Clinical trial results:
A 7-Day, Open-Label, Multicenter, Pharmacokinetic (PK) Study (Part 1) Followed by A 7-Day, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Dose-Ranging, Parallel Group Study (Part 2) of Intravenous (IV) Sildenafil in the Treatment of Neonates With Persistent Pulmonary Hypertension of the Newborn (PPHN) or Hypoxic Respiratory Failure and at Risk for PPHH

Summary

EudraCT number	2014-004166-23
Trial protocol	Outside EU/EEA
Global end of trial date	16 May 2005

Results information

Result version number	v1 (current)
This version publication date	25 May 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	A1481157

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc. , 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000671-PIP01-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes
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 April 2006
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 May 2005
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1. To evaluate the pharmacokinetics (PK) 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 to determine doses for Part 2 of the study (Part1).
2. To determine the efficacy of IV sildenafil in near-term and term newborns with PPHN or with hypoxic respiratory failure and at risk for PPHN (Part 2).

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	02 November 2003
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	France: 4
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	36
EEA total number of subjects	13

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	36
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 was initiated on 02 November 2003 and ended on 16 May 2005 in France, United Kingdom and United States.

Period 1

Period 1 title	Sildenafil (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Sildenafil

Arm description:

Subjects received loading dose of sildenafil infusion intravenously over 5 min (minutes) (treatment group 1), over 30 min (treatment groups 2-6), and over 180 min (treatment group 8) on Day 1, followed by a maintenance dose infused continuously at reduced rate for up to and no more than 7 days. Treatment group 7 did not receive a loading dose, the sildenafil infusion was begun at the reduced rate of the maintenance dose. Doses were escalated for each of the subsequent treatment group based on PK data from the previous treatment group. The rate of infusion was weight dependent.

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:

Subjects received loading dose of sildenafil infusion intravenously on Day 1 as 0.008±0.005 milligram per kilogram (mg/kg) over 5 min (treatment group 1), 0.011±0.0005 mg/kg to 0.243±0.03 mg/kg over 30 min (treatment groups 2-6), 0.427±0.046 mg/kg over 180 min (treatment group 8) followed by maintenance dose infused continuously at reduced rate for up to and no more than 7 days as 0.07 mg/kg/day (treatment group 1), 0.08 ±0.003 mg/kg/day to 1.59±0.302 mg/kg/day (treatment groups 2-6), 1.64±0.17 mg/kg/day (treatment group 8). Treatment group 7 did not receive a loading dose, the sildenafil infusion was begun at the reduced rate of the maintenance dose of 1.64±0.17 mg/kg/day. Doses were escalated for each of the subsequent treatment group based on PK data from the previous treatment group. The rate of infusion was weight dependent.

Number of subjects in period 1	Sildenafil
Started	36
Completed	31
Not completed	5
'Death '	1
'Adverse event, not serious '	3
'Adverse event, serious non-fatal '	1

Baseline characteristics

Reporting groups	
Reporting group title	Sildenafil

Reporting group description:

Subjects received loading dose of sildenafil infusion intravenously on Day 1 as 0.008±0.005 mg/kg over 5 min (treatment group 1), 0.011±0.0005 mg/kg to 0.243±0.03 mg/kg over 30 min (treatment groups 2-6), 0.427±0.046 mg/kg over 180 min (treatment group 8) followed by maintenance dose infused continuously at reduced rate for up to and no more than 7 days as 0.07 mg/kg/day (treatment group 1), 0.08±0.003 mg/kg/day to 1.59±0.302 mg/kg/day (treatment groups 2-6), 1.64±0.17 mg/kg/day (treatment group 8). Treatment group 7 did not receive a loading dose, the sildenafil infusion was begun at the reduced rate of the maintenance dose of 1.64±0.17 mg/kg/day. Doses were escalated for each of the subsequent treatment group based on PK data from the previous treatment group. The rate of infusion was weight dependent.

Reporting group values	Sildenafil	Total	
Number of subjects	36	36	
Age categorical Units: Subjects			
Age continuous Units: hours arithmetic mean standard deviation	 34.3 ± 16.7	 -	
Gender categorical Units: Subjects			
Female	19	19	
Male	17	17	

End points

End points reporting groups

Reporting group title	Sildenafil

Reporting group description:

Subjects received loading dose of sildenafil infusion intravenously over 5 min (minutes) (treatment group 1), over 30 min (treatment groups 2-6), and over 180 min (treatment group 8) on Day 1, followed by a maintenance dose infused continuously at reduced rate for up to and no more than 7 days. Treatment group 7 did not receive a loading dose, the sildenafil infusion was begun at the reduced rate of the maintenance dose. Doses were escalated for each of the subsequent treatment group based on PK data from the previous treatment group. The rate of infusion was weight dependent.

Subject analysis set title	UK-103320
Subject analysis set type	Safety analysis

Subject analysis set description:

UK-103320 is the metabolite of sildenafil produced via biotransformation.

Subject analysis set title	iNO or ECMO
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received standard therapy (inhaled nitrogen oxide [iNO] or extracorporeal membrane oxygen [ECMO]) as a concomitant medication during the study.

Subject analysis set title	Standard Therapy (iNO)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received standard therapy (iNo) as a concomitant medication during the study.

Primary: Plasma Concentration of Sildenafil (Part 1)

End point title	Plasma Concentration of Sildenafil (Part 1)[1]

End point description:

Thirty Five subjects of safety population included those subjects who have received study medication during the Part 1 of the study. Results of plasma concentration of sildenafil were not summarized. Hence it has been reported as a graphical presentation attached as Plasma concentration of Sildenafil.pdf.

End point type	Primary

End point timeframe:

5, 30 minutes post-infusion; every 24 hours from start of infusion; before end of infusion; at 1, 4, 8, 12, 24, 48, 72 hours post-infusion in Part 1

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: No statistical analysis was planned to be analyzed for this outcome.

End point values	Sildenafil			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: nanogram per milliliter (ng/mL)				
geometric mean (standard deviation)	()			

Notes:

[2] - Data for this outcome was presented graphically as data was not summarized.

Attachments (see zip file)	Plasma concentration of Sildenafi.pdf

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of UK-103320 (Part 1)

End point title	Plasma Concentration of UK-103320 (Part 1)[3]

End point description:

Thirty Five subjects of safety population included those subjects who have received study medication during the Part 1 of the study. Results of plasma concentration of UK-103320 were not summarized. Hence it has been reported as a graphical presentation attached as plasma concentration of UK-103320.pdf.

End point type	Primary

End point timeframe:

5, 30 minutes post-infusion; every 24 hours from start of infusion; before end of infusion; at 1, 4, 8, 12, 24, 48, 72 hours post-infusion in Part 1

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: No statistical analysis was planned to be analyzed for this outcome.

End point values	UK-103320			
Subject group type	Subject analysis set			
Number of subjects analysed	0[4]			
Units: ng/mL				
geometric mean (standard deviation)	()			

Notes:

[4] - Data for this outcome was presented graphically as data was not summarized.

Attachments (see zip file)	Plasma Concentration of UK-103320.pdf

Statistical analyses

No statistical analyses for this end point

Primary: Population Pharmacokinetics of Sildenafil and UK-103320 (Part 1): Clearance (Cl)

End point title	Population Pharmacokinetics of Sildenafil and UK-103320 (Part 1): Clearance (Cl)[5]

End point description:

Cl is a quantitative measure of the rate at which a drug substance is removed from the body. 1 and 2 compartmental PK models were used to evaluate Cl as population PK. The safety population for Part 1 included all subjects who had received study medication.

End point type	Primary

End point timeframe:

5, 30 minutes post-infusion; every 24 hours from start of infusion; before end of infusion; at 1, 4, 8, 12, 24, 48, 72 hours post-infusion in Part 1

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: No statistical analysis was planned to be analyzed for this outcome.

End point values	Sildenafil	UK-103320		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	35[6]	35[7]		
Units: liter per hour (L/hr)				
arithmetic mean (standard error)	1.72 (± 0.192)	3.8 (± 0.466)		

Notes:

[6] - Number of subjects analyzed signifies those subjects who were evaluable for this measure.

[7] - Number of subjects analyzed signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Population Pharmacokinetics of Sildenafil and UK-103320 (Part 1): Central Volume of Distribution (V1)

End point title	Population Pharmacokinetics of Sildenafil and UK-103320 (Part 1): Central Volume of Distribution (V1)[8]

End point description:

V1 is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug. 1 and 2 compartmental PK models were used to evaluate V1 as population PK. The safety population for Part 1 included all subjects who had received study medication.

End point type	Primary

End point timeframe:

5, 30 minutes post-infusion; every 24 hours from start of infusion; before end of infusion; at 1, 4, 8, 12, 24, 48, 72 hours post-infusion in Part 1

Notes:

[8] - 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: No statistical analysis was planned to be analyzed for this outcome.

End point values	Sildenafil	UK-103320		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	35[9]	35[10]		
Units: liter				
arithmetic mean (standard error)	10.4 (± 0.964)	7.56 (± 3.36)		

Notes:

[9] - Number of subjects analyzed signifies those subjects who were evaluable for this measure.

[10] - Number of subjects analyzed signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Population Pharmacokinetics of Sildenafil and UK-103320 (Part 1): Peripheral Volume of Distribution(V2)

End point title	Population Pharmacokinetics of Sildenafil and UK-103320 (Part 1): Peripheral Volume of Distribution(V2)[11]

End point description:

V2 is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug. 1 and 2 compartmental PK models were to evaluate V2 as population PK. The safety population for Part 1 included all subjects who had received study medication.

End point type	Primary

End point timeframe:

5, 30 minutes post-infusion; every 24 hours from start of infusion; before end of infusion; at 1, 4, 8, 12, 24, 48, 72 hours post-infusion in Part 1

Notes:

[11] - 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: No statistical analysis was planned to be analyzed for this outcome.

End point values	Sildenafil	UK-103320		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	35[12]	35[13]		
Units: liter				
arithmetic mean (standard error)	12 (± 5.19)	25.9 (± 6.95)		

Notes:

[12] - Number of subjects analyzed signifies those subjects who were evaluable for this measure.

[13] - Number of subjects analyzed signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Population Pharmacokinetics of Sildenafil and UK-103320 (Part 1): Inter-Compartmental Clearance (Q)

End point title	Population Pharmacokinetics of Sildenafil and UK-103320 (Part 1): Inter-Compartmental Clearance (Q)[14]

End point description:

Q is a quantitative measure of the rate at which a drug substance is removed from the body. 1 and 2 compartmental PK models were used to evaluate Q as population PK. The safety population for Part 1 included all subjects who had received study medication.

End point type	Primary

End point timeframe:

5, 30 minutes post-infusion; every 24 hours from start of infusion; before end of infusion; at 1, 4, 8, 12, 24, 48, 72 hours post-infusion in Part 1

Notes:

[14] - 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: No statistical analysis was planned to be analyzed for this outcome.

End point values	Sildenafil	UK-103320		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	35[15]	35[16]		
Units: liter				
arithmetic mean (standard error)	0.188 (± 0.053)	3.26 (± 0.888)		

Notes:

[15] - Number of subjects analyzed signifies those subjects who were evaluable for this measure.

[16] - Number of subjects analyzed signifies those subjects who were evaluable for this measure.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects who Received Standard Therapy (Inhaled Nitrogen Oxide [iNO] or Extracorporeal Membrane Oxygen [ECMO]): Part 2

End point title	Number of Subjects who Received Standard Therapy (Inhaled Nitrogen Oxide [iNO] or Extracorporeal Membrane Oxygen [ECMO]): Part 2[17]

End point description:

Results for this outcome have not been reported since Part 2 of the study was not conducted due to premature termination of the study.

End point type	Primary

End point timeframe:

Baseline up to 7 days in Part 2

Notes:

[17] - 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: No statistical analysis was planned to be analyzed for this outcome.

End point values	iNO or ECMO			
Subject group type	Subject analysis set			
Number of subjects analysed	0[18]			
Units: subjects				

Notes:

[18] - Data for this outcome was not reported since the study (Part 2) was terminated prematuraley.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Duration of Standard Therapy (inhaled nitrogen oxide [iNO]) Therapy: Part 2

End point title	Total Duration of Standard Therapy (inhaled nitrogen oxide [iNO]) Therapy: Part 2

End point description:

Results for this measure have not been reported since Part 2 was not conducted due to premature termination of the study.

End point type	Secondary

End point timeframe:

Baseline up to 7 days in Part 2

End point values	Standard Therapy (iNO)			
Subject group type	Subject analysis set			
Number of subjects analysed	0[19]			
Units: hours				
arithmetic mean (standard deviation)	()			

Notes:

[19] - Data for this outcome was not reported since the study (Part 2) was terminated prematurely.

Statistical analyses

No statistical analyses for this end point

Secondary: Time From Initiation of Study Drug to Receipt of Standard Therapy

(inhaled nitrogen oxide [iNO] or extracorporeal membrane oxygen [ECMO]): Part 2	
End point title	Time From Initiation of Study Drug to Receipt of Standard Therapy (inhaled nitrogen oxide [iNO] or extracorporeal membrane oxygen [ECMO]): Part 2

End point description:

Results for this measure have not been reported since Part 2 was not conducted due to premature termination of the study.

End point type	Secondary

End point timeframe:

Baseline up to 7 days in Part 2

End point values	iNO or ECMO			
Subject group type	Subject analysis set			
Number of subjects analysed	0[20]			
Units: hours				
arithmetic mean (standard deviation)	()			

Notes:

[20] - Data for this outcome was not reported since the study (Part 2) was terminated prematurely.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 7 days (end of study treatment) in Part 1

Adverse event reporting additional description:

The same event may appear as both an adverse event and a serious adverse event. However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Sildenafil

Reporting group description:

Subjects received loading dose of sildenafil infusion intravenously on Day 1 as 0.008±0.005 mg/kg over 5 min (treatment group 1), 0.011±0.0005 mg/kg to 0.243±0.03 mg/kg over 30 min (treatment groups 2-6), 0.427±0.046 mg/kg over 180 min (treatment group 8) followed by maintenance dose infused continuously at reduced rate for up to and no more than 7 days as 0.07 mg/kg/day (treatment group 1), 0.08±0.003 mg/kg/day to 1.59±0.302 mg/kg/day (treatment groups 2-6), 1.64±0.17 mg/kg/day (treatment group 8). Treatment group 7 did not receive a loading dose, the sildenafil infusion was begun at the reduced rate of the maintenance dose of 1.64±0.17 mg/kg/day. Doses were escalated for each of the subsequent treatment group based on PK data from the previous treatment group. The rate of infusion was weight dependent.

Serious adverse events	Sildenafil		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 36 (11.11%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Congenital, familial and genetic disorders			
Anomalous pulmonary venous connection			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Pneumothorax			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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	20 / 36 (55.56%)		
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Cardiac murmur			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Oxygen saturation decreased			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
White blood cell count increased			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Patent ductus arteriosus			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Ventricular septal defect			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Hypotension			

subjects affected / exposed	7 / 36 (19.44%)		
occurrences (all)	8		
Labile blood pressure			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Thrombophlebitis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Peripheral swelling			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Feeling jittery			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Gastrointestinal disorders			
Ileus			

subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	 3 / 36 (8.33%) 3		
Respiratory, thoracic and mediastinal disorders Atelectasis subjects affected / exposed occurrences (all) Lung disorder subjects affected / exposed occurrences (all) Laryngeal oedema subjects affected / exposed occurrences (all) Lung infiltration subjects affected / exposed occurrences (all) Pneumothorax subjects affected / exposed occurrences (all)	 1 / 36 (2.78%) 1 1 / 36 (2.78%) 1 1 / 36 (2.78%) 1 1 / 36 (2.78%) 1 2 / 36 (5.56%) 3		
Skin and subcutaneous tissue disorders Decubitus ulcer subjects affected / exposed occurrences (all)	 1 / 36 (2.78%) 1		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	 1 / 36 (2.78%) 1 1 / 36 (2.78%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2003	Changed the loading dose duration from a 5 minute to a 30 minute infusion.

Notes:

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.

Study part 2 was not performed. Use of inhaled NO to treat persistent pulmonary hypertension of newborn suggested that indication for sildenafil monotherapy may not be possible. A primary endpoint to support labelled indication has yet to be defined.

Notes: