Clinical trial results:
A Randomized, Double-Blind, Placebo Controlled, Dose Ranging, Parallel Group Study of Oral Sildenafil in the Treatment of Children, Aged 1-17 Years, With Pulmonary Arterial Hypertension.

Summary

EudraCT number	2006-002235-25
Trial protocol	GB FI SK Outside EU/EEA
Global end of trial date	05 June 2008

Results information

Result version number	v2 (current)
This version publication date	07 May 2016
First version publication date	29 July 2015
Version creation reason	• Correction of full data set update is required regarding the unit of measurement of a secondary endpoint.

Trial information

Trial identification

Sponsor protocol code	A1481131

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00159913
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000671-PIP01-09
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	27 November 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 June 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the efficacy of 16 weeks of chronic treatment with oral sildenafil in pediatric subjects, aged 1 to 17 years, with primary arterial hypertension (PAH).
Secondary objective were-
1) To assess safety, tolerability, and pharmacokinetics of 16 weeks of chronic treatment with oral sildenafil in pediatric subjects, aged 1 to 17 years with PAH,
2) To assess the survival status of subjects who did not enter A1481156 [(NCT number: NCT00159874) and (EudraCT number: 2005-000963-25)].

Protection of trial subjects:

The study was in compliance with 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	28 August 2003
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	Russian Federation: 13
Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Chile: 2
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	United States: 39
Country: Number of subjects enrolled	Japan: 1
Country: Number of subjects enrolled	Guatemala: 25
Country: Number of subjects enrolled	Colombia: 34
Country: Number of subjects enrolled	India: 27
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Malaysia: 8
Country: Number of subjects enrolled	Taiwan: 5

Worldwide total number of subjects	234
EEA total number of subjects	59

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)	6
Children (2-11 years)	129
Adolescents (12-17 years)	99
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 32 centers in North, Latin and South America, Europe and Asia.

Pre-assignment

Screening details:

Of the 324 subjects screened, 235 subjects were randomized. 234 received treatment. One subject (sildenafil medium dose group) withdrew prior to taking any study treatment as the hemodynamic entrance criteria were not met.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Sildenafil Low Dose

Arm description:

Day 1-7 10 milligram (mg), followed by 10 mg TID (3 times daily) for body weights greater than (>)20-45 kilogram (kg) and >45 kg, through Day 112. Modeling of the plasma concentrations for each dose level showed that the low and medium doses were predicted to be similar for the 8 to 20 kg subjects [that is (i.e.), subjects would receive the same dose because of the available tablet strengths]; consequently there was no low dose for the greater than or equal to (>=)8-20 kg weight group.

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:

Day 1-7 10 mg, followed by 10 mg TID for body weights >20-45 kg and >45 kg, through Day 112.

Arm title	Sildenafil Medium Dose

Arm description:

Day 1-7 10 mg, followed by 10, 20, 40 mg TID based on the body weight, through Day 112.

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:

Day 1-7 10 mg, followed by 10, 20, 40 mg TID for body weights >=8-20 kg, >20-45 kg, >45 kg respectively through Day 112.

Arm title	Sildenafil High Dose

Arm description:

Day 1-7 10 mg, followed by 20, 40, 80 mg TID based on body weight, through Day 112.

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:

Day 1-7 10 mg, followed by 20, 40, 80 mg TID for body weights >=8-20 kg, >20-45 kg, >45 kg respectively, through Day 112.

Arm title	Placebo

Arm description:

Subjects randomized to this arm received placebo TID for 112 days.

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:

Placebo was given TID for 112 days.

Number of subjects in period 1	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose
Started	42	55	77
Completed	40	55	75
Not completed	2	0	2
Consent withdrawn by subject	-	-	-
Protocol violation	1	-	1
Adverse event	1	-	1
Lost to follow-up	-	-	-

Number of subjects in period 1	Placebo
Started	60
Completed	58
Not completed	2
Consent withdrawn by subject	1
Protocol violation	-
Adverse event	-
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Sildenafil Low Dose
Reporting group description:	
Day 1-7 10 milligram (mg), followed by 10 mg TID (3 times daily) for body weights greater than (>)20-45 kilogram (kg) and >45 kg, through Day 112. Modeling of the plasma concentrations for each dose level showed that the low and medium doses were predicted to be similar for the 8 to 20 kg subjects [that is (i.e.), subjects would receive the same dose because of the available tablet strengths]; consequently there was no low dose for the greater than or equal to (>=)8-20 kg weight group.	
Reporting group title	Sildenafil Medium Dose
Reporting group description:	
Day 1-7 10 mg, followed by 10, 20, 40 mg TID based on the body weight, through Day 112.	
Reporting group title	Sildenafil High Dose
Reporting group description:	
Day 1-7 10 mg, followed by 20, 40, 80 mg TID based on body weight, through Day 112.	
Reporting group title	Placebo
Reporting group description:	
Subjects randomized to this arm received placebo TID for 112 days.	

Reporting group values	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose
Number of subjects	42	55	77
Age categorical Units: Subjects			
1-4 Years	0	9	19
5-12 Years	25	28	36
13-17 Years	17	18	22
>= 18 Years	0	0	0
Gender categorical Units: Subjects			
Female	25	31	51
Male	17	24	26

Reporting group values	Placebo	Total	
Number of subjects	60	234	
Age categorical Units: Subjects			
1-4 Years	7	35	
5-12 Years	37	126	
13-17 Years	16	73	
>= 18 Years	0	0	
Gender categorical Units: Subjects			
Female	38	145	
Male	22	89	

End points

End points reporting groups

Reporting group title	Sildenafil Low Dose
Reporting group description:	
Day 1-7 10 milligram (mg), followed by 10 mg TID (3 times daily) for body weights greater than (>)20-45 kilogram (kg) and >45 kg, through Day 112. Modeling of the plasma concentrations for each dose level showed that the low and medium doses were predicted to be similar for the 8 to 20 kg subjects [that is (i.e.), subjects would receive the same dose because of the available tablet strengths]; consequently there was no low dose for the greater than or equal to (>=)8-20 kg weight group.	
Reporting group title	Sildenafil Medium Dose
Reporting group description:	
Day 1-7 10 mg, followed by 10, 20, 40 mg TID based on the body weight, through Day 112.	
Reporting group title	Sildenafil High Dose
Reporting group description:	
Day 1-7 10 mg, followed by 20, 40, 80 mg TID based on body weight, through Day 112.	
Reporting group title	Placebo
Reporting group description:	
Subjects randomized to this arm received placebo TID for 112 days.	
Subject analysis set title	Sildenafil Low Dose
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Day 1-7 10 mg, followed by 10 mg TID for body weights >20-45 kg and >45 kg, through Day 112. Modeling of the plasma concentrations for each dose level showed that the low and medium doses were predicted to be similar for the 8 to 20 kg subjects (ie, subjects would receive the same dose because of the available tablet strengths); consequently there was no low dose for the >=8-20 kg weight group.	
Subject analysis set title	Sildenafil Medium Dose
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Day 1-7 10 mg, followed by 10, 20, 40 mg TID for body weights >=8-20 kg, >20-45 kg, >45 kg respectively, through Day 112.	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects randomized to this arm received placebo TID for 112 days.	
Subject analysis set title	Sildenafil High Dose
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Day 1-7 10 mg, followed by 20, 40, 80 mg TID for body weights >=8-20 kg, >20-45 kg, >45 kg respectively, through Day 112.	
Subject analysis set title	Combined Sildenafil
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
This includes all subjects in the low, medium and high dose group of sildenafil.	

Primary: Percent Change From Baseline in Peak Volume of Oxygen (VO2) Consumed: Intent To Treat Population

End point title	Percent Change From Baseline in Peak Volume of Oxygen (VO2) Consumed: Intent To Treat Population
End point description:	
Peak VO2 (normalized for body weight) at trough plasma levels assessed by Cardiopulmonary excercise (CPX) testing (bicycle ergometry) at the end of treatment (Week 16 for those who completed the study). Mean Percent change = [(week 16 value minus baseline mean)/mean at baseline]*100%. Intent to treat (ITT) population included all subjects randomized and who received at least one dose of study medication. All subjects developmentally able to perform the exercise test. Subjects assumed	

developmentally able if they had a CPX exercise assessment at any visit during study using a LOCF (last observation carried forward) (end-of-treatment) approach for handling missing data.

End point type	Primary

End point timeframe:

Baseline, Week 16

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Placebo	Sildenafil High Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	26	29	27
Units: percent change				
arithmetic mean (standard deviation)	6.44 (± 20.16)	13.4 (± 19.5)	0.53 (± 15.91)	10.58 (± 15.51)

End point values	Combined Sildenafil			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: percent change				
arithmetic mean (standard deviation)	10.24 (± 18.39)			

Statistical analyses

Statistical analysis title	Combined Sildenafil vs. Placebo

Statistical analysis description:

Analyses performed using analysis of covariance (ANCOVA) with etiology, weight and baseline peak VO2 as the covariates. No adjustments for multiple comparisons have been made.

Comparison groups	Combined Sildenafil v Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.056
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	15.6
Variability estimate	Standard error of the mean
Dispersion value	3.98

Statistical analysis title	Sildenafil Low Dose vs. Placebo
Statistical analysis description:	
Analyses performed using analysis of covariance with etiology, weight and baseline peak VO2 as the covariates.	
Comparison groups	Sildenafil Low Dose v Placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.11
upper limit	13.73
Variability estimate	Standard error of the mean
Dispersion value	5

Statistical analysis title	Sildenafil Medium Dose vs. Placebo
Statistical analysis description:	
Analyses performed using analysis of covariance with etiology, weight and baseline peak VO2 as the covariates.	
Comparison groups	Sildenafil Medium Dose v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	11.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.72
upper limit	20.94
Variability estimate	Standard error of the mean
Dispersion value	4.84

Statistical analysis title	Sildenafil High Dose vs. Placebo
Statistical analysis description:	
Analyses performed using analysis of covariance with etiology, weight and baseline peak VO2 as the covariates.	
Comparison groups	Sildenafil High Dose v Placebo

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.64
upper limit	17.6
Variability estimate	Standard error of the mean
Dispersion value	4.85

Primary: Percent Change From Baseline in Peak Volume of Oxygen (VO2) Consumed: Per Protocol Population

End point title	Percent Change From Baseline in Peak Volume of Oxygen (VO2) Consumed: Per Protocol Population

End point description:

Peak VO2 (normalized for body weight) at trough plasma levels assessed by CPX testing (bicycle ergometry) at the end of treatment (Week 16 for those who completed the study). Percent change = [(week 16 value minus baseline mean)/mean at baseline]*100%. Per protocol population was used for the analysis.

End point type	Primary

End point timeframe:

Baseline, Week 16

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Placebo	Sildenafil High Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	23	24	27
Units: percent change				
arithmetic mean (standard deviation)	5.43 (± 20.69)	15.66 (± 21.48)	2.81 (± 13.17)	9.34 (± 17.13)

End point values	Combined Sildenafil			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: percent change				
arithmetic mean (standard deviation)	10.1 (± 19.87)			

Statistical analyses

Statistical analysis title	Combined Sildenafil vs. Placebo
Statistical analysis description:	
Analyses performed using analysis of covariance with etiology, weight and baseline peak VO2 as the covariates.	
Comparison groups	Combined Sildenafil v Placebo
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.179
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.74
upper limit	14.53
Variability estimate	Standard error of the mean
Dispersion value	4.35

Statistical analysis title	Sildenafil Low Dose vs. Placebo
Statistical analysis description:	
Analyses performed using analysis of covariance with etiology, weight and baseline peak VO2 as the covariates.	
Comparison groups	Sildenafil Low Dose v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.49
upper limit	11.77
Variability estimate	Standard error of the mean
Dispersion value	5.35

Statistical analysis title	Sildenafil Medium Dose vs. Placebo
Statistical analysis description:	
Analyses performed using analysis of covariance with etiology, weight and baseline peak VO2 as the covariates.	
Comparison groups	Sildenafil Medium Dose v Placebo

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	21.94
Variability estimate	Standard error of the mean
Dispersion value	5.36

Statistical analysis title	Sildenafil High Dose vs. Placebo
Statistical analysis description:	
Analyses performed using analysis of covariance with etiology, weight and baseline peak VO2 as the covariates	
Comparison groups	Sildenafil High Dose v Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.02
upper limit	15.5
Variability estimate	Standard error of the mean
Dispersion value	5.16

Secondary: Change From Baseline to Week 16 in Mean Pulmonary Artery Pressure (mPAP)

End point title	Change From Baseline to Week 16 in Mean Pulmonary Artery Pressure (mPAP)
End point description:	
mPAP, a hemodynamic parameter, was measured using a pressure transducer positioned at the mid-axillary line with the subject in the supine position. Change is observed value at Week 16 minus Baseline value. ITT population, using a Last Observation Carried Forward (LOCF) (end-of-treatment) approach for handling missing data.	
End point type	Secondary
End point timeframe:	
Baseline, Week 16	

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Placebo	Sildenafil High Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	55	56	71
Units: mm Hg				
arithmetic mean (standard deviation)	0.9 (± 12.3)	-3.9 (± 12)	-0.4 (± 15.9)	-7.4 (± 15.4)

End point values	Combined Sildenafil			
Subject group type	Subject analysis set			
Number of subjects analysed	165			
Units: mm Hg				
arithmetic mean (standard deviation)	-4.3 (± 13.9)			

Statistical analyses

Statistical analysis title	Combined Sildenafil vs. Placebo
Statistical analysis description:	
Covariates: etiology, weight group, capability performing exercise test. Normality assumptions not met with main analysis: alternative=excluding outliers.	
Comparison groups	Combined Sildenafil v Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.172
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	1.3
Variability estimate	Standard error of the mean
Dispersion value	2.2

Statistical analysis title	Sildenafil Low Dose vs. Placebo
Statistical analysis description:	
Covariates: etiology, weight group, capability performing exercise test. Normality assumptions not met with main analysis: alternative=excluding outliers.	
Comparison groups	Sildenafil Low Dose v Placebo

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	7.6
Variability estimate	Standard error of the mean
Dispersion value	3.1

Statistical analysis title	Sildenafil Medium Dose vs. Placebo
Statistical analysis description:	
Covariates: etiology, weight group, capability performing exercise test. Normality assumptions not met with main analysis: alternative=excluding outliers.	
Comparison groups	Sildenafil Medium Dose v Placebo
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.9
upper limit	1.9
Variability estimate	Standard error of the mean
Dispersion value	2.7

Statistical analysis title	Sildenafil High Dose vs. Placebo
Statistical analysis description:	
Covariates: etiology, weight group, capability performing exercise test. Normality assumptions not met with main analysis: alternative=excluding outliers.	
Comparison groups	Sildenafil High Dose v Placebo
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.4
upper limit	-2.1
Variability estimate	Standard error of the mean
Dispersion value	2.6

Secondary: Change From Baseline to Week 16 in Pulmonary Vascular Resistance Index (PVRI)

End point title	Change From Baseline to Week 16 in Pulmonary Vascular Resistance Index (PVRI)

End point description:

PVRI equals Pulmonary Vascular Resistance (PVR) times Body Surface Area (BSA). Wood unit = 80 dyn*s/cm^5. Change is observed value at Week 16 minus baseline value. ITT population, LOCF.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Placebo	Sildenafil High Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	36	49	50	67
Units: wood units*m^2				
arithmetic mean (standard deviation)	0.1 (± 10.9)	-2.9 (± 11.5)	1.6 (± 9.2)	-5.1 (± 14.7)

End point values	Combined Sildenafil			
Subject group type	Subject analysis set			
Number of subjects analysed	152			
Units: wood units*m^2				
arithmetic mean (standard deviation)	-3.2 (± 13)			

Statistical analyses

Statistical analysis title	Combined Sildenafil vs. Placebo

Statistical analysis description:

Covariates: etiology, weight group, capability performing exercise test. Normality assumptions not met with main analysis: alternative=natural log transformed.

Comparison groups	Combined Sildenafil v Placebo

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	2

Statistical analysis title	Sildenafil Low Dose vs. Placebo
Statistical analysis description:	
Covariates: etiology, weight group, capability performing exercise test. Normality assumptions not met with main analysis: alternative=natural log transformed.	
Comparison groups	Sildenafil Low Dose v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	4.7
Variability estimate	Standard error of the mean
Dispersion value	2.7

Statistical analysis title	Sildenafil Medium Dose vs. Placebo
Statistical analysis description:	
Covariates: etiology, weight group, capability performing exercise test. Normality assumptions not met with main analysis: alternative=natural log transformed.	
Comparison groups	Sildenafil Medium Dose v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.3
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	2.4

Statistical analysis title	Sildenafil High Dose vs. Placebo
Statistical analysis description:	
Covariates: etiology, weight group, capability performing exercise test. Normality assumptions not met with main analysis: alternative=natural log transformed.	
Comparison groups	Sildenafil High Dose v Placebo
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.7
upper limit	-2.7
Variability estimate	Standard error of the mean
Dispersion value	2.3

Secondary: Percent Change From Baseline to Week 16 in: Respiratory Exchange Ratio (RER)	
End point title	Percent Change From Baseline to Week 16 in: Respiratory Exchange Ratio (RER)
End point description:	
RER is the ratio of carbon dioxide produced to oxygen consumed (VCO2/VO2). Percent change is ([Week 16 value minus Baseline value]/Baseline value) * 100% . ITT population, LOCF (end-of-treatment) approach for handling missing values.	
End point type	Secondary
End point timeframe:	
Baseline, Week 16	

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Placebo	Sildenafil High Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	26	29	27
Units: percent change				
arithmetic mean (standard deviation)	0.01 (± 11.69)	-3.96 (± 10.69)	-2.68 (± 10.37)	-2.01 (± 10.33)

End point values	Combined Sildenafil			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: percent change				
arithmetic mean (standard deviation)	-2.04 (± 10.87)			

Statistical analyses

Statistical analysis title	Combined Sildenafil vs. Placebo
Statistical analysis description: The model included the covariates etiology and weight group.	
Comparison groups	Combined Sildenafil v Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.795
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.07
upper limit	5.3
Variability estimate	Standard error of the mean
Dispersion value	2.36

Statistical analysis title	Sildenafil Low Dose vs. Placebo
Statistical analysis description: The model included the covariates etiology and weight group.	
Comparison groups	Sildenafil Low Dose v Placebo

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.31
upper limit	8.54
Variability estimate	Standard error of the mean
Dispersion value	2.99

Statistical analysis title	Sildenafil Medium Dose vs. Placebo
Statistical analysis description: The model included the covariates etiology and weight group.	
Comparison groups	Sildenafil Medium Dose v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.09
upper limit	4.5
Variability estimate	Standard error of the mean
Dispersion value	2.92

Statistical analysis title	Sildenafil High Dose vs. Placebo
Statistical analysis description: The model included the covariates etiology and weight group.	
Comparison groups	Sildenafil High Dose v Placebo
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.24
upper limit	6.28

Variability estimate	Standard error of the mean
Dispersion value	2.9

Secondary: Percent Change From Baseline to Week 16 in Time to Maximum Volume of Oxygen Consumed (VO2)	
End point title	Percent Change From Baseline to Week 16 in Time to Maximum Volume of Oxygen Consumed (VO2)
End point description: Time to maximum VO2 was assessed on the subset of subjects who are developmentally able to perform the exercise test. Percent change is [(value at Week 16 minus Baseline value)/Baseline value] * 100% . ITT population, LOCF (end-of-treatment) approach for handling missing values.	
End point type	Secondary
End point timeframe: Baseline, Week 16	

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Placebo	Sildenafil High Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	26	29	27
Units: percent change				
arithmetic mean (standard deviation)	15.21 (± 26.28)	15.97 (± 22.92)	4.56 (± 34.85)	11.16 (± 28.62)

End point values	Combined Sildenafil			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: percent change				
arithmetic mean (standard deviation)	14.04 (± 25.82)			

Statistical analyses

Statistical analysis title	Combined Sildenafil vs. Placebo
Statistical analysis description: The model included the covariates etiology and weight group.	
Comparison groups	Combined Sildenafil v Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.139
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	9.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.05
upper limit	21.54
Variability estimate	Standard error of the mean
Dispersion value	6.2

Statistical analysis title	Sildenafil Low Dose vs. Placebo
Statistical analysis description: The model included the covariates etiology and weight group.	
Comparison groups	Sildenafil Low Dose v Placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	10.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.21
upper limit	25.9
Variability estimate	Standard error of the mean
Dispersion value	7.84

Statistical analysis title	Sildenafil Medium Dose vs. Placebo
Statistical analysis description: The model included the covariates etiology and weight group.	
Comparison groups	Sildenafil Medium Dose v Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	11.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.78
upper limit	26.64
Variability estimate	Standard error of the mean
Dispersion value	7.67

Statistical analysis title	Sildenafil High Dose vs. Placebo

Statistical analysis description:	
The model included the covariates etiology and weight group.	
Comparison groups	Sildenafil High Dose v Placebo
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	5.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.16
upper limit	21.08
Variability estimate	Standard error of the mean
Dispersion value	7.62

Secondary: Change From Baseline to Week 16 in Pulmonary Vascular Resistance (PVR)

End point title	Change From Baseline to Week 16 in Pulmonary Vascular Resistance (PVR)
End point description:	
Change calculated as (mean PAP - pulmonary capillary wedge pressure [PCWP])/COpulm in PVR is observed value at Week 16 minus Baseline value. ITT population, using LOCF (end of treatment) approach for handling missing data.	
End point type	Secondary
End point timeframe:	
Baseline, Week 16	

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Placebo	Sildenafil High Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	36	49	50	67
Units: woods units				
arithmetic mean (standard deviation)	-0.1 (± 10.4)	-3.3 (± 10.5)	0.1 (± 11.8)	-5.2 (± 15.7)

End point values	Combined Sildenafil			
Subject group type	Subject analysis set			
Number of subjects analysed	152			
Units: woods units				
arithmetic mean (standard deviation)	-3.4 (± 13.1)			

Statistical analyses

Statistical analysis title	Combined Sildenafil vs. Placebo
Statistical analysis description: The model included the covariates etiology, weight group and capability of performing the exercise test.	
Comparison groups	Combined Sildenafil v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.172
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	1.3
Variability estimate	Standard error of the mean
Dispersion value	2.1

Statistical analysis title	Sildenafil Low Dose vs. Placebo
Statistical analysis description: The model included the covariates etiology, weight group and capability of performing the exercise test.	
Comparison groups	Sildenafil Low Dose v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	5.9
Variability estimate	Standard error of the mean
Dispersion value	2.9

Statistical analysis title	Sildenafil Medium Dose vs. Placebo
Statistical analysis description: The model included the covariates etiology, weight group and capability of performing the exercise test.	
Comparison groups	Sildenafil Medium Dose v Placebo

Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	1.7
Variability estimate	Standard error of the mean
Dispersion value	2.6

Statistical analysis title	Sildenafil High Dose vs. Placebo
Statistical analysis description: The model included the covariates etiology, weight group and capability of performing the exercise test.	
Comparison groups	Sildenafil High Dose v Placebo
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.3
upper limit	-0.7
Variability estimate	Standard error of the mean
Dispersion value	2.4

Secondary: Change From Baseline to Week 16 in Cardiac Index (CI)	
End point title	Change From Baseline to Week 16 in Cardiac Index (CI)
End point description: CI is observed value at Week 16 minus Baseline value. Calculated as cardiac output in systemic circulation (COsys) / body surface area (BSA). ITT population, using LOCF (end of treatment) approach for handling missing data.	
End point type	Secondary
End point timeframe: Baseline, Week 16	

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Placebo	Sildenafil High Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	49	52	68
Units: liters/minute/meters ^2				
arithmetic mean (standard deviation)	0.2 (± 1.17)	0.02 (± 1.44)	-0.6 (± 2.12)	0.24 (± 2.19)

End point values	Combined Sildenafil			
Subject group type	Subject analysis set			
Number of subjects analysed	154			
Units: liters/minute/meters ^2				
arithmetic mean (standard deviation)	0.16 (± 1.76)			

Statistical analyses

Statistical analysis title	Combined Sildenafil vs. Placebo
Statistical analysis description: The model included the covariates etiology, weight group and capability of performing the exercise test.	
Comparison groups	Combined Sildenafil v Placebo
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	1.34
Variability estimate	Standard error of the mean
Dispersion value	0.3

Statistical analysis title	Sildenafil Low Dose vs. Placebo
Statistical analysis description: The model included the covariates etiology, weight group and capability of performing the exercise test .	
Comparison groups	Sildenafil Low Dose v Placebo

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	1.52
Variability estimate	Standard error of the mean
Dispersion value	0.41

Statistical analysis title	Sildenafil Medium Dose vs. Placebo
Statistical analysis description: The model included the covariates etiology, weight group and capability of performing the exercise test .	
Comparison groups	Sildenafil Medium Dose v Placebo
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	1.35
Variability estimate	Standard error of the mean
Dispersion value	0.37

Statistical analysis title	Sildenafil High Dose vs. Placebo
Statistical analysis description: The model included the covariates etiology, weight group and capability of performing the exercise test.	
Comparison groups	Sildenafil High Dose v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	1.58

Variability estimate	Standard error of the mean
Dispersion value	0.35

Secondary: Change From Baseline to Week 16 in Right Atrial Pressure (RAP)

End point title	Change From Baseline to Week 16 in Right Atrial Pressure (RAP)

End point description:

RAP was measured using a pressure transducer positioned at the mid-axillary line with the subject in the supine position. Change is observed value at Week 16 minus Baseline value. ITT population, using LOCF (end of treatment) approach for missing data.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Placebo	Sildenafil High Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	55	56	71
Units: mm Hg				
arithmetic mean (standard deviation)	0.23 (± 3.95)	0.07 (± 4.1)	0.23 (± 4.48)	-0.96 (± 4.01)

End point values	Combined Sildenafil			
Subject group type	Subject analysis set			
Number of subjects analysed	165			
Units: mm Hg				
arithmetic mean (standard deviation)	-0.33 (± 4.04)			

Statistical analyses

Statistical analysis title	Combined Sildenafil vs. Placebo

Statistical analysis description:

The model included the covariates etiology, weight group and capability of performing the exercise test.

Comparison groups	Combined Sildenafil v Placebo
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.77
upper limit	0.77
Variability estimate	Standard error of the mean
Dispersion value	0.64

Statistical analysis title	Sildenafil Low Dose vs. Placebo
Statistical analysis description: The model included the covariates etiology, weight group and capability of performing the exercise test.	
Comparison groups	Sildenafil Low Dose v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.91
upper limit	1.57
Variability estimate	Standard error of the mean
Dispersion value	0.88

Statistical analysis title	Sildenafil Medium Dose vs. Placebo
Statistical analysis description: The model included the covariates etiology, weight group and capability of performing the exercise test.	
Comparison groups	Sildenafil Medium Dose v Placebo
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.73
upper limit	1.36
Variability estimate	Standard error of the mean
Dispersion value	0.78

Statistical analysis title	Sildenafil High Dose vs. Placebo
Statistical analysis description:	
The model included the covariates etiology, weight group and capability of performing the exercise test.	
Comparison groups	Sildenafil High Dose v Placebo
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.61
upper limit	0.33
Variability estimate	Standard error of the mean
Dispersion value	0.75

Secondary: Change From Baseline to Week 16 in Child Health Questionnaire Parent Form (CHQ-PF28), Physical Scale	
End point title	Change From Baseline to Week 16 in Child Health Questionnaire Parent Form (CHQ-PF28), Physical Scale
End point description:	
CHQ-PF28: validated generic Quality of Life (QoL) questionnaire for subjects >=5 years. Includes 12 domain scores of QoL concepts including physical functioning, social & school activities, mental health, parent/family concepts. Scores range 0-100: lower scores = lower QoL. Change is observed value at Week 16 minus Baseline value. ITT population, includes subjects >=5 years with a valid questionnaire available in the subject's first language.	
End point type	Secondary
End point timeframe:	
Baseline, Week 16	

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Placebo	Sildenafil High Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	29	40	43
Units: score on scale				
arithmetic mean (standard deviation)	14 (± 13.1)	9.8 (± 11.8)	8.3 (± 12)	5.9 (± 10.5)

End point values	Combined Sildenafil			
Subject group type	Subject analysis set			
Number of subjects analysed	103			
Units: score on scale				
arithmetic mean (standard deviation)	9.4 (± 12.1)			

Statistical analyses

Statistical analysis title	Combined Sildenafil vs. Placebo
Statistical analysis description:	
The covariates included in the model were baseline scale, etiology, weight and capability of performing the exercise test.	
Comparison groups	Combined Sildenafil v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.75
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.45
upper limit	3.21
Variability estimate	Standard error of the mean
Dispersion value	1.93

Statistical analysis title	Sildenafil Low Dose vs. Placebo
Comparison groups	Sildenafil Low Dose v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.21
upper limit	5.95
Variability estimate	Standard error of the mean
Dispersion value	2.57

Statistical analysis title	Sildenafil Medium Dose vs. Placebo
Comparison groups	Sildenafil Medium Dose v Placebo

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.68
upper limit	5.15
Variability estimate	Standard error of the mean
Dispersion value	2.49

Statistical analysis title	Sildenafil High Dose vs. Placebo
Comparison groups	Sildenafil High Dose v Placebo
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.37
upper limit	1.45
Variability estimate	Standard error of the mean
Dispersion value	2.23

Secondary: Change From Baseline to Week 16 in Child Health Questionnaire Parent Form (CHQ-PF28), Psychosocial Scales

End point title	Change From Baseline to Week 16 in Child Health Questionnaire Parent Form (CHQ-PF28), Psychosocial Scales

End point description:

CHQ-PF28: validated generic Quality of Life (QoL) questionnaire for subjects >=5 years. Includes 12 domain scores of QoL concepts including physical functioning, social & school activities, mental health, parent/family concepts. Scores range 0-100: lower scores = lower QoL. Change is observed value at Week 16 minus Baseline value. ITT population, includes subjects >=5 years with a valid questionnaire available in the subject's first language.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Placebo	Sildenafil High Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	29	40	43
Units: score on scale				
arithmetic mean (standard deviation)	5.1 (± 6.9)	4.1 (± 8.1)	5.6 (± 10.3)	4.3 (± 10)

End point values	Combined Sildenafil			
Subject group type	Subject analysis set			
Number of subjects analysed	103			
Units: score on scale				
arithmetic mean (standard deviation)	4.5 (± 8.6)			

Statistical analyses

Statistical analysis title	Combined Sildenafil vs. Placebo
Statistical analysis description:	
The covariates included in the model were baseline scale, etiology, weight and capability of performing the exercise test.	
Comparison groups	Combined Sildenafil v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.784
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.41
upper limit	2.58
Variability estimate	Standard error of the mean
Dispersion value	1.51

Statistical analysis title	Sildenafil Low Dose vs. Placebo
Comparison groups	Sildenafil Low Dose v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.41

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.49
upper limit	4.3
Variability estimate	Standard error of the mean
Dispersion value	1.97

Statistical analysis title	Sildenafil Medium Dose vs. Placebo
Comparison groups	Sildenafil Medium Dose v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.99
upper limit	1.77
Variability estimate	Standard error of the mean
Dispersion value	1.96

Statistical analysis title	Sildenafil High Dose vs. Placebo
Comparison groups	Sildenafil High Dose v Placebo
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.06
upper limit	3.97
Variability estimate	Standard error of the mean
Dispersion value	1.77

Secondary: Change From Baseline to Week 16 in World Health Organization (WHO) Pulmonary Hypertension (PH) Functional Class

End point title	Change From Baseline to Week 16 in World Health Organization (WHO) Pulmonary Hypertension (PH) Functional Class

End point description:	
WHO PH functional class definitions adapted from New York Heart Association Criteria for Functional Capacity and Therapeutic Class Definitions. Class I = PH without resulting limitation of physical activity, Class II = PH resulting in slight limitation of physical activity, Class III = PH resulting in marked limitation of physical activity, Class IV = PH with inability to carry out any physical activity without symptoms. Improved by 1 class = Class 4 to 3, Class 3 to 2, Class 2 to 1. Improved by 2 classes = Class 4 to 2, Class 3 to 1. Change is observed value at Week 16 minus Baseline value. ITT population.	
End point type	Secondary
End point timeframe:	
Baseline, Week 16	

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Placebo	Sildenafil High Dose
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	34	35	55
Units: Subjects				
number (not applicable)				
No change	25	24	31	38
Improved by 1 class	6	10	4	16
Improved by 2 classes	0	0	0	1

End point values	Combined Sildenafil			
Subject group type	Subject analysis set			
Number of subjects analysed	120			
Units: Subjects				
number (not applicable)				
No change	84			
Improved by 1 class	32			
Improved by 2 classes	1			

Statistical analyses

Statistical analysis title	Combined Sildenafil vs. Placebo
Statistical analysis description:	
Proportional odds method (LOCF). Model covariates were baseline WHO functional class, etiology, weight group and capability of performing the exercise test. Number of subjects displayed in the table is number of subjects with observations at Week 16. For the treatment comparison, results were based on LOCF analyses, with N=230.	
Comparison groups	Combined Sildenafil v Placebo
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.184
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	4.45

Statistical analysis title	Sildenafil Low Dose vs. Placebo

Statistical analysis description:

Proportional odds method (LOCF). Model covariates were baseline WHO functional class, etiology, weight group and capability of performing the exercise test. Number of subjects displayed in the table is number of subjects with observations at Week 16. For the treatment comparison, results were based on LOCF analyses, with N=100.

Comparison groups	Sildenafil Low Dose v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.409
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	2.01

Statistical analysis title	Sildenafil Medium Dose vs. Placebo

Statistical analysis description:

Proportional odds method (LOCF). Model covariates were baseline WHO functional class, etiology, weight group and capability of performing the exercise test. Number of subjects displayed in the table is number of subjects with observations at Week 16. For the treatment comparison, results were based on LOCF analyses, with N=114.

Comparison groups	Sildenafil Medium Dose v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.146
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	6.69

Statistical analysis title	Sildenafil High Dose vs. Placebo

Statistical analysis description:

Proportional odds method (LOCF). Model covariates were baseline WHO functional class, etiology, weight group and capability of performing the exercise test. Number of subjects displayed in the table is number of subjects with observations at Week 16. For the treatment comparison, results were based on LOCF analyses, with N=136.

Comparison groups	Sildenafil High Dose v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.56
upper limit	13.1

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 7 days after last dose of study drug	
Adverse event reporting additional description:	
EU BR specific AE tables were generated separately as per EU format. Latest coding dictionary has been used for EU BR tables.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects randomized to this arm received placebo TID (three times daily) for 112 days.	
Reporting group title	Sildenafil Low Dose
Reporting group description:	
Day 1-7 10 mg, followed by 10 mg TID (3 times daily) for body weights >20-45 kg and >45 kg, through Day 112. Modeling of the plasma concentrations for each dose level showed that the low and medium doses were predicted to be similar for the 8 to 20 kg subjects (i.e, subjects would receive the same dose because of the available tablet strengths); consequently there was no low dose for the >=8-20 kg weight group.	
Reporting group title	Combined Sildenafil
Reporting group description:	
This includes all subjects in the low, medium and high dose groups.	
Reporting group title	Sildenafil High Dose
Reporting group description:	
Day 1-7 10 mg, followed by 20, 40, 80 mg TID (3 times daily) for body weights >=8-20 kg, >20-45 kg, >45 kg respectively, through Day 112.	
Reporting group title	Sildenafil Medium Dose
Reporting group description:	
Day 1-7 10 mg, followed by 10, 20, 40 mg TID (3 times daily) for body weights >=8-20 kg, >20-45 kg, >45 kg respectively, through Day 112.	

Serious adverse events	Placebo	Sildenafil Low Dose	Combined Sildenafil
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 60 (3.33%)	1 / 42 (2.38%)	9 / 174 (5.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			

subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cyanosis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 42 (2.38%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 60 (0.00%)	1 / 42 (2.38%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 60 (1.67%)	0 / 42 (0.00%)	0 / 174 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 42 (2.38%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			

subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 60 (0.00%)	1 / 42 (2.38%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stridor			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	3 / 174 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 60 (1.67%)	0 / 42 (0.00%)	0 / 174 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	2 / 174 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Sildenafil High Dose	Sildenafil Medium Dose	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 77 (9.09%)	1 / 55 (1.82%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 77 (1.30%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyanosis			
subjects affected / exposed	0 / 77 (0.00%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 77 (0.00%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 77 (0.00%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			

subjects affected / exposed	0 / 77 (0.00%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 77 (1.30%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 77 (0.00%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stridor			
subjects affected / exposed	1 / 77 (1.30%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 77 (2.60%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 77 (0.00%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 77 (1.30%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Placebo	Sildenafil Low Dose	Combined Sildenafil
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 60 (51.67%)	21 / 42 (50.00%)	103 / 174 (59.20%)
Vascular disorders			
Flushing			
subjects affected / exposed	3 / 60 (5.00%)	1 / 42 (2.38%)	2 / 174 (1.15%)
occurrences (all)	8	6	7
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 60 (3.33%)	2 / 42 (4.76%)	6 / 174 (3.45%)
occurrences (all)	4	2	9
Headache			
subjects affected / exposed	8 / 60 (13.33%)	5 / 42 (11.90%)	23 / 174 (13.22%)
occurrences (all)	20	6	31
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 42 (0.00%)	2 / 174 (1.15%)
occurrences (all)	2	0	2
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 60 (3.33%)	2 / 42 (4.76%)	5 / 174 (2.87%)
occurrences (all)	4	2	6
Fatigue			
subjects affected / exposed	1 / 60 (1.67%)	2 / 42 (4.76%)	4 / 174 (2.30%)
occurrences (all)	4	2	4
Pyrexia			
subjects affected / exposed	1 / 60 (1.67%)	3 / 42 (7.14%)	19 / 174 (10.92%)
occurrences (all)	2	3	21
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	3 / 60 (5.00%)	1 / 42 (2.38%)	3 / 174 (1.72%)
occurrences (all)	6	1	3
Abdominal pain lower			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	3 / 174 (1.72%)
occurrences (all)	0	0	3
Abdominal pain upper			
subjects affected / exposed	1 / 60 (1.67%)	0 / 42 (0.00%)	6 / 174 (3.45%)
occurrences (all)	2	0	6
Diarrhoea			
subjects affected / exposed	4 / 60 (6.67%)	2 / 42 (4.76%)	12 / 174 (6.90%)
occurrences (all)	8	2	15
Dyspepsia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 42 (0.00%)	2 / 174 (1.15%)
occurrences (all)	2	0	2
Nausea			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	8 / 174 (4.60%)
occurrences (all)	0	0	8
Vomiting			
subjects affected / exposed	4 / 60 (6.67%)	3 / 42 (7.14%)	19 / 174 (10.92%)
occurrences (all)	10	7	27
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 60 (0.00%)	1 / 42 (2.38%)	3 / 174 (1.72%)
occurrences (all)	0	1	3
Erection increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	3 / 174 (1.72%)
occurrences (all)	0	0	3
Priapism			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	1 / 174 (0.57%)
occurrences (all)	0	0	1
Spontaneous penile erection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	3 / 174 (1.72%)
occurrences (all)	0	0	3
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	3 / 60 (5.00%)	2 / 42 (4.76%)	8 / 174 (4.60%)
occurrences (all)	8	2	9
Epistaxis			
subjects affected / exposed	2 / 60 (3.33%)	1 / 42 (2.38%)	6 / 174 (3.45%)
occurrences (all)	4	1	7
Haemoptysis			
subjects affected / exposed	1 / 60 (1.67%)	1 / 42 (2.38%)	3 / 174 (1.72%)
occurrences (all)	2	1	3
Nasal congestion			
subjects affected / exposed	2 / 60 (3.33%)	0 / 42 (0.00%)	0 / 174 (0.00%)
occurrences (all)	4	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	6 / 174 (3.45%)
occurrences (all)	0	0	6
Skin and subcutaneous tissue disorders			
Rash macular			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	3 / 174 (1.72%)
occurrences (all)	0	0	3
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	2 / 174 (1.15%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 60 (3.33%)	2 / 42 (4.76%)	2 / 174 (1.15%)
occurrences (all)	4	2	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 60 (1.67%)	1 / 42 (2.38%)	8 / 174 (4.60%)
occurrences (all)	2	1	9
Influenza			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	2 / 174 (1.15%)
occurrences (all)	0	0	2
Conjunctivitis			

subjects affected / exposed	2 / 60 (3.33%)	0 / 42 (0.00%)	2 / 174 (1.15%)
occurrences (all)	4	0	2
Laryngitis			
subjects affected / exposed	2 / 60 (3.33%)	1 / 42 (2.38%)	2 / 174 (1.15%)
occurrences (all)	4	1	2
Nasopharyngitis			
subjects affected / exposed	4 / 60 (6.67%)	3 / 42 (7.14%)	8 / 174 (4.60%)
occurrences (all)	10	3	11
Pharyngitis			
subjects affected / exposed	0 / 60 (0.00%)	3 / 42 (7.14%)	7 / 174 (4.02%)
occurrences (all)	0	4	8
Pneumonia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 42 (0.00%)	2 / 174 (1.15%)
occurrences (all)	0	0	2
Rhinitis			
subjects affected / exposed	1 / 60 (1.67%)	1 / 42 (2.38%)	5 / 174 (2.87%)
occurrences (all)	2	1	5
Upper respiratory tract infection			
subjects affected / exposed	4 / 60 (6.67%)	4 / 42 (9.52%)	18 / 174 (10.34%)
occurrences (all)	10	6	25
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 60 (3.33%)	1 / 42 (2.38%)	2 / 174 (1.15%)
occurrences (all)	4	1	2

Non-serious adverse events	Sildenafil High Dose	Sildenafil Medium Dose	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 77 (58.44%)	37 / 55 (67.27%)	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 77 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 77 (2.60%)	2 / 55 (3.64%)	
occurrences (all)	4	2	
Headache			

subjects affected / exposed	12 / 77 (15.58%)	6 / 55 (10.91%)	
occurrences (all)	14	11	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 77 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 77 (2.60%)	1 / 55 (1.82%)	
occurrences (all)	2	2	
Fatigue			
subjects affected / exposed	2 / 77 (2.60%)	0 / 55 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	8 / 77 (10.39%)	8 / 55 (14.55%)	
occurrences (all)	8	10	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 77 (2.60%)	0 / 55 (0.00%)	
occurrences (all)	2	0	
Abdominal pain lower			
subjects affected / exposed	3 / 77 (3.90%)	0 / 55 (0.00%)	
occurrences (all)	3	0	
Abdominal pain upper			
subjects affected / exposed	3 / 77 (3.90%)	3 / 55 (5.45%)	
occurrences (all)	3	3	
Diarrhoea			
subjects affected / exposed	7 / 77 (9.09%)	3 / 55 (5.45%)	
occurrences (all)	10	3	
Dyspepsia			
subjects affected / exposed	0 / 77 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	4 / 77 (5.19%)	4 / 55 (7.27%)	
occurrences (all)	4	4	
Vomiting			

subjects affected / exposed	11 / 77 (14.29%)	5 / 55 (9.09%)	
occurrences (all)	14	6	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 77 (1.30%)	1 / 55 (1.82%)	
occurrences (all)	1	1	
Erection increased			
subjects affected / exposed	2 / 77 (2.60%)	1 / 55 (1.82%)	
occurrences (all)	2	1	
Priapism			
subjects affected / exposed	1 / 77 (1.30%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Spontaneous penile erection			
subjects affected / exposed	1 / 77 (1.30%)	2 / 55 (3.64%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 77 (2.60%)	4 / 55 (7.27%)	
occurrences (all)	3	4	
Epistaxis			
subjects affected / exposed	3 / 77 (3.90%)	2 / 55 (3.64%)	
occurrences (all)	3	3	
Haemoptysis			
subjects affected / exposed	0 / 77 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
Nasal congestion			
subjects affected / exposed	0 / 77 (0.00%)	0 / 55 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	2 / 77 (2.60%)	4 / 55 (7.27%)	
occurrences (all)	2	4	
Skin and subcutaneous tissue disorders			
Rash macular			
subjects affected / exposed	1 / 77 (1.30%)	2 / 55 (3.64%)	
occurrences (all)	1	2	
Renal and urinary disorders			

Enuresis			
subjects affected / exposed	0 / 77 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 77 (0.00%)	0 / 55 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 77 (2.60%)	5 / 55 (9.09%)	
occurrences (all)	2	6	
Influenza			
subjects affected / exposed	0 / 77 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
Conjunctivitis			
subjects affected / exposed	2 / 77 (2.60%)	0 / 55 (0.00%)	
occurrences (all)	2	0	
Laryngitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	2 / 77 (2.60%)	3 / 55 (5.45%)	
occurrences (all)	3	5	
Pharyngitis			
subjects affected / exposed	1 / 77 (1.30%)	3 / 55 (5.45%)	
occurrences (all)	1	3	
Pneumonia			
subjects affected / exposed	0 / 77 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
Rhinitis			
subjects affected / exposed	1 / 77 (1.30%)	3 / 55 (5.45%)	
occurrences (all)	1	3	
Upper respiratory tract infection			
subjects affected / exposed	6 / 77 (7.79%)	8 / 55 (14.55%)	
occurrences (all)	7	12	
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	0 / 55 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2003	1) Safety follow-up days were increased from 30 days to 40 days for the subjects who were not electing to participate in the extension study. 2) Funduscopy was added instead of contrast sensitivity to the ocular safety measurement parameter. 3) Discontinuation criteria was updated to include unexpected pregnancy.
18 May 2004	1) Adverse event section was updated to include Abnormal test findings; Clinically significant symptoms and signs; Changes in physical examination findings; Hypersensitivity; Progression/worsening of underlying disease Drug overdose; Drug withdrawal; Drug abuse; Drug misuse; Drug interactions; Drug dependency; Extravasation; Exposure in utero. 2)Severity Assessment was distinctively defined to mild, moderate and severe. 3) Exposure in utero was defined.
27 September 2005	1) Causality assessment definition was added wherein the investigators assessment of causality must be provided for all adverse events (serious and non-serious). If the investigator's final determination of causality was unknown and the investigator does not know whether or not investigational product caused the event, then the event was handled as "related to investigational product" for reporting purposes. If the investigator's causality assessment was "unknown but not related to investigational product", this was clearly documented on trial records. 2) Serious adverse event Reporting Requirements were defined. 3) Clarification to the methodology for the Farnsworth-Munsell test and other ocular safety assessments were made.
07 July 2006	1) The amendment clarified the assessments that should be undertaken by subjects who permanently discontinue study drug (but have not withdrawn consent). 2) The addition of annual follow-up of subjects for the evaluation of survival status was done. 3) Addition of "male exposure, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure)" was done in in-utero section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22963001

http://www.ncbi.nlm.nih.gov/pubmed/22128226