Clinical trial results:
A SINGLE ARM SINGLE CENTRE STUDY TO INVESTIGATE SAFETY AND EFFICACY OF SILDENAFIL IN NEAR TERM AND TERM NEWBORNS WITH PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN)

Summary

EudraCT number	2009-016248-37
Trial protocol	GB
Global end of trial date	01 November 2011

Results information

Result version number	v1 (current)
This version publication date	01 June 2016
First version publication date	01 August 2015

Trial information

Trial identification

Sponsor protocol code	A1481276

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01069861
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 October 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 November 2011
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1. To determine the efficacy of intravenous (IV) Sildenafil in near term and term newborns with Persistent pulmonary hypertension of the newborn (PPHN) or with hypoxic respiratory failure and at risk for PPHN. The primary measure of efficacy will be the reduced need for Inhaled Nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO).
2. To assess the safety and tolerability of IV Sildenafil in near term and term newborns with PPHN or with hypoxic respiratory failure and at risk of developing PPHN.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 December 2010
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: 4
Worldwide total number of subjects	4
EEA total number of subjects	4

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	4
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	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study started on 18 December 2010 and ended on 01 November 2011. Overall, 4 subjects were enrolled in United Kingdom.

Period 1

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

Arms

Arm title	Sildenafil

Arm description:

Sildenafil citrate administered, based on the need of individual subject.

Arm type	Experimental
Investigational medicinal product name	Sildenafil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Sildenafil citrate administered intravenously at a loading dose of 0.1 mg/kg over 30 minutes infusion followed by a maintenance dose of 0.03 mg/kg/hr intravenous infusion up to 14 days, based on the need of individual subject.

Number of subjects in period 1	Sildenafil
Started	4
Completed	1
Not completed	3
Did not meet entrance criteria	1
Adverse event, non-fatal	1
Death	1

Baseline characteristics

Reporting groups	
Reporting group title	Sildenafil
Reporting group description:	
Sildenafil citrate administered, based on the need of individual subject.	

Reporting group values	Sildenafil	Total	
Number of subjects	4	4	
Age categorical Units: Subjects			
Age continuous Units: days			
arithmetic mean	1.5		
standard deviation	± 0.5	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	0	0	

End points

End points reporting groups

Reporting group title	Sildenafil

Reporting group description:

Sildenafil citrate administered, based on the need of individual subject.

Primary: Percentage of Subjects Requiring Inhaled Nitric Oxide (iNO) or Extracorporeal Membrane Oxygenation (ECMO)

End point title	Percentage of Subjects Requiring Inhaled Nitric Oxide (iNO) or Extracorporeal Membrane Oxygenation (ECMO)[1]

End point description:

Percentage of subjects who required standard therapy (iNO or ECMO) after failure of study treatment.

End point type	Primary

End point timeframe:

From start of infusion (baseline) up to Day 14

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: Data for this pre-specified outcome measure was collected and reported in individual subject listings but not statistically summarized for analysis due to early study termination.

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: percentage of subjects				
number (not applicable)				

Notes:

[2] - Data for this Outcome Measure was not reported due to early study termination.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Adverse Events (AEs) Based on Severity

End point title	Number of Subjects With Adverse Events (AEs) Based on Severity[3]

End point description:

AE:any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. Serious Adverse Event (SAE):AE resulting in any of following outcomes or deemed significant for any other reason: death; initial/prolonged inpatient hospitalization; life-threatening experience; persistent/significant disability/incapacity; congenital anomaly. Severity criteria: "mild=does not interfere with subject's usual function; moderate=interferes to some extent with subject's usual function and severe=interferes significantly with subject's usual function".

End point type	Primary

End point timeframe:

Baseline up to 28 days after last dose

Notes:

[3] - 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: Data for this pre-specified outcome measure was collected and reported in individual

subject listings but not statistically summarized for analysis due to early study termination.

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: subjects				

Notes:

[4] - Data for this Outcome Measure was not reported due to early study termination.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Abnormal Laboratory Data

End point title	Number of Subjects With Abnormal Laboratory Data[5]

End point description:

Following laboratory parameters were to be analyzed: Hemoglobin, hematocrit, RBC count, platelet count, WBC count, total neutrophils, eosinophils, lymphocytes, urea, creatinine, calcium, sodium, potassium, chloride, total CO2 (bicarbonate), aspartate aminotransferase, Alanine transaminase, total bilirubin, conjugated bilirubin, alkaline phosphatase and total protein.

End point type	Primary

End point timeframe:

Screening, once daily for 3 days, every 48 hours thereafter till the end of infusion (up to Day 14)

Notes:

[5] - 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: Data for this pre-specified outcome measure was collected and reported in individual subject listings but not statistically summarized for analysis due to early study termination.

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: subjects				

Notes:

[6] - Data for this Outcome Measure was not reported due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Oxygenation Index at Hour 6 and 12

End point title	Change From Baseline in Oxygenation Index at Hour 6 and 12

End point description:

Oxygenation Index (OI) was calculated as the product of fraction of inspired oxygen (FiO2) and Mean Airway Pressure divided by partial pressure of oxygen in arterial blood [(FiO2*Mean Airway Pressure)/PaO2] measured in centimeter of water/millimeter of mercury (cmH2O/mmHg). FiO2 is the measure of oxygen concentration that is breathed. Mean airway pressure is defined as an average of the airway pressure throughout the respiratory cycle. PaO2 is the measure of oxygen level in the arterial

End point type	Secondary

End point timeframe:

Baseline, Hour 6, 12

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	0[7]			
Units: cmH2O/mmHg				
arithmetic mean (full range (min-max))	(to)			

Notes:

[7] - Data for this Outcome Measure was not reported due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Differential Saturation (Pre- And Post-ductal) at Hour 6 and 12

End point title	Change From Baseline in Differential Saturation (Pre- And Post-ductal) at Hour 6 and 12

End point description:

Differential oxygenation saturation between preductal and postductal sites as measured by pulse oximetry. A difference of greater than (>) 5 percent (%) to 10% in saturation indicates right-to-left shunt through the ductus arteriosus. Oxygenation saturation is measured as percentage of hemoglobin binding sites occupied by oxygen in the blood.

End point type	Secondary

End point timeframe:

Baseline, Hour 6, 12

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	0[8]			
Units: subjects				

Notes:

[8] - Data for this Outcome Measure was not reported due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Ratio of Partial Pressure of Oxygen in Arterial Blood to the Fraction of Inspired Oxygen (P/F) at Hour 6 and 12

End point title	Change From Baseline in Ratio of Partial Pressure of Oxygen in Arterial Blood to the Fraction of Inspired Oxygen (P/F) at Hour 6 and 12

End point description:

The ratio of partial pressure of arterial oxygen and fraction of inspired oxygen (PaO2 / FiO2) is a comparison between the oxygen level in the arterial blood and the oxygen concentration that is breathed. It helps to determine the degree of any problems with how the lungs transfer oxygen to the blood.

End point type	Secondary

End point timeframe:

Baseline, Hour 6, 12

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	0[9]			
Units: PaO2 / FiO2				
arithmetic mean (full range (min-max))	(to)			

Notes:

[9] - Data for this Outcome Measure not reported due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Mechanical Ventilation

End point title	Duration of Mechanical Ventilation

End point description:

The number of days from the start to the stop of mechanical ventilation, if multiple ventilations occurred during the follow-up, the sum of the duration of each ventilation was used for analyses. Mechanical ventilation was defined as use of mechanical assistance or replacement of spontaneous breathing.

End point type	Secondary

End point timeframe:

Baseline up to 28 days after last dose

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	0[10]			
Units: days				
median (full range (min-max))	(to)			

Notes:

[10] - Data for this Outcome Measure was not reported due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Receipt of Standard Therapy (Inhaled Nitric Oxide [iNO] or Extracorporeal Membrane Oxygenation [ECMO])

End point title	Time to Receipt of Standard Therapy (Inhaled Nitric Oxide [iNO] or Extracorporeal Membrane Oxygenation [ECMO])

End point description:

Time from start of treatment up to introduction of standard therapy. If subjects did not receive standard therapy within 14 days after initiation of the study treatment, then Day 14 was the censoring time.

End point type	Secondary

End point timeframe:

Baseline up to 28 days after last dose

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			
Units: hours				
median (full range (min-max))	(to)			

Notes:

[11] - Data for this Outcome Measure was not reported due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Sildenafil and Metabolite (UK-103320)

End point title	Maximum Observed Plasma Concentration (Cmax) of Sildenafil and Metabolite (UK-103320)

End point description:

End point type	Secondary

End point timeframe:

Pre-dose, 5 and 30 minutes post-loading infusion, within 48 to 72, 96 to 120 hours during infusion, within 4 to 8, 18 to 24 and 44 to 48 hours post-maintenance infusion

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	0[12]			
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)	()			

Notes:

[12] - Data for this Outcome Measure was not reported due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Population Pharmacokinetics of Sildenafil and Metabolite (UK-103320)

End point title	Population Pharmacokinetics of Sildenafil and Metabolite (UK-103320)

End point description:

Data for this Outcome Measure are not reported here because the analysis population also includes subjects who were not enrolled in this study.

End point type	Secondary

End point timeframe:

Pre-dose, 5 and 30 minutes post-loading infusion, within 48 to 72, 96 to 120 hours during infusion, within 4 to 8, 18 to 24 and 44 to 48 hours post-maintenance infusion

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	0[13]			
Units: milligram per milliliter (mg/mL)				
arithmetic mean (standard deviation)	()			

Notes:

[13] - Data for this Outcome Measure was not reported due to early study termination.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Duration of Study Medication

End point title	Duration of Study Medication

End point description:

The duration of the infusion was determined as per investigator’s discretion up to Day 7 or Day 14.

End point type	Other pre-specified

End point timeframe:

Baseline up to Day 14

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	0[14]			
Units: days				
median (full range (min-max))	(to)			

Notes:

[14] - Data for this Outcome Measure was not reported due to early study termination.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 28 days after last dose

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorized as serious in 1 subject and as nonserious in another, or 1 subject may have experienced both a serious and nonserious event during study. 1 subject died due to 2 fatal SAEs: persistent fetal circulation and congenital pneumonia.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Sildenafil

Reporting group description:

Sildenafil citrate administered intravenously at a loading dose of 0.1 mg/kg over 30 minutes infusion followed by a maintenance dose of 0.03 mg/kg/hr intravenous infusion up to 14 days, based on the need of individual subject.

Serious adverse events	Sildenafil		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Congenital pneumonia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Persistent foetal circulation			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Sildenafil		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)		
Investigations			
Blood lactic acid increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
C-reactive protein increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Incorrect drug administration duration			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Pericardial effusion			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Nervous system disorders			
Intraventricular haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Infusion site erythema			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Hypoxia			

subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Pleural effusion			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pneumothorax			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pulmonary haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Respiratory distress			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was prematurely discontinued, therefore not all data was analyzed.

Notes: