# Clinical trial results:
# Can sonographic assessment of pulmonary vascular reactivity following maternal hyperoxygenation therapy predict neonatal outcome in fetuses at risk of pulmonary hypertension?

## Summary

| | |
|---|---|
| EudraCT number | 2016-003181-12 |
| Trial protocol | IE |
| Global end of trial date | 22 July 2018 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 15 August 2020 |
| First version publication date | 15 August 2020 |
| Summary attachment (see zip file) | Clinical Trial Report (EudraCT 201600318112 Summary.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | HOTPOT1 |

### Additional study identifiers

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

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Royal College of Surgeons Ireland |
| Sponsor organisation address | 111 St Stephens Green, dublin, Ireland, DUBLIN 2 |
| Public contact | RCSI Education & Research Centre, Royal College of Surgeons in Ireland, +353 018093863, mandyjackson@rcsi.ie |
| Scientific contact | RCSI Education & Research Centre, Royal College of Surgeons in Ireland, 5318093683 018093863, mandyjackson@rcsi.ie |

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 | 13 February 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 22 July 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 July 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary study objective is to predict the occurrence of neonatal pulmonary hypertension by measuring the pulmonary artery reactivity to maternal hyperoxygenation in fetuses at risk of neonatal respiratory morbidity.

Protection of trial subjects:

Pregnant patients were administered the IMP in a semi recumbent position in order to prevent any discomfort during administration of IMP.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 September 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Ireland: 66 |
| Worldwide total number of subjects | 66 |
| EEA total number of subjects | 66 |

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) | 66 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The first patient was recruited to the trial on 06-Feb-2017 and the last patient visit was 22-Jul-2018.

### Pre-assignment

Screening details:

Patients were screened to assess if they met the eligibility criteria. There were no screen fails and all 66 women screened were enrolled and dosed in this trial.
Please see Clinical Trial Report attached for details of the inclusion and exclusion criteria.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable. Trial was open label.

### Arms

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

Arm description:

Forty-six pregnant subjects out of 65 subjects were recruited

| | |
|---|---|
| Arm type | Pregnant subjects |
| Investigational medicinal product name | Medical Oxygen |
| Investigational medicinal product code | AATC Code V03AN01 |
| Other name | Oxygen |
| Pharmaceutical forms | Medicinal gas, compressed |
| Routes of administration | Inhalation use |

Dosage and administration details:

Oxygen was administered to the subjects while in a semi recumbent position in the hospital ultrasound department. Oxygen was administered at a rate of 8-10L/min for a duration of 10 minutes via a non-rebreather mask

| | |
|---|---|
| **Arm title** | Non-pregnant |

Arm description:

20 of the 65 subjects recruited to the trial were non pregnant women.

| | |
|---|---|
| Arm type | Non-pregnant subjects |
| Investigational medicinal product name | Medical Oxygen |
| Investigational medicinal product code | AATC Code V03AN01 |
| Other name | Oxygen |
| Pharmaceutical forms | Medicinal gas, compressed |
| Routes of administration | Inhalation use |

Dosage and administration details:

Oxygen was administered to the subjects while in a semi recumbent position in the hospital ultrasound department. Oxygen was administered at a rate of 8-10L/min for a duration of 10 minutes via a non-rebreather mask

| **Number of subjects in period 1** | Pregnant | Non-pregnant |
|---|---|---|
| Started | 46 | 20 |
| Completed | 46 | 20 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Overall Trial |
| Reporting group description: | |
| All subjects received the IMP and therefore baseline characteristics are reported as one group | |

| Reporting group values | Overall Trial | Total | |
|---|---|---|---|
| Number of subjects | 66 | 66 | |
| 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 | | | |
| Median age of all 66 subjects recruited was 33 years (interquartile range, 26-38 years) | | | |
| Units: years | | | |
| median | 33 | | |
| inter-quartile range (Q1-Q3) | 26 to 38 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 66 | 66 | |
| Male | 0 | 0 | |
| Gestational Age | | | |
| The median gestational age was 35 weeks (33-37 weeks) | | | |
| Units: weeks | | | |
| median | 35 | | |
| inter-quartile range (Q1-Q3) | 33 to 37 | - | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Pregnant |
| Reporting group description: | |
| Forty-six pregnant subjects out of 65 subjects were recruited | |
| Reporting group title | Non-pregnant |
| Reporting group description: | |
| 20 of the 65 subjects recruited to the trial were non pregnant women. | |

### Primary: Diagnosis of Persistent pulmonary hypertension PPHN

| | |
|---|---|
| End point title | Diagnosis of Persistent pulmonary hypertension PPHN |

End point description:

Persistent pulmonary hypertension will be defined by echocardiography as well as by clinical indicators as follows.

1) A requirement of at least 0.4 Fractional Inspired Oxygen to maintain a preductal saturation of ≥ 95%; and,
2) Normal Structural anatomy of the heart on echocardiogram; and,
3) In the presence of tricuspid regurgitant (TR) jet, an estimated right ventricular systolic pressure (using the Bernoulli Equation) ≥ 50% of the systemic systolic pressure measured at the start of the echocardiogram; or
4) In the presence of a patent ductus arteriosus (PDA of a low velocity shunt across the PDA from left to right such that the estimated Right Ventricular/ Pulmonary artery pressures was >50% systemic
5) In the absence of a TR jet or a PDA, an intraventricular septum bowing into the left ventricular cavity.

| | |
|---|---|
| End point type | Primary |
| End point timeframe: | |
| Within 24 hours of delivery | |

| End point values | Pregnant | Non-pregnant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 | 20[1] | | |
| Units: Number of cases | 0 | 0 | | |

Notes:

[1] - The endpoint does not apply to this reporting group as they were non-pregnant.

### Statistical analyses

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

Statistical analysis description:

Descriptive statistics were used to summarise the findings into two groups, responders and non-responders. Normally distributed data are reported as means and standard deviations (SD) while non-normally distributed data are reported as medians and interquartile ranges (IQR).

| | |
|---|---|
| Comparison groups | Pregnant v Non-pregnant |

| | |
|---|---|
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | other[2] |
| P-value | < 0.05 [3] |
| Method | t-test, 2-sided |
| Parameter estimate | descriptive statistics |

Notes:

[2] - Not applicable as descriptive statistics were used.

[3] - All tests were two-tailed and the significance level for all analyses was set at p <0.05. Statistical analysis was performed using SPSS (version 24.0).

## Adverse events

### Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events were captured from enrolment until 2 hours post IMP administration

Adverse event reporting additional description:

All AEs occurring during the 2 hour post IMP period were captured. These AEs were either observed by the investigator or reported by the subject, whether or not they were attributed to the study medication. The CRF captured AE description, date of onset and end date, severity, assessment of relatedness to the study medication.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

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: Adverse events were captured until 1 hour post administration of the IMP and no subjects reported any adverse events. The IMP is commonly used in this patient population and the investigators did not anticipate any adverse events.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 22 November 2017 | 1) Sample Size analysis section was revised to increase the sample size from a total of 60-75 participants to 80-95 participants. The rationale for the sample size amendment was the addition of a new cohort population (non-pregnant controls) to the study.<br>2) For key inclusion criteria, an additional category of subjects was added: Non-pregnant controls. The rationale for this new category was to compare the haemodynamic changes in both maternal and non-maternal controls following the test product.<br>3) The Data Safety Monitoring Board was removed from the trial protocol. The rationale for this was due to the small number of subjects recruited to the trial and the high safety profile of the IMP administered over 10 minutes, a DSMB was not considered necessary by the Sponsor. The side effect profile of the IMP administered for a total duration of 10 minutes is negligible and at the time of the substantial amendment, no safety concerns or adverse outcomes had arisen. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported