



## Clinical trial results:

### A Phase 3, Multi-Center, Open-Label Study To Confirm Safety, Efficacy And Tolerability Of Sildenafil Citrate 20 Mg Three Times a Day (TID) In Subjects With Pulmonary Arterial Hypertension

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2014-004167-20   |
| Trial protocol           | Outside EU/EEA   |
| Global end of trial date | 18 February 2009 |

#### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 17 June 2016  |
| First version publication date | 04 July 2015  |
| Version creation reason        | • Correction of full data set<br>typographical error was observed in one of the outcome<br>measure titles |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | A1481252 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00454207 |
| 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               | ClinicalTrials.gov Call Center, Pfizer Inc, 001 800-718-1021,<br>ClinicalTrials.govCallCenter@pfizer.com |
| Scientific contact           | ClinicalTrials.gov Call Center, Pfizer Inc, 001 800-718-1021,<br>ClinicalTrials.govCallCenter@pfizer.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 26 August 2009   |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 18 February 2009 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To confirm the safety of sildenafil 20 milligram (mg) three time a day (TID) orally administered to Pulmonary Arterial Hypertension (PAH) subjects. To confirm the efficacy after 12 Weeks of treatment of sildenafil 20 mg TID orally administered to PAH subjects (Part I).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 16 April 2007 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Japan: 44 |
| Worldwide total number of subjects   | 44        |
| EEA total number of subjects         | 0         |

Notes:

### Subjects enrolled per age group

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 1  |
| Adults (18-64 years)                      | 39 |
| From 65 to 84 years                       | 4  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Eight centers in Japan

### Pre-assignment

Screening details:

Twenty-one pulmonary arterial hypertension subjects who have never received sildenafil therapy entered the study from Part I period and could continue to study part II period. Twenty-three subjects who were continuously using sildenafil entered the study from Part II period.

### Period 1

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

### Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes  |
| <b>Arm title</b>             | Sildenafil: Subjects Who Entered the Study From Part I |

Arm description:

Consists of subjects who entered the study from Part I period in Week 0. The subjects were treated with sildenafil in Part I period (12 weeks) and Part II period (long-term treatment period, until a proper system was established to provide sildenafil to subjects after approval for the indication of pulmonary arterial hypertension). 19 subjects completed Part I period. 17 of 19 subjects continued from part I into Part II.

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

Dosage and administration details:

Subjects received sildenafil 20 mg three times a day orally in Part I period (12 weeks).

|                  |   |
|------------------|---|
| <b>Arm title</b> | Sildenafil: Subjects Who Entered the Study From Part II |
|------------------|---|

Arm description:

Consists of subjects who newly entered the study from Part II period in Week 0. The subjects were treated with sildenafil in Part II period (long-term treatment period, until a proper system was established to provide sildenafil to subjects after approval for the indication of pulmonary arterial hypertension).

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

Dosage and administration details:

Subjects received sildenafil 20 mg three times a day orally in Part II period.

| <b>Number of subjects in period 1</b> | Sildenafil: Subjects Who Entered the Study From Part I | Sildenafil: Subjects Who Entered the Study From Part II |
|---------------------------------------|--|---|
| Started                               | 21   | 23  |
| Completed                             | 17   | 21  |
| Not completed                         | 4  | 2   |
| Protocol violation                    | -  | 1   |
| Adverse event                         | 3  | 1   |
| Lack of efficacy                      | 1  | -   |

## Baseline characteristics

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Sildenafil: Subjects Who Entered the Study From Part I |
|-----------------------|--|

Reporting group description:

Consists of subjects who entered the study from Part I period in Week 0. The subjects were treated with sildenafil in Part I period (12 weeks) and Part II period (long-term treatment period, until a proper system was established to provide sildenafil to subjects after approval for the indication of pulmonary arterial hypertension). 19 subjects completed Part I period. 17 of 19 subjects continued from part I into Part II.

|                       |   |
|-----------------------|---|
| Reporting group title | Sildenafil: Subjects Who Entered the Study From Part II |
|-----------------------|---|

Reporting group description:

Consists of subjects who newly entered the study from Part II period in Week 0. The subjects were treated with sildenafil in Part II period (long-term treatment period, until a proper system was established to provide sildenafil to subjects after approval for the indication of pulmonary arterial hypertension).

| Reporting group values                       | Sildenafil: Subjects Who Entered the Study From Part I | Sildenafil: Subjects Who Entered the Study From Part II | Total |
|--|--|---|-------|
| Number of subjects                           | 21   | 23  | 44    |
| Age categorical<br>Units: Subjects           |  |   |       |
| Less than or equal to ( $\leq$ ) 18 years    | 0  | 1   | 1     |
| Between 18 and 65 years                      | 19   | 20  | 39    |
| greater than or equal to ( $\geq$ ) 65 years | 2  | 2   | 4     |
| Gender categorical<br>Units: Subjects        |  |   |       |
| Female                                       | 17   | 21  | 38    |
| Male   | 4  | 2   | 6     |
| Region of enrollment<br>Units: Subjects      |  |   |       |
| Japan  | 21   | 23  | 44    |

## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | Sildenafil: Subjects Who Entered the Study From Part I  |
| Reporting group description:<br>Consists of subjects who entered the study from Part I period in Week 0. The subjects were treated with sildenafil in Part I period (12 weeks) and Part II period (long-term treatment period, until a proper system was established to provide sildenafil to subjects after approval for the indication of pulmonary arterial hypertension). 19 subjects completed Part I period.17 of 19 subjects continued from part I into Part II.   |   |
| Reporting group title   | Sildenafil: Subjects Who Entered the Study From Part II |
| Reporting group description:<br>Consists of subjects who newly entered the study from Part II period in Week 0. The subjects were treated with sildenafil in Part II period (long-term treatment period, until a proper system was established to provide sildenafil to subjects after approval for the indication of pulmonary arterial hypertension).   |   |
| Subject analysis set title  | Sildenafil:Part I, Functional Class at Baseline: II     |
| Subject analysis set type   | Full analysis   |
| Subject analysis set description:<br>Consists of subjects who entered the study from Part I period in Week 0, and whose WHO functional class at baseline were II. The subjects were treated with sildenafil 20 mg three times a day orally in Part I period (12 weeks) and Part II period (long-term treatment period, until a proper system was established to provide sildenafil to subjects after approval for the indication of pulmonary arterial hypertension).   |   |
| Subject analysis set title  | Sildenafil, Part I, Functional Class at Baseline: III   |
| Subject analysis set type   | Full analysis   |
| Subject analysis set description:<br>Consists of subjects who entered the study from Part I period in Week 0, and whose WHO functional class at baseline were III. The subjects were treated with sildenafil 20 mg three times a day orally in Part I period (12 weeks) and Part II period (long-term treatment period, until a proper system was established to provide sildenafil to subjects after approval for the indication of pulmonary arterial hypertension).  |   |
| Subject analysis set title  | Sildenafil:Part II, Functional Class at Baseline: I     |
| Subject analysis set type   | Full analysis   |
| Subject analysis set description:<br>Consists of subjects who newly entered the study from Part II period in Week 0, and whose WHO functional class at baseline were I. The subjects had been receiving sildenafil at doses higher than 60 mg/day before the start of this study.The subjects were treated with sildenafil 20 mg three times a day orally in Part II period (long-term treatment period, until a proper system was established to provide sildenafil to subjects after approval for the indication of pulmonary arterial hypertension).   |   |
| Subject analysis set title  | Sildenafil:Part II, Functional Class at Baseline: II    |
| Subject analysis set type   | Full analysis   |
| Subject analysis set description:<br>Consists of subjects who newly entered the study from Part II period in Week 0, and whose WHO functional class at baseline were II. The subjects had been receiving sildenafil at doses higher than 60 mg/day before the start of this study.The subjects were treated with sildenafil 20 mg three times a day orally in Part II period (long-term treatment period, until a proper system was established to provide sildenafil to subjects after approval for the indication of pulmonary arterial hypertension).  |   |
| Subject analysis set title  | Sildenafil:Pharmacokinetic Analysis Subject             |
| Subject analysis set type   | Per protocol  |
| Subject analysis set description:<br>Consists of subjects who received sildenafil monotherapy, without administration of other treatment drugs for pulmonary arterial hypertension, in Part I or II, and satisfied the inclusion criteria for pharmacokinetics evaluation without violating the exclusion criteria. The subjects were treated with sildenafil 20 mg three times a day orally in Part I period (12 weeks) and Part II period (long term treatment period, until a proper system was established to provide sildenafil to subjects after approval for the indication of pulmonary arterial hypertension). |   |
| Subject analysis set title  | Sildenafil:Part II                                      |

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

#### Subject analysis set description:

Consists of subjects who newly entered the study from Part II period in Week 0 and had been receiving sildenafil at doses higher than 60 mg/day before the start of this study. The subjects were treated with sildenafil 20 mg three times a day orally in Part II period (long-term treatment period, until a proper system was established to provide sildenafil to subjects after approval for the indication of pulmonary arterial hypertension).

|                            |                                |
|----------------------------|--------------------------------|
| Subject analysis set title | Sildenafil: Part I and Part II |
|----------------------------|--------------------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

#### Subject analysis set description:

Consists of subjects who entered the study from Part I period plus subjects who entered the study from Part II period.

### Primary: Change in the 6-minute Walk Distance From Baseline at Week 12 in Subjects Who Entered the Study From Part I

|                 |   |
|-----------------|---|
| End point title | Change in the 6-minute Walk Distance From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[1][2]</sup> |
|-----------------|---|

#### End point description:

Change 6-minute walk distance at Week 12 minus 6-minute walk distance at baseline. The 6-minute walk distance: total distance walked during the 6-minute walk test. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

#### End point timeframe:

Baseline, Week 12

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be reported for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was reported for Part I and Part II separately.

| End point values                     | Sildenafil: Subjects Who Entered the Study From Part I |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: meters                        |  |  |  |  |
| arithmetic mean (standard deviation) | 84.2 (± 74.9)  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Change in the Mean Pulmonary Arterial Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I

|                 |   |
|-----------------|---|
| End point title | Change in the Mean Pulmonary Arterial Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[3][4]</sup> |
|-----------------|---|

#### End point description:

Change: Mean pulmonary arterial pressure at Week 12 minus mean pulmonary arterial pressure at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had

efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Week 12

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be reported for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: millimeter of mercury (mm Hg) |  |  |  |  |
| arithmetic mean (standard deviation) | -4.7 (± 8.2)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Change in the Pulmonary Vascular Resistance From Baseline at Week 12 in Subjects Who Entered the Study From Part I

|                 |  |
|-----------------|--|
| End point title | Change in the Pulmonary Vascular Resistance From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[5]</sup> <sup>[6]</sup> |
|-----------------|--|

End point description:

ChangePulmonary vascular resistance at Week 12 minus pulmonary vascular resistance at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Week 12

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be reported for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: dyne*second per centimeter^5  |  |  |  |  |
| arithmetic mean (standard deviation) | -246.49 (±   |  |  |  |



## Statistical analyses

No statistical analyses for this end point

### Primary: Change in the Cardiac Output From Baseline at Week 12 in Subjects Who Entered the Study From Part I

|                 |   |
|-----------------|---|
| End point title | Change in the Cardiac Output From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[7][8]</sup> |
|-----------------|---|

End point description:

ChangeCardiac output at Week 12 minus cardiac output at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Week 12

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be reported for this endpoint.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

| End point values                 | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group  |  |  |  |
| Number of subjects analysed      | 20   |  |  |  |
| Units: liter per minute          |  |  |  |  |
| arithmetic mean (standard error) | 0.556 (± 1)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in the 6-minute Walk Distance From Baseline at Week 8 in Subjects Who Entered the Study From Part I

|                 |   |
|-----------------|---|
| End point title | Change in the 6-minute Walk Distance From Baseline at Week 8 in Subjects Who Entered the Study From Part I <sup>[9]</sup> |
|-----------------|---|

End point description:

Change6-minute walk distance at Week 8 minus 6-minute walk distance at baseline.The 6-minute walk distance:Total distance walked during the 6- minute walk test. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 8

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: This endpoint was planned to be represented in Part 1 only.

| End point values                     | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 19   |  |  |  |
| Units: meters                        |  |  |  |  |
| arithmetic mean (standard deviation) | 87.5 ( $\pm$ 75.3)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in the Systolic Pulmonary Arterial Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I

|                 |   |
|-----------------|---|
| End point title | Change in the Systolic Pulmonary Arterial Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[10]</sup> |
|-----------------|---|

End point description:

ChangeSystolic pulmonary arterial pressure at Week 12 minus Systolic pulmonary arterial pressure at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

| End point values                     | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: mm Hg                         |  |  |  |  |
| arithmetic mean (standard deviation) | -3.4 ( $\pm$ 13.4)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Change in the Diastolic Pulmonary Arterial Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I**

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|                 |  |
|-----------------|--|
| End point title | Change in the Diastolic Pulmonary Arterial Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[11]</sup> |
|-----------------|--|

End point description:

ChangeDiastolic pulmonary arterial pressure at Week 12 minus diastolic pulmonary arterial pressure at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: mm Hg                         |  |  |  |  |
| arithmetic mean (standard deviation) | -3.2 (± 8.3)   |  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Change in the Systolic Systemic Blood Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I**

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|                 |   |
|-----------------|---|
| End point title | Change in the Systolic Systemic Blood Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[12]</sup> |
|-----------------|---|

End point description:

ChangeSystolic systemic blood pressure at Week 12 minus systolic systemic blood pressure at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

| End point values                     | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: mm Hg                         |  |  |  |  |
| arithmetic mean (standard deviation) | 0.7 (± 16.5)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in the Diastolic Systemic Blood Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I

|                 |  |
|-----------------|--|
| End point title | Change in the Diastolic Systemic Blood Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[13]</sup> |
|-----------------|--|

End point description:

ChangeDiastolic systemic blood pressure at Week 12 minus diastolic systemic blood pressure at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

| End point values                     | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: mmHg                          |  |  |  |  |
| arithmetic mean (standard deviation) | -3.1 (± 9)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in the Mean Systemic Blood Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I

|                 |   |
|-----------------|---|
| End point title | Change in the Mean Systemic Blood Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[14]</sup> |
|-----------------|---|

End point description:

Mean systemic blood pressure:(diastolic blood pressure+(systolic blood pressure-diastolic blood

pressure) divided by 3. ChangeMean systemic blood pressure at Week 12 minus mean systemic blood pressure at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 12    |           |

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: mm Hg                         |  |  |  |  |
| arithmetic mean (standard deviation) | -0.9 (± 12.9)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in the Pulmonary Capillary Wedge Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I

|                 |   |
|-----------------|---|
| End point title | Change in the Pulmonary Capillary Wedge Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[15]</sup> |
|-----------------|---|

End point description:

ChangePulmonary capillary wedge pressure at Week 12 minus pulmonary capillary wedge pressure at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 12    |           |

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: mm Hg                         |  |  |  |  |
| arithmetic mean (standard deviation) | 0.68 (± 3.14)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in the Right Atrial Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I

|                 |  |
|-----------------|--|
| End point title | Change in the Right Atrial Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[16]</sup> |
|-----------------|--|

End point description:

ChangeRight atrial pressure at Week 12 minus right atrial pressure at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was reported for Part I and Part II separately.

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: mm Hg                         |  |  |  |  |
| arithmetic mean (standard deviation) | -0.3 (± 4.4)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in the Cardiac Index From Baseline at Week 12 in Subjects Who Entered the Study From Part I

|                 |  |
|-----------------|--|
| End point title | Change in the Cardiac Index From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[17]</sup> |
|-----------------|--|

End point description:

ChangeCardiac index at Week 12 minus cardiac index at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

| End point values                               | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
|--|--|--|--|--|
| Subject group type                             | Reporting group  |  |  |  |
| Number of subjects analysed                    | 20   |  |  |  |
| Units: liter per minute per meter <sup>2</sup> |  |  |  |  |
| arithmetic mean (standard deviation)           | 0.32 (± 0.62)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in the Heart Rate From Baseline at Week 12 in Subjects Who Entered the Study From Part I

|                 |   |
|-----------------|---|
| End point title | Change in the Heart Rate From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[18]</sup> |
|-----------------|---|

End point description:

ChangeHeart rate at Week 12 minus heart rate at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

| End point values                     | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: beats/minute                  |  |  |  |  |
| arithmetic mean (standard deviation) | -4.14 (± 7.45)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

---

**Secondary: Change in the Pulmonary Vascular Resistance Index From Baseline at Week 12 in Subjects Who Entered the Study From Part I**

---

|                 |  |
|-----------------|--|
| End point title | Change in the Pulmonary Vascular Resistance Index From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[19]</sup> |
|-----------------|--|

End point description:

Change:Pulmonary vascular resistance index at Week 12 minus pulmonary vascular resistance index at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

|  |  |  |  |  |
|--|--|--|--|--|
| <b>End point values</b>                    | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
| Subject group type                         | Reporting group  |  |  |  |
| Number of subjects analysed                | 20   |  |  |  |
| Units:<br>dyne*second/centimeter^5/meter^2 |  |  |  |  |
| arithmetic mean (standard deviation)       | -382 (± 491.8)   |  |  |  |

---

**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Change in the Systemic Vascular Resistance From Baseline at Week 12 in Subjects Who Entered the Study From Part I**

---

|                 |   |
|-----------------|---|
| End point title | Change in the Systemic Vascular Resistance From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[20]</sup> |
|-----------------|---|

End point description:

ChangeSystemic vascular resistance at Week 12 minus systemic vascular resistance at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.



| End point values                     | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: dyne*second/centimeter^5      |  |  |  |  |
| arithmetic mean (standard deviation) | -265.77 (±<br>785.52)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in the Systemic Vascular Resistance Index From Baseline at Week 12 in Subjects Who Entered the Study From Part I

|                 |   |
|-----------------|---|
| End point title | Change in the Systemic Vascular Resistance Index From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[21]</sup> |
|-----------------|---|

End point description:

ChangeSystemic vascular resistance index at Week 12 minus systemic vascular resistance index at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

| End point values                           | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
|--|--|--|--|--|
| Subject group type                         | Reporting group  |  |  |  |
| Number of subjects analysed                | 20   |  |  |  |
| Units:<br>dyne*second/centimeter^5/meter^2 |  |  |  |  |
| arithmetic mean (standard deviation)       | -409.89 (±<br>1271.3)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in the Mixed Venous Oxygen Saturation From Baseline at Week 12 in Subjects Who Entered the Study From Part I

|                 |  |
|-----------------|--|
| End point title | Change in the Mixed Venous Oxygen Saturation From Baseline |
|-----------------|--|

## End point description:

ChangeMixed venous oxygen saturation at Week 12 minus mixed venous oxygen saturation at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

## Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

| End point values                     | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: percent saturation            |  |  |  |  |
| arithmetic mean (standard deviation) | 2.91 (± 9.05)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Change in the Arterial Oxygen Saturation From Baseline at Week 12 in Subjects Who Entered the Study From Part I**

|                 |   |
|-----------------|---|
| End point title | Change in the Arterial Oxygen Saturation From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[23]</sup> |
|-----------------|---|

## End point description:

ChangeArterial oxygen saturation at Week 12 minus arterial oxygen saturation at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

## Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

| End point values                     | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: percent saturation            |  |  |  |  |
| arithmetic mean (standard deviation) | 0.44 (± 5.437)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in the Arterial Oxygen Partial Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I

|                 |   |
|-----------------|---|
| End point title | Change in the Arterial Oxygen Partial Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[24]</sup> |
|-----------------|---|

End point description:

ChangeArterial oxygen partial pressure at Week 12 minus arterial oxygen partial pressure at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: mm Hg                         |  |  |  |  |
| arithmetic mean (standard deviation) | -2.02 (±<br>11.17)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in the Partial Pressure of Mixed Venous Oxygen From Baseline at Week 12 in Subjects Who Entered the Study From Part I

|                 |  |
|-----------------|--|
| End point title | Change in the Partial Pressure of Mixed Venous Oxygen From Baseline at Week 12 in Subjects Who Entered the Study From Part I <sup>[25]</sup> |
|-----------------|--|

End point description:

ChangePartial pressure of mixed venous oxygen at Week 12 minus partial pressure of mixed venous oxygen at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to be represented in Part 1 only.

| End point values                     | Sildenafil: Subjects Who Entered the Study From Part I |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 19   |  |  |  |
| Units: mm Hg                         |  |  |  |  |
| arithmetic mean (standard deviation) | 0.57 (± 4.35)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Changes in the World Health Organization (WHO) Functional Class of Pulmonary Arterial Hypertension From Baseline at Weeks 12 in Subjects Who Entered the Study From Part I

|                 |  |
|-----------------|--|
| End point title | Changes in the World Health Organization (WHO) Functional Class of Pulmonary Arterial Hypertension From Baseline at Weeks 12 in Subjects Who Entered the Study From Part I |
|-----------------|--|

End point description:

The cross-tabulation table on the WHO functional classes of pulmonary arterial hypertension at baseline and Week 12. The WHO functional classes of pulmonary arterial hypertension: Class I (pulmonary arterial hypertension patients with no limitation in physical activity) to Class IV (pulmonary arterial hypertension patients who can not perform a physical activity without any symptoms). There were no subjects reported under WHO Functional Class I and IV. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

| End point values                | Sildenafil: Part I, Functional Class at Baseline: II | Sildenafil, Part I, Functional Class at Baseline: III |  |  |
|---------------------------------|--|---|--|--|
| Subject group type              | Subject analysis set                                 | Subject analysis set                                  |  |  |
| Number of subjects analysed     | 7  | 13  |  |  |
| Units: subjects                 |  |   |  |  |
| Functional class at Week 12:I   | 0  | 1   |  |  |
| Functional class at Week 12:II  | 6  | 5   |  |  |
| Functional class at Week 12:III | 1  | 7   |  |  |
| Functional class at Week 12:IV  | 0  | 0   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Changes in the BORG Dyspnoea Score From Baseline at Week 8 and Week 12 in Subjects Who Entered the Study From Part I

|                 |  |
|-----------------|--|
| End point title | Changes in the BORG Dyspnoea Score From Baseline at Week 8 and Week 12 in Subjects Who Entered the Study From Part I <sup>[26]</sup> |
|-----------------|--|

End point description:

Change BORG dyspnoea score at Week 8 and Week 12 minus BORG dyspnoea score at baseline. BORG dyspnoea score: Scale 0 (no breathlessness at all) to 10 (maximum). The score reflected the maximum degree of dyspnoea that the subjects experienced at any time during the 6-minute walk distance. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward (Week 12).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 8, Week 12

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was reported for Part I and Part II separately.

| End point values                     | Sildenafil:<br>Subjects Who<br>Entered the<br>Study From<br>Part I |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: scores on a scale             |  |  |  |  |
| arithmetic mean (standard deviation) |  |  |  |  |
| Week 8 (n=19)                        | -0.84 (± 1.89)   |  |  |  |
| Week 12 (n=20)                       | -0.95 (± 1.94)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Changes in the the Plasma Brain Natriuretic Peptide Level From Baseline at Week 4, Week 8 and Week 12 in Subjects Who Entered the Study From Part I

|                 |   |
|-----------------|---|
| End point title | Changes in the the Plasma Brain Natriuretic Peptide Level From Baseline at Week 4, Week 8 and Week 12 in Subjects Who Entered the Study From Part I <sup>[27]</sup> |
|-----------------|---|

End point description:

Change Plasma brain natriuretic peptide level at Week 4, Week 8 and Week 12 minus plasma brain

natriuretic peptide level at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward (Week 12).

|                                   |           |
|-----------------------------------|-----------|
| End point type                    | Secondary |
| End point timeframe:              |           |
| Baseline, Week 4, Week 8, Week 12 |           |

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was reported for Part I and Part II separately.

| End point values                     | Sildenafil: Subjects Who Entered the Study From Part I |  |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 20   |  |  |  |
| Units: picograms/milliliter          |  |  |  |  |
| arithmetic mean (standard deviation) |  |  |  |  |
| Week 4 (n=20)                        | -78 (± 166.41)   |  |  |  |
| Week 8 (n=19)                        | -88.25 (± 178.39)                                      |  |  |  |
| Week 12 (n=20)                       | -61.82 (± 209.96)                                      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in the 6-minute Walk Distance From Baseline at Week 12 in Subjects Who Newly Entered the Study From Part II

|                 |  |
|-----------------|--|
| End point title | Change in the 6-minute Walk Distance From Baseline at Week 12 in Subjects Who Newly Entered the Study From Part II |
|-----------------|--|

End point description:

Change 6-minute walk distance at Week 12 minus 6-minute walk distance at baseline. The 6-minute walk distance: Total distance walked during the 6-minute walk test. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 12    |           |

| End point values                     | Sildenafil: Part II  |  |  |  |
|--------------------------------------|----------------------|--|--|--|
| Subject group type                   | Subject analysis set |  |  |  |
| Number of subjects analysed          | 6                    |  |  |  |
| Units: meters                        |                      |  |  |  |
| arithmetic mean (standard deviation) | -23.5 (± 34.1)       |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in the World Health Organization (WHO) Functional Class From Baseline at Week 12 in Subjects Who Newly Entered the Study From Part II

|                 |  |
|-----------------|--|
| End point title | Change in the World Health Organization (WHO) Functional Class From Baseline at Week 12 in Subjects Who Newly Entered the Study From Part II |
|-----------------|--|

#### End point description:

The cross-tabulation table on the WHO functional classes of pulmonary arterial hypertension at baseline and Week 12. The WHO functional classes of pulmonary arterial hypertension: Class I (pulmonary arterial hypertension patients with no limitation in physical activity) to Class IV (pulmonary arterial hypertension patients who can not perform a physical activity without any symptoms). There were no subjects reported under WHO Functional Class III and IV. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

#### End point timeframe:

Baseline, Week 12

| End point values                 | Sildenafil:Part II, Functional Class at Baseline: I | Sildenafil:Part II, Functional Class at Baseline: II |  |  |
|----------------------------------|---|--|--|--|
| Subject group type               | Subject analysis set                                | Subject analysis set                                 |  |  |
| Number of subjects analysed      | 1   | 6  |  |  |
| Units: subjects                  |   |  |  |  |
| Functional class at Week 12: I   | 1   | 0  |  |  |
| Functional class at Week 12: II  | 0   | 5  |  |  |
| Functional class at Week 12: III | 0   | 1  |  |  |
| Functional class at Week 12: IV  | 0   | 0  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Changes in the BORG Dyspnoea Score From Baseline at Week 12 in Subjects Who Newly Entered the Study From Part II

|                 |  |
|-----------------|--|
| End point title | Changes in the BORG Dyspnoea Score From Baseline at Week 12 in Subjects Who Newly Entered the Study From Part II |
|-----------------|--|

#### End point description:

Change BORG dyspnoea score at Week 12 minus BORG dyspnoea score at baseline. BORG dyspnoea score: Scale 0 (no breathlessness at all) to 10 (maximum). The score reflected the maximum degree of

dyspnoea that the subjects experienced at any time during the 6-minute walk distance. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 12    |           |

|                                      |                      |  |  |  |
|--------------------------------------|----------------------|--|--|--|
| <b>End point values</b>              | Sildenafil:Part II   |  |  |  |
| Subject group type                   | Subject analysis set |  |  |  |
| Number of subjects analysed          | 6                    |  |  |  |
| Units: scores on a scale             |                      |  |  |  |
| arithmetic mean (standard deviation) | 0.33 ( $\pm$ 1.21)   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Changes in the Plasma Brain Natriuretic Peptide Level From Baseline at Week 12 in Subjects Who Newly Entered the Study From Part II

|                 |   |
|-----------------|---|
| End point title | Changes in the Plasma Brain Natriuretic Peptide Level From Baseline at Week 12 in Subjects Who Newly Entered the Study From Part II |
|-----------------|---|

End point description:

ChangePlasma brain natriuretic peptide level at Week 12 minus plasma brain natriuretic peptide level at baseline. Full Analysis Set, including subjects who took at least one dose of study medication and had efficacy measurements at both baseline and post-baseline. Last observation carried forward.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Week 12    |           |

|                                      |                      |  |  |  |
|--------------------------------------|----------------------|--|--|--|
| <b>End point values</b>              | Sildenafil:Part II   |  |  |  |
| Subject group type                   | Subject analysis set |  |  |  |
| Number of subjects analysed          | 6                    |  |  |  |
| Units: picograms/milliliter          |                      |  |  |  |
| arithmetic mean (standard deviation) | 15.91 ( $\pm$ 55.94) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum Plasma Concentrations (C<sub>max</sub>) of Sildenafil and Sildenafil's



**Metabolite, UK-103,320**

|                 |  |
|-----------------|--|
| End point title | Maximum Plasma Concentrations (Cmax) of Sildenafil and Sildenafil's Metabolite, UK-103,320 |
|-----------------|--|

End point description:

Maximum plasma concentrations was calculated from the observed value of plasma concentrations in each subjects.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8 hours after dosing

|                                      |   |  |  |  |
|--------------------------------------|---|--|--|--|
| <b>End point values</b>              | Sildenafil:Pharmacokinetic Analysis Subject |  |  |  |
| Subject group type                   | Subject analysis set                        |  |  |  |
| Number of subjects analysed          | 9   |  |  |  |
| Units: nanograms/milliliter          |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |
| Sildenafil                           | 164.88 (± 74.78)                            |  |  |  |
| Sildenafil's Metabolite, UK-103,320  | 87.27 (± 30.67)                             |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Time to First Occurrence of Maximum Plasma Concentrations (Tmax) of Sildenafil and Sildenafil's Metabolite, UK-103,320**

|                 |  |
|-----------------|--|
| End point title | Time to First Occurrence of Maximum Plasma Concentrations (Tmax) of Sildenafil and Sildenafil's Metabolite, UK-103,320 |
|-----------------|--|

End point description:

Time to first occurrence of maximum plasma concentrations were calculated from the observed value of plasma concentrations in each subject.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8 hours after dosing

|                                      |   |  |  |  |
|--------------------------------------|---|--|--|--|
| <b>End point values</b>              | Sildenafil:Pharmacokinetic Analysis Subject |  |  |  |
| Subject group type                   | Subject analysis set                        |  |  |  |
| Number of subjects analysed          | 9   |  |  |  |
| Units: hours                         |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |

|                                     |                      |  |  |  |
|-------------------------------------|----------------------|--|--|--|
| Sildenafil                          | 1.102 ( $\pm$ 0.499) |  |  |  |
| Sildenafil's Metabolite, UK-103,320 | 1.611 ( $\pm$ 1.024) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: The Area Under the Curve (AUC) From Time 0 to Time 8 Hour of Sildenafil and Sildenafil's Metabolite, UK-103,320

|                 |   |
|-----------------|---|
| End point title | The Area Under the Curve (AUC) From Time 0 to Time 8 Hour of Sildenafil and Sildenafil's Metabolite, UK-103,320 |
|-----------------|---|

End point description:

The area under the curve from time 0 to time 8 hour was calculated from area under the curve in each subject on the date of blood sampling using the linear/log trapezoidal rule.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8 hours after dosing

|                                      |   |  |  |  |
|--------------------------------------|---|--|--|--|
| <b>End point values</b>              | Sildenafil:Phar<br>macokinetic<br>Analysis<br>Subject |  |  |  |
| Subject group type                   | Subject analysis set                                  |  |  |  |
| Number of subjects analysed          | 9   |  |  |  |
| Units: nanogram*hour/milliliter      |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |
| Sildenafil                           | 545.14 ( $\pm$ 294.88)                                |  |  |  |
| Sildenafil's Metabolite, UK-103,320  | 365.85 ( $\pm$ 186.55)                                |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: The Average Plasma Concentration (C<sub>ss,av</sub>) of Sildenafil at Steady State

|                 |  |
|-----------------|--|
| End point title | The Average Plasma Concentration (C <sub>ss,av</sub> ) of Sildenafil at Steady State |
|-----------------|--|

End point description:

The average plasma concentration of sildenafil at steady state was calculated from the area under the curve from time 0 to 8 hour/dosing interval (8 hours).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8 hours after dosing

|                                      |   |  |  |  |
|--------------------------------------|---|--|--|--|
| <b>End point values</b>              | Sildenafil:Phar<br>macokinetic<br>Analysis<br>Subject |  |  |  |
| Subject group type                   | Subject analysis set                                  |  |  |  |
| Number of subjects analysed          | 9   |  |  |  |
| Units: nanograms/milliliter          |   |  |  |  |
| arithmetic mean (standard deviation) | 68.14 ( $\pm$<br>36.86)                               |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: The Average Plasma Trough Concentration (C<sub>trough</sub>) of Sildenafil

|                 |  |
|-----------------|--|
| End point title | The Average Plasma Trough Concentration (C <sub>trough</sub> ) of Sildenafil |
|-----------------|--|

End point description:

The average plasma trough concentration of sildenafil was calculated from the observed value before administration of the drug in each subjects.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8 hours after dosing

|                                      |   |  |  |  |
|--------------------------------------|---|--|--|--|
| <b>End point values</b>              | Sildenafil:Phar<br>macokinetic<br>Analysis<br>Subject |  |  |  |
| Subject group type                   | Subject analysis set                                  |  |  |  |
| Number of subjects analysed          | 9   |  |  |  |
| Units: nanograms/milliliter          |   |  |  |  |
| arithmetic mean (standard deviation) | 19.608 ( $\pm$<br>12.438)                             |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Laboratory Test Abnormalities (Without Regard to Baseline Abnormality)

|                 |  |
|-----------------|--|
| End point title | Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) |
|-----------------|--|

---

End point description:

The total number of subjects with laboratory test abnormalities without regard to baseline abnormality. All subjects who received at least one dose of the study medication and had any evaluable laboratory test data after treatment.

---

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

---

End point timeframe:

Baseline up to 1.3 years

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|                             |                                |  |  |  |
|-----------------------------|--------------------------------|--|--|--|
| <b>End point values</b>     | Sildenafil: Part I and Part II |  |  |  |
| Subject group type          | Subject analysis set           |  |  |  |
| Number of subjects analysed | 43                             |  |  |  |
| Units: subjects             | 35                             |  |  |  |

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after last dose of study treatment .

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 | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

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

### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Sildenafil Part I and Part II |
|-----------------------|-------------------------------|

Reporting group description:

Consists of subjects who entered the study from Part I period plus subjects who entered the study from Part II period.

| Serious adverse events                            | Sildenafil Part I and Part II |  |  |
|---|-------------------------------|--|--|
| Total subjects affected by serious adverse events |                               |  |  |
| subjects affected / exposed                       | 7 / 44 (15.91%)               |  |  |
| number of deaths (all causes)                     | 0                             |  |  |
| number of deaths resulting from adverse events    | 0                             |  |  |
| Investigations                                    |                               |  |  |
| Platelet count decreased                          |                               |  |  |
| subjects affected / exposed                       | 1 / 44 (2.27%)                |  |  |
| occurrences causally related to treatment / all   | 0 / 1                         |  |  |
| deaths causally related to treatment / all        | 0 / 0                         |  |  |
| Cardiac disorders                                 |                               |  |  |
| Cardiac failure                                   |                               |  |  |
| subjects affected / exposed                       | 2 / 44 (4.55%)                |  |  |
| occurrences causally related to treatment / all   | 0 / 3                         |  |  |
| deaths causally related to treatment / all        | 0 / 0                         |  |  |
| Eye disorders                                     |                               |  |  |
| Cataract  |                               |  |  |
| subjects affected / exposed                       | 1 / 44 (2.27%)                |  |  |
| occurrences causally related to treatment / all   | 0 / 1                         |  |  |
| deaths causally related to treatment / all        | 0 / 0                         |  |  |
| Gastrointestinal disorders                        |                               |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Nausea  |                |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Pulmonary hypertension                          |                |  |  |
| subjects affected / exposed                     | 2 / 44 (4.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Scleroderma renal crisis                        |                |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Nasopharyngitis                                 |                |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia                                       |                |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Decreased appetite                              |                |  |  |
| subjects affected / exposed                     | 2 / 44 (4.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

|   |                               |  |  |
|---|-------------------------------|--|--|
| <b>Non-serious adverse events</b>                     | Sildenafil Part I and Part II |  |  |
| Total subjects affected by non-serious adverse events |                               |  |  |
| subjects affected / exposed                           | 34 / 44 (77.27%)              |  |  |

|  |   |  |  |
|--|---|--|--|
| Investigations<br>Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)   | 3 / 44 (6.82%)<br>3                               |  |  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all)   | 4 / 44 (9.09%)<br>4                               |  |  |
| Vascular disorders<br>Flushing<br>subjects affected / exposed<br>occurrences (all)   | 10 / 44 (22.73%)<br>11                            |  |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)                                    | 4 / 44 (9.09%)<br>4<br><br>11 / 44 (25.00%)<br>12 |  |  |
| General disorders and administration site conditions<br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)<br><br>Pyrexia<br>subjects affected / exposed<br>occurrences (all) | 3 / 44 (6.82%)<br>3<br><br>5 / 44 (11.36%)<br>5   |  |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 4 / 44 (9.09%)<br>4                               |  |  |
| Reproductive system and breast disorders<br>Dysmenorrhoea<br>subjects affected / exposed<br>occurrences (all)  | 2 / 44 (4.55%)<br>2                               |  |  |
| Respiratory, thoracic and mediastinal disorders  |   |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| Cough<br>subjects affected / exposed<br>occurrences (all)  | 3 / 44 (6.82%)<br>4    |  |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)  | 3 / 44 (6.82%)<br>5    |  |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                            | 3 / 44 (6.82%)<br>3    |  |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 3 / 44 (6.82%)<br>3    |  |  |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)               | 17 / 44 (38.64%)<br>21 |  |  |



## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported