veerle Verheyden

### Contact details

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## Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

RCCKD - 001

## Study information

**Scientific Title**

A phase I study to determine the pharmacokinetic profile, safety and tolerability of Sildenafil (REVATIO®) in cardiac surgery patients with chronic kidney disease

**Acronym**

REVAKI-001

**Study objectives**

1. To evaluate the pharmacokinetic profile of Sildenafil in cardiac surgery patients with chronic kidney disease.
2. To determine the safety and tolerability of Sildenafil in cardiac surgery patients with chronic kidney disease.

**Ethics approval required**

Old ethics approval format

**Ethics approval(s)**

Not provided at time of registration

**Study design**

Phase I multi-centre open-label non-randomised single-dose study

**Primary study design**

Interventional

**Secondary study design**

Randomised controlled trial

**Study setting(s)**

Hospital

**Study type(s)**

Screening

**Participant information sheet**

Not available in web format, please use the contact details below to request a patient information sheet

**Health condition(s) or problem(s) studied**

Cardiac surgery patients with chronic kidney disease

**Interventions**

Patients will be screened by the investigators to assess eligibility for entry into the study. Eligible patients undergoing cardiac surgery with CPB who consent to participate will be consecutively allocated, in a 6:6:6:6:6 sequence to:

Treatment group 1: Sildenafil 2.5 mg bolus IV (3.125 mL)

Treatment group 2: Sildenafil 2.5 mg bolus IV + Sildenafil 2.5 mg as a 2hrs continuous infusion (6.250 mL)

Treatment group 3: Sildenafil 5.0 mg bolus IV (6.250 mL)

Treatment group 4: Sildenafil 5 mg bolus IV + Sildenafil 2.5 mg as a 2hrs continuous infusion (9.375 mL)

Treatment group 5: Sildenafil 10 mg bolus IV (12.5 mL)

Treatment group 6: Sildenafil 10 mg bolus IV+ Sildenafil 2.5 mg as a 2hrs continuous infusion (15.625 mL)

## **Intervention Type**

Drug

## **Phase**

Phase I

## **Drug/device/biological/vaccine name(s)**

Sildenafil

## **Primary outcome measure**

1. Safety will be assessed by means of the following:

1.1. Physical examination at screening and clinical outcome monitoring during hospitalization and at 4-6 weeks follow-up visit

1.2. Vital sign measurements during study drug administration

1.3. Clinical laboratory assessments including haematology, biochemistry and urinalysis (at screening and at 6 hrs, 24 hrs, 48 hrs and 96 hrs after study drug administration and at hospital discharge)

1.4. Adverse events and concomitant medications/therapies

2. Pharmacokinetic assessments will include evaluation of plasma levels of Sildenafil and N-desmethyl-Sildenafil (at start of infusion, end of the bolus infusion and at 15 min, 30 min, 45 min, 1 hr, 2 hrs (end of CPB), 4 hrs (CICU admission), 6 hrs and 24 hrs after end of bolus infusion)

3. Plasma levels of Sildenafil and the following pharmacokinetic parameters calculated from it:

3.1. Incremental recovery (peak recorded within the first hour after infusion)

3.2. Maximum plasma concentrations (C<sub>max</sub>)

3.3. Time to C<sub>max</sub> (T<sub>max</sub>)

3.4. Terminal half-life (t<sub>1/2</sub>)

3.5. Terminal elimination rate constant (k<sub>el</sub>)

3.6. Area under the plasma time versus concentration curve from time 0 to time of last measurable concentration (AUC(0-t)); linear trapezoidal method

3.7. Area under the plasma time versus concentration curve from time 0 to extrapolated to infinity (AUC(0-∞))

3.8. Clearance (CL)

3.9. Apparent volume of distribution (V<sub>z</sub>)

3.10. Mean residence time (MRT)

## **Secondary outcome measures**

No secondary outcome measures

## **Overall study start date**

01/04/2013

## **Completion date**

01/10/2013

## **Eligibility**

**Key inclusion criteria**

1. Adult cardiac surgery patients (>16 years and <80 years) undergoing cardiac surgery with moderately hypothermic cardiopulmonary bypass (CPB) (32-34°C) and blood cardioplegia
2. eGFR >15 and <90ml/min (International classification of Chronic Kidney Disease, CKD, Stage 2-4)

**Participant type(s)**

Patient

**Age group**

Adult

**Sex**

Both

**Target number of participants**

36

**Key exclusion criteria**

1. Emergency or salvage procedure
2. Ejection fraction <30%
3. CKD Stage 1, defined as eGFR>90ml/min
4. CKD Stage 5, defined as eGFR<15ml/min or renal replacement therapy
5. Administration of potent CYP 3A4 inhibitors within 1 month prior to study participation
6. Any ongoing malignancy, or prior malignancy that currently requires treatment.
7. Patients allergic to any other PDE-5 Inhibitor
8. Patients who are participating in another interventional clinical study

**Date of first enrolment**

01/04/2013

**Date of final enrolment**

01/10/2013

**Locations****Countries of recruitment**

England

United Kingdom

**Study participating centre**

University of Leicester

Leicester

United Kingdom

LE3 9PQ

# Sponsor information

## Organisation

University of Leicester (UK)

## Sponsor details

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England  
United Kingdom  
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uolsponsor@le.ac.uk

## Sponsor type

University/education

## Website

<http://www2.le.ac.uk/>

## ROR

<https://ror.org/04h699437>

# Funder(s)

## Funder type

Charity

## Funder Name

British Heart Foundation (UK)

## Alternative Name(s)

the\_bhf, The British Heart Foundation, BHF

## Funding Body Type

Private sector organisation

## Funding Body Subtype

Trusts, charities, foundations (both public and private)

## Location

United Kingdom

# Results and Publications

## Publication and dissemination plan

Not provided at time of registration

## Intention to publish date

## Individual participant data (IPD) sharing plan

## IPD sharing plan summary

Not provided at time of registration

## Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Results article</a>	results:	01/04/2017		Yes	No