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 typographical error was observed in one of the outcome 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, ClinicalTrials.govCallCenter@pfizer.com
Scientific contact	ClinicalTrials.gov Call Center, Pfizer Inc, 001 800-718-1021, 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
Arm title	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).

Arm title	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.

Number of subjects in period 1	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 Units: Subjects			
Less than or equal to (<=) 18 years	0	1	1
Between 18 and 65 years	19	20	39
greater than or equal to (>=) 65 years	2	2	4
Gender categorical Units: Subjects			
Female	17	21	38
Male	4	2	6
Region of enrollment 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:

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).

Subject analysis set title	Sildenafil:Part I, Functional Class at Baseline: II
Subject analysis set type	Full analysis

Subject analysis set description:

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:

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:

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:

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:

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[1][2]

End point description:

Change6-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[3][4]

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.

End point values	Sildenafil: Subjects Who Entered the Study From 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[5][6]

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.

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

	301.17)

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[7][8]

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: Subjects Who Entered the Study From 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[9]

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: Subjects Who Entered the Study From Part I			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: meters				
arithmetic mean (standard deviation)	87.5 (± 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[10]

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: Subjects Who Entered the Study From Part I			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: mm Hg				
arithmetic mean (standard deviation)	-3.4 (± 13.4)			

Statistical analyses

No statistical analyses for this end point

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

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

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.

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Change in the Systolic Systemic Blood Pressure From Baseline at Week 12 in Subjects Who Entered the Study From Part I[12]

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: Subjects Who Entered the Study From 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[13]

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: Subjects Who Entered the Study From 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[14]

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.

End point values	Sildenafil: Subjects Who Entered the Study From 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[15]

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.

End point values	Sildenafil: Subjects Who Entered the Study From 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[16]

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.

End point values	Sildenafil: Subjects Who Entered the Study From 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[17]

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: Subjects Who Entered the Study From Part I			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: liter per minute per meter^2				
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[18]

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: Subjects Who Entered the Study From 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[19]

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.

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

Statistical analyses

No statistical analyses for this end point

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[20]

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: Subjects Who Entered the Study From Part I			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: dyne*second/centimeter^5				
arithmetic mean (standard deviation)	-265.77 (± 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[21]

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

	at Week 12 in Subjects Who Entered the Study From Part I[22]

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: Subjects Who Entered the Study From 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[23]

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: Subjects Who Entered the Study From 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[24]

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.

End point values	Sildenafil: Subjects Who Entered the Study From Part I			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: mm Hg				
arithmetic mean (standard deviation)	-2.02 (± 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[25]

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[26]

End point description:

ChangeBORG 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: Subjects Who Entered the Study From 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[27]

End point description:

ChangePlasma 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) Week 8 (n=19) Week 12 (n=20)	-78 (± 166.41) -88.25 (± 178.39) -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:

Change6-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:

ChangeBORG 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

End point values	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 (± 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

End point values	Sildenafil:Part II			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: picograms/milliliter				
arithmetic mean (standard deviation)	15.91 (± 55.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentrations (Cmax) 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

End point values	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

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

Sildenafil Sildenafil's Metabolite, UK-103,320	1.102 (± 0.499) 1.611 (± 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

End point values	Sildenafil:Pharmacokinetic Analysis Subject			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: nanogram*hour/milliliter				
arithmetic mean (standard deviation)				
Sildenafil Sildenafil's Metabolite, UK-103,320	545.14 (± 294.88) 365.85 (± 186.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Average Plasma Concentration (Css,av) of Sildenafil at Steady State

End point title	The Average Plasma Concentration (Css,av) 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

End point values	Sildenafil:Pharmacokinetic Analysis Subject			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: nanograms/milliliter				
arithmetic mean (standard deviation)	68.14 (± 36.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Average Plasma Trough Concentration (Ctrough) of Sildenafil

End point title	The Average Plasma Trough Concentration (Ctrough) 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

End point values	Sildenafil:Pharmacokinetic Analysis Subject			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: nanograms/milliliter				
arithmetic mean (standard deviation)	19.608 (± 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

End point values	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 %

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported