

**Clinical trial results:**

A multinational, multicentre, randomized, double-blind study to assess the efficacy and safety of oral sildenafil 20mg TID or placebo dosed concomitantly with Bosentan in the treatment of subjects , aged 18 years and above, with pulmonary arterial hypertension (PAH)

Summary

EudraCT number	2006-001464-23
Trial protocol	CZ DE GB IT GR
Global end of trial date	20 August 2013

Results information

Result version number	v1 (current)
This version publication date	31 May 2016
First version publication date	05 August 2015

Trial information**Trial identification**

Sponsor protocol code	A1481243
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00323297
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 March 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect on exercise capacity (as measured by the 6 Minute Walk Distance) after 12 weeks of treatment of sildenafil (20 milligram [mg] three times a day [TID]) or placebo when dosed concomitantly to subjects with PAH who are stabilized on bosentan therapy.

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 Harmonisation (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	15 September 2006
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	Czech Republic: 13
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	United States: 5
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Taiwan: 5
Worldwide total number of subjects	103
EEA total number of subjects	71

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)	65
From 65 to 84 years	38
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 29 active centers in 10 countries (10 centers in Germany, 5 centers in the United States of America [USA], 3 centers in France, 2 centers in Australia, Czech Republic, Italy, and Israel, and 1 center in Greece, Taiwan and United Kingdom [UK]).

Pre-assignment

Screening details:

Subjects were on bosentan therapy for 3 months prior. Subjects were randomized to sildenafil or placebo. Part A study was double-blind phase (12 weeks) and Part B was 12 months open-label phase. 53 and 51 subjects were randomized to placebo and sildenafil arm respectively. One subject in sildenafil arm did not receive any treatment.

Period 1

Period 1 title	Part A (Double Blind Randomized)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

In Part A of the study: the subjects received placebo, dosed concomitantly with their existing stable bosentan treatment, for Double-Blind Phase of the study.

In Part B of the study: All the subjects received sildenafil.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo TID, dosed concomitantly with their existing stable bosentan treatment (62.5 mg two times a day (BID) or 125 mg BID for minimum 3 months prior to randomization), for 12-Week Double-Blind Phase of the study.

Arm title	Sildenafil
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Arm description:

In Part A of the study: the subjects received sildenafil, dosed concomitantly with their existing stable bosentan treatment, for Double-Blind Phase of the study.

In Part B of the study: All the subjects received sildenafil.

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

Dosage and administration details:

Subjects received sildenafil 20 mg TID, dosed concomitantly with their existing stable bosentan treatment (62.5 mg BID or 125 mg BID for minimum 3 months prior to randomization), for 12-Week Double-Blind Phase of the study.

Number of subjects in period 1	Placebo	Sildenafil
Started	53	50
Completed	48	43
Not completed	5	7
Related and Unrelated adverse event	1	-
Death	-	1
Related adverse event	2	2
Reason unspecified	-	1
Protocol Violation	1	3
Unrelated adverse event	1	-

Period 2

Period 2 title	Part B (Open-label)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

In Part A of the study: the subjects received placebo, dosed concomitantly with their existing stable bosentan treatment, for Double-Blind Phase of the study.

In Part B of the study: All the subjects received sildenafil.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo TID, dosed concomitantly with their existing stable bosentan treatment (62.5 mg BID or 125 mg BID for minimum 3 months prior to randomization), for 12-Week Double-Blind Phase of the study.

Arm title	Sildenafil
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Arm description:

In Part A of the study: the subjects received sildenafil, dosed concomitantly with their existing stable bosentan treatment, for Double-Blind Phase of the study.

In Part B of the study: All the subjects received sildenafil.

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

Dosage and administration details:

All the subjects received sildenafil 20 mg TID for 12 months.

Number of subjects in period 2	Placebo	Sildenafil
Started	48	43
Completed	39	31
Not completed	9	12
Consent withdrawn by subject	1	3
Adverse Event	5	5
Death	-	1
Reason unspecified	-	1
Protocol Violation	-	1
Lack of efficacy	3	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
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Reporting group description:

In Part A of the study: the subjects received placebo, dosed concomitantly with their existing stable bosentan treatment, for Double-Blind Phase of the study.

In Part B of the study: All the subjects received sildenafil.

Reporting group title	Sildenafil
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Reporting group description:

In Part A of the study: the subjects received sildenafil, dosed concomitantly with their existing stable bosentan treatment, for Double-Blind Phase of the study.

In Part B of the study: All the subjects received sildenafil.

Reporting group values	Placebo	Sildenafil	Total
Number of subjects	53	50	103
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	56.9	55.2	-
standard deviation	± 14.14	± 15.1	

Gender categorical			
Units: Subjects			
Female	41	37	78
Male	12	13	25

World Health Organization Functional Class in Subjects with Pulmonary Arterial Hypertension			
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Pulmonary Arterial Hypertension criteria for WHO Class: Class I (Subjects with no limitation of physical activity); Class II (Subjects with slight limitation of physical activity); Class III (Subjects with marked limitation of physical activity); Class IV (Subjects with inability to carry out any physical activity).

Units: Subjects			
Class I	0	0	0
Class II	15	20	35
Class III	38	29	67
Class IV	0	1	1

Six Minute Walk Test (6MWT)			
6MWT is the distance that a subject could walk in 6 minutes. Subjects were asked to perform the test at a pace that was comfortable to them, with as many breaks as they needed. Continuous pulse oximetry was conducted during the test for safety.			

Units: meters			
arithmetic mean	350.38	354.44	-
standard deviation	± 87.587	± 73.121	

Mean Pulmonary Artery Pressure (mPAP)			
Units: Millimeter (mm) of mercury (Hg)			
arithmetic mean	44.9	46.9	

standard deviation	± 13.33	± 12.47	-
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End points

End points reporting groups

Reporting group title	Placebo
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Reporting group description:

In Part A of the study: the subjects received placebo, dosed concomitantly with their existing stable bosentan treatment, for Double-Blind Phase of the study.

In Part B of the study: All the subjects received sildenafil.

Reporting group title	Sildenafil
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Reporting group description:

In Part A of the study: the subjects received sildenafil, dosed concomitantly with their existing stable bosentan treatment, for Double-Blind Phase of the study.

In Part B of the study: All the subjects received sildenafil.

Reporting group title	Placebo
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Reporting group description:

In Part A of the study: the subjects received placebo, dosed concomitantly with their existing stable bosentan treatment, for Double-Blind Phase of the study.

In Part B of the study: All the subjects received sildenafil.

Reporting group title	Sildenafil
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Reporting group description:

In Part A of the study: the subjects received sildenafil, dosed concomitantly with their existing stable bosentan treatment, for Double-Blind Phase of the study.

In Part B of the study: All the subjects received sildenafil.

Primary: Change From Baseline in the Total Distance Walked During 6 Minute Walk Time (6MWT) at Week 12

End point title	Change From Baseline in the Total Distance Walked During 6 Minute Walk Time (6MWT) at Week 12
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End point description:

6MWT is the distance that a subject could walk in 6 minutes. Subjects were asked to perform the test at a pace that was comfortable to them, with as many breaks as they needed. Continuous pulse oximetry was conducted during the test for safety. Intent-to-Treat (ITT) Population (Full Analysis Set [FAS]) consisted of all subjects who had been randomly assigned to study drug and received at least one dose of study medication. Missing values were replaced according to the last observation carried forward (LOCF) approach. Statistical analysis was carried out on LOCF values.

End point type	Primary
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End point timeframe:

Week 12

End point values	Placebo	Sildenafil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	50		
Units: meters				
arithmetic mean (standard deviation)				
Change from baseline at Week 12 (n=46,44)	17.42 (± 57.27)	14.08 (± 63.679)		

Change from baseline at Week 12 LOCF (n=53,49)	14.08 (± 57.557)	13.62 (± 60.95)		
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Statistical analyses

Statistical analysis title	6MWT at Week 12
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Statistical analysis description:

The estimated sample size was based upon the primary endpoint. A sample size of 51 subjects per treatment group was required to detect a difference of 30 meters between treatments with 80% power at a one sided significance level of 0.05, assuming a standard deviation of 60 meters. The mean difference in method of estimation is the difference between Sildenafil - placebo.

Comparison groups	Placebo v Sildenafil
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5802 ^[1]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.38
Confidence interval	
level	90 %
sides	2-sided
lower limit	-21.843
upper limit	17.087
Variability estimate	Standard error of the mean
Dispersion value	11.722

Notes:

[1] - Sequential closed-testing procedure was implemented for all secondary endpoints. If no statistically significant treatment effect was found for primary endpoint then statistical tests were not to be performed on the secondary endpoints.

Secondary: Number of Subjects With Change From Baseline in World Health Organization (WHO) Functional Class in Subjects With PAH at Week 12 LOCF

End point title	Number of Subjects With Change From Baseline in World Health Organization (WHO) Functional Class in Subjects With PAH at Week 12 LOCF
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End point description:

WHO functional classification for PAH range from Class I (no limitation in physical activity, no dyspnea with normal activity) to Class IV (can not perform a physical activity without any symptoms, dyspnea at rest). Improvement=reduction in functional class; deterioration = increase in functional class, no change = no change in functional class. ITT Population (FAS) consisted of all subjects who had been randomly assigned to study drug and received at least one dose of study medication. Missing values were replaced according to the LOCF approach.

End point type	Secondary
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End point timeframe:

week 12

End point values	Placebo	Sildenafil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	50		
Units: subjects				
Worsened 2 Classes	0	0		
Worsened 1 Class	1	0		
No Change	45	39		
Improved 1 Class	7	10		
Improved 2 Classes	0	0		
Discontinued	0	0		
Died	0	1		
Missing	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Worsening Events

End point title	Clinical Worsening Events
End point description:	No survival analysis was carried out for the study due to very few events of clinical worsening. Hence, we present a summary of clinical worsening events instead. Events of clinical worsening were categorized as (A). Death, (B). Heart/lung transplantation, (C). Hospitalization due to pulmonary arterial hypertension (PAH), and (D). Clinical deterioration of PAH requiring additional therapy. ITT Population (FAS) consisted of all subjects who had been randomly assigned to study drug and received at least one dose of study medication.
End point type	Secondary
End point timeframe:	Week 12

End point values	Placebo	Sildenafil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	50		
Units: subjects				
None	51	47		
(A)	0	1		
(B)	0	0		
(C)	2	2		
(D)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Borg Dyspnea Score at Week 12

End point title	Change From Baseline in Borg Dyspnea Score at Week 12
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End point description:

Borg dyspnea scale is a 10-point scale where following scores stands for severity of dyspnea: 0 (no breathlessness at all); 0.5 (very very slight [just noticeable]); 1.(very slight); 2.(slight breathlessness); 3.(moderate); 4 (some what severe); 5 (severe breathlessness); 7 (very severe breathlessness); 9 (very very severe [almost maximum]); and 10 (maximum). ITT Population (FAS) consisted of all subjects who had been randomly assigned to study drug and received at least one dose of study medication. Missing values were replaced according to the last observation carried forward LOCF approach.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Placebo	Sildenafil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	50		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change from Baseline at Week 12 (n=46,43)	0.16 (\pm 1.637)	-0.73 (\pm 1.656)		
Change from Baseline at Week 12 LOCF (n=53,49)	0.24 (\pm 1.709)	-0.62 (\pm 1.583)		

Statistical analyses

No statistical analyses for this end point

Secondary: One Year Survival Probability From the Start of Sildenafil Treatment

End point title	One Year Survival Probability From the Start of Sildenafil Treatment
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End point description:

The survival probability of all subjects up to 1-year post start of Sildenafil treatment; for subjects who were randomized to Sildenafil, this was the week 52 from randomization, and for subjects who were originally randomized to Placebo group, this was the Week 64 from Baseline (Week 52 from Week 12, when the first dose of Sildenafil was administered to these subjects).Subjects who discontinued from the study prior to 1 year after start of sildenafil were considered as censored at time of discontinuation and those who discontinued from study post 1-year after start of sildenafil were considered as censored at the time of 1-year post start of sildenafil. ITT Population (FAS) consisted of all subjects who had been randomly assigned to study drug and received at least one dose of study medication. Missing values were replaced according to the last observation carried forward LOCF approach. The subjects in placebo arm have received Sildenafil on or after Week 12.

End point type	Secondary
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End point timeframe:

One year from the time of starting sildenafil

End point values	Placebo	Sildenafil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	50		
Units: Probability of death				
number (confidence interval 90%)	0.042 (0.013 to 0.127)	0.04 (0.013 to 0.124)		

Statistical analyses

No statistical analyses for this end point

Secondary: One Year Survival From the Start of Sildenafil Treatment

End point title	One Year Survival From the Start of Sildenafil Treatment
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End point description:

The survival status of all subjects who discontinued from the study, including those subjects who discontinued during the double-blind phase, was to be assessed at one year post their Week 12 visit/ End of treatment visit. ITT Population (FAS) consisted of all subjects who had been randomly assigned to study drug and received at least one dose of study medication. Missing values were replaced according to the last observation carried forward LOCF approach. The subjects in placebo arm have received Sildenafil on or after Week 12.

End point type	Secondary
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End point timeframe:

One year from the time of starting sildenafil

End point values	Placebo	Sildenafil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	50		
Units: subjects who died	2	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time that the subject provides informed consent through and including 28 calendar days after the last administration of the investigational product

Adverse event reporting additional description:

The same event may appear as both an adverse event (AE) and a serious adverse event (SAE). 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Sildenafil
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Reporting group description:

In Part A of the study: the subjects received sildenafil, dosed concomitantly with their existing stable bosentan treatment, for Double-Blind Phase of the study.

In Part B of the study: All the subjects received sildenafil.

Reporting group title	Placebo
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Reporting group description:

In Part A of the study: the subjects received placebo, dosed concomitantly with their existing stable bosentan treatment, for Double-Blind Phase of the study.

In Part B of the study: All the subjects received sildenafil.

Serious adverse events	Sildenafil	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 50 (44.00%)	23 / 53 (43.40%)	
number of deaths (all causes)	4	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			

subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic neoplasm			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Skin graft			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine haemorrhage			

subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 50 (4.00%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 50 (0.00%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	2 / 50 (4.00%)	6 / 53 (11.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 3	
Psychiatric disorders			
Mania			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Walking distance test abnormal			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural haematoma			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 50 (2.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular disorder			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			

subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	3 / 50 (6.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Paresis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 50 (2.00%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 50 (0.00%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Inguinal hernia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	2 / 50 (4.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 50 (0.00%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis viral			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 50 (0.00%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 50 (2.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Sildenafil	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 50 (66.00%)	38 / 53 (71.70%)	
Vascular disorders			
Flushing			
subjects affected / exposed	5 / 50 (10.00%)	4 / 53 (7.55%)	
occurrences (all)	5	4	
Hypertension			
subjects affected / exposed	1 / 50 (2.00%)	3 / 53 (5.66%)	
occurrences (all)	1	3	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 50 (0.00%)	4 / 53 (7.55%)	
occurrences (all)	0	5	
Oedema peripheral			

subjects affected / exposed occurrences (all)	7 / 50 (14.00%) 9	8 / 53 (15.09%) 9	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 50 (2.00%)	3 / 53 (5.66%)	
occurrences (all)	1	3	
Dyspnoea			
subjects affected / exposed	3 / 50 (6.00%)	8 / 53 (15.09%)	
occurrences (all)	4	12	
Pulmonary arterial hypertension			
subjects affected / exposed	2 / 50 (4.00%)	4 / 53 (7.55%)	
occurrences (all)	2	5	
Pulmonary hypertension			
subjects affected / exposed	3 / 50 (6.00%)	0 / 53 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 50 (6.00%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Investigations			
Weight increased			
subjects affected / exposed	0 / 50 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Cardiac disorders			
Palpitations			
subjects affected / exposed	5 / 50 (10.00%)	3 / 53 (5.66%)	
occurrences (all)	5	3	
Right ventricular failure			
subjects affected / exposed	0 / 50 (0.00%)	4 / 53 (7.55%)	
occurrences (all)	0	5	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 50 (14.00%)	7 / 53 (13.21%)	
occurrences (all)	9	8	
Presyncope			

subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3	3 / 53 (5.66%) 3	
Syncope subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	3 / 53 (5.66%) 5	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2	4 / 53 (7.55%) 6	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 7	2 / 53 (3.77%) 2	
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3	0 / 53 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	7 / 50 (14.00%) 8	5 / 53 (9.43%) 7	
Nausea subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 2	5 / 53 (9.43%) 6	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	4 / 53 (7.55%) 6	
Back pain subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	5 / 53 (9.43%) 5	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	3 / 53 (5.66%) 3	
Infections and infestations			

Bronchitis			
subjects affected / exposed	5 / 50 (10.00%)	5 / 53 (9.43%)	
occurrences (all)	7	9	
Nasopharyngitis			
subjects affected / exposed	5 / 50 (10.00%)	8 / 53 (15.09%)	
occurrences (all)	7	9	
Respiratory tract infection			
subjects affected / exposed	4 / 50 (8.00%)	1 / 53 (1.89%)	
occurrences (all)	5	1	
Sinusitis			
subjects affected / exposed	1 / 50 (2.00%)	5 / 53 (9.43%)	
occurrences (all)	1	7	
Upper respiratory tract infection			
subjects affected / exposed	2 / 50 (4.00%)	5 / 53 (9.43%)	
occurrences (all)	3	9	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 50 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2006	The safety language has been revised to address new reporting requirements related to Exposure in Utero.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported