Clinical trial results:
A Multicenter, Long-Term Extension Study to Assess Safety of Oral Sildenafil in the Treatment of Subjects Who Have Completed Study A1481131.

Summary

EudraCT number	2005-000963-25
Trial protocol	SE GB FI SK Outside EU/EEA
Global end of trial date	24 December 2012

Results information

Result version number	v1 (current)
This version publication date	25 May 2016
First version publication date	01 August 2015

Trial information

Trial identification

Sponsor protocol code	A1481156

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00159874
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	Clinical Trials gov Call center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Clinical Trials gov Call center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000671-PIP01-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	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	28 August 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 December 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the safety and tolerability of oral sildenafil in the chronic treatment of pediatric subjects with Pulmonary arterial hypertension (PAH).

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	13 January 2004
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	Sweden: 3
Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	Chile: 2
Country: Number of subjects enrolled	Japan: 1
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Colombia: 34
Country: Number of subjects enrolled	Guatemala: 25
Country: Number of subjects enrolled	India: 27
Country: Number of subjects enrolled	Malaysia: 8
Country: Number of subjects enrolled	United States: 39
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Canada: 1
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:

This extension study included 220 subjects at 31 sites. 14 subjects did not go from A1481131 (2006-002235-25) to A1481156. Subject from one center in Canada participated in base study A1481131 (2006-002235-25) but not in this extension study.

Pre-assignment

Screening details:

Sildenafil subjects remained in the same dose group as in study A1481131(2006-002235-25).Subjects randomized to placebo in 2006-002235-25 were rerandomized to sildenafil in A1481156. Placebo subjects in low weight category were rerandomized to medium or high dose(1:2) and other weight categories were re randomized to low, medium or high dose(1:1:1)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sildenafil Low/Low Dose

Arm description:

Subjects randomized to sildenafil low dose in study A1481131 (2006-002235-25) and in the extension study A1481156.

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 10 milligram (mg) thrice a day (TID) for body weights between 20-45 kilogram (kg) and >45 kg.

Arm title	Sildenafil Medium/ Medium Dose

Arm description:

Subjects randomized to sildenafil medium dose in study A1481131 (2006-002235-25) and in the extension study A1481156.

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 10, 20, 40 mg TID for body weights greater than or equal to (>=) 8-20 kg, > 20-45 kg, > 45 kg respectively.

Arm title	Sildenafil High/ High Dose

Arm description:

Subjects randomized to sildenafil high dose in study A1481131 (2006-002235-25) and in the extension study A1481156.

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 10 mg for body weight <=20 kg or 20, 40, 80 mg TID for body weights >= 8-20 kg, > 20-45 kg, > 45 kg respectively.

Arm title	Placebo/ Low Dose

Arm description:

Subjects randomized to placebo in study A1481131 (2006-002235-25) and randomized to sildenafil low dose in study A1481156.

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 10 mg TID for body weights between 20-45 kg and >45 kg.

Arm title	Placebo/ Medium Dose

Arm description:

Subjects randomized to placebo in study A1481131 (2006-002235-25) and randomized to sildenafil medium dose in study A1481156.

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 10, 20, 40 mg TID for body weights >= 8-20 kg, > 20-45 kg, > 45 kg respectively.

Arm title	Placebo/ High Dose

Arm description:

Subjects randomized to placebo in study A1481131 (2006-002235-25) and randomized to sildenafil high dose in study A1481156.

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 10 mg for body weight <=20 kg or 20, 40, 80 mg TID for body weights >= 8-20 kg, > 20-45 kg, > 45 kg respectively.

Arm title	Placebo Non-randomized

Arm description:

This group comprised those placebo subjects who either discontinued from base study A1481131 (2006-002235-25) or chose not to enter study A1481156 and hence not randomly assigned to a sildenafil dose group at the start of study A1481156.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose
Started	42	55	77
Completed	22	25	34
Not completed	20	30	43
Does Not Meet Entrance Criteria	1	-	1
Consent withdrawn by subject	2	6	8
Adverse Event	2	2	5
Death	3	8	15
Not specified	8	8	8
Pregnancy	1	1	-
Protocol Violation	-	5	2
Lost to follow-up	1	-	3
Lack of efficacy	2	-	1

Number of subjects in period 1	Placebo/ Low Dose	Placebo/ Medium Dose	Placebo/ High Dose
Started	13	19	23
Completed	7	11	11
Not completed	6	8	12
Does Not Meet Entrance Criteria	-	-	-
Consent withdrawn by subject	4	3	2
Adverse Event	1	1	2
Death	-	1	2
Not specified	-	2	1
Pregnancy	-	-	-
Protocol Violation	-	-	-
Lost to follow-up	-	1	2
Lack of efficacy	1	-	3

Number of subjects in period 1	Placebo Non-randomized
Started	5
Completed	0
Not completed	5
Does Not Meet Entrance Criteria	-
Consent withdrawn by subject	1
Adverse Event	-
Death	-
Not specified	3
Pregnancy	-

Protocol Violation	-
Lost to follow-up	1
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	Sildenafil Low/Low Dose
Reporting group description:	
Subjects randomized to sildenafil low dose in study A1481131 (2006-002235-25) and in the extension study A1481156.	
Reporting group title	Sildenafil Medium/ Medium Dose
Reporting group description:	
Subjects randomized to sildenafil medium dose in study A1481131 (2006-002235-25) and in the extension study A1481156.	
Reporting group title	Sildenafil High/ High Dose
Reporting group description:	
Subjects randomized to sildenafil high dose in study A1481131 (2006-002235-25) and in the extension study A1481156.	
Reporting group title	Placebo/ Low Dose
Reporting group description:	
Subjects randomized to placebo in study A1481131 (2006-002235-25) and randomized to sildenafil low dose in study A1481156.	
Reporting group title	Placebo/ Medium Dose
Reporting group description:	
Subjects randomized to placebo in study A1481131 (2006-002235-25) and randomized to sildenafil medium dose in study A1481156.	
Reporting group title	Placebo/ High Dose
Reporting group description:	
Subjects randomized to placebo in study A1481131 (2006-002235-25) and randomized to sildenafil high dose in study A1481156.	
Reporting group title	Placebo Non-randomized
Reporting group description:	
This group comprised those placebo subjects who either discontinued from base study A1481131 (2006-002235-25) or chose not to enter study A1481156 and hence not randomly assigned to a sildenafil dose group at the start of study A1481156.	

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

Reporting group values	Placebo/ Low Dose	Placebo/ Medium Dose	Placebo/ High Dose
Number of subjects	13	19	23

Age categorical Units: Subjects			
1-4	1	3	2
5-12	11	10	14
13-17	1	6	7
>=18	0	0	0
Gender categorical Units: Subjects			
Female	9	11	15
Male	4	8	8

Reporting group values	Placebo Non-randomized	Total	
Number of subjects	5	234	
Age categorical Units: Subjects			
1-4	1	35	
5-12	2	126	
13-17	2	73	
>=18	0	0	
Gender categorical Units: Subjects			
Female	3	145	
Male	2	89	

End points

End points reporting groups

Reporting group title	Sildenafil Low/Low Dose
Reporting group description:	
Subjects randomized to sildenafil low dose in study A1481131 (2006-002235-25) and in the extension study A1481156.	
Reporting group title	Sildenafil Medium/ Medium Dose
Reporting group description:	
Subjects randomized to sildenafil medium dose in study A1481131 (2006-002235-25) and in the extension study A1481156.	
Reporting group title	Sildenafil High/ High Dose
Reporting group description:	
Subjects randomized to sildenafil high dose in study A1481131 (2006-002235-25) and in the extension study A1481156.	
Reporting group title	Placebo/ Low Dose
Reporting group description:	
Subjects randomized to placebo in study A1481131 (2006-002235-25) and randomized to sildenafil low dose in study A1481156.	
Reporting group title	Placebo/ Medium Dose
Reporting group description:	
Subjects randomized to placebo in study A1481131 (2006-002235-25) and randomized to sildenafil medium dose in study A1481156.	
Reporting group title	Placebo/ High Dose
Reporting group description:	
Subjects randomized to placebo in study A1481131 (2006-002235-25) and randomized to sildenafil high dose in study A1481156.	
Reporting group title	Placebo Non-randomized
Reporting group description:	
This group comprised those placebo subjects who either discontinued from base study A1481131 (2006-002235-25) or chose not to enter study A1481156 and hence not randomly assigned to a sildenafil dose group at the start of study A1481156.	
Subject analysis set title	Sildenafil Low Dose
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects randomized to sildenafil low dose in study A1481131 (2006--002235--25) and continued in the low dose group in the extension study A1481156, and subjects randomized to placebo dose in study A1481131 (2006--002235--25) and randomized to sildenafil low dose in the extension study A1481156.	
Subject analysis set title	Sildenafil Medium Dose
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects randomized to sildenafil medium dose in study A1481131 (2006--002235--25) and continued in the medium dose group in the extension study A1481156, and subjects randomized to placebo dose in study A1481131 (2006--002235--25) and randomized to sildenafil medium dose in the extension study A1481156.	
Subject analysis set title	Sildenafil High Dose
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects randomized to sildenafil high dose in study A1481131 (2006--002235--25)and continued in the high dose group in the extension study A1481156, and subjects randomized to placebo dose in study A1481131 (2006--002235--25) and randomized to sildenafil high dose in the extension study A1481156.	

Primary: Number of Subjects Reporting at Least One Adverse Event

End point title	Number of Subjects Reporting at Least One Adverse Event[1]

End point description:

Safety was measured according to standard adverse event collection as described in the adverse event (AE) section of the results. Complete tables of the AEs according to the A1481156 treatment groups are provided in the reported AE section.The safety population consisted of all subjects who had taken at least one dose of study medication in A1481131 (2006-002235-25).

End point type	Primary

End point timeframe:

Up to Follow-Up visit (30 to 40 days after study completion or treatment discontinuation)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	55	77	13
Units: Subjects	41	55	73	13

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	23	5	
Units: Subjects	19	22	3	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting Treatment-related Adverse Events

End point title	Number of Subjects Reporting Treatment-related Adverse Events[2]

End point description:

Safety was measured according to standard AE collection as described in the AE section of the results. The safety population consisted of all subjects who had taken at least one dose of study medication in A1481131 (2006-002235-25).

End point type	Primary

End point timeframe:

Up to Follow-Up visit (30 to 40 days after study completion or treatment discontinuation)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	55	77	13
Units: Subjects	20	24	41	9

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	23	5	
Units: Subjects	9	11	3	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting at Least One Serious Adverse Event

End point title	Number of Subjects Reporting at Least One Serious Adverse Event[3]

End point description:

Safety was measured according to standard AE collection as described in the adverse event section of the results. Complete tables of the serious adverse events (SAEs) according to the A1481156 treatment groups are provided in the reported AE section. The safety population consisted of all subjects who had taken at least one dose of study medication in A1481131 (2006-002235-25).

End point type	Primary

End point timeframe:

Up to Follow-Up visit (30 to 40 days after study completion or treatment discontinuation)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	55	77	13
Units: subjects	13	33	38	1

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	23	5	
Units: subjects	4	10	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting Treatment-related Serious Adverse Events

End point title	Number of Subjects Reporting Treatment-related Serious Adverse Events[4]

End point description:

All SAEs regardless of treatment group or suspected relationship to study drug were reported. Investigators were to provide independent determination of possible causality of any SAE. The safety population consisted of all subjects who had taken at least one dose of study medication in A1481131 (2006-002235-25).

End point type	Primary

End point timeframe:

Up to Follow-Up visit (30 to 40 days after study completion or treatment discontinuation)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	55	77	13
Units: Subjects	1	1	4	0

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	23	5	
Units: Subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Deaths Reported in the Study Prior to the Data Monitoring Committee (DMC) Recommendation of Dose Down Titration

End point title	Number of Deaths Reported in the Study Prior to the Data Monitoring Committee (DMC) Recommendation of Dose Down Titration[5]

End point description:

Deaths were reported immediately independent of the circumstances or suspected cause at any time during the study through the last follow-up visit or 30 days after the last administration of study drug, whichever comes later.The safety population consisted of all subjects who had taken at least one dose of study medication in A1481131 (2006-002235-25).

End point type	Primary

End point timeframe:

Pre-DMC Recommendation dose down titration (04 August 2011)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	55	74	100	
Units: Subjects	5	10	22	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Deaths Reported During This Study

End point title	Number of Deaths Reported During This Study[6]

End point description:

Deaths were reported immediately independent of the circumstances or suspected cause at any time during the study through the last follow-up visit or 30 days after the last administration of study drug, whichever comes later. The safety population consisted of all subjects who had taken at least one dose of study medication in A1481131 (2006-002235-25).

End point type	Primary

End point timeframe:

Last follow-up visit or 30 days after the last administration of study drug

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	55	74	100	
Units: Subjects	5	13	24	

Statistical analyses

No statistical analyses for this end point

Primary: Discontinuation Due to Intolerability

End point title	Discontinuation Due to Intolerability[7]

End point description:

Subject who experienced drug-related intolerance, the subject's dose was reduced by 50 percent (%). If, after a dose reduction, the subject continued to appear intolerant, they were discontinued from study treatment. Safety population included all randomly assigned subjects who took at least 1 dose of study medication in Study A1481131 (2006-002235-25).

End point type	Primary

End point timeframe:

Throughout the treatment duration (median treatment duration 1689 to 1744 days)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	55	74	100	
Units: Subjects	2	1	3	

Statistical analyses

No statistical analyses for this end point

Primary: Down Titration in Dose Due to Intolerability

End point title	Down Titration in Dose Due to Intolerability[8]

End point description:

Based on review of the survival data, DMC concluded that the high dose of sildenafil was associated with a harmful effect on survival when compared to the low dose. The DMC also expressed concern as to the potential dose-response relationship between increasing dose and mortality. Therefore, on 04 August 2011, the DMC recommended discontinuation of the 40 mg and 80 mg TID doses, as well as the 20 mg TID dose in children with body weight less than (<=)20 kg. The protocol was amended per DMC recommendations. Safety population included all randomly assigned subjects who took at least 1 dose of study medication in Study A1481131 (2006-002235-25).

End point type	Primary

End point timeframe:

Pre-DMC recommendation (04 August 2011)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	55	77	13
Units: Subjects	0	0	3	0

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	

Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	23	5	
Units: Subjects	2	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Deterioration Post Baseline in Visual Acuity Safety Tests

End point title	Number of Subjects With Deterioration Post Baseline in Visual Acuity Safety Tests[9]

End point description:

Visual Acuity is measured either using the reduced Snellen test or via Teller cards, and was assessed in the left and right eyes separately. There were 9 lines on the reduced Snellen chart which were coded as 6/60, 6/36, 6/24, 6/18, 6/12, 6/9, 6/6, 6/5, 6/4 (where 6/60 was the easiest to read and 6/4 was the most difficult to read). If a subject experienced a visual AE the investigator was asked to perform additional ocular assessments either at the visit when the subject reported the visual Ae or at an unplanned visit. Safety population included all randomly assigned subjects who took at least 1 dose of study medication in Study A1481131 (2006-002235-25).

End point type	Primary

End point timeframe:

Week 36

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	55	77	13
Units: Subjects	10	11	17	0

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	23	5	
Units: Subjects	4	4	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Deterioration Post Baseline in Color Vision Monitoring Safety Tests

End point title	Number of Subjects With Deterioration Post Baseline in Color

	Vision Monitoring Safety Tests[10]

End point description:

Color vision was measured where appropriate via the Farnsworth-Munsell D-15 Hue test. This test was performed in both eyes simultaneously or just in a single specific eye. If using a single eye the same eye was used throughout the study. In case of young subjects an age-and-ability-appropriate evaluation such as the Ishihara Test for Unlettered Persons were conducted. Safety population included all randomly assigned subjects who took at least 1 dose of study medication in Study A1481131 (2006-002235-25).

End point type	Primary

End point timeframe:

Week 36

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	55	77	13
Units: Subjects	2	2	1	0

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	23	5	
Units: Subjects	0	1	1	

Statistical analyses

No statistical analyses for this end point

Primary: Pediatric Cognitive Development Status at Week 16

End point title	Pediatric Cognitive Development Status at Week 16[11]

End point description:

Subject's cognitive development status was assessed at A1481156 baseline (Week 16 in A1481131; 2006--002235--25) using the physician assessment questions. Assessment question (i.e., compared to other children the subject’s age group is this subject’s cognitive development limited?) included the following criteria: severely limited, moderately limited, mildly limited and not limited. Safety population included all randomly assigned subjects who took at least 1 dose of study medication in Study A1481131 (2006--002235--25). Subjects with observed data were included in table.

End point type	Primary

End point timeframe:

Week 16

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	55	77	13
Units: Subjects				
Severely Limited	2	4	2	0
Moderately Limited	5	6	8	1
Mildly Limited	6	7	12	1
Not limited	26	38	54	11

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	23	5	
Units: Subjects				
Severely Limited	1	1	0	
Moderately Limited	5	2	1	
Mildly Limited	1	1	0	
Not limited	12	19	1	

Statistical analyses

No statistical analyses for this end point

Primary: Pediatric Cognitive Development Status at Week 52

End point title	Pediatric Cognitive Development Status at Week 52[12][13]

End point description:

Subject's cognitive development status was assessed at Week 52 using the physician assessment questions. Assessment question (i.e., compared to other children the subject's age group is this subject's cognitive development limited?) included the following criteria: severely limited, moderately limited, mildly limited and not limited. Safety population included all randomly assigned subjects who took at least 1 dose of study medication in Study A1481131 (2006-002235-25). Subjects with observed data were included in table.

End point type	Primary

End point timeframe:

Week 52

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Placebo Non-randomized group was not assigned any treatment in the extension study. Hence no data was analyzed for it at Week 52.

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	55	77	13
Units: Subjects				
Severely limited	1	1	2	0
Moderately Limited	5	10	6	1
Mildly Limited	3	5	8	0
Not Limited	27	36	50	11

End point values	Placebo/ Medium Dose	Placebo/ High Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	23		
Units: Subjects				
Severely limited	0	0		
Moderately Limited	5	2		
Mildly Limited	3	3		
Not Limited	10	15		

Statistical analyses

No statistical analyses for this end point

Primary: Pediatric Motor Development Status at Week 16

End point title	Pediatric Motor Development Status at Week 16[14]

End point description:

Subject's motor development status was assessed at A1481156 baseline (Week 16 in A1481131; 2006-002235-25) using the physician assessment questions. Assessment question (i.e., compared to other children the subject's age group is this subject's motor development limited?) included the following criteria: severely limited, moderately limited, mildly limited and not limited. Safety population included all randomly assigned subjects who took at least 1 dose of study medication in Study A1481131 (2006-002235-25). Subjects with observed data were included in table.

End point type	Primary

End point timeframe:

Week 16

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	55	77	13
Units: Subjects				
Severely Limited	0	0	0	0
Moderately Limited	5	5	7	0

Mildly Limited	10	11	20	1
Not Limited	24	39	49	12

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	23	5	
Units: Subjects				
Severely Limited	1	0	0	
Moderately Limited	4	1	1	
Mildly Limited	5	2	0	
Not Limited	9	20	1	

Statistical analyses

No statistical analyses for this end point

Primary: Pediatric Motor Development Status at Week 52

End point title	Pediatric Motor Development Status at Week 52[15][16]

End point description:

Subject's motor development status was assessed at Week 52 using the physician assessment questions. Assessment question (i.e., compared to other children the subject's age group is this subject's motor development limited?) included the following criteria: severely limited, moderately limited, mildly limited and not limited. Safety population included all randomly assigned subjects who took at least 1 dose of study medication in Study A1481131 (2006-002235-25). Subjects with observed data were included in table.

End point type	Primary

End point timeframe:

Week 52

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Placebo Non-randomized group was not assigned any treatment in the extension study. Hence no data was analyzed for it at Week 52.

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	55	77	13
Units: Subjects				
Severely Limited	0	0	0	0
Moderately Limited	4	9	5	0
Mildly Limited	8	8	15	3
Not Limited	24	35	46	9

End point values	Placebo/ Medium Dose	Placebo/ High Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	23		
Units: Subjects				
Severely Limited	0	0		
Moderately Limited	2	0		
Mildly Limited	6	3		
Not Limited	10	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Peak Volume of Oxygen (VO2) Consumed at Year 1 Using a Bicycle Ergometry Cardiopulmonary Exercise Test (CPX)

End point title	Peak Volume of Oxygen (VO2) Consumed at Year 1 Using a Bicycle Ergometry Cardiopulmonary Exercise Test (CPX)

End point description:

Exercise Tolerance Test (CPX test) was performed on developmentally able subjects to determine peak volume of VO2 consumed. Subjects were assumed to be developmentally able if they had a CPX exercise assessment at any visit during study A1481131(N2006-002235-25). The CPX tests were performed as close to trough plasma levels of sildenafil as possible, i.e., prior to dosing and at least 4 hours after previous dose.If subjects were able to perform CPX test in Study A1481131(2006-002235-25), they were expected to be able to perform the exercise paradigm in extension study (A1481156) unless their clinical condition had deteriorated and investigator considered this was unsafe for the subject. An intent to treat (ITT) population included all randomized subjects who took at least 1 dose of study medication in base study and certain analyses were conducted at pre-specified time points:1, 2 years and 3, 4 and 5 years (where data quantity allowed) from A1481131(2006-002235-25) baseline.

End point type	Secondary

End point timeframe:

1 year

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	38	36	40	
Units: milliliter/Kilogram/minute (mL/kg/min)				
arithmetic mean (standard error)	19.97 (± 5.17)	18.69 (± 5.92)	17.93 (± 4.02)	

Statistical analyses

Statistical analysis title	Sildenafil Low Dose vs. Sildenafil Medium Dose

Statistical analysis description:

Analyses were performed using analysis of covariance (ANCOVA) with etiology, weight, day of assessment and baseline peak VO2 as the covariates. Least square mean difference of -7.02 was calculated as ' Sildenafil Medium Dose – Low Dose' for percent change from baseline in Peak VO2. For the treatment comparison, results were based on total 65 subjects, 33 from low dose and 32 from medium dose Sildenfil reporting groups.

Comparison groups	Sildenafil Low Dose v Sildenafil Medium Dose
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.253
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-7.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.13
upper limit	5.09
Variability estimate	Standard error of the mean
Dispersion value	6.1

Statistical analysis title	Sildenafil Low Dose vs. Sildenafil High Dose

Statistical analysis description:

Analyses were performed using ANCOVA with etiology, weight, day of assessment and baseline peak VO2 as the covariates. Least square mean difference of -9.84 was calculated as ' Sildenafil High Dose – Low Dose' for percent change from baseline in Peak VO2. For the treatment comparison, results were based on total 68 subjects, 33 from low dose and 35 from high dose Sildenafil reporting groups.

Comparison groups	Sildenafil High Dose v Sildenafil Low Dose
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	ANCOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-9.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.6
upper limit	1.93
Variability estimate	Standard error of the mean
Dispersion value	5.92

Statistical analysis title	Sildenafil Medium Dose vs. Sildenafil High Dose

Statistical analysis description:

Analyses were performed using ANCOVA with etiology, weight, day of assessment and baseline peak

VO2 as the covariates.Least square mean difference of -2.82 was calculated as ' Sildenafil High Dose – Medium Dose' for percent change from baseline in Peak VO2. For the treatment comparison, results were based on total 67 subjects, 32 from medium dose and 35 from high dose Sildenafil reporting groups.

Comparison groups	Sildenafil Medium Dose v Sildenafil High Dose
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-2.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.75
upper limit	9.11
Variability estimate	Standard error of the mean
Dispersion value	6.01

Secondary: Percentage Change From Baseline in Percent Predicted Peak VO2 at Year 1

End point title	Percentage Change From Baseline in Percent Predicted Peak VO2 at Year 1

End point description:

CPX test was performed on developmentally able subjects to measure the percent predicted peak VO2 at Week 16, and Year 1. Subjects were assumed to be developmentally able if they had a CPX exercise assessment at any visit during study A1481131 (2006-002235-25). CPX tests were performed as close to trough plasma levels of sildenafil as possible, i.e., prior to dosing and at least 4 hours after previous dose. If subjects were able to perform CPX test in Study A1481131(2006-002235-25), they were expected to be able to perform exercise paradigm in extension study (A1481156) unless their clinical condition had deteriorated and the investigator considered this was unsafe for the subject. ITT population. Only developmentally able subjects were used for this analysis. Here,99999 in the arithmetic mean and standard deviation signifies "Not estimable".Since number of subjects in the reporting group(Placebo Non-randomized) was 1, arithmetic mean and standard deviation could not be estimated.

End point type	Secondary

End point timeframe:

Baseline, Year 1

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	28	29	10
Units: percent				
arithmetic mean (standard deviation)	12.79 (± 22.71)	7.65 (± 34.57)	5.83 (± 23.54)	8.7 (± 25.99)

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	11	1	
Units: percent				
arithmetic mean (standard deviation)	0.2 (± 22.32)	-6.13 (± 7.46)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Time to Maximum VO2 at Year 1

End point title	Percent Change From Baseline in Time to Maximum VO2 at Year 1

End point description:

CPX testwas performed on developmentally able subjects to determine the time to maximum VO2. Subjects were assumed to be developmentally able if they had a CPX exercise assessment at any visit during study A1481131 (2006-002235-25). The CPX tests were performed as close to trough plasma levels of sildenafil as possible, i.e., prior to dosing and at least 4 hours after the previous dose. If subjects were able to perform the CPX test in Study A1481131 (2006-002235-25), they were expected to be able to perform the exercise paradigm in the extension study (A1481156) unless their clinical condition had deteriorated and the investigator considered this was unsafe for the subject. ITT population. Only developmentally able subjects were used for this analysis. Here, 99999 in the arithmetic mean and standard deviation signifies "Not estimable". Since number of subjects in the reporting group (Placebo Non-randomized) was 1, arithmetic mean and standard deviation could not be estimated.

End point type	Secondary

End point timeframe:

Baseline, Year 1

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	28	29	10
Units: percent				
arithmetic mean (standard deviation)	25.47 (± 35.67)	13.08 (± 33.42)	7.7 (± 33.01)	21.17 (± 57.25)

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	11	1	
Units: percent				
arithmetic mean (standard deviation)	36.68 (± 101.65)	-9.64 (± 15.21)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Respiratory Exchange Ratio at Year 1

End point title	Percent Change From Baseline in Respiratory Exchange Ratio at Year 1

End point description:

This is the ratio of carbon dioxide (CO2) produced to O2 consumed [VCO2/VO2]. Exercise Tolerance Test was performed on developmentally able subjects to determine the respiratory exchange ratio on week 16 and Year 1. Subjects were assumed to be developmentally able if they had a CPX exercise assessment at any visit during study A1481131 (2006-002235-25). An ITT population included all randomized subjects who took at least 1 dose of study medication in base study and certain analyses were conducted at pre-specified time points: 1, 2 years and 3, 4 and 5 years (where data quantity allowed) from A1481131 (2006-002235-25) baseline. Only developmentally able subjects were used for this analysis.Here, 99999 in the arithmetic mean and standard deviation signifies "Not estimable". Since number of subjects in the reporting group (Placebo Non-randomized) was 1, arithmetic mean and standard deviation could not be estimated.

End point type	Secondary

End point timeframe:

Baseline, Year 1

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	28	29	10
Units: percent				
arithmetic mean (standard deviation)	2.15 (± 8.73)	5.63 (± 13.37)	0.68 (± 11.5)	-3.69 (± 7.24)

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	11	1	
Units: percent				
arithmetic mean (standard deviation)	0.27 (± 11.04)	10.75 (± 17.76)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Start of Sildenafil in Total Ventilation (VE) to Year 1

End point title	Percent Change From Start of Sildenafil in Total Ventilation (VE) to Year 1

End point description:

CPX test was performed on developmentally able subjects to determine total ventilation. Subjects were assumed to be developmentally able if they had a CPX exercise assessment at any visit during study A1481131(2006-002235-25). The CPX tests were performed as close to trough plasma levels of sildenafil possible,i.e., prior to dosing and at least 4 hours after the previous dose. If subjects were able to perform CPX test in Study A1481131(2006-002235-25), they were expected to be able to perform the exercise paradigm in the extension study (A1481156) unless their clinical condition had deteriorated and investigator considered this was unsafe for the subject. ITT population included all randomized subjects who took at least 1 dose of study medication in base study and certain analyses were conducted at pre-specified time points: 1,2 years and 3,4 and 5 years(where data quantity allowed) from A1481131(2006-002235-25) baseline. Only developmentally able subjects were used for this analysis.

End point type	Secondary

End point timeframe:

Year 1

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	38	36	40	
Units: percent				
arithmetic mean (standard deviation)	14.29 (± 21.38)	12.38 (± 32.64)	11.8 (± 19.79)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in End Tidal Oxygen (O2) at Year 1

End point title	Percentage Change From Baseline in End Tidal Oxygen (O2) at Year 1

End point description:

CPX test was performed on developmentally able subjects to measure the End Tidal O2 at Year 1. Subjects were assumed to be developmentally able if they had CPX exercise assessment at any visit during study A1481131(2006-002235-25). The CPX tests were performed as close to trough plasma levels of sildenafil possible,i.e., prior to dosing and at least 4 hours after previous dose. If subjects were able to perform the CPX test in Study A148113(2006-002235-25), they were expected to be able to perform exercise paradigm in extension study (A1481156) unless their clinical condition had deteriorated and the investigator considered this was unsafe for the subject. ITT population included all randomized subjects who took at least 1 dose of study medication in base study and certain analyses were conducted at pre-specified time points: 1,2 years and 3,4, 5 years(where data quantity allowed) from A1481131(2006-002235-25) baseline. Only developmentally able subjects were used for this analysis.

End point type	Secondary

End point timeframe:

Baseline, Year 1

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	22	24	
Units: percent				
arithmetic mean (standard deviation)	0.59 (± 3.79)	-0.52 (± 3.55)	0.08 (± 3.68)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in End Tidal Carbon Dioxide (CO2) at Year 1

End point title	Percentage Change From Baseline in End Tidal Carbon Dioxide (CO2) at Year 1

End point description:

CPX test was performed on developmentally able subjects to measure the End Tidal CO2 at Year 1. Subjects were assumed to be developmentally able if they had a CPX exercise assessment at any visit during study A1481131(2006-002235-25). The CPX tests were performed as close to trough plasma levels of sildenafil possible,i.e., prior to dosing and at least 4 hours after previous dose. If subjects were able to perform the CPX test in Study A1481131(2006-002235-25), they were expected to be able to perform exercise paradigm in extension study (A1481156) unless their clinical condition had deteriorated and investigator considered this was unsafe for the subject. ITT population included all randomized subjects who took at least 1 dose of study medication in base study and certain analyses were conducted at pre-specified time points:1, 2 years and 3, 4, 5 years (where data quantity allowed) from A1481131(2006-002235-25) baseline. Only developmentally able subjects were used for this analysis.

End point type	Secondary

End point timeframe:

Baseline, Year 1

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	24	20	22	
Units: percent				
arithmetic mean (standard deviation)	7.83 (± 16.35)	7.68 (± 18.74)	13.16 (± 31.38)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in Anaerobic Threshold at Year 1

End point title	Percentage Change From Baseline in Anaerobic Threshold at Year 1

End point description:

CPX test was performed on developmentally able subjects to measure the anaerobic threshold at Week 16 and Year 1. Subjects were assumed to be developmentally able if they had a CPX exercise assessment at any visit during study A1481131(2006-002235-25). The CPX tests were performed as close to trough plasma levels of sildenafil as possible, i.e., prior to dosing and at least 4 hours after the previous dose. If subjects were able to perform the CPX test in Study A1481131(2006-002235-25), they were expected to be able to perform the exercise paradigm in the extension study (A1481156) unless their clinical condition had deteriorated and the investigator considered this was unsafe for the subject. ITT population. Only developmentally able subjects were used for this analysis. Here, 99999 in the arithmetic mean and standard deviation signifies "Not estimable". Since there was no observation at year 1 for reporting group (Placebo Non-randomized).

End point type	Secondary

End point timeframe:

Baseline, Year 1

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	27	28	10
Units: Percent Mean				
arithmetic mean (standard deviation)	-1.22 (± 23.06)	1.99 (± 29.54)	3.28 (± 29.36)	7.23 (± 12.31)

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	10	1	
Units: Percent Mean				
arithmetic mean (standard deviation)	-3.59 (± 28.29)	8.96 (± 32.55)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Shift in Changes From Start of Sildenafil in World Health Organization Pulmonary Hypertension (WHO PH) Functional Class by A1481156 Treatment Group at Year 1

End point title	Summary of Shift in Changes From Start of Sildenafil in World Health Organization Pulmonary Hypertension (WHO PH) Functional Class by A1481156 Treatment Group at Year 1

End point description:

The WHO PH functional classification was as follows: Class I: Subjects with PH but without resulting limitation of physical activity. Class II: Subjects with PH resulting in slight limitation of physical activity. Class III: Subjects with PH resulting in marked limitation of physical activity. Class IV: Subjects with PH with inability to carry out any physical activity without symptoms. Changes from baseline in functional class were summarized at Years 1, 2, 3 and 4. Numbers of subjects improving by 3 classes, improving

by 2 classes, improving by 1 class, not changing, worsening by 1 class, worsening by 2 classes or worsening by 3 classes from A1481131 baseline at Years 1, 2, 3 and 4 were evaluated. An ITT population included all randomly assigned subjects who took at least 1 dose of study medication in base study and certain analyses were conducted at pre-specified time points: 1, 2 years and 3, 4 and 5 years (where data quantity allowed) from A1481131 (2006-002235-25) baseline.

End point type	Secondary

End point timeframe:

Baseline, Year 1

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	55	74	100	
Units: Subjects				
Improved by 3 Classes	0	0	0	
Improved by 2 Classes	1	0	1	
Improved by 1 Class	13	15	19	
No change	30	48	64	
Worsened by 1 Class	4	6	3	
Worsened by 2 Classes	1	0	0	
Worsened by 3 Classes	0	0	0	
Discontinued	5	4	10	
Died	0	0	1	
Missing	1	1	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Shift in Changes From Start of Sildenafil in WHO PH Functional Class by A1481156 Treatment Group at Year 2

End point title	Summary of Shift in Changes From Start of Sildenafil in WHO PH Functional Class by A1481156 Treatment Group at Year 2

End point description:

The WHO PH functional classification was as follows: Class I: Subjects with PH but without resulting limitation of physical activity. Class II: Subjects with PH resulting in slight limitation of physical activity. Class III: Subjects with PH resulting in marked limitation of physical activity. Class IV: Subjects with PH with inability to carry out any physical activity without symptoms. Changes from baseline in functional class were summarized at Years 1, 2, 3, and 4. Numbers of subjects improving by 3 classes, improving by 2 classes, improving by 1 class, not changing, worsening by 1 class, worsening by 2 classes or worsening by 3 classes from A1481131 baseline at Years 1, 2, 3 and 4 were evaluated. An ITT population included all randomly assigned subjects who took at least 1 dose of study medication in base study and certain analyses were conducted at pre-specified time points: 1, 2 years and 3, 4 and 5 years (where data quantity allowed) from A1481131 (2006-002235-25) baseline.

End point type	Secondary

End point timeframe:

Baseline, Year 2

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	55	74	100	
Units: Subjects				
Improved by 3 Classes	0	0	0	
Improved by 2 Classes	0	1	1	
Improved by 1 Class	11	11	16	
No change	28	47	55	
Worsened by 1 Class	3	2	5	
Worsened by 2 Classes	0	0	0	
Worsened by 3 Classes	0	0	0	
Discontinued	9	9	16	
Died	1	2	5	
Missing	3	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Shift in Changes From Start of Sildenafil in WHO PH Functional Class by A1481156 Treatment Group at Year 3

End point title	Summary of Shift in Changes From Start of Sildenafil in WHO PH Functional Class by A1481156 Treatment Group at Year 3

End point description:

The WHO PH functional classification was as follows: Class I:Subjects with PH but without resulting limitation of physical activity. Class II:Subjects with PH resulting in slight limitation of physical activity. Class III:Subjects with PH resulting in marked limitation of physical activity. Class IV:Subjects with PH with inability to carry out any physical activity without symptoms. Changes from baseline in functional class were summarised at Years 1,2,3, and 4. Numbers of subjects improving by 3 classes, improving by 2 classes,improving by 1 class,not changing, worsening by 1 class,worsening by 2 classes or worsening by 3 classes from A1481131 (2006-002235-25)baseline at Years 1,2,3 and 4 were evaluated. An ITT population included all randomized subjects who took at least 1 dose of study medication in base study and certain analyses were conducted at pre-specified time points: 1, 2 years and 3, 4 and 5 years(where data quantity allowed)from A1481131 (2006-002235-25) baseline.

End point type	Secondary

End point timeframe:

Baseline, Year 3

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	55	74	100	
Units: Subjects				
Improved by 3 Classes	0	0	0	
Improved by 2 Classes	1	0	1	
Improved by 1 Class	11	16	17	
No change	21	36	44	
Worsened by 1 Class	3	3	5	
Worsened by 2 Classes	1	0	1	

Worsened by 3 Classes	0	0	0	
Discontinued	14	13	19	
Died	2	3	9	
Missing	2	3	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Shift in Changes From Start of Sildenafil in WHO PH Functional Class by A1481156 Treatment Group at Year 4

End point title	Summary of Shift in Changes From Start of Sildenafil in WHO PH Functional Class by A1481156 Treatment Group at Year 4

End point description:

The WHO PH functional classification was as follows: Class I : Subjects with PH but without resulting limitation of physical activity. Class II : Subjects with PH resulting in slight limitation of physical activity. Class III:Subjects with PH resulting in marked limitation of physical activity. Class IV:Subjects with PH with inability to carry out any physical activity without symptoms. Changes from baseline in functional class were summarised at Years 1, 2, 3, and 4. Numbers of subjects improving by 3 classes, improving by 2 classes, improving by 1 class, not changing, worsening by 1 class, worsening by 2 classes or worsening by 3 classes from A1481131 baseline at Years 1, 2, 3 and 4 were evaluated. An ITT population included all randomly assigned subjects who took at least 1 dose of study medication in base study and certain analyses were conducted at pre-specified time points: 1, 2 years and 3, 4 and 5 years (where data quantity allowed) from A1481131(2006-002235-25) baseline.

End point type	Secondary

End point timeframe:

Baseline, Year 4

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	55	74	100	
Units: Subjects				
Improved by 3 Classes	0	0	0	
Improved by 2 Classes	0	0	2	
Improved by 1 Class	13	14	16	
No change	15	29	41	
Worsened by 1 Class	6	4	5	
Worsened by 2 Classes	1	2	1	
Worsened by 3 Classes	0	0	0	
Discontinued	15	18	20	
Died	2	5	13	
Missing	3	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Additions From Baseline in Background Therapy up to the End of Study

End point title	Additions From Baseline in Background Therapy up to the End of Study

End point description:

This was defined as an addition or discontinuation in the class(es) of drugs used as background medication (e.g., anticoagulants, oxygen, diuretics, calcium channel blockers, and digoxin) compared to baseline of Study A1481131 (2006-002235-25). An ITT population included all randomly assigned subjects who took at least 1 dose of study medication in base study and certain analyses were conducted at pre-specified time points: 1, 2 years and 3, 4 and 5 years (where data quantity allowed) from A1481131 (2006-002235-25) baseline.

End point type	Secondary

End point timeframe:

Up to the end of study

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	55	77	13
Units: Subjects				
All Classes (N = 18, 26, 43, 7, 8, 14, 4)	6	5	11	2
At least one class (N = 42, 55, 77, 13, 19, 23, 5)	13	13	23	3

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	23	5	
Units: Subjects				
All Classes (N = 18, 26, 43, 7, 8, 14, 4)	1	2	1	
At least one class (N = 42, 55, 77, 13, 19, 23, 5)	5	2	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Child Health Questionnaire-Parent Form (CHQ-PF28) as Assessed by the Psychosocial Scale at Year 1

End point title	Change From Baseline in Child Health Questionnaire-Parent Form (CHQ-PF28) as Assessed by the Psychosocial Scale at Year 1

End point description:

CHQ:50-item, 15 subscale parent or legal guardian assessed instrument of child's physical, emotional, social well-being,and relative burden of disease on the parents; rated on Likert-type scale: range 0 to 100; higher scores indicate a more positive health status. Global indicators for Physical Health and

Psychosocial Health are weighted composites derived from subscale items using scoring algorithms(transformed scores); range 0 to 100:higher scores indicate more positive health status. ITT population included all randomized subjects who took at least 1 dose of study drug in base study; certain analyses were conducted at pre-specified time points:1, 2 years and 3, 4, 5 years(where data quantity allowed) from A1481131(2006-002235-25) baseline. Subjects >=5 years at baseline with questionnaire translated were included.Here, 99999 in the arithmetic mean and standard deviation signifies "Not estimable". Since there was no observation at year 1 for reporting group (Placebo Non-

End point type	Secondary

End point timeframe:

Baseline, Year 1

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34	30	45	11
Units: Units on a scale				
arithmetic mean (standard deviation)	5.63 (± 7.7)	3.92 (± 10.25)	3.48 (± 12.55)	13.74 (± 12.42)

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	15	1	
Units: Units on a scale				
arithmetic mean (standard deviation)	5.3 (± 9.3)	4.27 (± 12.19)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Child Health Questionnaire-Parent Form (CHQ-PF28) as Assessed by the Physical Scale at Year 1

End point title	Change From Baseline in Child Health Questionnaire-Parent Form (CHQ-PF28) as Assessed by the Physical Scale at Year 1

End point description:

CHQ: 50-item, 15 subscale parent or legal guardian assessed instrument of child's physical, emotional, social well-being,and relative burden of disease on the parents; rated on Likert-type scale:range 0 to 100; higher scores indicate a more positive health status. Global indicators for Physical Health and Psychosocial Health are weighted composites derived from subscale items using scoring algorithms(transformed scores); range 0 to 100:higher scores indicate more positive health status.ITT population included all randomized subjects who took at least 1 dose of study drug in base study; certain analyses were conducted at pre-specified time points:1, 2 years and 3, 4, 5 years(where data quantity allowed) from A1481131(2006-002235-25) baseline.Subjects >= 5 years at baseline with questionnaire translated were included. Here, 99999 in the arithmetic mean and standard deviation signifies "Not estimable". Since there was no observation at year 1 for reporting group (Placebo Non-

End point type	Secondary

End point timeframe:

Baseline, Year 1

End point values	Sildenafil Low/Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34	30	45	11
Units: Units on a scale				
arithmetic mean (standard deviation)	14.29 (± 11.06)	9.34 (± 13.45)	5.91 (± 10.17)	8.51 (± 13.27)

End point values	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	15	1	
Units: Units on a scale				
arithmetic mean (standard deviation)	9.86 (± 17.93)	4.64 (± 12.03)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subject (Parent) Global Assessment at Year 1

End point title	Subject (Parent) Global Assessment at Year 1

End point description:

The subject (parent) global assessment of disease severity was assessed at Year 1 in this extension study. The number and percentage of subjects markedly improved, moderately improved, mild improvement, no change, slightly worse, moderately worse, markedly worse were evaluated. Subjects who withdrew from study treatment after at least 10 weeks of treatment were requested to perform the global assessments. An ITT population included all randomly assigned subjects who took at least 1 dose of study medication in base study and certain analyses were conducted at pre-specified time points: 1, 2 years and 3, 4 and 5 years (where data quantity allowed) from A1481131 (2006-002235-25) baseline.

End point type	Secondary

End point timeframe:

Year 1

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	55	74	100	
Units: Subjects				
Markedly Improved	9	14	21	
Moderately Improved	13	27	26	
Mild Improvement	12	15	15	

No Change	13	6	21	
Slightly Worse	1	2	0	
Moderately Worse	0	1	0	
Markedly Worse	0	0	0	
Discontinued	5	4	10	
Died	0	0	1	
Missing	2	5	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Physician Global Assessment at Year 1

End point title	Physician Global Assessment at Year 1

End point description:

The physician global assessment of disease severity was assessed at Year 1 in this extension study. The number and percentage of subjects with markedly improved, moderately improved, mild improvement, no change, slightly worse, moderately worse, markedly worse were evaluated. Subjects who withdrew from study treatment after at least 10 weeks of treatment were requested to perform the global assessments. An ITT population included all randomly assigned subjects who took at least 1 dose of study medication in base study and certain analyses were conducted at pre-specified time points: 1, 2 years and 3, 4 and 5 years (where data quantity allowed) from A1481131 (2006--002235--25) baseline.

End point type	Secondary

End point timeframe:

Year 1

End point values	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	55	74	100	
Units: Subjects				
Markedly Improved	6	6	6	
Moderately Improved	8	18	27	
Mild Improvement	19	26	37	
No Change	15	16	17	
Slightly Worse	1	1	0	
Moderately Worse	0	1	0	
Markedly Worse	0	0	0	
Discontinued	5	4	10	
Died	0	0	1	
Missing	1	2	2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Follow--Up visit (30 to 40 days after study completion or treatment discontinuation)

Adverse event reporting additional description:

The same event may appear as both an AE/SAE. However, what is presented are distinct events. An event may be categorized as serious in 1 subject and as nonserious in another subject, or 1 subject may have experienced both a serious/nonserious event during the study. On treatment deaths during the study were reported in SAE section.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Sildenafil Low Dose

Reporting group description:

Subjects randomized to sildenafil low dose in study A1481131 (2006-002235-25) and continued in the lo w dose group in the extension study A1481156, and subjects randomized to placebo dose in study A1481131 (2006-002235-25) and randomized to sildenafil low dose in the extension study A1481156.

Reporting group title	Sildenafil Medium Dose

Reporting group description:

Subjects randomized to sildenafil medium dose in study A1481131 (2006-002235-25) and continued in t he medium dose group in the extension study A1481156, and subjects randomized to placebo dose in study A1481131 (2006-002235-25) and randomized to sildenafil medium dose in the extension study A1481156.

Reporting group title	Sildenafil High Dose

Reporting group description:

Subjects randomized to sildenafil high dose in study A1481131 (2006-002235-25) and continued in the high dose group in the extension study A1481156, and subjects randomized to placebo dose in study A1481131 (2006-002235-25) and randomized to sildenafil high dose in the extension study A1481156.

Serious adverse events	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 55 (25.45%)	37 / 74 (50.00%)	48 / 100 (48.00%)
number of deaths (all causes)	3	8	17
number of deaths resulting from adverse events			
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cardiac operation			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central venous catheterisation			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 55 (5.45%)	0 / 74 (0.00%)	2 / 100 (2.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gait disturbance			
subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	3 / 100 (3.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menorrhagia			

subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
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	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 55 (0.00%)	2 / 74 (2.70%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			

subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	2 / 100 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal turbinate hypertrophy			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
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 aspiration			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 55 (0.00%)	2 / 74 (2.70%)	7 / 100 (7.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary embolism			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	2 / 55 (3.64%)	4 / 74 (5.41%)	5 / 100 (5.00%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stridor			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar hypertrophy			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anorexia nervosa			
subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Catheterisation cardiac			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oxygen saturation decreased			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial pressure increased			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exposure via father			
subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Congenital, familial and genetic disorders			
Cystic fibrosis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eisenmenger's syndrome			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip dysplasia			
subjects affected / exposed	1 / 55 (1.82%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular septal defect			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
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			
subjects affected / exposed	2 / 55 (3.64%)	2 / 74 (2.70%)	6 / 100 (6.00%)
occurrences causally related to treatment / all	0 / 13	0 / 7	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	2 / 100 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Cyanosis			
subjects affected / exposed	1 / 55 (1.82%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	2 / 55 (3.64%)	3 / 74 (4.05%)	3 / 100 (3.00%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (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
Tachycardia paroxysmal			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	2 / 100 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 55 (1.82%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			

subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 55 (3.64%)	2 / 74 (2.70%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polycythaemia			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Corneal oedema			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Keratoconus			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vision blurred			
subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dental caries			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	3 / 100 (3.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 55 (0.00%)	2 / 74 (2.70%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			

subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (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
Vomiting			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Excessive granulation tissue			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Acute tonsillitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain abscess			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 55 (1.82%)	1 / 74 (1.35%)	3 / 100 (3.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 55 (1.82%)	1 / 74 (1.35%)	3 / 100 (3.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 55 (0.00%)	3 / 74 (4.05%)	3 / 100 (3.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis salmonella			

subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingivitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal viral infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			

subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 55 (1.82%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 55 (1.82%)	7 / 74 (9.46%)	10 / 100 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 11	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			

subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	6 / 100 (6.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 74 (0.00%)	3 / 100 (3.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Viral infection			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 55 (1.82%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypoalbuminaemia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 74 (1.35%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 55 (92.73%)	70 / 74 (94.59%)	87 / 100 (87.00%)
Investigations			
Blood pressure diastolic decreased			
subjects affected / exposed	3 / 55 (5.45%)	3 / 74 (4.05%)	4 / 100 (4.00%)
occurrences (all)	4	6	5
Weight decreased			
subjects affected / exposed	3 / 55 (5.45%)	2 / 74 (2.70%)	3 / 100 (3.00%)
occurrences (all)	5	2	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 55 (12.73%)	4 / 74 (5.41%)	10 / 100 (10.00%)
occurrences (all)	9	7	17
Headache			
subjects affected / exposed	18 / 55 (32.73%)	18 / 74 (24.32%)	26 / 100 (26.00%)
occurrences (all)	39	36	43
Syncope			
subjects affected / exposed	5 / 55 (9.09%)	7 / 74 (9.46%)	5 / 100 (5.00%)
occurrences (all)	7	12	7
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 55 (7.27%)	8 / 74 (10.81%)	7 / 100 (7.00%)
occurrences (all)	5	12	15
Chest pain			
subjects affected / exposed	5 / 55 (9.09%)	4 / 74 (5.41%)	12 / 100 (12.00%)
occurrences (all)	7	5	21
Pyrexia			
subjects affected / exposed	7 / 55 (12.73%)	16 / 74 (21.62%)	16 / 100 (16.00%)
occurrences (all)	9	40	31
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	3 / 55 (5.45%)	5 / 74 (6.76%)	6 / 100 (6.00%)
occurrences (all)	6	6	6
Conjunctivitis			

subjects affected / exposed	1 / 55 (1.82%)	3 / 74 (4.05%)	9 / 100 (9.00%)
occurrences (all)	1	3	13
Conjunctivitis allergic			
subjects affected / exposed	0 / 55 (0.00%)	4 / 74 (5.41%)	3 / 100 (3.00%)
occurrences (all)	0	4	3
Retinal vascular disorder			
subjects affected / exposed	1 / 55 (1.82%)	4 / 74 (5.41%)	6 / 100 (6.00%)
occurrences (all)	2	5	6
Visual impairment			
subjects affected / exposed	3 / 55 (5.45%)	1 / 74 (1.35%)	2 / 100 (2.00%)
occurrences (all)	3	1	3
Visual acuity reduced			
subjects affected / exposed	2 / 55 (3.64%)	4 / 74 (5.41%)	5 / 100 (5.00%)
occurrences (all)	3	7	9
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 55 (7.27%)	4 / 74 (5.41%)	13 / 100 (13.00%)
occurrences (all)	5	5	15
Abdominal pain upper			
subjects affected / exposed	3 / 55 (5.45%)	5 / 74 (6.76%)	9 / 100 (9.00%)
occurrences (all)	5	6	12
Dental caries			
subjects affected / exposed	6 / 55 (10.91%)	3 / 74 (4.05%)	2 / 100 (2.00%)
occurrences (all)	8	8	2
Diarrhoea			
subjects affected / exposed	10 / 55 (18.18%)	11 / 74 (14.86%)	16 / 100 (16.00%)
occurrences (all)	11	18	41
Dyspepsia			
subjects affected / exposed	3 / 55 (5.45%)	6 / 74 (8.11%)	5 / 100 (5.00%)
occurrences (all)	3	7	6
Gastritis			
subjects affected / exposed	2 / 55 (3.64%)	4 / 74 (5.41%)	5 / 100 (5.00%)
occurrences (all)	2	4	11
Vomiting			
subjects affected / exposed	14 / 55 (25.45%)	13 / 74 (17.57%)	24 / 100 (24.00%)
occurrences (all)	29	18	45

Nausea			
subjects affected / exposed	2 / 55 (3.64%)	5 / 74 (6.76%)	12 / 100 (12.00%)
occurrences (all)	3	7	14
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 55 (7.27%)	6 / 74 (8.11%)	6 / 100 (6.00%)
occurrences (all)	4	6	8
Cough			
subjects affected / exposed	11 / 55 (20.00%)	14 / 74 (18.92%)	17 / 100 (17.00%)
occurrences (all)	14	22	34
Haemoptysis			
subjects affected / exposed	3 / 55 (5.45%)	4 / 74 (5.41%)	2 / 100 (2.00%)
occurrences (all)	3	5	3
Epistaxis			
subjects affected / exposed	6 / 55 (10.91%)	12 / 74 (16.22%)	9 / 100 (9.00%)
occurrences (all)	8	18	18
Pulmonary arterial hypertension			
subjects affected / exposed	4 / 55 (7.27%)	4 / 74 (5.41%)	9 / 100 (9.00%)
occurrences (all)	4	5	9
Oropharyngeal pain			
subjects affected / exposed	3 / 55 (5.45%)	5 / 74 (6.76%)	5 / 100 (5.00%)
occurrences (all)	3	6	6
Rhinitis allergic			
subjects affected / exposed	3 / 55 (5.45%)	1 / 74 (1.35%)	2 / 100 (2.00%)
occurrences (all)	4	1	2
Pulmonary hypertension			
subjects affected / exposed	2 / 55 (3.64%)	4 / 74 (5.41%)	3 / 100 (3.00%)
occurrences (all)	4	6	3
Rhinorrhoea			
subjects affected / exposed	0 / 55 (0.00%)	5 / 74 (6.76%)	2 / 100 (2.00%)
occurrences (all)	0	7	2
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 55 (5.45%)	1 / 74 (1.35%)	3 / 100 (3.00%)
occurrences (all)	3	1	4
Psychiatric disorders			

Insomnia			
subjects affected / exposed	3 / 55 (5.45%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences (all)	3	0	3
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 55 (0.00%)	4 / 74 (5.41%)	0 / 100 (0.00%)
occurrences (all)	0	5	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 55 (5.45%)	0 / 74 (0.00%)	1 / 100 (1.00%)
occurrences (all)	4	0	1
Pain in extremity			
subjects affected / exposed	5 / 55 (9.09%)	3 / 74 (4.05%)	2 / 100 (2.00%)
occurrences (all)	6	4	6
Infections and infestations			
Bronchitis			
subjects affected / exposed	10 / 55 (18.18%)	16 / 74 (21.62%)	16 / 100 (16.00%)
occurrences (all)	27	38	28
Gastroenteritis			
subjects affected / exposed	4 / 55 (7.27%)	3 / 74 (4.05%)	7 / 100 (7.00%)
occurrences (all)	4	3	12
Bronchopneumonia			
subjects affected / exposed	0 / 55 (0.00%)	4 / 74 (5.41%)	2 / 100 (2.00%)
occurrences (all)	0	5	2
Ear infection			
subjects affected / exposed	3 / 55 (5.45%)	8 / 74 (10.81%)	4 / 100 (4.00%)
occurrences (all)	5	17	4
Laryngitis			
subjects affected / exposed	5 / 55 (9.09%)	1 / 74 (1.35%)	4 / 100 (4.00%)
occurrences (all)	8	4	4
Influenza			
subjects affected / exposed	10 / 55 (18.18%)	6 / 74 (8.11%)	12 / 100 (12.00%)
occurrences (all)	16	12	20
Otitis media			
subjects affected / exposed	2 / 55 (3.64%)	4 / 74 (5.41%)	4 / 100 (4.00%)
occurrences (all)	2	5	6

Nasopharyngitis			
subjects affected / exposed	15 / 55 (27.27%)	11 / 74 (14.86%)	17 / 100 (17.00%)
occurrences (all)	23	29	39
Pharyngitis			
subjects affected / exposed	16 / 55 (29.09%)	13 / 74 (17.57%)	13 / 100 (13.00%)
occurrences (all)	73	63	45
Pharyngitis streptococcal			
subjects affected / exposed	3 / 55 (5.45%)	3 / 74 (4.05%)	2 / 100 (2.00%)
occurrences (all)	4	5	4
Respiratory tract infection			
subjects affected / exposed	2 / 55 (3.64%)	4 / 74 (5.41%)	5 / 100 (5.00%)
occurrences (all)	2	4	7
Pneumonia			
subjects affected / exposed	2 / 55 (3.64%)	4 / 74 (5.41%)	0 / 100 (0.00%)
occurrences (all)	2	5	0
Rhinitis			
subjects affected / exposed	6 / 55 (10.91%)	10 / 74 (13.51%)	7 / 100 (7.00%)
occurrences (all)	9	19	9
Sinusitis			
subjects affected / exposed	2 / 55 (3.64%)	3 / 74 (4.05%)	8 / 100 (8.00%)
occurrences (all)	2	4	10
Tonsillitis			
subjects affected / exposed	9 / 55 (16.36%)	6 / 74 (8.11%)	13 / 100 (13.00%)
occurrences (all)	15	12	17
Upper respiratory tract infection			
subjects affected / exposed	9 / 55 (16.36%)	22 / 74 (29.73%)	37 / 100 (37.00%)
occurrences (all)	30	68	93
Urinary tract infection			
subjects affected / exposed	3 / 55 (5.45%)	2 / 74 (2.70%)	6 / 100 (6.00%)
occurrences (all)	3	2	7
Varicella			
subjects affected / exposed	3 / 55 (5.45%)	3 / 74 (4.05%)	4 / 100 (4.00%)
occurrences (all)	3	3	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2006	1. Made revisions to address the European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use guideline on the exposure to medicinal products during pregnancy, need for post-authorization data. 2. Made revisions to address the European Commission Decision in June 2006 that Revatio and Viagra (sildenafil citrate) should be contraindicated in the EU in subjects who have loss of vision in 1 eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous Phosphodiesterase 5 (PDE5) inhibitor exposure (new exclusion criterion added and safety information provided).
15 April 2009	1. Increased survival follow up frequency from yearly to every 3 months.
19 August 2011	1. The DMC concluded that in the context of this clinical trial the high dose of sildenafil was associated with a harmful effect on survival when compared to the low dose. The DMC also expressed concern as to the apparent dose response relationship between increasing dose and mortality, including when comparing the medium dose to the low dose. Therefore, the DMC recommended immediate discontinuation of the 40 mg and 80 mg doses, as well as the 20 mg dose in children with body weight <=20 kg. Those subjects on ''High Dose", irrespective of weight group, were to be immediately down-titrated based on the clear relationship between mortality and "High Dose" use. Advised physicians to exercise great caution in prescribing "Medium Dose" sildenafil for children weighing <45 kg, but to evaluate the responses of each subject individually in order to make an assessment of risk:benefit. The Summary of dosing based on weight groups is listed below: - For children <20 kg in weight: Either consider using alternative therapies if available, or use sildenafil in a dose no greater than 10 mg TID. - For children between 20 and 45 kg, consider using 'Low Dose" (10 mg TID) and under no circumstances should the dose exceed 20 mg TID. - For children greater than 45 kg a dose of 20 mg TID is the maximal dose that should be used. 2. Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy’s Law cases) and should always be considered important medical events. 3. If the trial subject’s partner becomes or is found to be pregnant while receiving the investigational product, the investigator should obtain agreement from the subject’s partner for the release of their pregnancy information for the purpose of safety monitoring.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported