



## 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
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##### 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:

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**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:

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**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:

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**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:

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**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
<b>Arm title</b>	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

<b>Arm title</b>	Non-pregnant
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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
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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

<b>Number of subjects in period 1</b>	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			
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			
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 $\geq$ 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) $\geq$ 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 <sup>[1]</sup>		
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 <sup>[2]</sup>
P-value	< 0.05 <sup>[3]</sup>
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

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

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

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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.

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Assessment type	Systematic
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### Dictionary used

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Dictionary name	MedDRA
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Dictionary version	20.0
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Frequency threshold for reporting non-serious adverse events: 0 %

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### 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	<p>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.</p> <p>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.</p> <p>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.</p>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported