



Clinical trial results:

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

Summary

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

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 |
| This version publication date | 22 April 2016 |
| First version publication date | 29 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | A1481131 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00159913 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000671-PIP01-09 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 27 November 2008 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 June 2008 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the efficacy of 16 weeks of chronic treatment with oral sildenafil in pediatric subjects, aged 1 to 17 years, with primary arterial hypertension (PAH).

Secondary objective were-

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 28 August 2003 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 6 |
| Children (2-11 years) | 129 |
| Adolescents (12-17 years) | 99 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

| | |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Sildenafil Low Dose |

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|------------------------|
| Arm title | Sildenafil Medium Dose |
|------------------|------------------------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|----------------------|
| Arm title | Sildenafil High Dose |
|------------------|----------------------|

Arm description:

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

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|------------|
| Investigational medicinal product name | Sildenafil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

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

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

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

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

Dosage and administration details:

Placebo was given TID for 112 days.

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

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

Baseline characteristics

Reporting groups

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

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

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

End points

End points reporting groups

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

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

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

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

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline, Week 16 | |

| End point values | Sildenafil Low Dose | Placebo | Combined Sildenafil | Sildenafil Medium Dose |
|--------------------------------------|----------------------|----------------------|----------------------|------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 24 | 29 | 77 | 26 |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | 6.44 (± 20.16) | 0.53 (± 15.91) | 10.24 (± 18.39) | 13.4 (± 19.5) |

| End point values | Sildenafil High Dose | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | 10.58 (± 15.51) | | | |

Statistical analyses

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|---|---------------------------------|
| Statistical analysis title | Combined Sildenafil vs. Placebo |
| Statistical analysis description: | |
| Analyses performed using analysis of covariance (ANCOVA) with etiology, weight and baseline peak VO2 as the covariates. No adjustments for multiple comparisons have been made. | |
| Comparison groups | Combined Sildenafil v Placebo |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.056 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 7.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.19 |
| upper limit | 15.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.98 |

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

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

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

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

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

| | |
|------------------------|---|
| End point title | Percent Change From Baseline in Peak Volume of Oxygen (VO2) Consumed : Per Protocol Population |
| End point description: | Peak VO2 (normalized for body weight) at trough plasma levels assessed by CPX testing (bicycle ergometry) at the end of treatment (Week 16 for those who completed the study). Percent change = [(week 16 value minus baseline mean)/mean at baseline]*100%. Per protocol population was used for the analysis. |
| End point type | Primary |
| End point timeframe: | |
| Baseline, Week 16 | |

| End point values | Sildenafil Low Dose | Placebo | Combined Sildenafil | Sildenafil Medium Dose |
|--------------------------------------|----------------------|----------------------|----------------------|------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 23 | 24 | 73 | 23 |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | 5.43 (± 20.69) | 2.81 (± 13.17) | 10.1 (± 19.87) | 15.66 (± 21.48) |

| End point values | Sildenafil High Dose | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | 9.34 (± 17.13) | | | |

Statistical analyses

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

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

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

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

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

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

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

| End point values | Sildenafil Low Dose | Placebo | Combined Sildenafil | Sildenafil Medium Dose |
|--------------------------------------|----------------------|----------------------|----------------------|------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 39 | 56 | 165 | 55 |
| Units: mm Hg | | | | |
| arithmetic mean (standard deviation) | 0.9 (\pm 12.3) | -0.4 (\pm 15.9) | -4.3 (\pm 13.9) | -3.9 (\pm 12) |

| End point values | Sildenafil High Dose | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 71 | | | |
| Units: mm Hg | | | | |
| arithmetic mean (standard deviation) | -7.4 (\pm 15.4) | | | |

Statistical analyses

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

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

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

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

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

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

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

| | |
|---|---|
| End point title | Change From Baseline to Week 16 in Pulmonary Vascular Resistance Index (PVRI) |
| End point description: PVRI equals Pulmonary Vascular Resistance (PVR) times Body Surface Area (BSA). Wood unit = 80 dyn*s/cm ⁵ . Change is observed value at Week 16 minus baseline value. ITT population, LOCF. | |
| End point type | Secondary |
| End point timeframe: Baseline, Week 16 | |

| End point values | Sildenafil Low Dose | Placebo | Combined Sildenafil | Sildenafil Medium Dose |
|--------------------------------------|----------------------|----------------------|----------------------|------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 36 | 50 | 152 | 49 |
| Units: wood units*m ² | | | | |
| arithmetic mean (standard deviation) | 0.1 (± 10.9) | 1.6 (± 9.2) | -3.2 (± 13) | -2.9 (± 11.5) |

| End point values | Sildenafil High Dose | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 67 | | | |
| Units: wood units*m ² | | | | |
| arithmetic mean (standard deviation) | -5.1 (± 14.7) | | | |

Statistical analyses

| | |
|--|---------------------------------|
| Statistical analysis title | Combined Sildenafil vs. Placebo |
| Statistical analysis description: Covariates: etiology, weight group, capability performing exercise test. Normality assumptions not met with main analysis: alternative=natural log transformed. | |
| Comparison groups | Combined Sildenafil v Placebo |

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

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

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

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

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

Secondary: Percent Change From Baseline to Week 16 in: Respiratory Exchange Ratio (RER)

| | |
|---|--|
| End point title | Percent Change From Baseline to Week 16 in: Respiratory Exchange Ratio (RER) |
| End point description: | |
| RER is the ratio of carbon dioxide produced to oxygen consumed (VCO ₂ /VO ₂). Percent change is ([Week 16 value minus Baseline value]/Baseline value) * 100% . ITT population, LOCF (end-of-treatment) approach for handling missing values. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 16 | |

| End point values | Sildenafil Low Dose | Placebo | Combined Sildenafil | Sildenafil Medium Dose |
|--------------------------------------|----------------------|----------------------|----------------------|------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 24 | 29 | 77 | 26 |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | 0.01 (\pm 11.69) | -2.68 (\pm 10.37) | -2.04 (\pm 10.87) | -3.96 (\pm 10.69) |

| End point values | Sildenafil High Dose | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | -2.01 (\pm 10.33) | | | |

Statistical analyses

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

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

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

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

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

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.9 |

Secondary: Percent Change From Baseline to Week 16 in Time to Maximum Volume of Oxygen Consumed (VO2)

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

| End point values | Sildenafil Low Dose | Placebo | Combined Sildenafil | Sildenafil Medium Dose |
|--------------------------------------|----------------------|----------------------|----------------------|------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 24 | 29 | 77 | 26 |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | 15.21 (± 26.28) | 4.56 (± 34.85) | 14.04 (± 25.82) | 15.97 (± 22.92) |

| End point values | Sildenafil High Dose | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | 11.16 (± 28.62) | | | |

Statistical analyses

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

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

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

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

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Sildenafil High Dose vs. Placebo |
|-----------------------------------|----------------------------------|

Statistical analysis description:

The model included the covariates etiology and weight group.

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

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

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

| End point values | Sildenafil Low Dose | Placebo | Combined Sildenafil | Sildenafil Medium Dose |
|--------------------------------------|----------------------|----------------------|----------------------|------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 36 | 50 | 152 | 49 |
| Units: woods units | | | | |
| arithmetic mean (standard deviation) | -0.1 (± 10.4) | 0.1 (± 11.8) | -3.4 (± 13.1) | -3.3 (± 10.5) |

| End point values | Sildenafil High Dose | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 67 | | | |
| Units: woods units | | | | |
| arithmetic mean (standard deviation) | -5.2 (± 15.7) | | | |

Statistical analyses

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

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

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

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

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

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

| End point values | Sildenafil Low Dose | Placebo | Combined Sildenafil | Sildenafil Medium Dose |
|--------------------------------------|----------------------|----------------------|----------------------|------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 | 52 | 154 | 49 |
| Units: liters/minute/meters ^2 | | | | |
| arithmetic mean (standard deviation) | 0.2 (± 1.17) | -0.6 (± 2.12) | 0.16 (± 1.76) | 0.02 (± 1.44) |

| End point values | Sildenafil High Dose | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 68 | | | |
| Units: liters/minute/meters ^2 | | | | |
| arithmetic mean (standard deviation) | 0.24 (± 2.19) | | | |

Statistical analyses

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

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

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

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

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

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.35 |

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

| | |
|--|--|
| End point title | Change From Baseline to Week 16 in Right Atrial Pressure (RAP) |
| End point description: RAP was measured using a pressure transducer positioned at the mid-axillary line with the subject in the supine position. Change is observed value at Week 16 minus Baseline value. ITT population, using LOCF (end of treatment) approach for missing data. | |
| End point type | Secondary |
| End point timeframe: Baseline, Week 16 | |

| End point values | Sildenafil Low Dose | Placebo | Combined Sildenafil | Sildenafil Medium Dose |
|--------------------------------------|----------------------|----------------------|----------------------|------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 39 | 56 | 165 | 55 |
| Units: mm Hg | | | | |
| arithmetic mean (standard deviation) | 0.23 (± 3.95) | 0.23 (± 4.48) | -0.33 (± 4.04) | 0.07 (± 4.1) |

| End point values | Sildenafil High Dose | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 71 | | | |
| Units: mm Hg | | | | |
| arithmetic mean (standard deviation) | -0.96 (± 4.01) | | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | Combined Sildenafil vs. Placebo |
| Statistical analysis description: The model included the covariates etiology, weight group and capability of performing the exercise test. | |
| Comparison groups | Combined Sildenafil v Placebo |
| Number of subjects included in analysis | 221 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.44 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.5 |

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

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

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

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

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

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

| End point values | Sildenafil Low Dose | Placebo | Combined Sildenafil | Sildenafil Medium Dose |
|--------------------------------------|----------------------|----------------------|----------------------|------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 31 | 40 | 103 | 29 |
| Units: score on s scale | | | | |
| arithmetic mean (standard deviation) | 14 (\pm 13.1) | 8.3 (\pm 12) | 9.4 (\pm 12.1) | 9.8 (\pm 11.8) |

| End point values | Sildenafil High Dose | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 43 | | | |
| Units: score on s scale | | | | |
| arithmetic mean (standard deviation) | 5.9 (\pm 10.5) | | | |

Statistical analyses

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

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

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

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

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

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

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

| End point values | Sildenafil Low Dose | Placebo | Combined Sildenafil | Sildenafil Medium Dose |
|--------------------------------------|----------------------|----------------------|----------------------|------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 31 | 40 | 103 | 29 |
| Units: score on scale | | | | |
| arithmetic mean (standard deviation) | 5.1 (\pm 6.9) | 5.6 (\pm 10.3) | 4.5 (\pm 8.6) | 4.1 (\pm 8.1) |

| End point values | Sildenafil High Dose | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 43 | | | |
| Units: score on scale | | | | |
| arithmetic mean (standard deviation) | 4.3 (\pm 10) | | | |

Statistical analyses

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

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

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

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

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

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

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

End point description:

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

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 16 | |

| End point values | Sildenafil Low Dose | Placebo | Combined Sildenafil | Sildenafil Medium Dose |
|-----------------------------|----------------------|----------------------|----------------------|------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 31 | 35 | 120 | 34 |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| No change | 25 | 31 | 84 | 24 |
| Improved by 1 class | 6 | 4 | 32 | 10 |
| Improved by 2 classes | 0 | 0 | 1 | 0 |

| End point values | Sildenafil High Dose | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 55 | | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| No change | 38 | | | |
| Improved by 1 class | 16 | | | |
| Improved by 2 classes | 1 | | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Combined Sildenafil vs. Placebo |
|----------------------------|---------------------------------|

Statistical analysis description:

Proportional odds method (LOCF). Model covariates were baseline WHO functional class, etiology, weight group and capability of performing the exercise test. Number of subjects displayed in the table is number of subjects with observations at Week 16. For the treatment comparison, results were based on LOCF analyses, with N=230.

| | |
|---|-------------------------------|
| Comparison groups | Combined Sildenafil v Placebo |
| Number of subjects included in analysis | 155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.184 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.83 |

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

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | Sildenafil Low Dose vs. Placebo |
|-----------------------------------|---------------------------------|

Statistical analysis description:

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

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

| | |
|-----------------------------------|------------------------------------|
| Statistical analysis title | Sildenafil Medium Dose vs. Placebo |
|-----------------------------------|------------------------------------|

Statistical analysis description:

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

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

| | |
|---|----------------------------------|
| Statistical analysis title | Sildenafil High Dose vs. Placebo |
| Statistical analysis description: | |
| Proportional odds method (LOCF). Model covariates were baseline WHO functional class, etiology, weight group and capability of performing the exercise test. Number of subjects displayed in the table is number of subjects with observations at Week 16. For the treatment comparison, results were based on LOCF analyses, with N=136. | |
| Comparison groups | Sildenafil High Dose v Placebo |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.006 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 4.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.56 |
| upper limit | 13.1 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 7 days after last dose of study drug

Adverse event reporting additional description:

EU BR specific AE tables were generated separately as per EU format. Latest coding dictionary has been used for EU BR tables.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects randomized to this arm received placebo TID (three times daily) for 112 days.

| | |
|-----------------------|---------------------|
| Reporting group title | Sildenafil Low Dose |
|-----------------------|---------------------|

Reporting group description:

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

| | |
|-----------------------|------------------------|
| Reporting group title | Sildenafil Medium Dose |
|-----------------------|------------------------|

Reporting group description:

Day 1-7 10 mg, followed by 10, 20, 40 mg TID (3 times daily) for body weights >= 8-20 kg, > 20-45 kg, > 45 kg respectively, through Day 112.

| | |
|-----------------------|----------------------|
| Reporting group title | Sildenafil High Dose |
|-----------------------|----------------------|

Reporting group description:

Day 1-7 10 mg, followed by 20, 40, 80 mg TID (3 times daily) for body weights >= 8-20 kg, > 20-45 kg, > 45 kg respectively, through Day 112.

| | |
|-----------------------|---------------------|
| Reporting group title | Combined Sildenafil |
|-----------------------|---------------------|

Reporting group description:

This includes all subjects in the low, medium and high dose groups.

| Serious adverse events | Placebo | Sildenafil Low Dose | Sildenafil Medium Dose |
|---|----------------|---------------------|------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 1 / 42 (2.38%) | 1 / 55 (1.82%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 42 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 42 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cyanosis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 42 (2.38%) | 0 / 55 (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 / 60 (0.00%) | 0 / 42 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 42 (2.38%) | 0 / 55 (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 | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 42 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 42 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 42 (2.38%) | 0 / 55 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchospasm | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 42 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 42 (2.38%) | 0 / 55 (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 |
| Stridor | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 42 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 42 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 42 (0.00%) | 1 / 55 (1.82%) |
| 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 bacterial | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 42 (0.00%) | 0 / 55 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 42 (0.00%) | 1 / 55 (1.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Sildenafil High Dose | Combined Sildenafil | |
|---|----------------------|---------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 77 (9.09%) | 9 / 174 (5.17%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

| | | | |
|--|----------------|-----------------|--|
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 174 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 174 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cyanosis | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 174 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 174 (0.57%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 174 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 174 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 0 / 174 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematochezia | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 174 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 174 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 1 / 174 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stridor | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 174 (0.57%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 174 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 3 / 174 (1.72%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 0 / 174 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 2 / 174 (1.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | Sildenafil Low Dose | Sildenafil Medium Dose |
|--|---|---|---|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 31 / 60 (51.67%) | 21 / 42 (50.00%) | 37 / 55 (67.27%) |
| Vascular disorders Flushing subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 8 | 1 / 42 (2.38%) 6 | 1 / 55 (1.82%) 1 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 4 8 / 60 (13.33%) 20 | 2 / 42 (4.76%) 2 5 / 42 (11.90%) 6 | 2 / 55 (3.64%) 2 6 / 55 (10.91%) 11 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 2 | 0 / 42 (0.00%) 0 | 2 / 55 (3.64%) 2 |
| General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 4 1 / 60 (1.67%) 4 1 / 60 (1.67%) 2 | 2 / 42 (4.76%) 2 2 / 42 (4.76%) 2 3 / 42 (7.14%) 3 | 1 / 55 (1.82%) 2 0 / 55 (0.00%) 0 8 / 55 (14.55%) 10 |
| Gastrointestinal disorders | | | |

| | | | |
|---|----------------------|---------------------|---------------------|
| Abdominal pain subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 6 | 1 / 42 (2.38%) 1 | 0 / 55 (0.00%) 0 |
| Abdominal pain lower subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 55 (0.00%) 0 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 2 | 0 / 42 (0.00%) 0 | 3 / 55 (5.45%) 3 |
| Diarrhoea subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 8 | 2 / 42 (4.76%) 2 | 3 / 55 (5.45%) 3 |
| Dyspepsia subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 2 | 0 / 42 (0.00%) 0 | 2 / 55 (3.64%) 2 |
| Nausea subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 42 (0.00%) 0 | 4 / 55 (7.27%) 4 |
| Vomiting subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 10 | 3 / 42 (7.14%) 7 | 5 / 55 (9.09%) 6 |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 42 (2.38%) 1 | 1 / 55 (1.82%) 1 |
| Erection increased subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 55 (1.82%) 1 |
| Priapism subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 55 (0.00%) 0 |
| Spontaneous penile erection subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 42 (0.00%) 0 | 2 / 55 (3.64%) 2 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Cough subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 8 | 2 / 42 (4.76%) 2 | 4 / 55 (7.27%) 4 |
| Epistaxis subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 4 | 1 / 42 (2.38%) 1 | 2 / 55 (3.64%) 3 |
| Haemoptysis subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 2 | 1 / 42 (2.38%) 1 | 2 / 55 (3.64%) 2 |
| Nasal congestion subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 4 | 0 / 42 (0.00%) 0 | 0 / 55 (0.00%) 0 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 42 (0.00%) 0 | 4 / 55 (7.27%) 4 |
| Skin and subcutaneous tissue disorders Rash macular subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 42 (0.00%) 0 | 2 / 55 (3.64%) 2 |
| Renal and urinary disorders Enuresis subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 42 (0.00%) 0 | 2 / 55 (3.64%) 2 |
| Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 4 | 2 / 42 (4.76%) 2 | 0 / 55 (0.00%) 0 |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 2 | 1 / 42 (2.38%) 1 | 5 / 55 (9.09%) 6 |
| Influenza subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 0 / 42 (0.00%) 0 | 2 / 55 (3.64%) 2 |
| Conjunctivitis | | | |

| | | | |
|------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 2 / 60 (3.33%) | 0 / 42 (0.00%) | 0 / 55 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Laryngitis | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 1 / 42 (2.38%) | 0 / 55 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 3 / 42 (7.14%) | 3 / 55 (5.45%) |
| occurrences (all) | 10 | 3 | 5 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 3 / 42 (7.14%) | 3 / 55 (5.45%) |
| occurrences (all) | 0 | 4 | 3 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 42 (0.00%) | 2 / 55 (3.64%) |
| occurrences (all) | 0 | 0 | 2 |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 42 (2.38%) | 3 / 55 (5.45%) |
| occurrences (all) | 2 | 1 | 3 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 4 / 42 (9.52%) | 8 / 55 (14.55%) |
| occurrences (all) | 10 | 6 | 12 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 1 / 42 (2.38%) | 0 / 55 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |

| Non-serious adverse events | Sildenafil High Dose | Combined Sildenafil | |
|---|----------------------|---------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 45 / 77 (58.44%) | 103 / 174 (59.20%) | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 2 / 174 (1.15%) | |
| occurrences (all) | 0 | 7 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 6 / 174 (3.45%) | |
| occurrences (all) | 4 | 9 | |
| Headache | | | |

| | | | |
|--|---|--|--|
| subjects affected / exposed occurrences (all) | 12 / 77 (15.58%) 14 | 23 / 174 (13.22%) 31 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 2 / 174 (1.15%) 2 | |
| General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) | 2 / 77 (2.60%) 2 2 / 77 (2.60%) 2 8 / 77 (10.39%) 8 | 5 / 174 (2.87%) 6 4 / 174 (2.30%) 4 19 / 174 (10.92%) 21 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain lower subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting | 2 / 77 (2.60%) 2 3 / 77 (3.90%) 3 3 / 77 (3.90%) 3 7 / 77 (9.09%) 10 0 / 77 (0.00%) 0 4 / 77 (5.19%) 4 | 3 / 174 (1.72%) 3 3 / 174 (1.72%) 3 6 / 174 (3.45%) 6 12 / 174 (6.90%) 15 2 / 174 (1.15%) 2 8 / 174 (4.60%) 8 | |

| | | | |
|--|------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 11 / 77 (14.29%) 14 | 19 / 174 (10.92%) 27 | |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 3 / 174 (1.72%) | |
| occurrences (all) | 1 | 3 | |
| Erection increased | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 3 / 174 (1.72%) | |
| occurrences (all) | 2 | 3 | |
| Priapism | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 1 / 174 (0.57%) | |
| occurrences (all) | 1 | 1 | |
| Spontaneous penile erection | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 3 / 174 (1.72%) | |
| occurrences (all) | 1 | 3 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 8 / 174 (4.60%) | |
| occurrences (all) | 3 | 9 | |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 77 (3.90%) | 6 / 174 (3.45%) | |
| occurrences (all) | 3 | 7 | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 3 / 174 (1.72%) | |
| occurrences (all) | 0 | 3 | |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 77 (0.00%) | 0 / 174 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 2 / 77 (2.60%) | 6 / 174 (3.45%) | |
| occurrences (all) | 2 | 6 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash macular | | | |
| subjects affected / exposed | 1 / 77 (1.30%) | 3 / 174 (1.72%) | |
| occurrences (all) | 1 | 3 | |
| Renal and urinary disorders | | | |

| | | | |
|--|---------------------|-------------------------|--|
| Enuresis subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 2 / 174 (1.15%) 2 | |
| Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 2 / 174 (1.15%) 2 | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 2 / 77 (2.60%) 2 | 8 / 174 (4.60%) 9 | |
| Influenza subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 2 / 174 (1.15%) 2 | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 2 / 77 (2.60%) 2 | 2 / 174 (1.15%) 2 | |
| Laryngitis subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 2 / 174 (1.15%) 2 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 77 (2.60%) 3 | 8 / 174 (4.60%) 11 | |
| Pharyngitis subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 7 / 174 (4.02%) 8 | |
| Pneumonia subjects affected / exposed occurrences (all) | 0 / 77 (0.00%) 0 | 2 / 174 (1.15%) 2 | |
| Rhinitis subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 5 / 174 (2.87%) 5 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 6 / 77 (7.79%) 7 | 18 / 174 (10.34%) 25 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|---------------------|----------------------|--|
| Decreased appetite subjects affected / exposed occurrences (all) | 1 / 77 (1.30%) 1 | 2 / 174 (1.15%) 2 | |
|--|---------------------|----------------------|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

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

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