# Clinical trial results:
# A single-centre, placebo-controlled, double-blinded, randomized, cross-over study of Iloprost (Ventavis®) in patients with Eisenmenger syndrome

## Summary

| | |
|---|---|
| EudraCT number | 2014-000091-25 |
| Trial protocol | GB |
| Global end of trial date | 27 March 2018 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 11 February 2021 |
| First version publication date | 11 February 2021 |
| Summary attachment (see zip file) | Iloprost study publication (1-s2.0-S0167527319314500-main.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 2014GU001B |

### Additional study identifiers

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

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Royal Brompton and Harefield NHS Foundation Trust, Royal Brompton Hospital |
| Sponsor organisation address | Sydney Street, Research Office, London , United Kingdom, SW3 6NP |
| Public contact | Dr John Wort, Royal Brompton and Harefield NHS Foundation Trust, +44 20 7351 8121 , i.jakupovic@rbht.nhs.uk |
| Scientific contact | Ira Jakupovic, Royal Brompton and Harefield NHS Foundation Trust, +44 20 7351 8121 , i.jakupovic@rbht.nhs.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 | 28 March 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 March 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 March 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

To assess the impact of iloprost - an inhaled pulmonary vasodilator (opens up the blood vessels in the lung)- on exercise capacity in patients with the congenital heart condition Eisenmenger Syndrome.

Protection of trial subjects:

Within the UK Commissioning Policy, administration of inhaled Iloprost is a recognised treatment for patients with PAH including Eisenmenger Syndrome. As we will not perform any invasive tests in this study we do not expect a higher risk profile in this study when compared to routine care in this setting. There is a theoretical risk that Iloprost may enhance the adverse/toxic effect of anticoagulants and antiplatelet agents. Specifically, the antiplatelet effects of Iloprost may, theoretically, lead to an increased risk of bleeding with the combination. Concomitant treatment with Iloprost and anticoagulants or antiplatelet agents is, however, not contraindicated and this effect has not been seen in previous studies involving many patients. Furthermore, it is not routine clinical practice to increase the frequency of INR measurement for patients commenced on Iloprost. INR will be checked as part of the standard care for such patients, as indicated in the schedule and study assessments.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 15 August 2014 |
| 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 | United Kingdom: 15 |
| Worldwide total number of subjects | 15 |
| EEA total number of subjects | 15 |

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) | 14 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Study participants were recruited between December 2014 and November 2015. Eligible patients were recruited from the PHT clinic at Adult Congenital Heart Centre and Centre for Pulmonary Hypertension, Royal Brompton Hospital, UK.

### Pre-assignment

Screening details:

The screening visit included the following assessments:
Physical Examination
Medical History
Concomitant medication review
WHO functional class
Pregnancy test for women of childbearing potential
Blood Pressure
Collection of blood
Measurement of oxygen saturation at rest
12 lead ECG
Echocardiography
Pulmonary function test
6MWT

### Period 1

| | |
|---|---|
| Period 1 title | Baseline |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

### Arms

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

Arm description:

Iloprost (Ventavis®) – Ventavis® 10 µg/ml clear colourless nebuliser solution. Each ampoule with 1ml solution contains 10 µg Iloprost (as Iloprost trometamol). Iloprost (Ventavis®) was manufactured by Bayer Pharma AG and distributed by Bayer plc in the UK. Iloprost was used in this study within its licensed indication.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Iloprost |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for nebuliser solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Iloprost concentration in the ampoules is 10 µg/ml.
The treatment dose will be initially a low dose of 0.25ml every 3 to 4 hours up-titrated to 0.5ml every 3 to 4 hours if tolerated (up to 8 times a day). If a patient treated with 0.5ml every 3 to 4 hours does not tolerate the treatment it will be reduced to 0.25ml every 3 to 4 hours.

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

Arm description:

Placebo a clear colourless nebuliser solution in 1ml ampoules. Bayer plc manufactured the matching placebo for this study.

| | |
|---|---|
| Arm type | Placebo |

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for nebuliser solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

The treatment dose will be initially a low dose of 0.25ml every 3 to 4 hours up-titrated to 0.5ml every 3 to 4 hours if tolerated (up to 8 times a day). If a patient treated with 0.5ml every 3 to 4 hours does not tolerate the treatment it will be reduced to 0.25ml every 3 to 4 hours.

| **Number of subjects in period 1** | Iloprost | Placebo |
|---|---|---|
| Started | 8 | 7 |
| Completed | 8 | 7 |

| **Period 2** | |
|---|---|
| Period 2 title | Cross-over |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

**Arms**

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

Arm description: -

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Iloprost |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for nebuliser solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Iloprost concentration in the ampoules is 10 µg/ml.
The treatment dose will be initially a low dose of 0.25ml every 3 to 4 hours up-titrated to 0.5ml every 3 to 4 hours if tolerated (up to 8 times a day). If a patient treated with 0.5ml every 3 to 4 hours does not tolerate the treatment it will be reduced to 0.25ml every 3 to 4 hours.

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

Arm description: -

| | |
|---|---|
| Arm type | Placebo |

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for nebuliser solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

The treatment dose will be initially a low dose of 0.25ml every 3 to 4 hours up-titrated to 0.5ml every 3 to 4 hours if tolerated (up to 8 times a day). If a patient treated with 0.5ml every 3 to 4 hours does not tolerate the treatment it will be reduced to 0.25ml every 3 to 4 hours.

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for nebuliser solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

The treatment dose will be initially a low dose of 0.25ml every 3 to 4 hours up-titrated to 0.5ml every 3 to 4 hours if tolerated (up to 8 times a day). If a patient treated with 0.5ml every 3 to 4 hours does not tolerate the treatment it will be reduced to 0.25ml every 3 to 4 hours.

| **Number of subjects in period 2[1]** | Ilopropst | Placebo |
|---|---|---|
| Started | 6 | 8 |
| Completed | 6 | 8 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Subjects withdrew due to SAEs (details of SAEs in the publication attached).

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Baseline |

Reporting group description: -

| Reporting group values | Baseline | Total | |
|---|---|---|---|
| Number of subjects | 15 | 15 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 14 | 14 | |
| From 65-84 years | 1 | 1 | |
| 85 years and over | 0 | 0 | |
| Gender categorical<br>Units: Subjects | | | |
| male | 4 | 4 | |
| female | 11 | 11 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Iloprost |

Reporting group description:

Iloprost (Ventavis®) – Ventavis® 10 µg/ml clear colourless nebuliser solution. Each ampoule with 1ml solution contains 10 µg Iloprost (as Iloprost trometamol). Iloprost (Ventavis®) was manufactured by Bayer Pharma AG and distributed by Bayer plc in the UK. Iloprost was used in this study within its licensed indication.

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

Reporting group description:

Placebo  a clear colourless nebuliser solution in 1ml ampoules. Bayer plc manufactured the matching placebo for this study.

| | |
|---|---|
| Reporting group title | Ilopropst |

Reporting group description: -

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

Reporting group description: -

### Primary: 6MWT distance

| | |
|---|---|
| End point title | 6MWT distance |

End point description:

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

End point timeframe:

Change in 6 minute walking distance (6MWT distance) after 12 weeks of therapy.

| End point values | Iloprost | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 4 | | |
| Units: meters | 8 | 4 | | |

### Statistical analyses

| Statistical analysis title | Statistical analysis |
|---|---|

Statistical analysis description:

It was used R version 3.4.3. Using a cross over design a sample size of 12 was calculated using the level of significance as 0.05, the power as 0.84, the estimated SD (of 6MWT) as 40 m and the minimal detectable difference in 6MWT as 50m.
Descriptive statistics were presented as number for categorical data and mean +- SD or median for continuous variables.
Subjects who were withdrawn before completion were not included in analysis. No substitution rules were used for missing data in analysis

| | |
|---|---|
| Comparison groups | Placebo v Iloprost |

| | |
|---|---|
| Number of subjects included in analysis | 12 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Median difference (net) |
| Variability estimate | Standard deviation |

## Adverse events

| Adverse events information[1] | |
|---|---|
| Timeframe for reporting adverse events: Duration of the study | |
| Assessment type | Non-systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

Frequency threshold for reporting non-serious adverse events: 1 %

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: While the Sponsor had requested recording of non serious adverse events in patient notes/ Sponsor's AE Log, we had only collected SAE for this study (details in the publication attached).

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 16 September 2014 | To inform the REC of the changes in the study protocol in response to GNA received on 05th August 2014. 22nd October 2014 – FAO |
| 12 January 2015 | Substantial:<br>Changes in the study protocol to clarify arrangements for un-blinding and randomization via RB&HFT pharmacy facilitated by LC2<br>Additional blood tests @ baseline and ECHO at cross over visit<br>Study assessments flowchart correction<br>Non-substantial:<br>NHS R&D Form changes at the CLRN Request<br>IMP tracking logs<br>REC approval -04 Jan 2015<br>MHRA approval 25th Jan 2015 |
| 12 May 2015 | Protocol changes to add open-label Iloprost for 3 years, include changes regarding accountability along with changes to inclusion criteria<br>PIS and ICF updated accordingly<br>Patient Invitation Letter to open-label added<br>REC approval 11 June 2015<br>MHRA approval 30 June 2015 |
| 09 March 2017 | Protocol - replace SARs with reference to SPC.<br>PIS/ICF ammended to update safety information<br>SPC updated 14th December 2016 |
| 27 April 2017 | Re-submission of the study protocol in responce to MHRA's notice of non acceptance<br>REC approval 31 May 2017<br>MHRA approval 23 May 2017 |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported